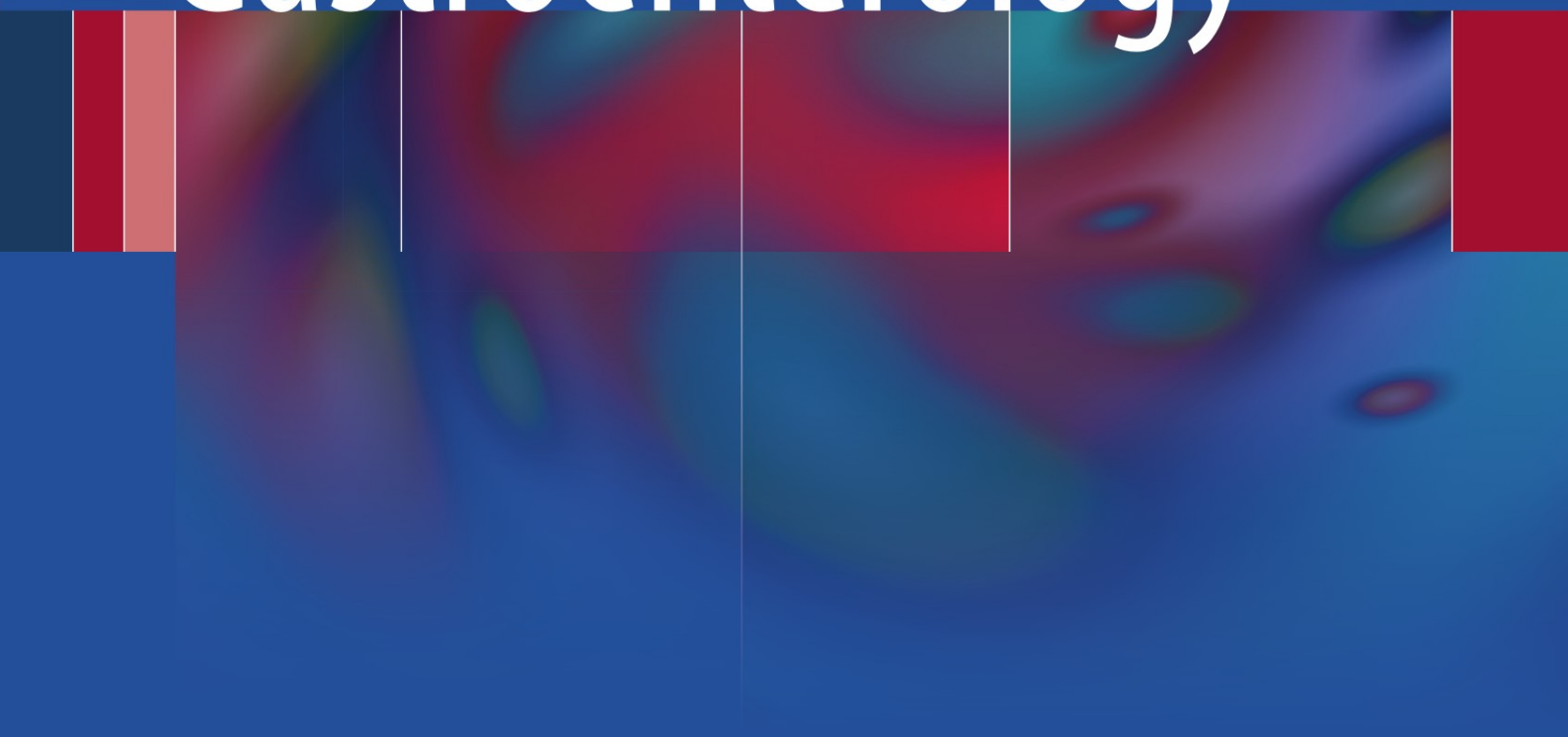
C. S. Pitchumoni
T. S. Dharmarajan
Editors

Geriatric Gastroenterology



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Geriatric Gastroenterology

C.S. Pitchumoni • T.S. Dharmarajan
Editors

Geriatric Gastroenterology

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Dedicated to my parents,
My wife, Prema
And children Sheila, Shoba and Suresh
For love, encouragement and understanding!

CSP

Dedicated to my mother,
My wife, Lekshmi,
And, Kumar and Kavita,
With love and gratitude,

TSD

Foreword

The definition of old age is not a clear one; most societies use arbitrary language to define 'the older adult.' One hundred years ago, old age was defined as 'any age after fifty.' Later, criteria such as pension schemes evolved to define the older adult, and ages 60 to 65 are numbers still accepted today. The term 'geriatrics' means 'related to the aged' and geriatric medicine deals with 'medical problems of old age.' Aging is associated with a gradual decline in physiologic processes, along with susceptibility to disease. The needs of the old differ from those of the young. Geriatric patients often present atypically. Both evaluation and care differ. Decision-making is influenced not only by the disease process itself, but also by life expectancy, quality of life issues and patient choices. This book deals with both the physiologic and pathologic changes in the gastrointestinal system as the aging process advances, and with the evaluation and care appropriate to the older age group.

The gastroenterology and geriatric medicine disciplines are fortunate to have two experienced editors in Dr. Pitchumoni and Dr. Dharmarajan: they have conceived this book and have brought it to fruition. They are distinguished educators and clinicians who have achieved national and international respect in the fields of gastroenterology, internal medicine and geriatrics. As authors and editors, they have been collaborating for over three decades. Having co-authored a series of articles in geriatric gastroenterology in peer-reviewed journals, they have now taken a step further in the design and execution of this work. The diverse backgrounds of the two editors bring strength and breadth to this ambitious text.

Both editors have spent the majority of their professional careers in academic gastroenterology and geriatric medicine respectively. They have published extensively and have served on the editorial boards of prestigious journals. Dr. Pitchumoni, a recognized master teacher, is a Master of both the American College of Physicians and the American College of Gastroenterology. He has advanced degrees and board certification in the fields of internal medicine, gastroenterology, clinical nutrition and public health. Although he considers this author to be his mentor, I have certainly reaped equal benefit from our personal and professional relationship over the years.

Dr. Dharmarajan, a dedicated geriatrician, developed one of the largest known acute care hospital geriatric programs and associated geriatric medicine fellowships. He also serves as Associate Dean of his affiliated medical school. In 1998, he published "Launching a Geriatric Unit" in *Health Progress*. The two continued their academic alliance in 2002 with the publication "Geriatric Medicine Programs in India: Has the Time Arrived?" in the *Journal of Association of Physicians India*. The present book joins several other textbooks previously edited by this fine team of scholars.

This is not just another gastroenterology textbook. The design is unique in providing contemporary information in the field of gastroenterology pertinent to the older adult.

Although not the first book in geriatric gastroenterology, this first edition is conceptually bold and novel. The text is a state of the art, comprehensive and practical approach to the clinical practice of internal medicine, geriatrics and gastroenterology. The references are updated

and current clinical practice guidelines are appropriately presented. The book impresses me as one meant for the practicing physician as well as the resident in training and the fellow in geriatric medicine or gastroenterology. Key points at the end of every chapter summarize the highlights. Every chapter is amply supplemented with easy- to-understand tables and figures. Two chapters are devoted to radiologic images of gastrointestinal disorders in the aged. A chapter dealing with gastrointestinal pathology is rich in photographs of virtually every common gastrointestinal disorder in the elderly. The book as a whole is liberally illustrated with high quality images and clear captions.

The editors have done an excellent job in their plan and execution of the contents. Seventy-two chapters are presented in fourteen sections. Introductory chapters present the perspectives of the editors as geriatrician and gastroenterologist. These are followed by a chapter on future trends in health care, and enable clinicians become knowledgeable on management of gastrointestinal disorders in the aged population, a view supported by the American College of Gastroenterology. Chapters follow on the basic sciences and principles of gastroenterology in the context of the older adult and the aging process. Subsequent chapters deal with the important topics of pharmacology and drug interactions. The next few focus on geriatric nutrition, with topics ranging from healthy diet to enteral feeding to ethical issues in end-of-life care. The chapters which follow deal with luminal disorders, malignancies of the gastrointestinal tract, the liver, gallbladder and pancreas, palliative care, systemic disorders, and psychiatric disease. Each chapter focuses on evaluation, differential diagnosis and management of gastrointestinal problems relevant to the older adult.

Over eighty authors have contributed to the writing of this book. Many are of national and international repute, and ably supported by junior faculty members. In addition to their role as editors, Dr. Pitchumoni and Dr. Dharmarajan have also contributed a significant share of book chapters.

In summary, this first edition of Geriatric Gastroenterology is a major attempt to be all-inclusive in the field of gastroenterology pertinent to the geriatric patient. The information therein is contemporary and basic to the practice of medicine. It is a privilege and honor to write this Foreword. The Editors are world-renowned educators and scholars who have designed and delivered a masterful textbook for clinicians of internal medicine, geriatrics and gastroenterology. They are to be congratulated for this effort.

Martin H. Floch, M.D.
Clinical Professor of Medicine
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Preface

Over the past several decades, trends in global aging have focused attention on the manner in which we care for older adults. How can we be best prepared to meet the demands of medical illness in our aging population? Many of the medical societies have increasingly promoted the blending of medical sub-specialty training with expertise in the care of the older adult. In this regard, the American Gastroenterologic Association Future Trends Committee Report recently highlighted several areas for improvement in health care delivery, including the need to identify 'best evidence-based care' for the older adult; to develop guidelines for care of specific gastrointestinal issues in geriatrics; to modify current practices in order to meet the complex needs of older individuals; and to adapt the healthcare workforce to meet the demands of specialized treatments in gastroenterology for older people. Until there are sufficient trained personnel in both geriatrics and gastroenterology, providers must handle the daunting task with knowledge gained in other ways.

As editors specialized in gastroenterologiy and geriatric medicine, we see the need for a textbook to address the physiology, pathology, evaluation and management of digestive disorders in the elderly. Too often, clinical complaints are attributed to 'old age' by patient and provider alike. Physicians must be better trained to discern physiological from pathological processes and normal aging from disease. Disorders such as constipation and diverticular disease are common in the old, but are they pathological, or the result of aging? As age is associated withimmune dysfunction, the role of the gut in the elderly has become a subject of increasing importance. How should the age-related decline in homestatic mechanisms, known as homeostenosis, alter medical care in the elderly? Added to the complex situation is the impact of polypharmacy and adverse drug events which often mimic gastrointestinal disorders, with increasing health care costs. How can we learn to be more focused and sensitive to these issues? This book attempts to clarity these challenging and controversial issues in the diagnosis and care of the geriatric individual.

A standard format has been adopted for this text, whereby most chapters conclude with key summary points. Numerous tables and figures are included to emphasize content. There are abundant pictures focusing on endoscopy, radiography and pathology. Several relevant gastrointestinal topics unique to the older person are included. We anticipate the book will be a valuable resource for residents, fellows, and practicing physicians alike. A section providing Questions with multiple choice Answers and brief discussions relating to the chapters is hosted in an electronic platform (Springer Extras); this may be an additional benefit particularly to residents and fellows in training.

This work is by no means all-inclusive, but does offer solid grounding in geriatric gastroenterology. It is also not the first text on the subject: the first comprehensive book was written in 1984 by Lawrence J. Brandt MD, Emeritus Chairman of Gastroenterology at Albert Einstein College of Medicine, entitled "Gastrointestinal Disorders of the Elderly." Tremendous credit is due to Peter R. Holt MD of Saint Luke's Hospital of New York-Presbyterian Medical Center

for pioneering the concept of 'Aging and the Gastrointestinal Tract'. These two provided the initial motivation for our efforts. We salute as well many pioneers in the field of Geriatrics: William R. Hazzard, Christine K. Cassel, Joseph G. Ouslander, Mary E. Tinetti, Laurence Z. Rubenstein, John E. Morley, and others; and the field of Gastroenterology: Howard M. Spiro, Henry L. Bockus, Sir Francis Avery Jones, Dame Sheila Sherlock, Marvin H. Sleisenger, John S. Fordtran, Edward J. Berk, and others. All of these scholar-mentors in medicine paved the path for us to follow.

Special thanks are due to Martin H. Floch MD of Yale University, who has graciously provided the Foreword for the book. We are grateful to the many contributors who responded to our call and gave generously of their time to provide chapters for the book. Springer has been supportive from the start of this venture and throughout the editing process. Both of us wrote a series of articles over the past fifteen years on the theme of geriatric gastroenterology, and Springer has been instrumental in bringing to fruition our dream of a textbook of geriatric gastroenterology.

Support and encouragement from our family was ever present, and for this we are eternally grateful. Our families were a source of strength and inspiration; their patience, understanding and sacrifices commendable. As teachers and mentors, we acknowledge our students, residents, fellows and professional colleagues for providing the opportunity to enrich our knowledge and clinical skills. And above all, we pay tribute to our older adult patients in community, hospital and nursing home settings, from whom we have learned so much.

It is our hope that this textbook serves as a resource towards fulfillment of a goal so aptly stated by Abraham Lincoln: "And in the end, it's not the years in your life that count. It's the life in your years."

C.S. Pitchumoni MD
T.S. Dharmarajan MD

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Part I

Perspectives and Trends

Geriatric Gastroenterology: The Geriatrician's Perspective

1

T.S. Dharmarajan

An Aging Society, an Era of Centenarians

Aging trends the world over have resulted in a dramatic increase in life expectancy of older adults. While the life expectancy at birth for a female and male born in the USA today has increased to 80 and 75 years, respectively (mean 77), it is even higher in Canada, Japan, France, Italy, Sweden, Greece, and some other countries. In spite of their functional limitations and comorbidity, the group over 85 years has been the fastest growing segment in the USA.

The U.S. Census Bureau used the term Century Club to denote the people aged over 100 years, a number around 50,000 in 2004; the centenarians have increased rapidly in the last 5 years to over 70,000 as of 2010, the highest number for any country in the world [1]. Even more impressive is the number of supercentenarians (aged 110 years or over) in the USA and European countries. Of the 60 oldest people in the world (as of December 2010), the top ten aged over 113 years, are mostly from the USA or Japan. The oldest person to meet Guinness standards was Jeanne Calment, a Frenchwoman who died at 122 in 1997. This age group would surely have kept health care providers perplexed; although the provider of care rarely has the opportunity to care for such cases, this is more likely to occur in the future [2]. Table 1.1 provides relevant age-related statistics.

Differentiate Physiology from Pathology: Age Versus Disease

With these aging trends, it is only to be expected that the old will be burdened by impaired function, often coupled with diseases of several systems, the gastrointestinal system being no exception [3, 4]. The difference between physiological changes expected with age and pathological changes or disease may be blurred or distinct. While menopause is a distinct physiological change expected at a certain stage of life in women and renal function declines at a certain rate with age, other physiologic processes are less well defined. Constipation is more prevalent in older adults but may be attributed to changes in life style, disease process, and adverse effects of medication, rather than a well-recognized alteration in gut transit time. But the patient tends to convince the doctor that "it is because I am getting old"; the providers of care must decide for constipation or any manifestation, whether it is an age-related physiological change that requires little care or a disease process needing intervention.

Too Much or Too Little Care: The Question

Health care providers including geriatricians and gastroenterologists caring for older patients will need to make several judgments: whether a patient is in good health and will live long enough to benefit from an intervention; whether the life expectancy is less than 6 months and a qualifier for hospice; or if death is imminent [5]. Life expectancy is influenced by age, disease, and disability [5]; predicting life expectancy is difficult and imprecise. It is equally important to assess the old by their physiological age rather than chronological age; many geriatric patients may benefit from treatments as much as the young, whereas some may require alternatives. People in their 90s or older (referred to as the oldest old) may be healthier and

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Table 1.1 A selection of age-related statistics [1, 17]

US population (Feb 2011)	310,862,271
Age 65 years and older in USA	
Total 65+ age group	38,000,870
Percentage of total population	12.6
Male:female ratio	42.2:57.8
Males >65 years, % population	10.8
Females >65 years, % population	14.4
Race	
White, alone	80.8%
African Americans	8.4%
Asian	3.2%
Hispanics	6.5%
Old age dependent	20.5%
Marital status, now married	53.4%
Education: high school or more	59.0%
Most common causes of death	
Cancer, all sites	
Cardiovascular disease	
Cerebrovascular disease	
Common comorbid conditions	
Musculoskeletal disease	
Heart disease	
Hypertension	
Diabetes mellitus	
Hearing and vision impaired	
Age 75 years and older in USA	
Percentage of total population	6.1
Males >75 years, % population	4.7
Females >75 years, % population	7.4
Centenarians across the world	
USA (Sept 2010)	70,490
Japan (Sept 2010)	44,449
China (2007)	17,800
France (Jan 2010)	15,459
England and Wales (2009)	11,600
Germany (2006)	8,839
Canada (2009)	5,981
Spain (Jan 2009)	5,891
Australia (June 2010)	3,700

more robust than some who are 20 years younger [6]. The use of physiological age, with a determination of functional status and social support, enables providers to make more appropriate decisions. The concept of "successful aging" was confined to persons with an excellent genetic background who had also lived an exemplary lifestyle [7], but as we know today, people can age with disease processes by overcoming disabilities, and may be termed "aging successfully" in contradistinction to "successful aging" [8]. Additionally, when addressing patients a word of caution: the term "old" is perceived to be associated with negative traits far more than the word "young."

Besides addressing physiologic age, the approach to an older adult must begin with assessment of life expectancy and incorporate evidence-based guidelines; short-term issues must focus on restoration of the previous state of health, mid-range issues must address preventive care and geriatric syndromes, and long-term issues require planning for decline and end-of-life [9].

How Is the Geriatric Patient Different?

"Is the geriatric GI older patient just like any other adult? No…. and Yes" is well addressed by a geriatrician–gastroenterologist in an American Gastroenterological Association Perspective and in depth in the Association's Future Trends Committee Report. Several gastrointestinal disorders such as constipation and cancer are known to be common in the geriatric age group; further, the older adult is likely to manifest additional comorbid conditions including but not limited to cardiac and renal diseases, alterations in weight and malnutrition, impaired cognition, hearing and visual impairment, and proneness to falls, delirium, and incontinence. With polypharmacy and inappropriate prescribing a concern in this age group, adverse drug events (ADEs) are common; they may manifest as GI illness, such as constipation, diarrhea, GI bleeding, peptic ulcer disease, and pill esophagitis, a partial list. Furthermore, ADEs are a common basis for hospitalization and health care costs. The older adult may not comprehend or adhere to recommendations for a procedure or its management, because of underlying dementia; rather than being labeled noncompliant, the patient needs additional help in view of impaired cognition. Dysphagia and aspiration are common basis for morbidity and mortality, more likely to be predisposed to by neurological disorders such as Parkinson's disease or Alzheimer's dementia, than by mechanical obstruction. The risk for aspiration is not minimized by gastrostomy tube feeding either. Older adults with dysphagia and reflux disease also find it difficult to swallow their medications and are prone to pill esophagitis. With these scenarios, a multidisciplinary approach is often required, coupled with care giver dependency.

Make the Right Decisions at End of Life

The geriatrician may believe that towards the later stages of life, there is a lower likelihood of cure for disease; aggressive therapy may be unwarranted and comfort is paramount. About half the older patients die in hospitals, a quarter in nursing homes and the rest in community settings. In the palliative care setting, data suggests that median survival may be longer in those receiving early palliative care; high-quality palliative care in any setting (home, hospital, or nursing home) helps patients and should be integrated into patient care in all settings [10].

The goals in care of the older adult with GI illness should be to respect the patient's and caregiver's wishes and keep the patient physically and psychologically comfortable. Quality of life consideration deserves importance. Early implementation of advance directives is a helpful approach; when directives are in place, it is the provider's responsibility to make every effort to fulfill the patient's wishes. A concept stated by a sixteenth century anonymous physician still makes sense: "to cure sometimes, to relieve often, to comfort always."

Be Knowledgeable in Geriatrics, in Preparing for the Future

With the awareness of current aging trends and an anticipated ongoing shortage of geriatricians, it is relevant for gastroenterologists (and other specialists) to familiarize themselves broadly with aspects of geriatric medicine and care of the elderly; at medical schools there is a real need for geriatricians to provide geriatrics educational component [11]; the specialists would also need to bear some of the burden. The Institute of Medicine has recommended that all physicians develop competency in geriatrics to prepare for the population changes; several specialties have drafted a roadmap for this training, because "these are the people who are going to care of older adults" [12]. The American Gastroenterological Association has come out with a position paper in this regard addressing the research and guidelines of care recommended, with emphasis on specific issues relevant to the aging GI tract [4]. Incorporation of assessment of function and cognition into routine GI practice involving geriatric patients is one "out of the box" inclusion [4].

Collaboration Between Geriatrician and Gastroenterologist

The wide array of diseases, medication effects, and presentations involving the GI system in the geriatric age group are sufficient reasons for a geriatrician to work in collaboration with a gastroenterologist. Despite the recognition that primary care physicians and specialist communication is important in clinical care, a recent study found only two of three primary physicians and four of five specialists communicate patient information always or most of the time; adequate visit time with patients and quality reports for chronic disorders are positive associations [13, 14]. A recent study in patients over age 70 with positive fecal occult blood test suggested that there was failure of adequate follow-up, suggesting that efforts must improve for the entire chain of decision-making, including screening and follow-up [15]. Finally, it is essential to determine early in the course of illness whether the patient has capacity to make informed decisions, understand the options, and choose appropriately based on the costs, risks, and benefits to that individual [16].

The older age group typically bears the burden of chronic disease. Gastrointestinal illness in the geriatric age group offers tremendous opportunity to the primary care physician or geriatrician to satisfactorily provide solutions to the patient in consultation with the gastroenterologist.

Key Points

- Population trends point to an aging population with multiple chronic illnesses, functional decline, and impaired cognition as associations.
- Providers should gain background knowledge in basic geriatric medicine to cope with these older patients [18].
- Gastrointestinal illness is common in geriatric patients, with the typical older adult manifesting additional chronic diseases.
- Adverse drug effects are common in the old with several presenting as GI manifestations.
- Physiological age must be prioritized over chronological age in decision-making, with attention paid to quality of life and functional status.
- Communication between primary care physician and gastroenterologist is essential to ensure patient satisfaction and favorable outcomes.
- Providers must address the full chain of decision-making, from screening, to management and follow-up.

References

1. http://en.wikipedia.org/wiki/centenarian. Accessed 21 Feb 2011.
2. Dharmarajan TS, Sohagia A. Urgent surgery in a near supercentenarian nursing home resident: possible with favorable outcome! J Am Med Dir Assoc. 2007;8:543–4.
3. Dharmarajan TS, Ugalino JT. The physiology of aging. In: Dharmarajan TS, Norman RA, editors. Clinical geriatrics. 1st ed. Boca Raton: CRC Press/Parthenon; 2003. p. 9–22.
4. Hall KE, Proctor DD, Fisher L, et al. American gastroenterological association future trends committee report: effect of aging of the population on gastroenterology practice, education and research. Gastroenterology. 2005;129:1305–38.
5. Coll PP. Determination of life expectancy: implications for the practice of medicine. Ann Longterm care. 2010;18(4):21–4.
6. Perls TT. The oldest old. Sci Am. 1995;14(3):6–11.
7. Rowe JW, Kahn RI. Human aging: usual and successful. Science. 1987;237:143–9.
8. Morley JE. Successful aging or aging successfully. J Am Med Dir Assoc. 2009;10:85–6.
9. Rueben DB. Medical care for the final years of life. "When you're 83, it's not going to be 20 years". JAMA. 2009;302:2686–94.

10. Gibson R. Resource use in the last 6 months of life. What does it mean for patients? Arch Intern Med. 2011;171(3):194–5.
11. Nusbaum NJ. What should geriatricians be doing? Ann Longterm Care. 2009;17:38–9.
12. Kuehn BM. Effort under way to prepare physicians to care for growing elderly population. JAMA. 2009;302:727–8.
13. O'Malley AS, Reschovsky JD. Referral and consultation communication between primary care and specialist physicians. Arch Intern Med. 2011;171(1):56–65.
14. Chen AH, Yee Jr HF. Improving primary care-specialty care communication. Lessons from the San Francisco safety net. Arch Intern Med. 2011;171(1):65–7.
15. Carlson CM, Kirby KA, Casadei MA, et al. Lack of follow-up after fecal occult blood testing in older adults. Inappropriate screening or failure to follow up? Arch Intern Med. 2011;171(3): 249–56.
16. Gambert SR. Capacity to make an informed decision: an essential component of every initial patient encounter. Clin Geriatr. http://factfinder.census.gov/servlet/. Accessed 21 Feb 2011;19(2): 9–11.
17. http://factfinder.census.gov/servlet/. Accessed 21 Feb 2011.
18. Leipzig RM, Hall WJ, Fried LP. Treating our societal scotoma: the case for investing in geriatrics, our nation's future, and our patients. Ann Intern Med. 2012;156:657–9.

Geriatric Gastroenterology: The Gastroenterologist's Perspective

2

C.S. Pitchumoni

Demographic change in the last few decades, showing a shift in the United States and elsewhere toward an older age distribution, is multifactorial. Contributory factors include substantial scientific advances in preventive and curative medicine, improved sanitation and water supply, and enhanced food production [1, 2]. The concurrent decline in both fertility and mortality, and the consequent increase in the percentage of the older adults (a term preferentially used in the book instead of the "elderly"), is a prominent global trend. In the USA the percentage of adults aged 65 and over has increased from 4% in 1900 to about 13% at present. By 1998 the number of older adults accounted for 34 million of the US population, a number estimated to grow to 50 million by 2020. Nineteen of the 20 world's "oldest countries" are in Europe. Even many of the so-called Third World countries—such as India, China, and Latin America—are demonstrating similar trends. This "graying" of the population has brought with it a number of economic and social challenges, including alarming financial pressures to meet health care needs. Aging of the population is hence a mixed blessing with challenges that will undoubtedly continue.

The demographic shift has also resulted in substantial changes in the incidence and prevalence of diseases, and in their associated morbidity and mortality. Among the many systemic disorders, the gastrointestinal tract warrants special attention.

With the burden of gastrointestinal disorders in the older population, and, with patients expecting improved quality of life, thoughtful and cost effective care is clearly warranted. The World Health Organization (WHO) has published Data measured by disability adjusted life years (DALY) for all ages, including those 60 and older, for select gastrointestinal disorders for several countries [3–5].

Because of the high prevalence of cerebrovascular disease, Parkinson's disease, and Alzheimer's disease among the elderly, oropharyngeal or transfer dysphagia is a more commonly encountered esophageal disorder than esophageal cancer. When polypharmacy is superimposed on functional decline in the elderly, pill esophagitis and esophageal strictures occur more often.

PUD has shown a considerable decline in the past few decades. Currently more cases are secondary to NSAID use and fewer are secondary to *Helicobacter pylori*. More than 80% of the deaths from bleeding PUD in the USA occur in those 65 and older. NSAID-induced PUD is often painless, occurs more often in women, and may be associated with severe underlying anemia and massive upper gastric intestinal bleeding [6].

Although the proton pump inhibitors (PPI) are unquestionably a major therapeutic advance in the treatment of acid-related disorders, their panacea-like over-use has resulted in an increase in the incidence of *Clostridium difficile* colitis, bacterial pneumonia, vitamin B12, iron and calcium malabsorption, diarrheal disorders, osteoporosis with fractures, and acute interstitial nephritis [7].

Small bowel disorders, including malabsorption of fat and B12 secondary to bacterial overgrowth (blind loop syndrome), are common but seldom diagnosed. Celiac disease, considered a pediatric problem until recently, is increasingly diagnosed for the first time in the older adults [8]. We are increasingly aware that anemia in the elderly may be a vexing diagnostic challenge. Once considered the "black box" of the gut, wireless capsule endoscopy has opened a window of opportunity to visualize the entire small bowel [9].

Constipation is extremely common in the elderly. The symptoms may be chronic, recalcitrant, and debilitating [10]. The dollars spent on laxatives exceed $400 million annually. Fecal impaction and incontinence, which bring patients repeatedly to the emergency rooms, lead to hospitalizations,

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nosocomial infections, and both invasive and expensive diagnostic procedures.

Diverticular disease increases in prevalence with age [11]. In many western countries more than half the population may have the disorder. Although often silent, diverticular disease [12] is the single most common cause for hospitalization in patients aged 75 and over [5].

Inflammatory bowel disorders (IBD), Crohn's as well as ulcerative colitis, have a dual peak of onset. This late onset peak creates diagnostic and therapeutic dilemma, as ischemic bowel disorders, lymphocytic or collagenous colitis, drug-induced colitis and infectious colitis are all part of the differential diagnosis. The increased incidence of *Clostridium*-associated colitis with the newly detected virulent form (Quebec Strain) has posed an epidemiological problem in the institutionalized as well as free living elderly [13, 14].

Gastrointestinal bleeding, upper more than lower, can be life-threatening. Its incidence is attributed to greater use of NSAIDs for pain in the aged. Estimates suggest that 35–45% of all patients presenting with upper gastrointestinal bleeding are over the age of 60 [15–17]. A greater than 200-fold increased incidence of LGI bleeding occurs as the age advances from the third to the ninth decade of life [18], based on an increased incidence of diverticular disease, colonic neoplasm, angiodysplasia, and ischemic colitis. Advances in diagnostic and therapeutic endoscopy have undoubtedly helped better manage gastrointestinal bleeding [19–21].

Hospital admissions with the principal diagnosis of cholecystitis increase sharply with age. Although generally more common in women, after age 75 the gender difference disappears [22]. Older adults may present atypically and/or with complications, such as acute cholecystitis, cholangitis, gall bladder perforation, gangrene, emphysematous cholecystitis, and gallstone pancreatitis.

Benign and malignant diseases of the pancreas pose serious threat to the geriatric patient, with older age in itself a prognostic marker for serious outcome [23]. Chronic alcoholic pancreatitis is rare in the geriatric age group, but idiopathic chronic pancreatitis of late onset ("senile pancreatitis") is a cause of pancreatic insufficiency. The risk for pancreatic malignancy dramatically increases with age with a median age of 72 at the time of diagnosis.

Chronic liver disease linked to alcohol abuse is seldom seen. On the other hand, other chronic liver diseases including hepatitis C, cryptogenic cirrhosis, nonalcoholic fatty liver disease, and malignant liver disease (primary and metastatic) are frequent.

Liver transplantation, once considered exclusively an option for the young is currently offered to the older adult. Transplant recipients over the age of 60 have the same postoperative mortality rate and life expectancy as those younger. Older recipients of liver transplants enjoy a quality of life similar to the younger recipients [23].

The gastrointestinal problems in the geriatric patient should not be dismissed as a problem of aging. Clinicians must become familiar with the epidemiology of common gastrointestinal problems in the elderly. Proper diagnosis and management demand an understanding of the interplay of comorbidity, gastrointestinal side effects of medications, impact of expensive and invasive diagnostic tests, and above all an understanding of the special needs and quality of life measures of the geriatric patient.

References

1. Gavrilov LA, Heuveline P. Aging of population. In: Demeny P, McNicoll G, editors. The encyclopedia of population. New York: Macmillan; 2003. p. 32–7.
2. Eberstadt N. World population implosion? Public Interest. 1997;129:3–22.
3. World Health Organization. Ageing and life course. 2011. http://www.who.int/ageing/en/.
4. World Health Organization. Global Burden of Disease (GBD). Health statistics and health information systems. 2011. http://www.who.int/healthinfo/global_burden_disease/en/index.html.
5. Goldacre MJ. Demography of aging and the epidemiology of gastrointestinal disorders in the elderly. Best Pract Res Clin Gastroenterol. 2009;23(6):793–804.
6. Griffin MR, Piper JM, Daugherty JR, Snowden M, Ray WA. Nonsteroidal anti-inflammatory drug use and increased risk for peptic ulcer disease in elderly persons. Ann Intern Med. 1991;114(4):257–63.
7. Khara HS, Pitchumoni CS. Proton pump inhibitors: a better prescription is needed. J Clin Gastroenterol. 2009;43(6):597–8.
8. Catassi C, Kryszak D, Bhatti B, Sturgeon C, Helzlsouer K, Clipp SL, et al. Natural history of celiac disease autoimmunity in a USA cohort followed since 1974. Ann Med. 2010;42(7):530–8.
9. Muhammad A, Pitchumoni CS. Evaluation of iron deficiency anemia in older adults: the role of wireless capsule endoscopy. J Clin Gastroenterol. 2009;43(7):627–31.
10. Lembo A, Camilleri M. Chronic constipation. N Engl J Med. 2003;349(14):1360–8.
11. Jacobs DO. Clinical practice. Diverticulitis. N Engl J Med. 2007;357(20):2057–66.
12. Munson KD, Hensien MA, Jacob LN, Robinson AM, Liston WA. Diverticulitis. A comprehensive follow-up. Dis Colon Rectum. 1996;39(3):318–22.
13. McDonald LC, Killgore GE, Thompson A, Owens Jr RC, Kazakova SV, Sambol SP, et al. An epidemic, toxin gene-variant strain of *Clostridium difficile*. N Engl J Med. 2005;353(23):2433–41.
14. Bartlett JG, Perl TM. The new *Clostridium difficile*–what does it mean? N Engl J Med. 2005;353(23):2503–5.
15. Trivedi CT, Pitchumoni CS. Gastrointestinal bleeding in older adults. Pract Gastroenterol. 2006;30(3):15–42.
16. Silverstein FE, Gilbert DA, Tedesco FJ, Buenger NK, Persing J. The national ASGE survey on upper gastrointestinal bleeding. I. Study design and baseline data. Gastrointest Endosc. 1981;27(2):73–9.
17. Segal WN, Cello JP. Hemorrhage in the upper gastrointestinal tract in the older patient. Am J Gastroenterol. 1997;92(1):42–6.

18. Longstreth GF. Epidemiology and outcome of patients hospitalized with acute lower gastrointestinal hemorrhage: a population-based study. Am J Gastroenterol. 1997;92(3):419–24.
19. Davila RE, Rajan E, Adler DG, Egan J, Hirota WK, Leighton JA, et al. ASGE Guideline: the role of endoscopy in the patient with lower-GI bleeding. Gastrointest Endosc. 2005;62(5):656–60.
20. Gostout CJ, Wang KK, Ahlquist DA, Clain JE, Hughes RW, Larson MV, et al. Acute gastrointestinal bleeding. Experience of a specialized management team. J Clin Gastroenterol. 1992;14(3):260–7.
21. Farrell JJ, Friedman LS. Gastrointestinal bleeding in the elderly. Gastroenterol Clin North Am. 2001;30(2):377–407, viii.
22. Ross SO, Forsmark CE. Pancreatic and biliary disorders in the elderly. Gastroenterol Clin North Am. 2001;30(2):531–45, x.
23. Singhal A, Sezginsoy B, Ghuloom AE, Hutchinson IV, Cho YW, Jabbour N. Orthotopic liver transplant using allografts from geriatric population in the United States: is there any age limit? Exp Clin Transplant. 2010;8(3):196–201.

Geriatric Gastroenterology: Future Trends

3

Karen E. Hall

"Difficult to see.... always in motion, is the future": famous words by the Jedi Master Yoda to Luke Skywalker. In one sense, it is not difficult to predict some general trends in practice for generalists or specialists based on current efforts—electronic medical records will likely be the standard documentation mode, new drugs and procedures will be developed, and the average patient will be more complex to manage…and older. Position papers/statements have highlighted new noninvasive testing for disease, such as colon cancer screening using stool DNA, which might supersede many procedures currently used for health screening [1]. Often the assumption is that the population being screened is relatively healthy (and relatively young), and are satisfied with medical care delivered by computer interaction. The majority of medical visits and healthcare costs are incurred by patients over age 65 who have preexisting chronic comorbidities that require management—this model may improve management of those patients, but there is no data yet that it works in that population. This section will focus on implications of treating an aging population, and attempt to predict issues that may be relevant for future practice.

There are important differences in the way that older patients present to physicians, due to a combination of changes in physiology that come with aging, and the burden of chronic disease. In the 2005 AGA Future Trends Committee Task Force on the effect of aging of the population on gastroenterology practice, education, and research [2], we included "out of the box" sections such as one advocating inclusion of assessment of physical function and cognition into routine GI assessments of geriatric patients, based on the high prevalence of impaired cognition and mobility in this population. Impairment in a patient's ability to perform Activities of Daily Living (ADLs), is more predictive of health outcome and subsequent mortality than any single disease entity [3, 4], and many medical centers are incorporating functional assessment into their electronic medical record as a resource for physicians to use when deciding when, how, and who to treat. This data has been available for some time in paper-based charting by nurses and physical therapists, but lack of access to the paper record makes use by other practitioners difficult. This is about to change, as the recently passed Patient Protection and Affordable Care Act [5] mandates implementation of electronic medical records by all practitioners. Practices can use this opportunity to incorporate information about a patient's physical function, social support, and proxy decision makers for medical care into their records. A model for obtaining this information are the screening surveys used by geriatricians for new patients, and those who have had a significant change in their health status such as recent hospitalization, subacute rehabilitation in a nursing facility to capture this data. The data can be collected by a nurse, a social worker or other paramedical staff, as a high level of specialized knowledge is not required.

At this stage it is important to highlight some other ways that an electronic medical record could impact future practice. The current generation of patients entering their sixth and seventh decades of life most likely have been using electronic devices such as smart phones and computers as a ubiquitous adjunct to daily life. This creates a specific type of behavior. Any question or uncertainty can be immediately searched, and sources of information that provide immediate answers are used to aid decision-making, While teachers may lament the use of Wikipedia by students, it is not a "bad" thing to use a rapid reference if the user has some ability to critically evaluate the source of the information. Patients look up their diagnoses and treatment on the Web, therefore many centers have developed resource centers for patients. I find it useful to endorse web searching by patients, and suggest that they use the Centers for Disease Control and Prevention website (http://www.cdc.gov) or National Institute of Health (http://health.nih.gov/category/SeniorsHealth) as

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alternative well-researched external sites. If you have material published on the web, your patients may actually be able to read it directly (this rarely used to happen unless your patient was another physician or medical provider with access to printed medical journals).

Another trend that is rapidly increasing is the use of quality indicators to identify disease risk, and monitor attempts to treat. Controlled trials have provided evidence of better outcomes with monitoring of parameters such as low density lipoprotein (LDL) and hemoglobin A1C (HbA1c), however objective evidence of improved outcomes at the population level in actual use has been lagging behind. Mandated reminder systems and monitoring are in place in many institutions, however the onus is on the medical practice to manage the data. In the future, it may be possible (or even essential) to have patients collaborate with their monitoring—assuming that patients agree that the outcome of the monitoring justifies the impact on their lifestyle. This raises an interesting philosophical question of how much medical interference in private life is acceptable, and the answer is often highly politically charged.

As geriatric patients enter the "middle-old" age range of 75–85 years, the functional reserve of physiologic systems decreases and patients are more vulnerable to perturbations of normal function by disease and iatrogenic causes [2]. A common scenario is resuscitation of a dehydrated 85-year-old patient with intravenous fluids at "standard flow rates," only to have them develop pulmonary edema, require diuresis which then causes renal impairment that requires more intravenous fluids…and so on. This decrease in physiologic reserve ("homeostenosis") requires modification of the "usual" approach to treatment [6]. Testing of treatments and drugs in younger patients that do not have the comorbidities and age-related decline in organ function of geriatric patients may be the explanation for "unexpected" complications and increased post-market drug-related adverse events in older patients. Instituting periodic review of protocols or rote orders that may be used on geriatric-aged patients, to identify potential problems will likely reap the benefits in patient-centered quality surveys, and in teaching of residents and gastroenterology fellows.

Another issue that will impact future practice is the increased prevalence of dementia in patients over age 75, as the impact of dementia on outcomes, institutionalization, and caregiver workload has been estimated to be $100 billion dollars annually [7]. Gastroenterologists should be aware of impaired cognition as a potential barrier to care and incorporate screening or results of screening into their care. In some cases the minimal additional work to identify cognitive impairment might even minimize the risk of future litigation.

The increasing economic pressure to "ration care" to those deemed most likely to benefit will impact practice in the next 10–20 years. While most people agree in principal that finite resources have to be used efficiently, applying this to a specific patient is difficult. Prior generations of older patients may have been more fatalistic about outcomes (possibly due to attitudes formed when young), but the "Baby Boom" generation is less likely to accept limits on their choice of care. Having a perceived "younger" age may actually improve patient's ability to cope with illness [8]. Response to standard treatment of many conditions (depression, constipation, peptic ulcer disease) appears to be very comparable between young and old patients if the latter have no serious comorbidities limit lifespan (such as the end stages of conditions such as dementia, congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), cancer, or severe impairment in ADLs). Utilizing functional data such as ADLs and life tables provides prognostic information that can allow you to predict whether the risk of intervention outweighs benefit for your older patient. A recent case-based article in JAMA demonstrates the use of this information [9] to decide whether colon cancer screening or other health maintenance screening should be performed in this 83-year-old man. The same data can be used to assist in decisions about performing invasive procedures with significant risk in geriatric patients, such as feeding tube insertion.

Recent discussions about the future of large-scale government plans such as Medicare and Medicaid have highlighted economic pressures on health care systems. Different venues of care ("home health care" vs. "office-based") have been suggested [10]; however, the home care model is unlikely to be practical for a proceduralists such as gastroenterologists. To save costs, there may be a strong push to increase use of physician "extenders" such as physician assistants (PAs) and nurse practitioners (NPs) in primary care and specialties [11]. This may cause problems as current reimbursement appears to be too low to keep most specialty and primary practices viable. The new health care legislation also proposes formation of global capitated medical associations (Associated Care Organizations (ACOs)) that are reminiscent of HMOs (Health Maintenance Organizations), however the salient difference between HMOs and ACOs is that the ACO structure is, in principal, physician-driven rather than insurer-driven. An ACO is a practice alliance/conglomeration of primary and specialty providers who agree to treat patients for "episodes of care" that generate a lump sum payment from insurers. The physicians and other providers divide the payment amongst themselves in whatever way they have agreed internally. This model addresses the major problem facing politicians, namely the inability to successfully lower specialist rates of reimbursement and overall costs. The ACO model puts the onus on physicians groups to lower costs, and in theory might give primary care physicians a much more powerful base from which to negotiate favorable terms. The main uncertainty is which parts of the bill will survive beyond the next election, as there has been considerable opposition. Hopefully there will be more public input into any new plan, which will be critical for public acceptance.

Finally, there is concern among physicians that the profession is evolving from a self-regulated business to an employee business model—a position that was articulated over 25 years ago at a lecture at the University of North Carolina School of Medicine by Dr. Arnold Relman, the then editor of the New England Journal of Medicine [12]. It may be inevitable, given the economic and societal pressures currently in play, however it will be interesting to see how this affects future recruitment into medicine and the various specialties. A proactive approach by specialists and generalists to provide appropriate and thoughtful care of the elderly will be essential to cope with future needs of our geriatric patients and practice requirements.

References

1. A Doctor's Vision of the Future of Medicine. Newsweek. 27 Jun 2009. http://www.newsweek.com/2009/06/26/a-doctor-s-vision-of-the-future-of-medicine.print.html.
2. Hall KE, Proctor DD, Fisher L, Rose S. American gastroenterological association future trends committee report: effects of aging of the population on gastroenterology practice, education, and research. Gastroenterology. 2005;129:1305–38.
3. Inouye SK, Peduzzi PN, Robison JT, Hughes JS, Horwitz RI, Concato J. Importance of functional measures in predicting mortality among older hospitalized patients. JAMA. 1998;279:1187–93.
4. Cigolle CT, Langa KM, Kabeto MU, Tian Z, Blaum CS. Geriatric conditions and disability: the health and retirement study. Ann Intern Med. 2007;147(3):156–64.
5. Patient Protection and Affordable Care Act, 2010. http://democrats.senate.gov/reform/patient-protection-affordable-care-act-as-passed.pdf.
6. Resnick NM. Geriatric medicine. In: Braunwald E, Fauci AS, Kasper DL, Hauser SL, editors. Harrison's principles of internal medicine, vol. 1. 15th ed. New York: McGraw-Hill; 2001. p. 36–9.
7. National Institute on Aging and National Institute on Health. Progress report on Alzheimer's disease, 1999. Silver Spring: Alzheimer's disease Education and Referral Center; 1999.
8. Boehmer S. Relationships between felt age and perceived disability. Satisfaction with recovery, self-efficacy beliefs and coping strategies. J Health Psychol. 2007;12(6):895–906.
9. Reuben DB. Medical care for the final years of life "When you're 83, it's not going to be 20 years". JAMA. 2009;302(24):2686–94.
10. Landers S. Why health care is going home. New Engl J Med. 2010;363(18):1691.
11. Horrocks S, Anderson E, Salisbury C. Systematic review of whether nurse practitioners working in primary care can provide equivalent care to doctors. BMJ. 2002;324:819–23.
12. Relman AS. The future of medical practice. Health Aff. 1983;2(2):5–19.

Part II

Basic Sciences, Principles and Epidemiology

The Physiology of Aging

4

T.S. Dharmarajan

The chapter provides an overview of basic physiological and morphological changes with aging. Primary care physicians and gastroenterologists are likely to benefit from knowledge of changes that occur with normal aging and the distinction of physiological alterations from disease. Information pertinent to aging physiology is helpful in the appropriate and individualized evaluation and management of older adults. Changes in the gastrointestinal system are detailed in another chapter.

Life Expectancy and Life Span

Life expectancy refers to the number of years an individual is anticipated to live following a certain reference age. The life expectancy at birth for females and males in the United States is 80.6 and 75.7 years respectively (including all races), and is higher for whites than blacks [1]. Life expectancy has a low of nearly 32 years in Swaziland and a high of 82.6 years in Japan [2]. The life expectancy in humans at birth has progressively increased. Statistically significant decline in mortality has been registered from 2008 to 2009 for age groups over 55 years; the decrease is 0.9% for those 55–64 years, 3.4% for 65–74 years, and 4.9% for 75–84 years [1]. Hence, the older old are living longer and contribute to the highest growth. However, as expected, the over 65 year group has the highest emergency room visits, hospitalization rates and prescription drug use based on the Center for Disease Control 2010 data. The United States also has the highest health care expenditure in the world, largely for the older age group.

In most countries, and at all ages, women have a lower mortality rate and outlive the men. The rule is true in practically all mammals. The precise reason is not clear, and may be a result of several factors including disease patterns, lifestyle, genetics, environment, impact of accidents, and more. Most centenarians are females. Japan has the highest ratio of centenarians to total population, at 347 per million inhabitants , but the United States has the highest number of centenarians in the world, with 70,490 in 2010 [3].

Maximum life span refers to the maximum number of years an individual lives from birth to death in a certain population; the term has been used for the longest living 10% in a cohort [4]. The longest living recorded human, a French woman (Jeanne Calment) lived to 122 years.

Mortality in developed countries of the world mainly occurs from heart disease, cancer, and stroke in order, followed by chronic lung disease and injuries (intentional and unintentional [5]). Heart disease related mortality has declined more rapidly in the United States than in other countries. Increase in longevity may be attributable to several factors, including better health care especially for coronary artery disease, availability of medications, preventive measures, and public health measures including smoking cessation and improved sanitation.

Aging refers to a gradual and progressive decline in cell or tissue structure and function, with resultant loss of homeostasis or reserves, or homeostenosis. Aging is associated with physiological decline in most organs or systems, along with the presence of pathology, disability and dissatisfaction, with some elders compensating well and others poorly [6–12].

Theories of Aging

Several theories address the theme of aging, although none offer a full, clear explanation. Overall, the view is that genes are preprogrammed to control the course of cell proliferation and death. An alternative concept involves the impact of exogenous factors that cause damage to DNA, mitochondria

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or telomeres, errors in RNA and protein synthesis, genetic abnormalities, accumulation of reactive or toxic free radicals, loss of hormonal function, immunosenescence, and others [8]. A family of antiaging genes, the sirtuins, may control pathways that increase life span and influence aging [13]. Caloric restriction with provision of essential nutrients has prolonged life in several animal species, but has not been practical for a prolonged study in humans [14, 15].

Chronological age denotes the time elapsed since birth or actual age of an individual; biological age represents the age based on physiological development and influence of health. Chronological age does not necessarily match biological age. One can live a prolonged life and maintain good health, cognition and a relatively young appearance. In a Danish study, a large proportion of the remaining life time in people between 92 and 100 was spent in good health, with physical independence and normal cognition [16].

Aging changes are universal, decremental, and progressive [10]. The general rule is a decline in organ function (or most systems) of about 1% each year after the third decade [10]. Subclinical functional decline results in loss of reserves or homeostenosis and impairs maximal performance [12]. However, in most studies, the influence of subtle disease cannot be effectively excluded. Dramatic decline in function is unlikely to be age related, and likely from disease.

At the other end of aging is "frailty," a common biological syndrome characterized by decreased reserves in multiple organ systems due to the combined effects of disease, inactivity, stress, poor nutritional intake, and altered physiology [17]. Although common, with a prevalence ranging from 5 to 58%, a clear consensus definition is not available [18]. One diagnosis requires three of the following characteristics: decreased walk time (using a 15-foot walk test), decreased grip strength, decreased physical activity, exhaustion, and over 10 lb or 5% weight loss in the last year [19]. Frailty is not inevitable in the old. Its presence is associated with falls, institutionalization, and mortality [17]. Frailty can be delayed or reversed in some by appropriate measures, most notably exercise [17].

Clinical Impact

Determining life expectancy has relevance in practice. Judgment is often called when assessing if a patient will live long enough to benefit from a certain intervention. A life expectancy less than 6 months may draw consideration for hospice; imminent death may require the family to prepare and visit the patient [20]. Healthy living (and better life expectancy) is summed up by adherence to four lifestyle factors: never smoking, keeping the body mass index below 30, adherence to dietary principles (high intake of fruits, vegetables, and whole grains, with low meat), and performing 3.5 h/week or more physical activity [21] (Table 4.1).

Table 4.1 Features of aging

Life expectancy is on the increase worldwide
Life expectancy is higher in females, a fact true in practically all mammalian species
Chronological and biological age do not necessarily match
Physiological changes of aging seldom cause manifestations
A decline in function by 1% per year occurs after the third decade in most systems
Pathological disorders need to be distinguished from physiological changes
Multiple comorbid processes, many silent, are often present in older adults
Atypical presentations of disease are common
Successful aging may result from an interplay of several factors including genetics, environmental influences, and a healthy lifestyle

Gait and Balance

Gait changes with age are particularly apparent after the seventh decade [22]. Gait depends on maintenance of normal neurological, musculoskeletal, autonomic, vascular, and cardiorespiratory function [22, 23]. The term "senile" gait in reality represents a gait disorder due to subclinical disease [23]. Gait slows by about 12–16% per decade with age [22]. A young adult or unimpaired person has a gait speed of 1.2–1.5 m/s; an older person's gait ranges from 0.9 to 1.3 m/s; an impaired person's gait may be <0.6 m/s. The classic older gait is slow, with more time spent in stance. Stride length is shorter, as is arm swing, with both feet on the ground for a longer period of time. There is slightly more knee and hip flexion (due to pelvic tilt), contributing a stooped posture. The older gait may mimic that of Parkinson's disease. In a study of people 50–96 years, the Baltimore Longitudinal Study of Aging found that women have greater ankle range of motion, while men exhibit greater hip range of motion [24]. Inflammatory markers such as IL-6 have been associated with gait speed decline in community seniors [25]. Gait abnormality also predicts dementia [23]. A nonlinear relationship is noted between gait speed and falls; a greater risk of outdoor falls is seen in faster walkers and greater risk of indoor falls in slow walkers [26].

Balance is the ability to control upright posture and maintain stability. With age, a larger base support is necessary to maintain balance. Sway increases with age and is exaggerated with illness (e.g., cerebellar or posterior column disease) or under the influence of certain medications. Gait and balance is tested by tandem walking, the Berg Balance scale, "functional reach test," Timed Up and Go Test (TUG), Performance Oriented Balance and Mobility Assessment (POMA), gait speed, one legged stance, and other means [27]. Only about 20% community dwelling oldest old can perform tandem walking without difficulty [23].

Clinical Impact

Gait and balance disorders are common in the old. The older gait must be distinguished from several disorders in the geriatric age group. The most common diagnoses associated with an abnormal gait are osteoarthritis, dementia, spinal disease, vertigo, and neurological disorders (e.g., hemiplegia, Parkinson's disease, normal pressure hydrocephalus) and following orthopedic surgery. Abnormal gait is a predictor of falls and injuries, and ultimately interferes with function and quality of life. A lot can be learned from merely observing the patient's gait as the person walks into the examination room.

Skin and Hair

The skin is the largest organ in the body and subject to systemic and environmental insults throughout life [28].

Morphology and Physiology

Many cell lines responsible for dermal functions decline with age; they include fibroblasts, mast cells, immune (Langerhans) cells, melanocytes, as well as sweat and sebaceous glands. Dermal functions affected include cell replacement, barrier protection, water proofing, immune response, wound healing, thermoregulation, sweat and sebum production, and vitamin D synthesis [29]. Dermal changes with age are mostly from photoaging, also known as extrinsic aging. Photoaging is the consequence of exposure to ultraviolet light, pollution, and smoking; it is cumulative, involves exposed areas (face, neck, arms) and is less prominent in darker persons [30]. Photoaging accounts for about 80% of extrinsic aging, including wrinkling, pigmentation, telangiectasia, and purpura, and follows exposure to both UVA and UVB rays [31]. This is in contrast to intrinsic aging, which is characterized by atrophy, thin transparent skin, loss of elasticity, loss of underlying fat, and fine wrinkles [32]. Dry skin or xerosis is common in the old, but not a sequel of normal aging [33].

Graying of hair is the most recognizable early sign of aging [34]. Graying occurs in both genders but varies among people, with Caucasians having earlier onset of graying compared to African Americans. Half the hair on average turns gray in half of Caucasians by age 50 [34]. Hair loss is universal with age, but varies with race. Hair growth goes through anogen (growth), catagen (involution), and telogen (rest) phases. At a given time, most hair is in the anogen (>90%) and least in catagen (<1%) phase; alterations with aging cause growth decline due to shift towards catagen [34]. Hair density is highest in the first few years of life and drops significantly even by the third decade. Loss occurs earlier in the scalp followed by the eyebrows, axilla, and pubis [35].

Table 4.2 Skin and aging

Skin structure and function decline observed in:
Sweat and sebaceous gland activity
Immune response (Langerhan cells)
Fibroblasts
Mast cells
Melanocytes (melanin production)
Elastic fibers (elasticity and turgor)
Subcutaneous fat
Dermal capacity for vitamin D synthesis
Hair and nails
Gradual decline in hair density
Graying of hair, with differences by race
Coarser texture of hair around the ears, upper lips, and eyebrows
Decline in rate of nail growth
Clinical impact
Dry skin with tendency to pruritus and skin injuries
Slower healing, including surgical wounds
Higher proneness to infections
Nail infections need to be treated for longer periods
Most visible changes from photoaging can be modified
Photoaging due to UV light exposure is associated with development of skin neoplasms

A Copenhagen study demonstrated lower mortality in males without gray hair [36]. Like hair, nail growth also declines with age.

Clinical Impact

Photoaging is linked to development of precancerous and malignant skin neoplasms [31]. Impaired dermal vitamin D synthesis contributes to deficiency. Smoking status influences visible skin aging [37]. Xerosis predisposes to pruritus and infections, and is addressed by increasing ambient humidity, modifying bathing schedules, increasing fluid intake, limiting sun exposure, and using of emollients and moisturizers [33, 38, 39]. In postprocedural patients, sutures may need to stay longer to allow for wound healing. Nail infections must be treated for longer periods, especially onychomycosis [29] (Table 4.2).

Anthropometrics and Body Composition

Physiological changes and age of onset in body composition are variable, and additionally influenced by gender, independent of physical activity and hormones [40, 41].

Height increases gradually from birth and stabilizes around the fourth decade. The gradual height loss with age results from spinal changes (thinning of vertebral discs from loss of water and decline in vertebral body height), mild flattening of the arch of the foot, and increased flexion at the

hip and knee joints. Vertebral fractures and kyphosis cause a greater decline in height. The arm span is one measure that remains constant through the years [6].

Weight is influenced by several factors. Although bone loss should cause weight decline, weight is more a reflection of lifestyle, in particular physical activity and caloric intake, and the influence of disease. In Western society, weight typically increases until around 50 years of age in men and thereafter declines, with similar patterns in women till about age 60 [6]. In active elderly women who engage in physical activity, body weight has been regarded as a reliable, low-cost indicator of fat-free mass [42].

In young and middle age adults, body water takes up about 60% of body weight. With age, a decline in body water occurs, with the water compartment closer to 50% of body weight. Increased insensible water loss through the skin and respiration increases with age, another component to age-related dehydration [43]. Lean body mass is body weight minus fat and includes muscle, bone, and nonfatty tissue. In health, an adult male's body has 6–24% fat while a female has 14–31% fat. The fat compartment increases through life to about 30% of body weight by the seventh decade; the lipid compartment is even larger in women. Even if the total weight is unchanged, there is a relative decrease in water and increase in the fat compartments. Fat tends to be centrally deposited and abdominal obesity becomes apparent.

Lean body mass may decline by as much as 40% between the third and eighth decade of life. CT scans of the diaphragm from the third to the eighth decade demonstrated no difference in muscle thickness with age, although diaphragmatic defects and pseudotumors appeared in older age [44]. Age-related decline in muscle mass, or sarcopenia, predominantly involves type 2 fibers. Sarcopenia is common over age 65 in men and women. Hand grip strength declines with age, but a greater loss of muscle strength occurs in the lower limbs. Efforts to slow the decline in muscle mass are achievable through appropriate nutrition and resistance training [45].

Aging is associated with changes in bone remodeling [46]. Like muscle, bone mass declines after age 30 by about 1% in women and 0.7% in men. The loss accelerates in women to 3–5% from estrogen loss in the postmenopausal period, the stage of most rapid bone loss in life. Eventually, the rate of bone loss decelerates to previous levels and equals that in men. In addition, alterations also occur with age in bone toughness due to increased nonenzymatic collagen cross-linking which suppresses plasticity [47]. Men have less microstructural damage and less pronounced changes [48].

Clinical Impact

Changes in body composition impact health [49]. A decline in body water increases the serum concentration of water-soluble drugs (e.g., digoxin, diuretics, warfarin, aminoglycosides, theophylline, etc.), enhancing their pharmacodynamic effects. The impact of alcohol is similarly enhanced by age, even more in women. Fluid administration must be judicious in older adults and requires awareness of differences in water distribution (in the intracellular, extracellular, and interstitial compartments). In addition, lipid-soluble drugs (e.g., benzodiazepines) are retained longer in fat stores, long after they are discontinued, with the potential for adverse effects on mind, gait, and balance.

Age-related sarcopenia can mask decline in renal function due to reductions in muscle derived creatinine. A decline in bone mass (osteopenia and osteoporosis) is typical with aging and may be modified favorably by altering lifestyle or use of medications such as bisphosphonates. Sarcopenia in association with an increase in abdominal fat impacts respiratory function, causing a decline in FEV_1 and FVC, accelerating age-related worsening of respiratory function [50]. The same changes in composition also contribute to insulin resistance.

Vital Signs

Age-related physiological changes influence vital signs to some extent, but a far greater impact results from pathological processes [51]. Stiffening of the vasculature with a high prevalence of systolic hypertension [52], widening of pulse pressure [53], dysregulated signaling with orthostatic hypotension [54], and postprandial hypotension [55] are common.

There is no appreciable change in the respiratory rate with normal aging; tachypnea or shallow breathing must raise concern about serious illness. Temperature measurements are fraught with interpretation difficulties in the old. Physiological changes in the skin, adipose layer, ability to sweat, volume status, sarcopenia, vascular response and immune system, coupled with the simultaneous presence of disease and drug effects combine to influence thermoregulation [51]. Poor thermoregulation results from reduced ability to maintain body heat, vulnerability to extremes of cold and heat, impaired ability to mount a febrile response, and disrupted circadian rhythm. Thus, even with infection and bacteremia, a febrile response may not be evident in the old. Even low-grade fever or minimal deviations in temperature may indicate serious underlying illness.

Clinical Impact

Vital signs are typically affected by the presence of disease. Hypertension is associated with heart failure from diastolic dysfunction, but the correlation with "dyspnea" in this setting may be poor [56]. Vascular aging is accelerated by coexisting risk factors such as hypertension, hyperlipidemia,

diabetes, and smoking [52]. Both hypo- and hyperthermia are common in older people and result from endocrine or infectious etiology or an adverse medication effect. Hypothermia may occur even in the absence of a cold environment and heralds a poor outcome, with high mortality, particularly in men [57–59].

Vision and Hearing

Morphology and Physiology

Several age-related changes occur with vision. Adaptation to dark and light take longer; the delay in dark adaptation is accurate enough to correlate with a patient's age [60]. Contrast sensitivity is blunted. The presence of cataracts scatters light, leading to glare, besides causing blue to be perceived as green due to photooxidation of the lens. The iris becomes more rigid, causing the pupillary reaction to light to become more sluggish. Floaters are increasingly common in the field of vision from condensation of vitreous gel. Diminished lacrimal secretion, ptosis from the weight of fibrous tissue in the eyelids, and both entropian and ectropian are common with age.

Hearing impairment is a common cause of disability in the old [61]. Despite this, the prevalence of hearing aid use appears low [62]. However, the prevalence of hearing impairment in those aged 65–74 years was lower in 1999–2006 compared to 1959–1962 [63]. The slight dominance of the right ear over the left in younger people is magnified further in people over 80 years.

The most common age-related hearing impairment is presbycusis, a bilateral, sensorineural, symmetrical disorder with high frequency hearing loss. In contrast, unilateral hearing loss and the presence of vertigo indicate that the disorder is not age-related, requiring meticulous evaluation of the ears, brain, vascular system and medication use. Other hearing defects can involve the external, middle, and inner ear. Cerumen in the external ear tends to become drier and tenacious, with blockage from wax a common, reversible cause of hearing loss. The ossicles in the middle ear ossify and fuse, impairing conduction. The inner ear experiences loss of sensory hair cells in the organ of Corti, loss of cochlear neurons, and thickening of the stria vascularis; a variable combination of these abnormalities predisposes to presbycusis. We need more data on the effect of age and noise exposure on high frequency hearing [64].

Clinical Impact

Refractory errors are common as one becomes older, with presbyopia a universal problem that is easily corrected. Glaucoma, cataracts, macular degeneration, and diabetic retinopathy all cause significant visual impairment, warranting and justifying periodic eye examination. Age is the most important risk factor for cataracts. The prevalence of glaucoma in the old is high; the reasons for increased intraocular pressure and reduced outflow are not clear [65]. Glare may be irritating, but can be reduced through glare-free lighting or use of sunglasses.

Visually impaired elderly participate in society less than their peers; the findings are relevant since participation is an indicator of successful aging [66]. Impaired vision is among the most common treatable causes of accidents and falls. In fact, both visual and hearing impairment are associated with falls, poor outcomes, and impaired quality of life; gender does not influence these outcomes [67].

As with vision, hearing loss can be addressed through the use of hearing aids for most forms of hearing impairment [63]. Patients, however, seldom acknowledge their hearing disability and even when diagnosed are reluctant to accept hearing aids [62]. The presence of hearing loss may result in an erroneous diagnosis of cognitive impairment and even dementia. In fact, greater hearing loss has been associated with lower scores on cognitive testing, even raising the question whether hearing loss is a modifiable risk factor or an early marker of cognitive decline [68]. The Baltimore Longitudinal Study has noted an independent association between hearing loss and lower scores for memory and executive function [69]. The contribution of adverse drug effects to hearing disability (e.g., aspirin, NSAIDs, diuretics, vancomycin, aminoglycosides, etc.) should be recognized. The consequences from hearing loss, health disorders and life satisfaction are closely related, emphasizing the role for audiological rehabilitation [70].

Cardiovascular System

Cardiovascular changes are common with aging. These include myocardial and vascular stiffening, diminished function of the electrical conduction system, and decreased sensitivity of the autonomic nervous system. All of these changes contribute to common cardiovascular conditions in older persons including heart failure with preserved ejection fraction, systolic hypertension, chronotropic incompetence, and orthostasis. These age-related alterations and associated impacts are summarized in Table 4.3.

Morphology and Physiology

Aging is associated with both structural and functional changes in the cardiac myocardium. Myocytes decline in number and are replaced with fibrous tissue. The remaining myocytes hypertrophy and align in a more disorganized

Table 4.3 Cardiovascular changes with aging

Cardiovascular system component	Age-related change	Clinical impact
Myocardium	Myocyte loss and hypertrophy Myocardial fibrosis Alteration in calcium handling	Heart failure with preserved ejection fraction
Electrical conduction system	Loss of sinoatrial node pacemaker cells Decreased maximum heart rate Decreased heart rate response to beta-agonists	Sinus node dysfunction Chronotropic incompetence
Vascular system	Thickening and stiffening of central arteries Endothelial dysfunction	Systolic hypertension
Autonomic nervous system	Decreased baroreceptor sensitivity Decreased alpha-adrenergic and beta-adrenergic sensitivity	Orthostasis

manner [71]. Additionally, myocyte contraction is prolonged due to alterations in intracellular calcium handling. As a result, a greater percentage of the cardiac cycle is spent in systole rather than diastole [72]. All of these changes increase ventricular stiffening and intraventricular diastolic pressures.

The cardiac conduction system similarly undergoes age-related alterations. By age 75, almost 90 percent of sinoatrial node pacemaker cells have disappeared [73]. In part due to the loss of these cells, maximum achievable heart rate is reduced as is the heart rate response to stimulants including beta-agonists [74]. The most widely used formula describing maximal-achievable heart rate therefore shows significant interaction with age ($HR_{max} = 220 - \text{age in years}$ for males; $190 - (\text{age in years} \times 0.8)$ for females). As with the loss of sinoatrial cells, degeneration of the more distal electrical conduction pathways is also frequent and results in varied forms of heart block and nonspecific conduction disease.

The extracardiac vascular and autonomic systems also show significant morphologic and physiologic change. The vascular system becomes stiffer and less responsive to local metabolic needs. Central arteries demonstrate thickening of intimal, medial, and adventitial layers due to increased collagen and smooth muscle content. These changes are compounded by reduction in elastin, an important distensible element in the vessel intima and media [75]. In addition, endothelial dysfunction results in impaired blood flow-mediated vasodilation and increased vasoconstriction [76]. In part due to these vascular changes and multiple other influences, the sensitivity of the autonomic nervous system declines with age. Carotid baroreceptor and beta-adrenergic receptor function are affected and less so alpha-adrenergic receptor response. Sympathetic activation is blunted and central vagal tone is enhanced [77]. As a result, the body's ability to compensate for postural change deteriorates [78] (Table 4.3).

Clinical Impact

The structural and functional age-related changes described above contribute to common cardiovascular disorders and syndromes in older persons. Vascular and ventricular stiffening increases the prevalence of isolated systolic hypertension, hypertensive heart disease, and heart failure with preserved ejection fraction (CHFpEF). Over half the persons older than 60 years and three-quarters of adults over 75 years have systolic hypertension, and the majority of older persons with heart failure have CHFpEF [79, 80].

Similarly, the combination of conduction system degeneration and autonomic dysfunction increases the prevalence of symptomatic sick sinus syndrome, atrioventricular block, chronotropic incompetence, and orthostasis. Both sick sinus syndrome and atrioventricular block may manifest as syncope and difficulties with rate control in atrial fibrillation—a pacemaker may therefore be required. Chronotropic incompetence may manifest as exercise intolerance and functional impairment; older persons are less able to augment stroke volume and therefore rely to a greater extent on heart rate increases to meet metabolic needs in situations of stress. Beta-blockade or use of calcium channel blockers can further worsen this symptomatology. Finally, orthostasis may result in falls, especially in the setting of polypharmacy. When both chronotropic incompetence and autonomic dysfunction are present, fall risk is especially magnified.

Respiratory System

Morphology and Physiology

Changes occur with age in the structure of almost every component of the respiratory system [81, 82]. The thoracic rib cage compliance is diminished as a result of calcification

of the costal cartilage and costochondral junctions and degenerative disease of the spine with or without kyphosis [82]. The changes alter the shape of the rib cage and increase the anteroposterior diameter. In contrast, the lung loses elastic recoil and becomes more compliant [83]. The pulmonary vasculature becomes stiffer, with increase in resistance. The alveolar size increases due to reduce elastic lung recoil. Respiratory muscle performance weakens and along with the stiffer chest wall results in an increase in residual volume. The decline in muscle strength does not spare the diaphragm; an older adult's diaphragmatic contractions are feebler than those of a young adult [83]. Despite these changes, there is no impact on breathing patterns or gas exchange to a significant degree [84].

The decline in PaO_2 with age can be determined by using either of the following formulae: $PaO_2 = 100 - (\text{age in years}/3)$ *or* $110 - (\text{age in years} \times 0.4)$. The A-a gradient which increases with age can be calculated from the formula: $(\text{age}/4) + 4$. The small decrease in oxygenation with aging does not get much worse beyond 70 years [85]. The pCO_2 and pH remain normal. Any deviations are explained by disease.

Aging effects can be primary or secondary [85]. The primary effects of age are an increase in distal airspace (alveolar ducts and alveoli) along with a reduction in chest wall compliance and muscle strength. The consequent reduced lung elastic recoil facilitates airway closure; secondary effects are manifest in lung volume changes [85] (Table 4.4). Closing volume and closing capacity (sum of closing volume and total lung capacity) increase with age; residual volume also increases, while FEV_1 declines. Genetic effects cannot be discounted; in a large Danish study, genetic influences appeared to contribute significantly to alterations in pulmonary function, especially FEV_1 and FVC, more so in males than in females [86].

Aging is also associated with decline in immune function. The respiratory system has a large epithelial surface and is much exposed to microbes and antigens. Mucociliary function, mucins, antibacterial proteins, and alveolar macrophages play a role in defense; alterations occur in cell mediated, humoral, and innate immunity [81]. Further, an age-related maladaptive response to cigarette smoke sensitizes the lung to inflammation and oxidation, and contributes to smoking induced chronic obstructive lung disease; the age factor may have a greater role in sensitizing smokers than hitherto realized [87] (Table 4.4).

Table 4.4 Respiratory system and aging

Structure
Increase in the anteroposterior diameter of rib cage
Calcification of the costochondral junction and costal cartilage
Thoracic rib cage increases in rigidity and decreases in compliance
Lung compliance increases
Loss of lung elasticity and recoil
Alveolar ducts enlarge, but there is loss of alveolar surface area
Increase in pulmonary vascular stiffness, pressures, and resistance
Lung volumes
Total lung capacity unchanged
Tidal volume unchanged
Residual volume and functional residual capacity increase
Closing volume increases (accounts for ventilation-perfusion mismatch)
Decline in vital capacity; FVC and FEV_1 decrease by 15–30 mL/year
Gas exchange
Decline in PaO_2 with age
$PaCO_2$ and pH remain unchanged
A-a gradient increases with age
Diffusion capacity of carbon monoxide declines
Defense to infection declines
Dysregulated cell mediated, humoral, and innate immune function
Decline in vigor of cough reflex
Decline in mucociliary function with poorer clearance
Clinical impact
Age-related physiological changes do not cause symptoms
Dyspnea at rest or minimal exertion suggests lung or other disease
Impact of smoking on lung structure and function is far more than physiological changes
Increased predisposition to aspiration

Clinical Impact

Changes in the respiratory system do not cause manifestations in the old even during routine exercise. Commonly, abnormal pulmonary function tests signify the presence of obstructive or interstitial lung disease, with or without a cardiac component. Smoking (including secondhand smoke) is deleterious to the lungs and must always be addressed [87, 88]. Profound changes in pH, pO_2 or pCO_2 are very likely a result of disease. A dysfunctional immune system in the presence of systemic disease, drug effects and predisposition to aspiration increase the risk of pneumonia [81].

Kidneys

Morphology and Physiology

The kidneys undergo structural and functional alteration with age [89–93]. Renal blood flow declines with age at the rate of 10% per decade from age 30 to 60, with the cortex affected most [87]. Both kidneys become smaller, with nephron volume beginning to shrink by about the third or fourth decade of life [94]; renal size lessens by up to 40% by age 80 [92]. The glomeruli manifest basement membrane thickening, hyalinization and sclerosis. Apoptosis

and proliferation of podocytes lead to sclerosis [95]. In a biopsy proven study, the prevalence of nephrosclerosis went up progressively from 2.7% in an age group 18–29 years to 73% for those 70–77 years [96]. There also occurs a decline in functioning tubules and increase in interstitial fibrosis. Collecting tubules may develop diverticuli. Glomerular filtration rate (GFR) tends to decline at a rate of about 8.0 mL/min/1.73 m^2/decade (or about 0.8–1% annually) after the third decade; however, based on longitudinal studies, the rate of decline is highly variable [93, 97]. The decline in GFR may be none, less than 1%, or over 1%. Tubular secretion also undergoes a decline of about 0.7% annually.

Serum creatinine levels would be expected to rise based on the diminished renal function; however, creatinine generation declines with age due to the decrease in muscle mass (sarcopenia) with aging. The expected rise in creatinine is offset by the decline in synthesis of creatinine, rendering creatinine level a poor indicator of renal function. Hence, renal function must be measured utilizing an acceptable formula. While GFR is an overall index of renal function, it is not measured directly. Derived eGFR using the Cockroft–Gault equation (CGF) [98] or the Modification of Diet in Renal Disease Study (MDRD) equation [99] is commonly used; the newer Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was introduced in 2009, but is not yet in common usage [100]. The CGF approximates eGFR from creatinine clearance, while the other two require computer assistance.

Several tubular functions become impaired as one gets older. The ability to conserve or excrete water is blunted. The capacity to conserve or excrete a sodium load is impaired. The ability to excrete a potassium load or an acid load decreases. There is controversy regarding the secretion and effectiveness of antidiuretic hormone [92]. Hormonal functions of the kidney are variably affected and are briefly stated in Table 4.5. Several functions are preserved with aging: these include tubular handling of calcium, phosphorus, and magnesium, as also erythropoietin synthesis [101]. The presence of diverticuli in the bladder suggests outlet obstruction, especially prostatic hyperplasia in males. Bladder capacity declines with age, but there is a small increase in postvoid residual volume; a large increase in residual volume suggests obstructive uropathy.

The cause of renal function decline with age is unclear. Postulates include decline in blood flow, activation of growth factors, and dietary factors such as protein. A recent study suggests that "hyperfiltration" may be a factor [102]; a decrease in glomerular density with aging appears associated with an increase in GFR and albumin excretion [94].The influence of even mild disease on renal function cannot be excluded.

Table 4.5 The kidneys and aging

Morphology
Decline in blood flow to the kidneys with age, as with other organs
Decline in size of both kidneys
Decline in number of functioning glomeruli, with increase in sclerosis, predominantly in the cortical region
Decline in functioning tubules, especially long tubules
Presence of diverticuli in renal tubules
Postvoid residue increases a little with age, not to the extent seen in obstructive uropathy
Bladder capacity declines with normal aging
Function
Decline in glomerular filtration rate (GFR) (from the third decade, highly variable)
Decline in tubular secretion
Filtration fraction (GFR/renal blood flow) increases with age
Decline in both tubular concentration and dilution capacity
Decline in ability to conserve sodium or excrete a large sodium load
Reduced ability to excrete a potassium or acid load
Reduced renal threshold for glucose (urine testing for glucose unreliable)
Preserved calcium, phosphorus and magnesium handling
Decline in hormonal function
Decline in 1,25-dihydroxy vitamin D synthesis
Decline in degradation of insulin, parathormone, calcitonin, glucagon
Decline in renin secretion
Erythropoietin synthesis intact until marked decline in renal function
Clinical impact
Older adults are susceptible to both dehydration and volume overload
Vulnerable to both hyponatremia and hypernatremia
Decline in GFR not accompanied by expected increase in the serum creatinine
Renal function must be estimated utilizing an acceptable formula
Medications handled by the kidney warrant dosing based on accurate assessment of renal function
Unilateral decrease or increase in renal size is not age related
Bladder diverticuli suggest the presence of obstructive uropathy

Clinical Impact

Measurement of renal function must be a routine part of patient evaluation, rather than reliance on serum creatinine levels. The implications for accurately assessing renal function are many: appropriate dosing (or avoidance) of medications, water, sodium, and potassium administration, diet prescription, better anticipation of health outcomes, and future planning. Renal function remains good enough in many older adults to receive consideration as suitable renal allograft donors. Interventions such as control of blood pressure, blood sugar, weight, diet and caloric restriction may help prevent renal aging [103].

Endocrine System

Morphology and Physiology

Normal aging is associated with a decline in hormone concentrations of estrogen (menopause), testosterone, and dehydroepiandrosterone (andropause), and growth hormone with insulin like growth factor 1 in parallel (somatopause) [104, 105]. However, interestingly, in the Baltimore Longitudinal Study of Aging, in a comparison of long-lived people (survivors >90 years) to short-lived participants (58–70 years), single biomarker levels for gut hormones, insulin, and testosterone were not significantly different, although global scores differentiated the two groups [106].

Thyroid function declines with age, with serum TSH levels increasing with age in the absence of autoimmune antibodies [107–110]. Free T_3 levels decline in the extreme old; but free T_4 remains intact, because a decline in its secretion is offset by a decline in clearance [108, 111]. The majority of women over 70 and men over 80 develop thyroid nodules, many of which are not felt on physical examination [107].

Insulin resistance, denoting a lower rate of glucose disposal for a given insulin level, develops in diabetes, with obesity and with aging [112]. Aging is associated with alterations in the fat and muscle compartments, and visceral obesity correlates with insulin resistance. Fasting blood glucose levels rise only 1–2 mg/dL/decade, but a greater rise occurs in postprandial glucose with healthy aging [107]. Inspiratory muscular training in healthy subjects (61–82 years) improves insulin sensitivity [113].

In men, there is also a decrease in estradiol [114, 115]; in women, besides estrogen, a decline occurs in progesterone, testosterone, and androstenedione. The ovaries decrease in weight from a normal of 20 g around menopause to about 2–3 g in old age; prominent ovaries on imaging studies in older women warrant evaluation.

Table 4.6 outlines endocrine changes with age.

Table 4.6 Endocrine system[a]

Thyroid
Decline in free T_3 levels
Normal free T_4 levels (decreased secretion and decreased clearance)
Gradual increase in TSH levels
Increasing nodularity of thyroid gland in both genders
Insulin
Marginal increase in fasting glucose (1–2 mg/dL/decade)
Larger increase in postprandial glucose
Decline in insulin production, offset by decreased clearance by kidneys
Insulin resistance develops with age, multifactorial in basis
Anti diuretic hormone (ADH)
Increase in basal levels due to tubular resistance
Increase ADH response to osmotic stimuli
Atrial natriuretic peptide
Basal and stimulated levels are elevated
Vitamin D
Diminished synthesis in the skin
Down regulation of vitamin D receptors in the gut
Erythropoietin
Production by kidneys preserved until marked decline in renal function
Adrenal hormones
Cortisol secretion decreases, offset by decreased clearance, diurnal rhythm is preserved
Reaction to ACTH and stress remains intact
Catecholamine production is normal
Renin and aldosterone
Renin and aldosterone levels decline predictably
Response to posture is blunted
Prone to hyperkalemia with dietary insults or medications
Parathyroid hormone
Levels increase from age 30 as a response to maintain calcium levels
Decline in degradation by the kidneys
Sex hormones
Males: decline in total and free testosterone, dehydroepiandrosterone, estrogen
Females: decline in estrogen, progesterone, testosterone, androstenedione
Growth hormone
Decline in secretion, to very low levels by age 80
Decrease insulin-like growth factor 1 levels parallel growth hormone
Melatonin
Decline in levels with loss of circadian rhythm

[a]Gastrointestinal hormones are detailed in Chap. 5

Clinical Impact

The previous belief that exogenous hormones slow the aging process appears a myth; replacement must be selective and intended to correct for deficiency (e.g., vitamin D) or for endocrine disease [116]. Thyroid function tests are commonly abnormal in the old; illness and medication effects compound the abnormal results, emphasizing the need to correctly interpret test results. Overt hypothyroid and hyperthyroid states must be distinguished from subclinical states, euthyroid sick syndrome, and age-related abnormalities [107, 117, 118]. Low thyroid activity is associated with longevity, while subclinical hyperthyroidism has the opposite effect; long-living people have higher TSH levels [109]. The treatment of subclinical hypothyroidism is hence of questionable benefit [118]. Likewise treatment of low serum thyrotropin levels (to merely correct biochemical abnormalities) does

not necessarily improve clinical outcomes [119]. Growth hormone levels come down markedly by age 70–80. There is little benefit in replacement of growth hormone or testosterone for the low levels seen with aging [107].

Alteration of body composition by diet and exercise has the potential to delay the onset of insulin resistance [112]. A diet rich in dairy products, whole grains, fruit, vegetables, poultry, and fish is associated with greater insulin sensitivity in older adults [120].

Nervous System

Morphology and Physiology

The brain mass declines with age, concomitant with a decline in blood flow. Brain atrophy evident in neuroimaging in older people may be associated with perfectly intact function. However, more atrophy is apparent even with mild dementia. Neuronal loss occurs maximally in the cerebellum, superior temporal gyrus, and subcortical areas. White matter asymmetry is a common finding in healthy male and female adults and remains stable during aging [121].White matter reduction may be causative in declines in episodic memory, executive function and information processing speed [122] The role for genetic effects are inconclusive [123]. Every person inherits two apolipoprotein alleles of the three isoforms E2, E3, and E4, one from each parent. The E2 allele, the longevity gene, is linked to increased life span, while the E4 allele is linked to Alzheimer's disease. White matter age-related changes are associated with myelin sheath degeneration rather than axonal degeneration, with no gender disparity [124].The presence and degree of white matter alterations correlate with declines in frontal function, including processing information, visuomotor function, and verbal fluency, although language and memory are less closely related [123].

The presence of intracellular tau protein and extracellular amyloid plaques may be markers of damage. While neurofibrillary tangles (composed of tau) and amyloid beta peptide may be seen in the normal brain, it is their distribution and extent that distinguishes aging from Alzheimer's disease. The significance of lipofuscin accumulation in the brain is not clear. Alterations in energy metabolism, mitochondrial function, neurotransmitters, and enzymes occur with brain aging.

The concept of cognitive reserve is important in that some people cope better with brain changes than others, and those with higher IQ or attainment often cope well even in the presence of Alzheimer's disease [125, 126]. Intelligence gained from prior experience remains generally intact, but fluid intelligence (involving problem solving) deteriorates. General vocabulary is preserved into the eighth decade. Older people take more time to perform complex tasks, as processing speed is slower; performing new executive tasks may be difficult. Recall is slower, reaction time is longer (as is processing time), but recognition is generally intact.

Clinical Impact

Changes in the nervous system occur with age. Diminished vibration sense, position sense, and gait abnormalities may occur in the absence of specific neurological disease. Most people undergo gradual cognitive decline, especially with memory, but can nevertheless function. A minority (1 in 100) does not experience this change and age successfully [127]. Mild cognitive impairment (MCI) represents the intermediate stage between cognitive function in aging and the decline in dementia [127]. A significant change in cognition or personality indicates disease. Future interventions should attempt boosting cognitive reserve to reduce age-related disorders [126].

Immune Function

A decline in immune function or "immune senescence" occurs with age and denotes deterioration in innate immune function (the first line of defense) and adaptive immunity (delayed response) [81, 128]. Thymic involution is complete by about 50 years, the thymus being largely replaced by fat; it accounts for the reduction of thymocytes and naive T cells [129]. Abnormal T and B lymphocyte function result in loss of cellular and humoral immunity. Immunosenescence is not characterized by unavoidable progressive deterioration of immune function, rather a remodeling where some functions are reduced, some are unchanged, and others are enhanced [130]. The progressive loss of T cell subsets may be responsible for poorer defense against viral and bacterial infections, a consequence of thymic involution and chronic antigenic stimulation [130]. The loss of B cell function may be due to inadequate T cell stimulation; diminished antibody production following immunizations is due to poor B cell function. Upregulation of inflammatory responses is another feature of aging and is unfavorable to longevity [130].

Microglial immunosenescence in the brain may explain the occurrence of neurofibrillary degeneration [131] and even relate to behavioral and cognitive deficits [132]. A postulate is that zinc homeostasis and signaling are vital in immune activation and that zinc deficiency may be responsible for impaired adaptive and innate immune function, and increased systemic inflammation [133] (Table 4.7).

Table 4.7 Immune function

Innate immunity
Loss of barrier function of skin and mucous membranes
Neutrophil function:
Decline in phagocytosis, bactericidal activity
No change in adherence or chemotaxis
Decline in macrophage function (phagocytosis, killing of pathogens)
Increase in cytokine activity through NK cells
Adaptive immunity
T cell function: production affected in parallel with thymic involution
T cell subsets change with age:
Decline in absolute number of total T cells, including CD4+ and CD8+ subsets (mostly the latter), and increase in NK cells (but with a decline in function)
Decrease in naïve T cells with proportionate increase in memory cells
Higher IgM, IgA, and IgG concentration
B cell function
Reduction in B cell number
Reduced antibody response; with faster drop in antibody levels
Increase in autoantibodies
Inflammatory response
Up regulation of chronic inflammatory response (detrimental)
Increase in IL-2, IFN-gamma, TNF-alpha, IL-4, IL-6, IL-10 positive CD8+ T cells
Clinical impact
Increased susceptibility to viral and bacterial infections
Antibody response to vaccines is suboptimal
May require additional booster steps (e.g., 2-step tuberculin test)
Susceptible to infections and cancers
Increase in development of auto antibodies (significance?)

Clinical Impact

Increased morbidity and mortality are well recognized in the old following bacterial and viral infections. Influenza, pneumonia, and septicemia are among the top causes of death in older adults in the United States [128]. Vaccines are less protective in the old than in the young as noticed with influenza and pneumococcal vaccines [128, 129]. An increase in cutaneous infections in older age may relate to defective cutaneous immunity [134].The increase in cancer after age 65 may partly relate to deleterious immune alterations [135]. Maintaining immune health is a concept that can be linked to lifestyle, including energy intake, physical training, sleep patterns, and psychological stress [135].

Sleep

Physiology

Aging is associated with significant changes to the daily sleep cycle, with about half of older adults encountering sleep disturbances [136]. Sleep requirements vary by person and range from 6 to 10 h, with 8 h considered reasonable. Older people tend to go to bed earlier with earlier awakening (phase advance), compared to younger adults who tend to sleep later and wake up later (phase delay). In addition, the time required to fall asleep increases (sleep latency), while sleep efficiency, the percentage of time actually asleep while in bed, declines. Sleep becomes more fragmented with nocturnal awakenings; the consequences are waking up not refreshed and day time sleepiness. Lastly, the time spent in deep sleep (non-rapid-eye-movement (NREM) stages 3 and 4) decline, with relatively more time spent in NREM sleep (stages 1 and 2) [137, 138]. Despite this, older adults tend to be more resistant to the cognitive effects of sleep deprivation than younger adults [138]. Terminology changes by the American Academy of Sleep Medicine in 2007 [137] and sleep alterations are described in Table 4.8.

Table 4.8 Sleep and aging

Terminology (American Academy of Sleep Medicine 2007) [137]
Rapid eye movement (REM) = R
Non-rapid-eye-movement 1 (NREM 1) = N1
Non-rapid-eye-movement 2 (NREM 2) = N2
Non-rapid-eye-movement 3, 4 (NREM 3, 4) = N3
Sleep phases
REM: decline in REM sleep
NREM: stages 1 and 2 increase, 3 and 4 decline
NREM stages 3 and 4 (deep, restorative sleep) most affected
Changes in sleep cycle
Total sleep time decreases
Tend to go to bed earlier, with earlier awakening (phase advance)
Delay in sleep latency (time required to fall asleep once in bed)
Sleep efficiency is impaired (time asleep while in bed)
Nocturnal awakenings are common
Sleep fragmentation increases
Daytime drowsiness and napping increase
Clinical impact
Insomnia needs evaluation to ascertain etiology
Acute insomnia often has an addressable cause
Chronic insomnia is managed by addressing sleep hygiene
Environment, diet, caffeine, alcohol, activity, regular sleep habits
Sedative hypnotics are short-term therapy, typically for acute insomnia
Adverse effects of sedative hypnotics include falls, impaired memory, loss of concentration, daytime drowsiness, accidents
Chronic use of hypnotics outweighs benefits in older persons

Clinical Impact

Insomnia increases morbidity and mortality [136]. Sleep disorders contribute to cognitive problems, falls, accidents, and impaired quality of life; many variables affect sleep [136]. It is essential to distinguish physiological sleep changes from the impact of diseases that interfere with sleep (heart failure,

nocturia, depression, dementia, sleep apnea, pain, etc.) and insomnia from adverse drug effects. Insomnia is primarily managed by addressing measures to promote sleep hygiene and treating any apparent cause. In acute insomnia a cause is usually evident and addressed; medications (sedative hypnotics) may have a temporary role for therapy. However, in chronic insomnia, adverse effects of hypnotics exceed benefits. Enhancing sleep may help improve cognition and performance [138].

Successful Aging

There has been much interest on prolonging aging and in the theme of "successful aging" [139]. The very definition of "successful aging" is complex. To some it reflects achieving one's dreams in spite of early death; for others, good health appears to be the priority; but would aging be considered successful if long life and death were associated with unhappiness? [140]. Improving health care to the highest quality has the potential to promote successful aging. Many practices persist without evidence of efficacy, while many models demonstrate the need to redesign systems to improve quality of care [141]. A multidimensional model defines successful aging as a state wherein an individual makes good use of psychological and social potentials to compensate for physiological limitations to achieve a personally satisfying quality of life and sense of fulfillment, even in the context of disease and disability [139]. Determinants of exceptional longevity as observed in centenarians show a substantial familial component in the ability to survive to extreme old age. These include a locus on chromosome 4 (linked to exceptional longevity), absence of genetic variants linked to premature death, and reduced risks for age-related diseases in the children [142]. Simply stated, successful aging may be dependent on genetics, lifestyle, and fortitude [143].

Aging reduces physiological reserves, leading to frailty when the reserve capacity is exceeded. These reserves can be estimated by cardiopulmonary testing. While sedentary lifestyle accelerates the aging effects in those susceptible, physical activity promotes a disease-free life expectancy and thereby has an antiaging effect [144].

The future holds promise for improved therapies based on a better understanding of the science of aging. New models or approaches may include cognitive enhancers, designer drugs, antioxidants, gene therapy, nutrition, and psychosocial health [145–148]. For now, physical inactivity is known to retard secondary aging and prevent some chronic risk conditions such as insulin resistance [149].

Old age did not prevent a centenarian from successfully running a marathon in 5 h 40 min in October 2011. The centenarian completed his first marathon at the age of 89 and since then ran the marathon seven more times, a feat unthinkable in the past. It is encouraging that "people in their late 90s or older are often healthier and more robust than those 20 years younger" [150], warranting a change in our traditional views of aging. There is much to be done in the future to promote healthy aging in older adults as stated by the American Geriatrics Society Task Force [151].

Key Points

- Aging is inevitable, slowly and relentlessly progressive and affects all systems.
- A general yearly decline of 1% applies to most functions, following the third decade.
- Physiological changes in function are expected, but must be differentiated from pathology or disease, although the two almost always often coexist.
- Decline in certain organs or systems can be measured, and followed over time. Typical examples include renal and cardiac function.
- Clinical manifestations are unlikely to result from physiological changes alone and usually signal coexisting disease.
- Manifestations from medications may be superimposed.
- Inactivity contributes to worsening systems function in general; on the other hand, physical activity promotes an antiaging effect.
- Inadequate reserves become apparent during periods of stress; frailty is an extreme situation of minimal reserves.
- Although no theory fully explains "aging," the process appears to be a result from a combination of genetic factors, environmental influences, and lifestyle factors.
- Addressing lifestyle (with emphasis on a healthy diet and physical activity) may be the best approach to minimize disease and promote longevity.
- Successful aging may be the result from the right combination of factors that include favorable genetics, healthy lifestyle to minimize disability and making the most to enjoy a good quality of life.

References

1. US Department of Health and Human Services, Center for Disease Control. National vital statistics reports. 2011;59(4).
2. Ikeda N, Saito E, Konda N, et al. What has made the population of Japan healthy? Lancet. 2011;378(9796):1094–105.
3. Centenarian. http://en.wikipedia.org/wiki/Centenarian. Accessed 26 Dec 2010.
4. Maximum life span. http://en.wikipedia.org/wiki/Maximum_life_span. Accessed 31 Oct 2011.
5. Mortality in developed countries. MMWR. http://www.cdc.gov/mmwr/preview/mmwrhtml/00001589.htm. Accessed 24 Nov 2011.
6. Taffet GE. Age related physiological changes. In: Cobbs EL, Duthie Jr EH, Murphy JB, editors. Geriatrics review syllabus: a core curriculum in geriatric medicine. 4th ed. Dubuque: Kendall/Hunt; 1999. p. 10–23.

7. Dharmarajan TS, Ugalino JT. The physiology of aging. In: Dharmarajan TS, Norman RA, editors. Clinical geriatrics. 1st ed. Boca Raton: CRC/Parthenon; 2001. p. 9–22.
8. Fedarko NS. Biology. In: Pacala JT, Sullivan GM, editors. Geriatrics review syllabus: a core curriculum in geriatric medicine. 7th ed. New York: American Geriatric Society; 2010. p. 9–19.
9. Zanni GR. Coping successfully with aging. Consult Pharm. 2010;25(8):476–91.
10. Perron VD, Robinson BE. The aging process and functional assessment. Arch Am Acad Orthop Surg. 1998;2(1):1–9.
11. Dharmarajan TS, Ugalino JT. The aging process. Geriatric Medicine Board Review Manual. Hosp Physician. 2000;1(1):1–12.
12. Hazzard WR. The clinical physiology of aging. In: Oreopoulos DG, Hazzard WR, Luke R, editors. Nephrology and geriatrics. 1st ed. Boston: Kluwer Academic; 2000. p. 1–16.
13. Guarente L. Sirtuins, aging and medicine. N Engl J Med. 2011;364:2235–44.
14. Yamaza H, Chiba T, Higami Y, Shimokawa I. Lifespan extension by caloric restriction: an aspect of energy metabolism. Microsc Res Tech. 2002;59(4):325–30.
15. Weiss EP, Fontana L. Caloric restriction: powerful protection for the aging heart and vasculature. Am J Physiol Heart Circ Physiol. 2011;301(4):H1205–19.
16. Bronnum-Hansen H, Petersen I, Jeune B, Christensen K. Lifetime according to health status amongst the oldest olds in Denmark. Age Ageing. 2009;38:47–51.
17. Ahmed N, Mandel R, Fain MJ. Frailty: an emerging geriatric syndrome. Am J Med. 2007;120:748–53.
18. Sternberg SA, Schwartz AW, Karunananantham S, et al. Identification of frailty: a systematic literature review. J Am Geriatr Soc. 2011;59:2129–38.
19. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol. 2001;56A:M146–56.
20. Coll PP. Determination of life expectancy: implications for the practice of medicine. Annals of Long-Term Care; Clinical Care and Aging. 2010;18(4):21–4.
21. Ford ES, Bergmann MM, Kroger J, et al. Healthy living is the best revenge. Findings from the European Prospective Investigation into Cancer and Nutrition-Potsdam Study. Arch Intern Med. 2009;169:1355–62.
22. Judge JO, Ounpuu S, Davis RB. Effects of age on the biomechanics and physiology of gait. Clin Geriatr Med. 1996;12(4):659–78.
23. Lam R. Office management of gait disorders in the elderly. Can Fam Physician. 2011;57:765–70.
24. Ko SU, Tolea MI, Hausdorff JM, Ferrucci L. Sex-specific differences in gait patterns of healthy older adults: results from the Baltimore Longitudinal Study of Aging. J Biomech. 2011;44(10): 1974–9.
25. Verghese J, Holtzer R, Oh-Park M, et al. Inflammatory markers and gait speed decline in older adults. J Gerontol A Biol Sci Med Sci. 2011;66(10):1083–9.
26. Quarch L, Galica AM, Jones RN, et al. The non-linear relationship between gait speed and falls: the MOBILIZE Boston Study. J Am Geriatr Soc. 2011;59(6):1069–73.
27. Alexander NB. Differential diagnosis of gait disorders in older adults. Clin Geriatr Med. 1996;12(4):689–703.
28. Dharmarajan TS. Aging and the skin: the geriatrician's perspective. In: Norman RA, editor. Diagnosis of aging skin diseases. London: Springer; 2008. p. 27–38.
29. Norman RA, Mendez R. Structure and function of aging skin. In: Norman RA, editor. Diagnosis of aging skin diseases. London: Springer; 2008. p. 5–10.
30. Siturn M, Buljan M, Cavka V, et al. Skin changes in the elderly people—how strong is the influence of the UV radiation on skin aging? Coll Antropol. 2010;34 Suppl 2:9–13.
31. Sjerobabski-Masnec I, Poduje S. Photoaging. Coll Antropol. 2008;32 Suppl 2:177–80.
32. Sjerobabski-Masnec I, Siturn M. Skin aging. Acta Clin Croat. 2010;49(4):515–8.
33. White-Chu EF, Reddy M. Dry skin in the elderly: complexities of a common problem. Clin Dermatol. 2011;29:37–42.
34. Hanjani NM, Cymet T. Gray hair: medical explanations and issues. Geriatrics. 2003;11(3):36–42.
35. Hordinsky M, Sawaya M, Roberts JL. Hair loss and hirsutism in the elderly. Clin Geriatr Med. 2002;18:121–33.
36. Schnohr P, Nyboe J, Lange P, Jensen G. Longevity and gray hair, baldness, facial wrinkles and arcus senilis in 13000 men and women: The Copenhagen City Heart Study. J Gerontol A Biol Sci Med Sci. 1998;53:347–50.
37. Asakura K, Nishiwaki Y, Milojevic A, et al. Lifestyle factors and visible skin aging in a population of Japanese elders. J Epidemiol. 2009;19:251–9.
38. Hurlow J, Bliss DZ. Dry skin in older adults. Geriatr Nurs. 2011;32:257–62.
39. Dyble T, Ashton J. Use of emollients in the treatment of dry skin conditions. Br J Community Nurs. 2011;16(5):214, 216.
40. Buffa R, Floris GU, Putzu PF, Marini E. Body composition variations in ageing. Coll Antropol. 2011;35(1):259–65.
41. Zamboni M, Zoico E, Scartezzini T, et al. Body composition changes in stable-weight elderly subjects: the effect of sex. Aging Clin Exp Res. 2003;15(4):321–7.
42. Sonati JG, Modeneze DM, Vilarta R, et al. Body weight as an indicator of fat-free mass in active elderly women. Maturitas. 2011; 68(4):378–81.
43. Dmitrieva NI, Burg MB. Increased insensible water loss contributes to aging related dehydration. PLoS One. 2011;6(5):e20691.
44. Caskey CI, Zerhouni EA, Fishman EK, Rahmouni AD. Aging of the diaphragm: a CT study. Radiology. 1989;171(2):385–9.
45. Iannuzzi-Sucich M, Prestwood KM, Kenny AM. Prevalence of sarcopenia and predictors of skeletal muscle mass in healthy, older men and women. J Gerontol A Biol Sci Med Sci. 2002;57(12):M772–7.
46. Schulman RC, Weiss AJ, Mechanick JL. Nutrition, bone and aging: an integrative physiology approach. Curr Osteoporos Rep. 2011;9(4):184–95.
47. Zimmerman EA, Schaible E, Bale H, et al. Age-related changes in the plasticity and toughness of human cortical bone at multiple length scales. Proc Natl Acad Sci U S A. 2011;108(35):14416–21.
48. Lambert JK, Zaidi M, Mechanick JI. Male osteoporosis: epidemiology and the pathogenesis of aging bones. Curr Osteoporos Rep. 2011;9(4):229–36.
49. Seidell JC, Visscher TL. Body weight and weight change and their health implications for the elderly. Eur J Clin Nutr. 2000;54 Suppl 3:S33–9.
50. Rossi AP, Watson NL, Newman AB, et al. Effects of body composition and adipose tissue distribution on respiratory function in elderly men and women: the health, aging and body composition study. J Gerontol A Biol Sci Med Sci. 2011;66(7):801–8.
51. Chester JG, Rudolph JL. Vital signs in older patients: age related changes. J Am Med Dir Assoc. 2011;12:337–43.
52. Lee HY, Oh BH. Aging and arterial stiffness. Circ J. 2010;74(11): 2257–62.
53. Steppan J, Barodka V, Berkowitz DE, Nyhan D. Vascular stiffness and increased pulse pressure in the aging cardiovascular system. Cardiol Res Pract. 2011;2011:263585.
54. Ooi WL, Hossain M, Lipsitz LA. The association between orthostatic hypotension and recurrent falls in nursing home residents. Am J Med. 2000;108:106–11.
55. LeCouteur DG, Fisher AA, Davis MW, McLean AJ. Postprandial systolic blood pressure response of older people in residential care: associated with risk of falling. Gerontology. 2003;49:260–4.

56. Germing A, Gotzmann M, Schikowski T, et al. High frequency of diastolic dysfunction in a population-based cohort of elderly women—but poor association with the symptom dyspnea. BMC Geriatr. 2011;11:71.
57. Dharmarajan TS, Bullecer ML, Gorich G. Drug related hyperthermia. J Am Med Dir Assoc. 2001;2:160–5.
58. Dharmarajan TS, Manalo MG, Manalac MM, Kanagala M. Hypothermia in the nursing home: adverse outcomes in two older men. J Am Med Dir Assoc. 2001;2:29–33.
59. Dharmarajan TS, Widjaja D. Hypothermia in the geriatric population. Aging Health. 2007;3(6):735–41.
60. Domey RC, McFarland MC, Chadwick E. Dark adaptation as a function of age and time: II. A derivation. J Gerontol. 1960;15(3): 267–79.
61. Zannert T. The differential diagnosis of hearing loss. Dtsch Arztebl Int. 2011;108(25):433–43.
62. Popelka MM, Cruickshanks KJ, Wiley TL, et al. Low prevalence of hearing aid use among older adults with hearing loss: the epidemiology of Hearing Loss Study. J Am Geriatr Soc. 1998;46(9): 1075–8.
63. Hoffman HJ, Dobie RA, Ko CW, et al. Hearing threshold levels at age 70 years (65-74 years) in the unscreened older adult population of the United States, 1959-1962 and 1999-2006. Ear Hear. 2012;33:437–40.
64. Ciorba A, Benatti A, Bianchin C, et al. High frequency hearing loss in the elderly: effect of age and noise exposure in an Italian group. J Laryngol Otol. 2011;125(8):776–80.
65. Guedes G, Tsai JC, Loewen NA. Glaucoma and aging. Curr Aging Sci. 2011;4(2):110–7.
66. Alma MA, van der Mei SF, Melis-Dankers BJ, et al. Participation of the elderly after vision tests. Disabil Rehabil. 2011;33(1):63–72.
67. Lopez D, McCaul KA, Hankey GJ, et al. Falls, injuries from falls, health related quality of life and mortality in older adult with vision and hearing impairment—is there a gender difference? Maturitas. 2011;69(4):359–64.
68. Lin FR. Hearing loss and cognition among older adults in the United States. J Gerontol A Biol Sci Med Sci. 2011;66(10):1131–6.
69. Lin FR, Ferrucci L, Metter EJ, et al. Hearing loss and cognition in the Baltimore Longitudinal Study of Aging. Neuropsychology. 2011;25(6):763–70.
70. Solheim J, Kvaerner KJ, Falkenberg ES. Daily life consequences of hearing loss in the elderly. Disabil Rehabil. 2011;33(23–34): 2179–85.
71. Mann DL. Pathophysiology of heart failure. In: Libby P, Bonow RO, Mann DL, Zipes DP, editors. Braunwald's heart disease. 8th ed. Philadelphia: Saunders; 2008.
72. Orchard CH, Lakatta EG. Intracellular calcium transients and developed tension in rat heart muscle. A mechanism for the negative interval-strength relationship. J Gen Physiol. 1985;86(5):637.
73. Craft N, Schwartz JB. Effects of age on intrinsic heart rate, heart rate variability, and AV conduction in healthy humans. Am J Physiol. 1995;268:H1441.
74. Stratton JR, Cerqueira MD, Schwartz RS, et al. Differences in cardiovascular responses to isoproterenol in relation to age and exercise training in healthy men. Circulation. 1992;86(2):504.
75. Zieman SJ, Melenovsky V, Kass DA. Mechanisms, pathophysiology, and therapy of arterial stiffness. Arterioscler Thromb Vasc Biol. 2005;25(5):932.
76. Celermajer DS, Sorensen KE, Spiegelhalter DJ, et al. Aging is associated with endothelial dysfunction in healthy men years before the age-related decline in women. J Am Coll Cardiol. 1994;24(2):471.
77. Folno AF, Migliore F, Marinelli A, et al. Age-related hemodynamic changes during vasovagal syncope. Auton Neurosci. 2010;156(1–2):131–7.
78. Low PA, Singer W. Management of neurogenic orthostatic hypotension: an update. Lancet Neurol. 2008;7(5):451.
79. O'Rourke MF, Nichols WW. Aortic diameter, aortic stiffness, and wave reflection increase with age and isolated systolic hypertension. Hypertension. 2005;45(4):652.
80. Owan TE, Hodge DO, Herges RM, et al. Trends in prevalence and outcomes of heart failure with preserved ejection fraction. N Engl J Med. 2006;355(3):251.
81. Meyer KC. Aging. Proc Am Thorac Soc. 2005;2:433–9.
82. Janssens JP. Aging of the respiratory system: impact on pulmonary function tests and adaptation to exertion. Clin Chest Med. 2005;26:469–84.
83. Taylor BJ. The pulmonary circulation and exercise responses in the elderly. Semin Respir Crit Care Med. 2010;31(5):528–38.
84. Britto RR, Zampa CC, De Oliveira TA, et al. Effects of the aging process on respiratory function. Gerontology. 2009;55:505–10.
85. Miller MR. Structural and physiological age-associated changes in aging lungs. Semin Respir Crit Care Med. 2010;31(5):521–7.
86. Ingebrigtsen TS, Thomsen SF, van der Sluis S, et al. Genetic influences on pulmonary function: a large sample twin study. Lung. 2011;189(4):323–30.
87. Gould NS, Min E, Gauthier S, et al. Aging adversely affects the cigarette smoke-induced glutathione adaptive response in the lung. Am J Respir Crit Care Med. 2010;182:1114–22.
88. Flouris AD, Koutedakis Y. Immediate and short-term consequences of secondhand smoke exposure on the respiratory system. Curr Opin Pulm Med. 2011;17(2):110.
89. Puyol DR. The aging kidney. Kidney Int. 1998;54:2247–65.
90. Dharmarajan TS, Venkatasamy D, Russell RO. Renal and electrolyte disorders in older adults. In: Dharmarajan TS, Norman RA, editors. Clinical geriatrics. 1st ed. London: Parthenon; 2003. p. 429–45.
91. Epstein M. Aging and the kidney. J Am Soc Nephrol. 1996;7: 1106–22.
92. Jassal SV, Oreopoulos DG. The aging kidney. In: Oreopoulos DG, Hazzard WR, Luke R, editors. Nephrology and geriatrics. 1st ed. Boston: Kluwer Academic; 2000. p. 27–36.
93. Rowe JW, Andres A, Tobin JD, et al. The effect of age on creatinine clearance in men: a cross sectional and longitudinal study. J Gerontol. 1976;32:155–63.
94. Glassock RJ. The aging kidney: more pieces to the puzzle. Mayo Clin Proc. 2011;86(4):271–2.
95. Camici M, Carpi A, Cini G, et al. Podocyte dysfunction in aging-related glomerulosclerosis. Front Biosci (Schol Ed). 2011;3: 995–1006.
96. Rule AD, Amer H, Cornell LD, et al. The association between age and nephrosclerosis on renal biopsy among healthy adults. Ann Intern Med. 2010;152:562–7.
97. Lindeman RD, Tobin J, Shock NW. Longitudinal studies on the rate of decline in renal function with age. J Am Geriatr Soc. 1985;33(4):278–85.
98. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31–41.
99. Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med. 1999;130(6):461–70.
100. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, Kusek JW, Eggers P, Van LF, Greene T, Coresh J. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150:604–12.
101. Musso CG, Preopoulos DG. Aging and physiological changes of the kidneys including changes in glomerular filtration rate. Nephron Physiol. 2011;119(Suppl):p1–5.
102. Rule AD, Semret MH, Amer H, et al. Association of kidney function and metabolic risk factors with density of glomeruli on renal biopsy samples from living donors. Mayo Clin Proc. 2011;86(4): 282–90.
103. Choudhry D, Levi M. Kidney aging—inevitable or preventable? Nat Rev Nephrol. 2011;7(12):706–17.

104. Lamberts SW, van den Beid AW, van der Lely AJ. The endocrinology of aging. Science. 1997;278(5337):419–24.
105. Anawalt BD, Merriam GR. Neuroendocrine aging in men. Andopause somatopause. Endocrinol Metab Clin North Am. 2001;30(3):647–69.
106. Stenholm A, Mette JE, Roth GS, et al. Relationship between plasma ghrelin, insulin, leptin, IL6, adinopectin, testosterone and longecity in the Baltimore Longitudinal Study of Aging. Aging Clin Exp Res. 2011;23:153–8.
107. Gruenewald DA, Kenny AM, Matsumoto AM. Endocrine and metabolic disorders. In: Pacala JT, Sullivan GM, editors. Geriatrics review syllabus: a core curriculum in geriatric medicine. 7th ed. New York: American Geriatric Society; 2010. p. 549–64.
108. Peeters RP. Thyroid function and longevity: new insights into an old dilemma. J Clin Endocrinol Metab. 2009;94(12): 4658–60.
109. Arzmon G, Barzilai N, Hollowell JG, et al. Extreme longevity is associated with increased serum thyrotropin. J Clin Endocrinol Metab. 2009;94:1251–4.
110. Surks MJ, Hollowell JG. Age-specific distribution of serum thyrotropin and anti-thyroid antibodies in the U.S. population: implications for the prevalence of subclinical hypothyroidism. J Clin Endocrinol Metab. 2007;92:4575–82.
111. Mazzoccol G, Pazienza V, Piepoli A, et al. Hypothalamus-hypophysis-thyroid axis function in healthy aging. J Biol Regul Homeost Agents. 2010;24(4):433–9.
112. Ryan AS. Insulin resistance with aging: effects of diet and exercise. Sports Med. 2000;30(5):327–46.
113. Silva MD, Martins AC, Cipriano G, et al. Inspiratory training increases insulin sensitivity in elderly patients. Geriatr Gerontol Int. 2012;12:345–51.
114. Leifke E, Gorenoi V, Wilchers C, et al. Age-related changes of serum sex hormones, insulin-like growth factor-1 and sex-hormone binding globuline levels in men: cross-sectional data from a healthy male cohort. Clin Endocrinol (Oxf). 2000;53(6): 689–95.
115. Van den Beid AW, Lamberts SW. The male climacterium: clinical signs and symptoms of a changing endocrine environment. Prostate Suppl. 2000;10:2–8.
116. Morley JE. Hormones and the aging process. J Am Geriatr Soc. 2003;51(7 Suppl):S333–7.
117. Peeters RP, Debaveye Y, Fliers E, Visser TJ. Changes within the thyroid axis during critical illness. Crit Care Clin. 2006;22: 41–55.
118. Mooradian AD. Subclinical hypothyroidism in the elderly: to treat or not to treat? Am J Ther. 2011;18(6):477–86.
119. Mitchell AL, Pearce SH. How should we treat patients with low serum thyrotropin concentrations? Clin Endocrinol (Oxf). 2010;72(3):292–6.
120. Anderson AL, Harris TB, Tylavasky FA, et al. Dietary patterns, insulin sensitivity and inflammation in older adults. Eur J Clin Nutr. 2012;66(1):18–24.
121. Takao H, Hayash N, Ontomor K. White matter asymmetry in healthy individuals: a diffusion tensor imaging study using tract-based spatial statistics. Neuroscience. 2011;193:291–9.
122. Gunning-Dixon FM, Brickman AM, Cheng JC, Alexopoulos GS. Aging of cerebral white matter: a review of MRI findings. Int J Geriatr Psychiatry. 2009;24(2):106–17.
123. Bartes-Faz D, Clemnete IC, Junque C. White matter changes and cognitive performance in aging. Rev Neurol. 2001;33(4):347–53.
124. Inano S, Takao H, Hayashi N, et al. Effects of age and gender on white matter integrity. AJNR Am J Neuroradiol. 2011;32(11): 2103–9.
125. Steffener J, Stern Y. Exploring the neural basis of cognitive reserve in aging. Biochim Biophys Acta. 2012;1822(3):467–73.
126. Tucker AM, Stern Y. Cognitive reserve in aging. Curr Alzheimer Res. 2011;8(4):354–60.
127. Petersen RC. Mild cognitive impairment. N Engl J Med. 2011;364:2227–34.
128. Kumar R, Burns EA. Age-related decline in immunity: implications for vaccine responsiveness. Expert Rev Vaccines. 2008;7(4): 467–79.
129. Caider AE, Hince MN, Dudakov JA, et al. Thymic involution: where endocrinology meets immunology. Neuroimmunomodulation. 2011;18(5):281–9.
130. Sansoni P, Vescovini R, Fagnoni F, et al. The immune system in extreme longevity. Exp Gerontol. 2008;43(2):61–5.
131. Streit WJ, Xue QS. The brain's aging immune system. Aging Dis. 2010;1(3):254–61.
132. Corona AW, Fenn AM, Godbout JP. Cognitive and behavioral consequences of impaired immunoregulation in aging. J Neuroimmune Pharmacol. 2012;7(1):7–23.
133. Wong CP, Ho E. Zinc and its role in age-related inflammation and immune dysfunction. Mol Nutr Food Res. 2012;56(1):77–87.
134. Vulmanovic-Stejic M, Rustin MH, Nikolich-Zugich J, Akbar AN. Immune responses in the skin old age. Curr Opin Immunol. 2011;23(4):525–31.
135. Walsh NP, Gleeson M, Pyne DB, et al. Position statement. Part two: maintaining immune health. Exerc Immunol Rev. 2011;17:64–103.
136. Crowley K. Sleep and sleep disorders in older adults. Neuropsychol Rev. 2011;21(1):41–53.
137. IIber C, Ancoli-Israel S, Chesson A, Quan SF. The AASM Manual for the scoring of sleep and associated events. Westchester, IL. American Academy of Sleep Medicine. 2007.
138. Pace-Schott EF, Spencer RM. Age-related changes in the cognitive function of sleep. Prog Brain Res. 2011;192:75–891.
139. Young Y, Frick KD, Phelan EA. Can successful aging and chronic illness coexist in the same individual? A multidimensional concept of successful aging. J Am Med Dir Assoc. 2009;10:87–92.
140. Callahan CM. Successful aging and the humility of perspective. Ann Intern Med. 2003;5(2):389–90.
141. Landefield CS. Improving health care for older persons. Ann Intern Med. 2003;5(2):421–4.
142. Perls T, Terry D. Understanding the determinants of exceptional longevity. Ann Intern Med. 2003;5(2):445–9.
143. Morley JE. Successful aging or aging successfully. J Am Med Dir Assoc. 2009;10:85–6.
144. Charansonney OL. Physical activity and aging: a life-long story. Discov Med. 2011;12(64):177–85.
145. Cassel CK. Successful aging. How life expectancy and medical advances are changing geriatric care. Geriatrics. 2001;56(1): 35–9.
146. Parslow RA, Lewis VJ, Nay R. Successful aging: development and testing of a multidimensional model using data from a large sample of older Australians. J Am Geriatr Soc. 2011; 59:2077–83.
147. Brummel-Smith K. Optimal aging, part II: evidence-based practical steps to achieve it. Ann Longterm Care. 2001;15(12): 32–40.
148. King AC, Guralnik JM. Maximizing the potential of an aging population. JAMA. 2010;304:1944–5.
149. Booth FW, Laye MJ, Roberts MD. Lifestyle sedentary living accelerates some aspects of secondary aging. J Appl Physiol. 2011;111(5):1497–504.
150. Perls TT. The oldest old. Sci Am. 2004;14(3):6–11.
151. Besdine R, Boult C, Brangman S, et al. Caring for older Americans: the future of geriatric medicine. American Geriatrics Society: core writing group of the Task Force on the Future of Geriatric Medicine. J Am Geriatr Soc. 2005;53:S245–56.

The Gastrointestinal System and Aging

5

T.S. Dharmarajan, Amit Sohagia, and C.S. Pitchumoni

Introduction

Normal aging is associated with gradual and subtle changes in the morphology and function of most organs and systems [1]. The gastrointestinal (GI) system is no exception; there are suggestions that physiological changes may accelerate in the oldest years. With the increase in life expectancy in the United States and world over, clinicians need awareness of the age-related physiological changes and their consequences, well detailed in a committee report by the American Gastroenterological Association [2]. Demographic changes have led to a disproportionate increase in the oldest segments of the population, many characterized to have several GI disorders including dysphagia, gastroesophageal reflux, gastroparesis, and discomfort due to constipation, stool impaction, and fecal incontinence. True physiologic changes due to aging may be difficult to distinguish from subclinical disease. Data on several age-related alterations have been largely derived from animal studies with implications in humans far from clear. Altered gut physiology, subtle as it might be, may play a role in many manifestations in the aged, including anorexia, constipation, fecal incontinence, and postprandial hypotension [1–4].

Gastrointestinal Motor Function

An increase in the prevalence of gastrointestinal disorders of function and motility occurs with age [5]. Although we recognize an increase in the prevalence of several gastrointestinal motor disorders such as dysphagia and constipation in older people, age per se has minimal direct effects, largely due to the enormous functional reserves. Alterations in motor function more likely result from disease, with clinical implications relating to weight loss or gain, taste disturbances, clinical outcome, and at times even socioeconomic burden [4–8].

The intestinal myenteric and submucosal plexus demonstrate age-related changes which begin in adulthood and worsen with advancing years; changes specifically involve the cholinergic neurons and include concurrent enteric glial cell losses. There appears to be greater losses in the distal GI tract compared to the proximal sites [9–11]. Dystrophic axonal swelling occurs in the sympathetic, vagal, dorsal root, and enteric nitrergic innervation of the gut; these autonomic nervous system changes may in part explain the age-related decline in function [1, 3, 11]. Motor dysfunction in older persons more commonly results from tumor, inflammatory or neurological disease, systemic disorders, and effects of medications. As management will relate to the presence or absence of disease, and not just age, a diagnostic work-up is usually required [11–13].

Oral Changes

Changes in the skin and oral mucosa are known to result from the variable influence of environment, diet, hormonal changes, and medications. Disorders of the oral cavity are detailed in chapter 45 on Oral Health.

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Teeth

With age, the appearance of teeth changes to a yellowish, darker hue from altered composition of the underlying dentin and covering enamel. The vascular supply of the tooth and enamel declines with age, one cause of altered sensitivity to environmental stimuli. There is proneness to caries or trauma, leading to thickening of the cementum (the substance covering the root surface); the total width of the tooth almost triples between ages 10 and 75 years [14–17]. Teeth wear occurs with age, to a large extent as a result of normal chewing; however, the number of edentulous people has declined in the past few decades, with more older people retaining their teeth [15].

The Tongue

The mucous membrane of the tongue accommodates four papillae: filiform, fungiform, circumvallate, and foliate. Although the filiform papillae do not contain taste buds, each circumvallate papilla contains about 250 taste buds, and the foliate papillae (vertical folds in the postero-lateral tongue) contain approximately 1,200 taste buds. Taste buds are found primarily around the tongue margin and dorsum, soft palate, pharynx, and epiglottis. Taste innervation is provided by the chorda tympani branch of the facial nerve and the glossopharyngeal nerve [18–20].

Xerostomia

Xerostomia, the subjective sensation of dry mouth, is the result of a decline in saliva production and affects 29–57% of older persons [21–23]. The functions of saliva include lubrication, promoting dental remineralization, prevention of decay, and protection against fungal and bacterial infections. Manifestations of xerostomia include burning sensation, altered taste, dysphagia, and dysarthria. Age by itself does not cause a decrease in stimulated salivation, but loss of teeth may cause a decline in stimulated salivary flow [22]. Xerostomia results from illness and more commonly as an adverse effect of medications. Examples of medications causing xersotomia include tricyclic antidepressants (amitriptyline, imipramine), serotoin reuptake inhibitors (fluoexitine, sertraline), antipsychotics (thioridazine, olanzapine), and antihistamines (diphenhydramine, cyproheptidine) [21–23].

Clinical Application

Xerstomia calls for a review of medications that decrease salivary flow, and elimination or substitution of the offending agent wherever possible. Patients are encouraged to sip water, avoid alcohol, and minimize consumption of food and drinks that promote xerostomia e.g., caffeinated beverages. Chewing sugarless gum or candy may serve as sialogogues (agents that induce salivation); mechanical foods that serve as stimulants include apples, carrots, and celery. Salivary substitutes may offer temporary relief. Oral moisturizers are an option. Pharmacological stimulants include pilocarpine and cevimeline; they are useful for dry mouth in keratoconjunctvitis sicca (Sjögren syndrome) [18–23]. Decreased salivation and buffering capacity may be associated with low carries risk but high dental erosion progression [22].

Taste Sensation

Taste sensation is appreciated during mastication and deglutition from the contact of food with neuroepithelial cells, the taste buds. The sense of smell contributes much to taste perception. Both taste and smell complement nicely to enhance food palatability. Oral tactile sensation helps determine food texture; flavoring agents and condiments help complete the taste experience. Taste buds in thousands sit atop the papillae. The ovoid taste bud has a life of about 10 days and is constituted by 50–100 taste receptors, essentially taste chemoreceptors. Balding of the tongue or glositis may indicate loss of papillae or malnutrition, among other causes [24–26].

A taste bud has receptors that essentially account for five primary taste sensation: sour, salty, sweet, bitter, and umami. Acids produce a sour taste; ionized salts, mainly cations, stimulate salty taste. Various chemicals, mainly organic, produce sweet and bitter sensations. Monosodium glutamate (MSG), a flavor enhancer, elicits umami taste. Diminishing taste is a consequence of degeneration or reduction in taste buds. In healthy adults, taste buds regenerate approximately every 10 days; the process declines in the old, and in women following menopause or with estrogen deficiency. Protein and zinc deficiency retards taste bud renewal [18, 19, 21]. Although taste perception may change with age, somatic sensations such as touch and burning pain in the tongue are preserved, suggesting that the tongue addresses these stimuli differently [24]. Data now supports an elevation in sensory threshold with age for somato-sensory (warm, cool, two point discrimination) and gustatory senses [26].

Olfaction

The sense of smell is often taken for granted, until it is lost! There is a consistent age-related decline in olfactory function. The loss of smell is gradual along with the ability to discriminate between odors. The decline is significant with the majority of adults over age 80 having olfactory impairment (i.e., elevated olfactory threshold). This is attributed to a decrease in olfactory bulb fibers and olfactory receptors. Olfactory receptors undergo apoptosis at a baseline rate in all; age enhances receptor cell death [19, 21, 25].

Table 5.1 Oral cavity, taste, and smell

Morphology
Teeth
Teeth wear gradually with age from normal chewing
Teeth width increases with age
Teeth loss is not an aging phenomenon, rather from disease
Tongue
Taste buds: several thousand in the tongue and sit on the papillae on the tongue surface
Taste buds house receptor cells; receptors located in the palate, tongue, and upper esophagus
Salivary glands: acinar cells structurally intact, but reduced in number
Functions
Smell: increased threshold in perception, with decline in abilities to perceive smell. Consistent decline with age
Taste, also, known as gestation; basic tastes are salty, sweet, bitter, sour, and umami. Taste sensitivity is located all over the tongue and other locations in the mouth. Taste preferences are altered with age, with a decline in taste discrimination, but alterations less consistent than olfaction
Saliva production: basal <0.5 mL/min and stimulated 1–2 mL/min are intact with age, both quantitative and qualitative, suggesting adequate acinar cell function
Implications
Proper dental care in early life leads to better preservation of teeth in old age
Taste and smell contribute to appetite, an extremely important factor in quality of life
Tastes can benefit or harm and hence stimulates or deteriorates appetite
Most often marked loss in taste and smell is secondary to:
Diseases alter the perception of taste and smell
Adverse effects of medications that alter taste and/or saliva production
Decline in saliva production with xerostomia is a result of disease, medications, or salivary loss (mouth breathing or drooling)

Clinical Application

Olfactory function is also influenced by disorders of liver, cancers, mild cognitive impairment (precursor to dementia), and Alzheimer's disease [19, 21]. Electrophysiological tests have confirmed impaired olfaction in preclinical and clinical Alzheimer's disease.

The human being always has the desire to eat and enjoy food, a process requiring all sensations to be intact. The pleasure of eating the apple comes from the sight of the apple (vision), smell and taste of the fruit, the crunch while eating (dentition and hearing), and intact swallowing function. Aguesia and dysguesia commonly result from nutrient deficiencies or adverse drug effects. Enjoyment of food can be helped by flavor enhancement, use of sugarless candy (to stimulate saliva) and by social dining. Older adults can thus better enjoy their meals [5]. While aging is largely associated with preservation of taste, subtle taste discrimination may be impaired (Table 5.1).

The Esophagus

Clinically significant esophageal dysfunction does not result solely from age although mild manometric changes have been described [27]. Alterations in the old include a decrease in the amplitude of contractions, number of peristaltic waves following a swallow, increase in disorganized contractions in the body of the esophagus and weakening of esophageal smooth muscle. Often, it is the associated neurological disorders that cause secondary esophageal dysfunction; esophageal function is usually well preserved even in advanced age [27–29].

Esophageal Motility

Dysphagia is common in old people. Oropharyngeal dysphagia occurs in 50% of nursing home residents, accounting for frequent aspiration pneumonia. Oropharyngeal (or transfer) dysphagia may result even from subtle changes in upper esophageal sphincter (UES) or pharyngeal function. UES dysfunction results from striated muscle disorders, myasthenia gravis, stroke, Parkinson's disease, and commonly advanced dementia [3, 4, 29]. Zenker's diverticulum and cervical osteophytes are unique mechanical causes of intrinsic and extrinsic obstruction, respectively. Zenker's diverticulum is an out-pouching in the posterior pharyngeal wall immediately above the UES; the diverticulum retains putrified food, with manifestations such as foul breath, cough, neck fullness or gurgling with meals, and the dreaded pulmonary aspiration. The UES, composed of the cricopharyngeus skeletal muscle, is a primary barrier to aspiration of gastric reflux. Subtle alterations in oropharyngeal function are observed through video swallowing studies [30, 31]. UES pressure may decline with age, causing a delay in relaxation after deglutition. Pharyngeal clearance during a swallow may be impaired, partly explaining the risk of aspiration in older age. In addition, a decline in sensory

discrimination in the oral cavity and the pharynx is also a predisposition. Quantitative evidence of age-related changes in tongue movement during natural swallowing is attributed to muscle weakening [30]. The amount of food and liquid required to stimulate a pharyngeal swallow is larger in the old. Secondary esophageal peristalsis in the elderly is either absent or evoked less frequently after esophageal distension; complete lower esophageal sphincter (LES) relaxation in response to esophageal air distension is impaired [32].

Esophageal (transit) dysphagia, as opposed to oropharyngeal dysphagia, may be due to a mechanical cause or a motility disorder. Motility dysfunction infrequently occurs in people over 70 years of age [4, 33]. In symptomatic persons, esophageal abnormalities may be present in 20–30% [2]. A decline in the amplitude of esophageal contractions is explained by a decline in cells of the enteric nervous system with age. The term "presbyesophagus" once popular refers to a constellation of age-associated changes: decreased contractile amplitude, polyphasic waves, incomplete relaxation of the LES, and esophageal dilatation, with frequent simultaneous contractions (symptomatic or asymptomatic diffuse esophageal spasm) [2]. The clinical significance of these findings remains unclear [29, 33].

Age is associated with a reduction in the enteric plexus neurons by 20–60% [6]. The UES and LES act as barriers against reflux. The UES pressure in the old is considerably lower [31]. Age-associated hiatal hernia pushes up the gastroesophageal junction above the diaphragm to decrease LES function. Age is associated with an increase in esophageal acid exposure due to progressive decrease in abdominal LES length and peristaltic activity [34]. Overall, intrinsic changes in esophageal function with age have little impact on function.

Clinical Application

Dysphagia should never be attributed solely to old age. Primary esophageal motility disorders associated with dysphagia would include achalasia, scleroderma, diffuse esophageal spasm, "nutcracker" esophagus, and nonspecific esophageal motor disorders. Achalasia in the elderly may be a manifestation of gastro-esophageal junctional cancer. Medication-induced esophageal injury is a common esophageal disorder in older adults, warranting a medication review, and focused history for substernal pain, odynophagia, and dysphagia. The injuries are generally self-limiting. Swallowing disorders in older adults predispose to aspiration pneumonia and malnutrition [33, 35]. While salivary secretion declines during sleep, the effect of hypnotics decreases secondary peristaltic activity and increases likelihood for esophageal mucosal injury through contact with regurgitated acid.

The Stomach

It is common for asymptomatic individuals over age 60 years to have atrophic gastritis [2–4, 33–37]. Gastric atrophy does not result from normal aging; rather, it is a consequence of other factors. Both basal and peak gastric acid output decrease with age, mostly a result of gastric mucosal atrophy. Yet, most healthy older people maintain normal gastric acid secretion [37]. The role of *Helicobacter pylori* infection in the pathogenesis of gastric atrophy and hypochlorhydria is now well recognized; prior or current *H. pylori* infection is seen in most patients with atrophic gastritis. Serum gastrin concentration increases in *H. pylori* infected subjects but not in older uninfected subjects [36]. Pepsin secretion does not decline, but a decline in gastric bicarbonate, sodium ion and nonparietal fluid secretion occurs with age [2]. In summary, the histological and functional changes in the stomach attributed in the past to aging are now better explained by the presence of *H. pylori* infection, a prevalence that increases with age [36–38].

Gastric mucosal blood flow decreases with age, as does the blood flow to most organs, leading to slower healing of mucosal injury [2]. Gastric prostaglandin synthesis may diminish increasing susceptibility to the adverse effects of NSAIDs on the mucosa. While gastric aging may induce abnormalities of the gastric epithelium, most alterations are a result of chronic insults; these include *H. pylori* infection, adverse effects of medications (NSAID gastritis) and comorbidity [39]. A consequence of gastric frailty with age is the vulnerability to peptic ulcer disease [39]. Mucosal protective mechanisms may be impaired with age [40]. The role for molecules implicated in repair such as trefoil peptides and matrix components is being studied [40].

Clinical Application

Life style factors that impact on gastric filling, distension and emptying, postmeal posture and GERD [41] may favor acid reflux. In large part, the influence of acid-reducing agents, NSAIDs, and *H. pylori* infection cause a variety of gastric disorders including a reduction of defense mechanisms [34, 35].

Gastric and Small Bowel Motility

The major functions of the stomach are to accept ingested food and convert the material to a suspension suitable for emptying into the duodenum and beyond. The presence of comorbidity and drug effects pose difficulties in interpreting motility studies in the elderly. The interstitial cells of Cajal (ICC) decline in the stomach and colon, influencing motility and response to insults from disease and drugs [42].

Isotope studies demonstrate a considerable prolongation of gastric emptying for liquids in healthy older subjects compared to younger controls [43]. However, gastric emptying for solids appears unchanged and the gastric electrical rhythm remains intact [44]. Aging is associated with diminished perception of gastric distension. Age does not alter fasting and postprandial antral motility, believed to play a role in the emptying of solids. Conversely, fundic activity may be affected, which may account for a disturbance in liquid emptying [43]. Gastroparesis is detailed in chapter 33.

Morphological changes in the small intestine include a reduction in number of neurons in myenteric plexus and a reduction in splanchnic blood flow [45]. The surface to volume ratio in the jejunum and enterocyte height remain unchanged, retaining the normal absorptive surface [46]. Mucosal regeneration increases with age [2]. The migrating motor complex (MMC) serves as the gut "housekeeper." MMC occurs in three phases: phase 1, a silent period with small bowel inactivity; phase 2, characterized by irregular patterns; phase 3, with migrating motor activity. Changes in MMC involve velocity and occur only in the eighth or ninth decade of life. Intestinal abnormalities in any age group such as malabsorption cannot be attributed to age-related intestinal motility changes. The control of *phase 3* motor activity is mainly neural; a reduction in propagation velocity may result from age-related alterations in receptors of the enteric nervous system [43, 45, 47].

With age there is little decline in small intestinal function, and malabsorption is uncommon [46]. Overall carbohydrate absorption is unaffected, and the duodenal brush border activity for glucose is maintained [2, 13]. Lipid absorption is maintained in older age, with little decline based on lower splanchnic blood flow [48]. Pancreatic exocrine function is well preserved, since only 10–20% of pancreatic enzyme required for digestion [46]. Fructose, a monosaccharide and a component of fruits and fruit beverages, is increasingly consumed with fructose intolerance (diarrhea) more recognized. The role of transporters will help better understand fructose absorption [49]. Lactase activity that declines during adolescence may become more common with age, as a result of infections and chronic disease, medications (chemotherapeutic agents), and radiation injury. A decline in vitamin D receptor activity lowers the active absorption and transport of calcium, predisposing to osteomalacia [49]. Human studies suggest that although there is little concern for macronutrient absorption, micronutrients such as B12, folic acid, zinc, and copper may be affected with age [2].

Small intestinal motility is a requirement for proper food digestion, nutrient absorption and clearance of cell debris, secretions, and residual undigested materials. Orocecal transit time does not change significantly with age in healthy adults, but is altered in disease; the transit time of facility residents, mean age 82 years, did not differ from younger adult controls [51]. In another study, although age did not affect small intestinal transit time nor gastric emptying time, it did slow colonic transit time [52] (Table 5.2).

Table 5.2 Age-related physiological changes

Esophagus
Decreased upper esophageal sphincter (UES) pressure, increased resistance, and delayed relaxation after deglutition
Decreased amplitude of peristalsis and an increase in synchronous contractions
Progressive decrease in abdominal lower esophageal sphincter (LES) length
Decline in esophageal clearance
Diminished esophageal perception
Stomach
Decline in gastric blood flow with age
Some delay in gastric emptying, noted particularly for liquids, with increase in postprandial antral volume
Little change in pepsin secretion with age
Basal and stimulated gastric acid secretion do not decline in healthy aging; a decline may in fact be due to atrophic gastritis
Decline in interstitial cells of Cajal (ICC) with age
Impaired mucosal protective mechanism; decline in mucosal prostaglandin
Small intestine
Alteration in villous architecture
Reduction in myenteric neuronal plexus
Decline in splanchnic blood flow
Decline in calcium absorption diminishes because of intestinal resistance to action of 1,25-dihydroxyvitamin D
Large intestine
Reduction in rectal wall sensitivity
Decrease in anal canal resting and squeeze pressure with age
Delay in colonic transit may be modest to none
Decline in ICC at 13% per decade
Enteric neurodegeneration (seen in animal models) with age
Higher prevalence of diverticular disease is noted with age
Pancreas
Decline in insulin secretions with age associated with insulin resistance
Exocrine function is largely intact, with no significant impact on absorption
Liver
Blood flow declines with age; decline in phase 1 activity, better preserved phase 2 activity
Liver function relatively preserved, with normal albumin synthesis
Gall bladder
Decrease in hepatic extraction of LDL with higher LDL level
Diminish sensitivity to cholecystokinin (CCK) with age is offset by an increase in endogenous CCK secretion facilitating gall bladder contractions
Increase incidence of cholelithasis, perhaps relating to lithogenic bile

Clinical Application

The delay in gastric emptying noted in pathological states or as a pharmacodynamic effect may allow for longer contact time between harmful medications such as NSAIDs or aspirin and the gastric mucosa, with resultant adverse effects. While small intestinal transit time does not change appreciably with age, diseases such as diabetes and systemic sclerosis may significantly affect prolonged orocecal transit time [53, 54].

Intestinal Microflora

Proximal small intestine in healthy adults usually contains less than 10^4 bacteria/mL, predominantly Gram-positive anerobes [55]. Changes are apparent in the gut bacteria in older persons. An overall decrease in the total number of bifidobacteria is accompanied by an increase in species diversity [56]. Fungi and enterobacteria tend to increase. Overall, no single marker has been identified to denote change in microbiota composition; the impact of age is little, while that from disease and medications modify the composition of the microbial community [57]. In a study of seniors and centenarians, age-related differences in microbiota were related to inflammation and disease processes, and could affect host physiology [58]. Translocation of pathogenic bacteria from the gut into the circulation or lymphatics may lead to release of endotoxins.

Clinical Application

Shifts in composition of microflora may lead to detrimental effects [59], for e.g., increased predisposition to *Clostridium difficile* associated diseases. Therapeutic strategies have been considered and recommended to counter these changes [59]. Aging associated with reduced immune function, coexisting disease, malnutrition, and effect of medications modifies the composition of the microbial community [60]. Small intestinal overgrowth with colonic type bacteria must be considered as a basis for chronic diarrhea, anorexia, or nausea [61]. Based on evidence that the elderly have distinct microbiomes, the healthy old rather than the young may be better donors for probiotics [62]. Probiotics are detailed in chapter 11. With decreased costs of DNA sequencing, it is possible to identify the evolution of microbiota and thereby select probiotics based on patient age [63]. It also appears possible that manipulation of the complex symbiotic ecosystem of gut microbiota may help extend healthy aging and life span [64]. An understanding of the mechanisms of host-gut microbiota cross talk would help design nutritional approaches in targeting immune reactivity [65].

Immune Function

Advanced age associated with breakdown of epithelial barriers of the skin, lung, and genito-urinary tract does not spare the GI system. The gut mucosal immune system is exposed to a large number of antigens [66]. The GI tract surface represents the single largest immunological organ with much of the body's immunoglobulin-producing cells [6]. Aging is accompanied by a decline in the mucosal and secretory immune response, with markedly higher GI infection-related mortality [6]. Changes include decline in regulatory-type cytokine production, T cell compartment, antibody responses to antigens, and the composition of the Peyer's patches lymphoid tissues [66]. Although total T and B cells are generally stable, subset alterations occur. Intrinsic and extrinsic factors dictate macrophage function, with the latter more influential [67]. A better understanding of T cell metabolism, hormones and microbiota may provide insights into immune responses associated with aging. Gut hormones such as leptin, ghrelin, insulin-like growth factor (IGF-1), and cytokines may play a role [68]. Little is known as to how the IgA plasma cells in Peyer's patches and their homing to the lamina propria are affected by age [69]. Intestinal mucosal immunosenescence may be a consequence of reduced homing of IgA plasma cells [69]. Although age does not correlate with surface epithelium and number of intraepithelial lymphocytes, absorption of lipids is somewhat impaired and may result from a decline in blood flow and ischemia [48].

Clinical Application

Gastrointestinal infections are common in older adults and may in part relate to altered immune function. More often, predispositions to infections are contributed by decline in gastric acidity, inappropriate use of antibiotics, presence of blind loops, and other causes.

Colonic Motility

Constipation and colonic motor functional alterations are not solely a consequence of aging. The role of enteric neurodegeneration in constipation has been noted in animal models; whether age affects the intrinsic and extrinsic innervation of colonic smooth muscle or degeneration from neurological disorders (such as Parkinson's disease) deserves study [70]. The number of neurons in human colon declines with age; neuronal nitric oxide synthase-positive neurons are spared and compensation has been noticed in the spared neurons [71]. In both stomach and colon, the number of ICC decrease with age at a rate of 13% per decade; ICC size is affected only in the myenteric plexus of the colon [42]. While the changes do not differ by gender, they may contribute to alteration in motility [42].

In a study of over 3,000 individuals, 26% of women and 16% of men reported recurrent constipation [72, 73]. The variables associated with constipation in the over 65 age group included age, female gender, medication use, and the presence of abdominal pain, diverticular disease, and hemorrhoids. Psychological illness correlated positively with self-reported constipation [73].

Studies on sigmoid function and colonic transit show little evidence of alterations [74]. The most consistent

physiological findings were decreased rectal compliance and an increase in the sensory threshold for the urge to defecate. A large, relatively noncompliant rectum correlates with an infrequent urge to defecate. The presence of stool in the rectum for lengthy periods of time may suggest poor sensation of the urge to defecate.

While there is data to implicate abnormalities in colonic motility in older adults, chronic constipation is associated more frequently with abnormalities of rectal function and afferent sensory mechanisms. Whether the findings are attributable to age-related physiological changes or poor bowel habits is unclear [4, 70, 73].

Anorectal Function

Data suggests a decrease in both resting and squeeze anal canal pressures with age, as noted in healthy volunteers aged 20–89 years and subjects over 50 years [75–77]. The rate of decline in resting anal canal pressures is more apparent in females, and unrelated to parity. While the data is less clear on changes in rectal sensation, the threshold sensation for rectal filling seems to increase with age. Anorectal dysfunction is common in those with fecal incontinence, common in the old and one reason for institutionalization. Fecal incontinence is detailed in chapter 56.

Clinical Application

Constipation is most often the result of disorders seen in the old and influenced by life style and adverse drug effects. Measures must hence address life style, acknowledging the coexistence of disease and adverse effects of medications.

Gastrointestinal Hormones

Neuroendocrine cells regulate homeostasis via neurocrine, endocrine, and paracrine means. Gut neuroendocrine cells demonstrate differential behavior with age and are key to regulatory processes [12]. Gut hormones may be encoded for circadian rhythms of motor and secretory activity, and cell proliferation rhythm [78]. The hormones have been implicated in relaying signals on nutritional status and energy intake to the nervous system; while ghrelin stimulates food intake, cholecystokinin (CCK), peptide YY, pancreatic polypeptide, and glucagon-like peptide-1 (GLP-1) suppress appetite [79].

It is also believed that hormonal interactions occur between gut and brain; hormones circulate in the blood and signal via vagal afferents to communicate with the hypothalamus and brainstem [80]. Circadian biological rhythms account for food intake, hunger, and satiety. Gut hormones such as motilin and ghrelin are responsible for generation of MCC starting in the stomach; gastrin, ghrelin, cholecystokinin, and serotonin are involved in generating contractions in the small and large bowel. Disruption of the gut clock and the circadian rhythm in the GI tract has the potential to cause weight changes [78].

A brief account on gut hormones follows; more information is eloquently detailed in other reviews [81–83].

Gastrin

Gastrin is a peptide hormone released by G cells in the antrum of the stomach, duodenum, and pancreas. The release of gastrin is stimulated by gastric distension, vagal stimulation, peptides in the lumen of the stomach, and hypercalcemia. The actions of gastrin include stimulation of parietal cells to secrete hydrochloric acid. Gastrin plays a role in parietal cell maturation and fundic mucosal cell growth. Further, gastrin increases antral contraction and relaxes the pyloric sphincter to facilitate stomach emptying. Its secretion is inhibited by acidity (negative feedback mechanism) and paracrine secretion of somatostatin. Although gastrin levels were believed to decline with age, it is now believed that basal and stimulated gastric secretion do not significantly decline in healthy aging [13]. Hypergastrinemia occurs in pathologic states e.g., atrophic gastritis, acid suppression from use of histamine receptor antagonists and proton pump inhibitors, and gastrin-producing tumors, a component of the Zollinger–Ellison syndrome [81–82].

Cholecystokinin

CCK is secreted by entero-endocrine I cells in the duodenum and jejunum in response to fat and protein in meals. The actions include gallbladder contraction and promotion of bile entry into the duodenum. CCK stimulates the pancreatic acinar cells to increase enzyme secretion. Other actions include inhibition of food intake and delay gastric emptying. Duodenal mucosal diseases such as celiac disease and surgical procedures that bypass the duodenum (e.g., Billroth II, surgical gastric bypass) decrease CCK production and release, and may be responsible for pancreatic atrophy. Gallbladder sensitivity to CCK is diminished in the elderly, but gallbladder emptying remains unchanged due to an increase in endogenous CCK secretion [81, 82].

Secretin

Secretin, the first hormone, discovered in 1902 (Baylis and Starling) is produced by the S cells of the duodenum and

is released by acid food entering the intestine. Secretin predominantly stimulates the ductal epithelial cells of the pancreas to secrete pancreatic fluid and bicarbonate, facilitating neutralization of acid chyme in the intestine. Secretin is a polypeptide with 27 amino acids; it is present in duodenal mucosa in the inactive prosecretin form. Chyme in the duodenum activates and enhances the release of secretin. Pancreatic alkaline secretion in the duodenum is a protective mechanism against acid mucosal injury. Alkaline pH provides the ideal pH required for action of pancreatic lipase. Age-related effects on secretin are not clear. In pharmacological doses, secretin increases bile flow and GI motility and decreases LES pressure [78–82].

Glucagon

Glucagon, released from pancreatic alpha cells, regulates glucose metabolism through several mechanisms including gluconeogenesis, glycogenolysis, and lipolysis, opposing the actions of insulin. There are no age-related changes. Glucagonoma is a pancreatic cell tumor that causes diabetes, normocytic, normochromic anemia, cheilitis, glossitis, mild diarrhea, psychiatric manifestations, and a predisposition to thromboembolic phenomena. A characteristic erythematous skin reaction (necrolytic migratory erythema) is an association [78–82].

Glucagon Peptide Superfamily

Glucagon Peptide Superfamily is comprised of two peptide hormones: glucagon-like peptide (GLP-1) and glucose-dependent insulin releasing polypeptide (GIP). Incretin hormones (GLP-1 and GIP) are intestinal hormones released following food intake which potentiates glucose-induced insulin response [83, 85–87].

Glucagon-Like Peptide

GLP-1 is produced from the proglucagon gene in L cells of the small intestine. GLP-1 levels are decreased in type 2 diabetes. GLP-1 inhibits gastric acid secretion and gastric emptying [83]. It inhibits food intake through a central nervous system effect and promotes satiety [83]. The incretin effect denotes the phenomenon of oral glucose intake promoting a much greater release of insulin compared to the parenteral isoglycemic glucose infusion. GLP-1 is responsible for incretin effect. Currently GLP-1 analogues are commercially available for the management of diabetes (exenatide, liraglutide, sitagliptin).

Glucose-Dependent Insulin-Releasing Polypeptide

Although not as potent as GLP-1, on a molar basis, GIP also plays a role in incretin effect. Originally termed gastric inhibitory polypeptide (GIP), it is produced by K cells in the small intestine and released in response to ingestion of glucose or fat. Through a complex mechanism, GIP stimulates insulin secretion, in the presence of hyperglycemia. Similar to GLP-1, GIP also inhibits gastric acid secretion and gastric emptying; it also inhibits food intake through a central nervous system effect and promotes satiety [83]. There is experimental evidence that GIP regulates fat metabolism through receptors on adipocytes.

Vasoactive Intestinal Polypeptide

Vasoactive intestinal polypeptide (VIP) is a 28 amino acid peptide with similarities to secretin. VIP is present in brain, spinal cord, lung, and other endocrine organs. The hormone is unresponsive to meals. It is a potent vasodilator that increases GI blood flow and causes smooth muscle relaxation. As a chemical messenger, VIP acts on receptors to stimulate intracellular cAMP generation. It belongs to a family of GI peptides, including secretin and glucagon. The role of VIP is well studied in the syndrome of watery diarrhea, hypokalemia, and achlorhydria. Age-related changes are unclear.

Pancretic Polypeptide (PP)

The PP family of hormones include PP, neuropeptide Y (NPY), and peptide tyrosine tyrosine (termed PYY), each with distinct distribution and function. PP cells are distributed in the pancreatic islets within the parenchyma of the head and uncinate lobe. The secretion of PP correlates with vagal tone and is biphasic. The physiological effects of PP are not clear, but presumed to be inhibitory of pancreatic exocrine secretion. Other roles are inhibitory effects on gallbladder contraction, intestinal motility, and hepatic glucose production. Hospitalized patients may have reduced appetite through excessive release of PP [88]. PP influences several physiological functions including gall bladder contraction and secretion, pancreatic exocrine secretion, intestinal motility, and ileal contractions.

PYY is a 36 amino acid peptide found in the pancreas and in L cells of the distal small intestine and colon. PYY acts an endocrine and paracrine hormone. The stimulants for PYY include fat and products of digestion. PYY in the circulation is reduced by fasting. PYY is a hormone with inhibitory effects on gastric secretion and gastrointestinal motility.

PYY has been termed an "ileal brake" as it increases nutrient–mucosal contact time. Levels are influenced by age and may regulate food intake in the older people, serving as a satiety factor [89]. While PYY cells increase with age in rodents, such change has not been observed in humans [90].

NPY is a 36 amino acid hormone with similarities to PYY, found in the central and peripheral system. NPY stimulates appetite, causes vasoconstriction, and alters circadian rhythm.

Pancreatic endocrine function is altered with age, with a decline in insulin secretion even after adjustment for adiposity and physical activity; this is accompanied with decline in insulin sensitivity and alterations in hepatic glucose production [91]. There appears a significant reduction in PP-positive cells in elderly rats compared to young control rats, suggesting that the distribution of pancreatic hormones is altered to a varying extent during the normal aging process [92].

Somatostatin

Somatostatin is predominantly a paracrine secretion and produced by D cells of gastric and intestinal mucosa and islets of the pancreas. The physiological effects of somatostatin are mostly inhibitory. It regulates gastric, pancreatic, biliary, and salivary secretion and a wide spectrum of GI hormones. The inhibitory effects on secretion have been utilized to treat diarrhea, fluid output from pancreatic fistulas, and to decrease splanchnic and portal blood flow. Radio-labeled somatostatin analogues, such as octreotide, help localize neuroendocrine tumor [93]. Levels of somatostatin increase with aging. The rare clinical syndrome of somatostinoma is characterized by diabetes, diarrhea, and gallstones.

Ghrelin

Ghrelin is a 28 amino acid peptide produced largely in the gastric fundus, with small amounts in the small intestine, pancreas, kidney, testis, placenta, and lung [94]. Ghrelin is the natural ligand growth hormone secretogogue (GHS) receptor; it increases food intake and weight gain [95]. Circulating ghrelin increases during fasting and under conditions associated with negative energy balance, such as starvation or anorexia [96]. In contrast, levels are low following feeds and in obesity. Ghrelin is a central neurohormonal regulator of food intake and energy homeostasis and serves as a signal for initiation of feeding. The usual premeal increase in levels is not observed in gastric bypass patients and may be one of the reasons for the effectiveness of gastric bypass surgery in inducing weight loss [94–97]. In old mice, the release and synthesis of ghrelin seem to be higher compared to that in younger mice, explained by compensation for decline of receptor functions [98]. Ghrelin levels may also decline with aging, and partially explain anorexia in the older adult [99].

Motilin

Motilin is a 22 amino acid peptide produced by endocrine cells of duodenal epithelium and regulates propulsive contractions from the antero-duodenal region to the distal gut. Alterations in gastric motor activity and serum motilin are not related to acid secretory capacity, rather to other alterations in neurohormonal control in the aged [100]. Drugs may serve as motilin agonists to cause abdominal discomfort and diarrhea.

Leptin

Leptin is a protein with 167 amino acids secreted primarily by adipocytes; small amounts are produced by the chief cells of the stomach. Its function is primarily to decrease food intake. Blood leptin levels reflect total body fat stores. Leptin "resistance" in obesity occurs at the level of the blood–brain barrier. Peripherally, leptin acts in synergy with CCK to reduce meal size. Blood levels of leptin increase with obesity, especially in sleep apneic patients and correlate with total fat content; they increase with fasting, stress, and sleep deprivation. *H. pylori* infection in patients over 75 years has been associated with decreased gastric leptin and ghrelin and plasma ghrelin levels [101]. Neuronal nitric acid synthase may be the pathway through which proinflammatory cytokines cause anorexia, and certainly for leptin. Leptin levels remain unchanged with age.

Oxyntomodulin

This is a hormone that has received recent attention. Oxyntomodulin is a 37 amino acid peptide with several actions; these include inhibition of gastric emptying, acid secretion and food intake, and stimulation of intestinal glucose uptake and insulin secretion [83]. It also induces satiety and increases energy expenditure [83]. When administered to humans, it caused weight loss through a reduction in caloric intake and increase in energy expenditure.

Clinical Application

The Baltimore Longitudinal Study of Aging compared healthy "long-lived" individuals (at least 90 years old) with "short-lived" persons (72–76 years), with samples collected between 58 and 70 years. Levels were obtained for ghrelin,

Table 5.3 Aging and gastrointestinal hormones

Hormone	Function	Effect of aging
Gastrin	Stimulates gastric acid secretion	No change with healthy aging
Cholecystokinin	Stimulates gallbladder contraction and pancreatic enzyme secretion	Increase in endogenous CCK, but gall bladder sensitivity is decreased
Secretin	Stimulates pancreatic bicarbonate secretion	Unknown
Vasoactive intestinal polypeptide (VIP)	Stimulates intracellular cAMP	Unknown
Glucagon-like peptide (GLP-1)	Participates in incretin effect. Inhibits gastric emptying, gastric acid secretion and food intake. Promotes satiety	No change
Glucose-dependent insulin-releasing polypeptide (GIP)	Participates in incretin effect. Inhibits gastric emptying, gastric acid secretion and food intake. Promotes satiety	No change
Glucagon	Promotes gluconeogenesis, glycogenolysis, and lipolysis	No change
Pancreatic polypeptide	Inhibits pancreatic exocrine secretion and gut motility	Increase
Somatostatin	Inhibits gut secretion and intestinal motility	Increase
Motilin	Stimulates gastric emptying	Increase
Leptin	Reduces food intake	No change
Ghrelin	Increases food intake, induces weight gain, and stimulates growth hormone	Decline?
Oxyntomodulin	Inhibits gastric emptying, acid secretion, and food intake. Induces satiety and increases glucose uptake and energy expenditure	Unknown

leptin, insulin, interleukin 6, testosterone, and adinopectin. None of the single biomarkers were significantly different, but after combining information from multiple biomarkers, the global score differentiated the two groups [102]. In another study, after weight loss induced by a very low energy diet in overweight or obese patients without diabetes, circulating levels of gut hormones were examined. The levels of ghrlein, GIP, and PP increased, whereas the levels of leptin, peptide YY, CCK, amylin, and insulin declined. This may call for strategies in long-term management to prevent recurrence of weight gain following diet-induced loss [103].

In summary, GI hormone changes in healthy aging result in minimal to no impairment, while the impact may be different in the ill, frail, and homeostenotic states. On the other hand, there may be an emerging role for gut hormones in the management of satiety, gut motility, nutrient absorption, energy handling, and managing disorders involving energy homeostasis [83] (Table 5.3).

Figure 5.1 summarizes the sites and actions of gut hormones.

Hepato-Biliary System

Liver volume decreases with age, with a decline in size but not in the number of hepatocytes. Minor alterations in serum alanine aminotransferase (ALT) are noted. In women, levels continue to increase with age, whereas in men levels increase up to around 50 years [104]. In the frail old, ALT levels demonstrate a bell-shaped curve with lower levels in the old-old [105]. Although liver function is little altered, there is a general decline in the P450 enzyme system in animals [105]. Of note, a greater decline occurs in the activity of rapid metabolism. The fact that age minimally alters liver physiology is supported by the fact that livers from donors over age 80 years are transplanted satisfactorily.

The biliary duct is marginally dilated with age, a result of increased connective tissue; the upper limit for normal is 8.5 mm [106, 107]. Lithogenicity of bile salts increases and leads to a propensity to form gallstones. The prevalence of cholelithiasis increases; however, gall bladder contractions are not affected by age.

Clinical Application

Marked alteration in liver function raises the possibility of diseases including drug-induced liver injury. Evaluation of abnormal liver function must include a medication review to minimize needless evaluation. Alterations in P450 system influence metabolism of numerous medications, additionally influenced by individual variability in enzyme activity with aging; some microsomal enzymes, such as CYP3A are more affected than others [105].

While several physiological changes have been described, one must reiterate that most age-related alterations will have little impact on function. Gastrointestinal dysfunction may be the result of physiological or structural changes in the GI tract or age-related diseases such as tumor, neurological or inflammatory diseases, malnutrition, or the effect of medications [108] (Table 5.4). Often, there is a chronic subclinical inflammation, with the intestine serving as a source of signals that amplify local and systemic inflammation [109]. Several manifestations seldom result solely from aging and

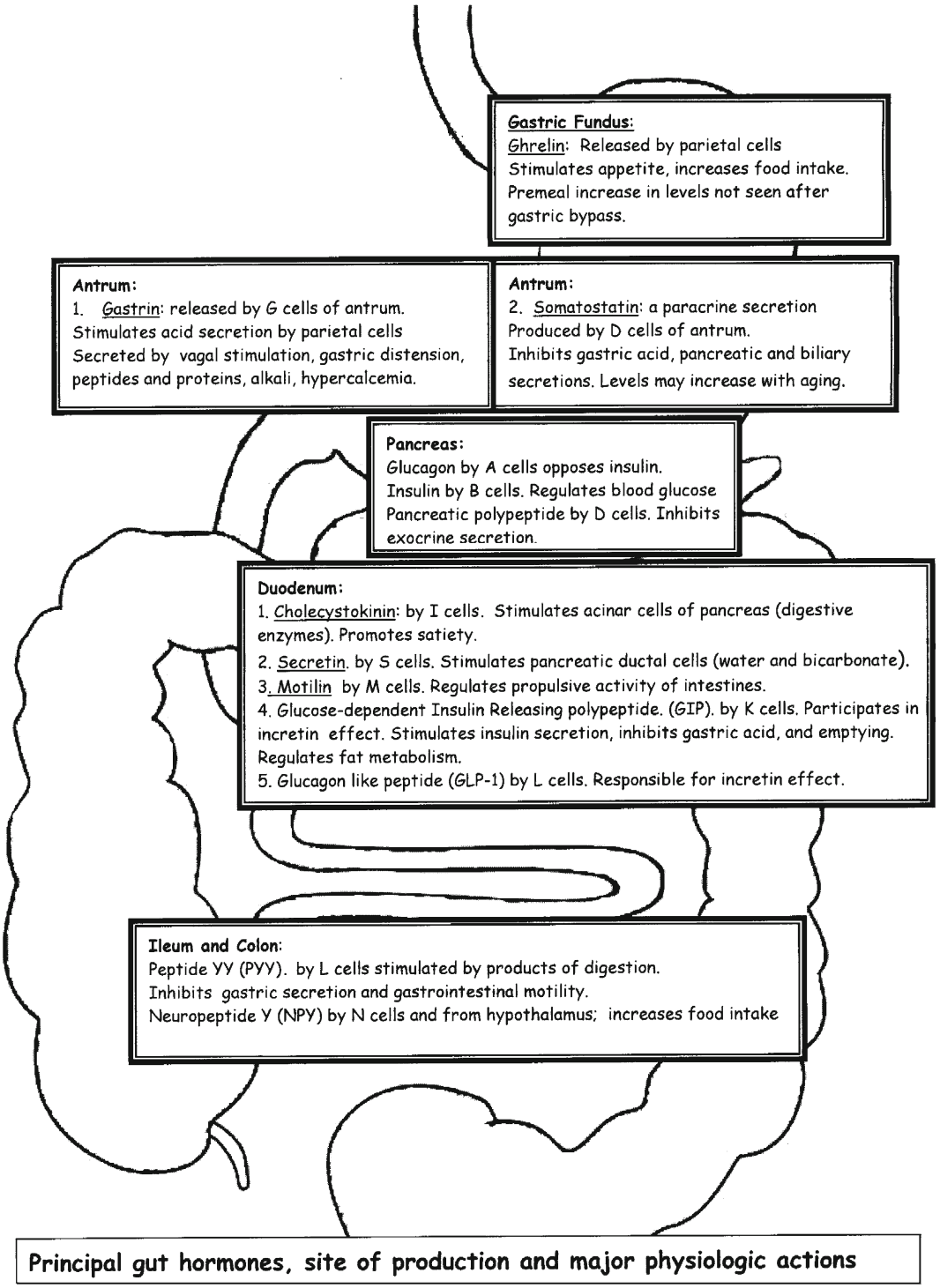

Fig. 5.1 Principal gut hormones, site of production, and major physiological actions

Table 5.4 The impact of medications on gastrointestinal function[a]

Alterations in appetite
Metronidazole
Angioconverting enzyme inhibitors
Iron preparations
Metformin
Dry mouth
Anticholinergics
Clonidine
Diuretics
Alterations in gastric acid secretion and pH
Antacids
H_2 receptor antagonists
Proton pump inhibitors
Constipation
Anticholinergics
Aluminum-containing antacids
Calcium-containing preparations
Calcium channel blockers
Iron preparation
Diarrhea
Antibiotic related (*Clostridium difficile* diarrhea)
Ferrous sulfate or other iron salts
Erythromycin induced
Metformin
Misoprostol
Serotonin reuptake inhibitors
Sorbitol containing preparations
Dysphagia
Large-sized medications (pill esophagitis)
Doxycycline, potassium chloride, ascorbic acid, aspirin, iron salts, bisphosphonates
Candidiasis (following antibiotic use)
Vomiting
Anticholinergic medications

[a]The stated medications are for illustration only and not a complete list

Table 5.5 Gastrointestinal disorders unlikely to result solely from aging

Anorexia
Aguesia, dysguesia
Anemia
Intractable constipation
Diarrhea
Dysphagia
Edentulous state
Fecal incontinence
Iron deficiency
Malnutrition
Malabsorption
Vomiting
Weight loss
Weight gain

are an indication for an evaluation to determine an etiology (Table 5.5).

Key Points

- Age-related physiological changes in the GI tract are minimal and by themselves are not impediments to daily living.
- Gastrointestinal dysfunction is most often the result of age-associated primary disorders of the GI tract or systemic disease.
- Medications often alter gastrointestinal function; adverse drug effects must be addressed before needless testing and evaluation.
- Because of therapeutic options for disease states (as opposed to physiological changes), a differential diagnosis and evaluation is often required in most older persons.
- Several common disorders such as anorexia, dysphagia, constipation, diarrhea, and malabsorption, all common in the old, do not result solely from aging.
- Age has little significant effect on gastric acid secretion, gastric emptying, and small intestinal transit time. Older individuals may have slower colonic transit than the young.
- Most gastrointestinal hormonal changes with age and their effects on body function are subtle; however, gut physiology may play a role in several gut manifestations seen in older age.
- The physiological effects of gut hormones may be utilized in future in the treatment of disorders such as type 2 diabetes mellitus.

References

1. Morley JE. The aging gut: physiology. Clin Geriatr Med. 2007;23(4):757–67, v–vi.
2. Hall KE, Proctor DD, Fisher L, Rose S. American gastroenterology future trends committee report: effects of aging of the population on gastroenterology practice, education and research. Gastroenterology. 2005;129:1305–38.
3. Bhutto A, Morley JE. The clinical significance of gastrointestinal changes with aging. Curr Opin Clin Nutr Metab Care. 2008;11(5):651–60.
4. Firth M, Prather CM. Gastrointestinal motility problems in the elderly patient. Gastroenterology. 2002;122(6):1688–700.
5. Dharmarajan TS, Kokkat AJ, Pitchumoni CS. The aging gut. Pract Gastroenterol. 2001;25(1):15–27.
6. Blechman MB, Gelb AM. Aging and gastrointestinal physiology. Clin Geriatr Med. 1999;15:429–38.
7. Donini LM, Savina C, Cannella C. Eating habits and appetite control in the elderly: the anorexia of aging. Int Psychogeriatr. 2003;15(1):73–87.
8. Moss C, Dhillo WS, Frost G, Hickson M. Gastrointestinal hormones: the regulation of appetite and the anorexia of aging. J Hum Nutr Diet. 2012; 25(1):3–15.

9. Salles N. Basic mechanisms of the aging gastrointestinal tract. Dig Dis. 2007;25(2):112–7.
10. Drozdowski L, Thomson AB. Aging and the intestine. World J Gastroenterol. 2006;12(47):7578–84.
11. Orr WC, Chen CL. Aging and neural control of the GI tract: IV. Clinical and physiological aspects of gastrointestinal motility and aging. Am J Physiol Gastrointest Liver Physiol. 2002;283(6): G1226–31.
12. Kvetnoy I, Popuichiev V, Mikhina L, et al. Gut neuroendocrine cells: relationship to the proliferative activity and apoptosis of mucous epitheliocytes in aging. Neuro Endocrinol Lett. 2001;22(5):337–41.
13. Holt PR. Effect of aging upon the small intestine and colon. In: Pilotto A, Malfertheiner P, Holt PR, editors. Aging and the gastrointestinal tract. New York: Karger; 2003. p. 57–64.
14. Mckenna G, Burke FM. Age-related oral changes. Dent Update. 2010;37(8):519–23.
15. Christensen GJ. The inevitable maladies of the mature dentition. J Am Dent Assoc. 2000;131:803–4.
16. De Rossi SS, Slaughter YA. Oral changes in older patients: a clinician's guide. Quintessence Int. 2007;38(9):773–80.
17. Guiglia R, Musciotto A, Compilato D, et al. Aging and oral health: effects in hard and soft tissues. Curr Pharm Des. 2010; 16(6):619–30.
18. Schiffman SS. Effects of aging on the human taste system. Ann N Y Acad Sci. 2009;1170:725–9.
19. Schiffman SS, Graham BG. Taste and smell perception affect appetite and immunity in the elderly. Eur J Clin Nutr. 2000;54 Suppl 3:S54–63.
20. Koehler J, Leonhaeuser IU. Changes in food preferences during aging. Ann Nutr Metab. 2008;52 Suppl 1:15–9.
21. Boyce JM, Shone GR. Effects of ageing on smell and taste. Postgrad Med J. 2006;82(966):239–41.
22. Filipi K, Halackova Z, Filipe V. Oral health status, salivary factors and microbial analysis in patients with active gastro-esophageal reflux disease. Int Dent J. 2011;61(4):231–7.
23. Gonsalves WC, Wrightson AS, Henry RG. Common oral conditions in older persons. Am Fam Physician. 2008;78(7): 845–52.
24. Fukunaga A, Uematsu H, Sugimoto K. Influences of aging on taste perception and oral somatic sensation. J Gerontol A Biol Sci Med Sci. 2005;60(1):109–13.
25. Kaneda H, Maeshima K, Goto N, et al. Decline inn taste and odor discrimination abilities with age, and relationship between gustation and olfaction. Chem Senses. 2000;25(3):331–7.
26. Heft MW, Robinson ME. Age differences in orofacial sensory thresholds. J Dent Res. 2010;89(10):1102–5.
27. Shaker R, Staff D. Esophageal disorders in the elderly. Gastroenterol Clin North Am. 2001;30:335–61.
28. Greenwald DA. Aging, the gastrointestinal tract, and risk of acid-related disease. Am J Med. 2004;117(Suppl 5A):8S–13.
29. Lee J, Anggiansah A, Anggiansah R, et al. Effects of age on the gastroesophageal junction, esophageal motility, and reflux disease. Clin Gastroenterol Hepatol. 2007;5(12):1392–8.
30. Tamine K, Ono T, Hori K, et al. Age-related changes in tongue pressure during swallowing. J Dent Res. 2010;89(10): 1097–101.
31. Shaker R, Ren J, Podvrsan B, et al. Effect of aging and bolus variables on pharyngeal and upper esophageal sphincter motor function. Am J Physiol. 1993;264(3 Pt 1):G427–32.
32. Ren J, Shaker R, Kusano M, et al. Effect of aging on secondary esophageal peristalsis: presbyesophagus revisited. Am J Physiol. 1995;268(5 Pt 1):G772–9.
33. Gutschow CA, Leers JM, Schroder W et al. Effect of aging on esophageal motility in patients with and without GERD. Ger Med Sci. 2011;9:Doc 22.
34. Lee J, Anggiansah A, Anggiansah R, et al. Effects of age on the gastroesophageal junction, esophageal motility and reflux disease. Clin Gastroenterol Hepatol. 2007;5(12):1392–8.
35. Pilotto A. Aging and upper gastrointestinal disorders. Best Pract Res Clin Gastroenterol. 2004;18(Suppl):73–81.
36. Haruma K, Kamada T, Kawaguchi H, et al. Effect of age and *Helicobacter pylori* infection on gastric acid secretion. J Gastroenterol Hepatol. 2000;15:277–83.
37. Nakamura K, Ogoshi K, Makuuchi H. Influence of aging, gastric mucosal atrophy and dietary habits on gastric secretion. Hepatogastroenterology. 2006;53(70):624–8.
38. Joseph IM, Zavros Y, Merchant JL, Kirschner D. A model for integrative study of human gastric acid secretion. J Appl Physiol. 2003;94:1602–18.
39. Salles N. Is stomach spontaneously ageing? Pathophysiology of aging stomach. Best Pract Res Clin Gastroenterol. 2009;23(6): 805–19.
40. Newtom JL. Changes in upper gastrointestinal physiology with age. Mech Ageing Dev. 2004;125(12):867–70.
41. Poh CH, Navarro-Rodriguez T, Fass R. Review: treatment of gastroesophageal reflux disease in the elderly. Am J Med. 2010;123: 496–501.
42. Takaki M. Gut pacemaker cells: the interstitial cells of Cajal (ICC). J Smooth Muscle Res. 2003;39(5):137–61.
43. Kuo P, Rayner CK, Horowitz M. Gastric emptying, diabetes, and aging. Clin Geriatr Med. 2007;23(4):785–808, vi.
44. Phillips RJ, Powley TL. Innervation of the gastrointestinal tract: patterns of aging. Auton Neurosci. 2007;136(1–2):1–19.
45. Wade PR, Cowen T. Neurodegeneration: a key factor in the ageing gut. Neurogastroenterol Motil. 2004;16 Suppl 1:19–23.
46. Nagar A, Roberts IM. Small bowel diseases in the elderly. Clin Geriatr Med. 1999;15(3):473–86.
47. Wade PR. Aging and neural control of the GI tract: I. Age-related changes in the enteric nervous system. Am J Physiol Gastrointest Liver Physiol. 2002;283(3):G489–95.
48. Meier J, Sturm A. The intestinal epithelial barrier: does it become impaired with age? Dig Dis. 2009;27(3):240–5.
49. Jones HF, Butler RN, Brooks DA. Intestinal fructose transport and malabsorption in humans. Am J Physiol Gastrointest Liver Physiol. 2011;300(2):G202–6.
50. Rosen CJ. Vitamin D insufficiency. N Engl J Med. 2011;364: 248–54.
51. Piccipme PR, Holt PR, Culpepper-Morgan JA, et al. Intestinal dysmotility syndromes in the elderly: measurement of orocecal transit time. Am J Gastroenterol. 1990;85(2):161–4.
52. Madsen JL. Effects of gender, age, and body mass index on gastrointestinal transit times. Dig Dis Sci. 1992;37(10):1548–53.
53. Rana S, Bhansali A, Bhadada S, et al. Orocecal transit time and small intestinal bacterial overgrowth in type 2 diabetes patients from North India. Diabetes Technol Ther. 2011;13(11): 1115–20.
54. Fynne L, Worsoe J, Gregersen T, et al. Gastrointestinal transit inpatients with systemic sclerosis. Scand J Gastroenterol. 2011;46(10):1187–93.
55. Simon GL, Gorbach SL. Intestinal flora in health and disease. Gastroenterology. 1984;86:174–93.
56. Cucchiara S, Iebba V, Conte MP, Schippa S. The microbiota in inflammatory bowel disease in different age groups. Dig Dis. 2009;27(3):252–8.
57. Tiihonen K, Ouwehand AC, Rautonen N. Human intestinal microbiota and healthy ageing. Ageing Res Rev. 2010;9(2):107–16.
58. Biagi E, Nylund L, Candela M, et al. Through ageing, and beyond: gut microbiota and inflammatory status in seniors and centenarians. PLoS One. 2010;5(5):e10667.
59. Woodmansey EJ. Intestinal bacteria and ageing. J Appl Microbiol. 2007;102(5):1178–86.

60. Tihonen K, Ouwehand AC, Rautonen N. Human intestinal microbiota and healthy aging. Ageing Res Rev. 2010;9(2):107–16.
61. Riordan SM, Mciver CJ, Wakefield D, et al. Small intestinal bacterial overgrowth in the symptomatic elderly. Am J Gastroenterol. 1997;92:47–51.
62. Claesson MJ, Cusack S, O'Sullivan O, et al. Composition, variability and temporal stability of the intestinal microbiota of the elderly. Proc Natl Acad Sci USA. 2011;108 Suppl 1:4586–91.
63. Dominquez-Bello MG, Blaser MJ, Ley RE, Knight R. Development of the human gastrointestinal microbiota and insights from high-throughput sequencing. Gastroenterology. 2011;140(6):1713–9.
64. Ottavian E, Ventura N, Mandrioli M, et al. Gut microbiota as a candidate for lifespan extension: an ecological/evolutionary perspective targeted on living organisms as metaorganisms. Biogerontology. 2011;12(6):599–609.
65. Guigoz Y, Dore J, Schiffrin EJ. The inflammatory status of old age can be nutured from the intestinal environment. Curr Opin Clin Nutr Metab Care. 2008;11(1):13–20.
66. Santiago AF, Alves AC, Oliveira RP, et al. Aging correlates with reduction in regulatory-type cytokines and T cells in the gut. Immunobiology. 2011;216(10):1085–93.
67. Gomez CR, Boehmer ED, Kovacs EJ. The aging innate immune system. Curr Opin Immunol. 2005;17(5):457–62.
68. Hsu HC, Mountz JD. Metabolic syndrome, hormones and maintenance of T cells during aging. Curr Opin Immunol. 2010;22(4): 541–8.
69. Schmucker DL, Owen RL, Outenreath R, Thoreux K. Basis for the age-related decline intestinal mucosal immunity. Clin Dev Immunol. 2003;10(2–4):167–72.
70. Wiskur B, Greenwood-Van Meerveld B. The aging colon: the role of enteric neurodegeneration in constipation. Curr Gastroenterol Rep. 2010;12(6):507–12.
71. Hanani M, Fellig Y, Udassin R, Freund HR. Age-related changes in the morphology of the myenteric plexus of the human colon. Auton Neurosci. 2004;113(1–2):71–8.
72. McCrea GL, Miaskowski C, Stotts NA, et al. Pathophysiology of constipation in the older adult. World J Gastroenterol. 2008;14(17):2631–8.
73. Camilleri M, Lee JS, Viramontes B, et al. Insights into the pathophysiology and mechanisms of constipation, irritable bowel syndrome, and diverticulosis in older people. J Am Geriatr Soc. 2000;48(9):1142–50.
74. Bernard CE, Gibbons SJ, Gomez-Pinilla PJ, et al. Effect of age on the enteric nervous system of the human colon. Neurogastroenterol Motil. 2009;21(7):746–e46.
75. Schnelle JF, Leung FW, Rao SS, et al. A controlled trial of an intervention to improve urinary and fecal incontinence and constipation. J Am Geriatr Soc. 2010;58(8):1504–11.
76. Kepenekci I, Keskinkilic B, Akinsu F, et al. Prevalence of pelvic floor disorders in the female population and the impact of age, mode of delivery, and parity. Dis Colon Rectum. 2011;54(1):85–94.
77. Gundling F, Seidl H, Scalercio N, et al. Influence of gender and age on anorectal function: normal values from anorectal manometry in a large Caucasian population. Digestion. 2010;81(4):207–13.
78. Konturek PC, Brzozowski T, Konturek SJ. Gut clock: implication of circadian rhythms in the gastrointestinal tract. J Physiol Pharmacol. 2011;62(2):139–50.
79. Suzuki K, Hayasena CN, Bloom SR. The gut hormones in appetite regulation. J Obes. 2011;2011:528401.
80. Zac-Varghese S, Tan T, Bloom SR. Hormonal interactions between gut and brain. Discov Med. 2010;10(55):543–52.
81. Liddle RA. Gastrointestinal hormones and neurotransmitters. In: Feldman M, Friedman LS, Brandt LJ, editors. Sleisenger and Fordtran's gastrointestinal and liver disease. 9th ed. Philadelphia: Saunders; 2010. p. 3–19.
82. Miller LJ. Gastrointestinal hormones and receptors. In: Yamada T, Alpers DH, Laine L, et al., editors. Text book of gastroenterology, vol. 1. 3rd ed. Philadelphia: Lippincott, Williams and Wilkins; 1999. p. 35–67.
83. Drucker DJ. The role of gut hormones in glucose homeostenosis. J Clin Invest. 2007;117(1):24–32.
84. Masclee AAM, Geuskens LM, Driessen WMM, et al. Effect of aging on plasma cholecystokinin secretion and gallbladder emptying. Age. 1988;11:136–40.
85. Gautier JF, Choukem SP, Girard J. Physiology of incretins (GIP and GLP-1) and abnormalities in type 2 diabetes. Diabetes Metab. 2008;34 Suppl 2:S65–72.
86. Elahi D, McAloon-Dyke M, Fukagawa NK, et al. The insulinotropic actions of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (7-37) in normal and diabetic subjects. J Steroid Biochem Mol Biol. 1994;51(1):63–74.
87. Meneilly GS, McIntosh CHS, Pederson RA, et al. Glucagon-like peptide-1 (7-37) augments insulin-mediated glucose uptake in elderly patients with diabetes. J Gerontol A Biol Sci Med Sci. 2001;56(11):M681–5.
88. Nematy M, Owell CA, Brynes AE, et al. Peptide YY (PYY) is increased in elderly patients with femoral neck fractures: a prospective study. J Parenter Enteral Nutr. 2006;30(6): 530–1.
89. Tovar SA, Seoane LM, Caminos JE, et al. Regulation of peptide YY levels by age, hormonal and nutritional status. Obes Res. 2001;12(12):1944–50.
90. Sandstrom O, El-Salhy M. Ontogeny and the effect of aging on pancreatic polypeptide and peptide YY. Peptides. 2002;23(2): 263–7.
91. Elahi D, Muller DC, Egan JM, et al. Glucose tolerance, glucose utilization and insulin secretion in ageing. Novartis Found Symp. 2002;242:222–42.
92. Howarth FC, Kitbi MKAA, Hameed RS, Adeghate E. Pancreatic peptides in young and elderly Zucker type 2 diabetic fatty rats. J Pancreas. 2011;12(6):567–73.
93. De Herder WW, Lamberts SW. Somatostatin and somatostatin analogues: diagnostic and therapeutic uses. Curr Opin Oncol. 2002;14:53–7.
94. Zhao Z, Sakai T. Characteristic features of ghrelin cells in the gastrointestinal tract and the regulation of stomach ghrelin expression and production. World J Gastroenterol. 2008;14(41):6306–11.
95. Chaudhri O, Small C, Bloom S. Gastrointestinal hormones regulating appetite. Philos Trans R Soc Lond B Biol Sci. 2006; 361(1471):1187–209.
96. Suzuki K, Simpson KA, Minnion JS, et al. The role of gut hormones and the hypothalamus in appetite regulation. Endocr J. 2010;57(5):359–72.
97. Cummings D, Weigle D, Frayo R, et al. Plasma ghrelin levels alter diet induced weight loss or gastric bypass. N Engl J Med. 2003;346(21):1623–30.
98. Akimoto Y, Kanai S, Ohta M, et al. Age-associated reduction of stimulatory effect of ghrelin on food intake in mice. Arch Gerontol Geriatr. 2011 [Ahead of print].
99. Rigamonti AE, Pincelli AI, Corra B, et al. Plasma ghrelin concentrations in elderly subjects: comparison with anorexic and obese patients. J Endocrinol. 2001;175(1):R1–5.
100. Bortolotti M, Frada G, Vezzadini P, et al. Influence of gastric acid secretion on interdigestive gastric motor activity and serum motilin in the elderly. Digestion. 1987;38(4):226–33.
101. Salles N, Menard A, Georges A, et al. Effects of *Helicobacter pylori* infection on gut appetite peptide (leptin, ghrelin) expression in elderly inpatients. J Gerontol A Biol Sci Med Sci. 2006;61(11): 1144–50.
102. Stenholm A, Mette JE, Roth GS, et al. Relationship between plasma ghrelin, insulin, leptin, IL6, adinopectin, testosterone and

longecity in the Baltimore Longitudinal Study of Aging. Aging Clin Exp Res. 2011;23:153–8.
103. Sumithran P, Prendergast LA, Delbridge E, et al. Long-term persistence of hormonal adaptations to weight loss. N Engl J Med. 2011;365(17):1597–604.
104. Elinav E, Ben-Dov IZ, Ackerman E, et al. Correlation between serum alanine aminotransferase activity and age: an inverted U curve pattern—age alters ALT activity. Am J Gastroenterol. 2005;100(10):2201–4.
105. McLachlan AJ, Pont LG. Drug metabolism in older people—a key consideration in achieving optimal outcomes with medicines. J Gerontol A Biol Sci Med Sci. 2012;67(2):175–80.
106. Ross SO, Forsmark CE. Pancreatic and biliary disorders in the elderly. Gastroenterol Clin North Am. 2001;30(2):531–45.
107. Tohno Y, Tohno S, Yamada MO, et al. Age-related changes of elements and relationships among elements in the common bile and pancreatic ducts. Biol Trace Elem Res. 2004;101(1):47–60.
108. Frieling T. [Age related functional gastrointestinal disorders]. Z Gastroenterol. 2011;49(1):47–53.
109. Schiffrin EJ, Morley JE, Donnet-Hughes A, Guigoz Y. The inflammatory status of the elderly: the intestinal contribution. Mutat Res. 2010;690(1–2):50–6.

Epidemiology of Gastrointestinal Disease

6

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Introduction

The United States and the world over progressively comprise a significantly larger proportion of older individuals. For the purposes of this chapter, the terms "older adult" and "elderly" define persons 65 years or older. In 2000, almost 35 million individuals in the United States were aged 65 and older, a group representing about half the total costs of healthcare. By 2030, almost 20% of the US population will be 65 years or older and are estimated to consume 75% of healthcare resources and subsequent costs. Table 6.1 displays the US Census data that tracks the growth of older cohorts and provides projections of their population representation in future years [1]. It is important to note that the greatest increase occurs among the "older" old—those aged 75–84 and 85 and over [2]. This chapter presents an overview of the epidemiology and unique features of benign and malignant gastrointestinal (GI) conditions in the geriatric population. While the chapter focuses on diseases in the United States, the information may be applicable to most developed nations.

Benign Disorders of the Gastrointestinal Tract

Numerous ailments that prevail during old age impact the gastrointestinal tract [3]. Conditions characteristically observed in the geriatric age group that affect gastrointestinal motility and pathology are presented in Table 6.2. The disease burden and mortality in the elderly are much higher compared to those in the general population; Tables 6.3, 6.4, and 6.5 depict the US rates of ambulatory visits, hospital discharges, and death rates, respectively, for common gastrointestinal diseases. The elderly constitute about 13% of the US population but account for 25–30% of all ambulatory care visits and hospital discharges, and 40–90% of all deaths related to gastrointestinal diseases.

Swallowing Disorders and Gastroesophageal Reflux

Symptoms commonly observed in older individuals include dysphagia, odynophagia, and dyspepsia due to the preponderance of neurological and neuromuscular diseases such as Parkinson's disease, amyotrophic lateral sclerosis, and cerebrovascular accidents [4]. Gastroesophageal reflux disease (GERD) is highly prevalent in the elderly and may be asymptomatic or present with atypical symptoms including asthma, hoarseness, chronic cough, sinusitis, halitosis, dental caries, chest pain, and sinus arrhythmia, all of which may be mistaken for other disorders in the old [5–8]. Older adults with intense symptoms of pyrosis demonstrate considerably greater esophageal mucosal damage (esophagitis, Barrett's) than the young [9]. Laparoscopic anti-reflux surgery is safe and effective in the geriatric age group [10].

Peptic Ulcer Disease, Upper Gastrointestinal Bleeding, and Gastroparesis

Peptic ulcer disease is a more serious entity in the old than that in the young because of the presence of more risk factors and complications, such as bleeding and perforation [11]. Nonsteroidal anti-inflammatory drug (NSAID)-induced ulcer disease is more prevalent, frequently more fatal, and atypical symptoms often delay diagnosis and treatment in

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Table 6.1 The US population projections according to the US Census data, to July 1, 2030

Day/year	Total population	Population 65+ years of age	% of population 65+ years of age
July 1, 2010	308,935,581	40,243,713	13.0
July 1, 2015	322,365,787	46,790,727	14.5
July 1, 2020	335,804,546	54,631,891	16.3
July 1, 2025	349,439,199	63,523,732	18.2
July 1, 2030	363,584,435	71,453,471	19.7

Data derived and adapted from [1]

Table 6.2 Conditions common in the geriatric population and associated with gastrointestinal dysfunction or pathology

Organ system	Condition	Gastrointestinal effect
Neurologic	Transient ischemic attack Cerebrovascular accident Parkinson's syndrome Alzheimer's disease Amyotrophic lateral sclerosis Peripheral neuropathies	Decreased peristalsis, dysphagia. aspiration, delayed gastric emptying, altered understanding of normal bowel habits
Endocrine/ metabolic	Diabetes mellitus Hypothyroidism Thyrotoxic myopathy Amyloidosis	Dysphagia, delayed gastric emptying, increased whole gut/ colonic transit time, anorexia, alterations in appetite, malabsorption, intestinal bacterial overgrowth
Neuropsychiatric	Depression	Chronic constipation, including medication induced
	Dementia	Medication-induced nausea, vomiting, weight loss, constipation
Cardiac	Congestive heart failure	Congestive hepatopathy, ischemic hepatitis, malabsorption
Musculoskeletal	Physical inactivity	Constipation, fecal impaction
Renal	Chronic kidney disease	Delayed gastric emptying, nausea
Pulmonary	COPD, emphysema	Nausea, constipation

Table 6.3 Rates of ambulatory care visits (first-listed diagnosis) for common gastrointestinal disorders in the United States, 2004

Disorder	Number of visits[a] (all age groups)	Rate[b]	Number of visits[a] (over age 65 years)	Rate[b]
Gastroesophageal reflux disease	6,849	2,332	1,611	4,433
Peptic ulcer disease	712	243	295	812
Liver disease	1,373	468	358	986
Gallstones	1,299	442	321	883
Pancreatitis	475	162	101	279
Abdominal wall hernia	3,742	1,274	976	2,686
Irritable bowel syndrome	1,605	547	469	1,290
Chronic constipation	3,149	1,072	880	2,423
Diverticular disease	1,864	635	947	2,607
Hemorrhoids	2,036	693	387	1,065

Data presented is adapted from [2]. Data in this publication was compiled from various government sources
Rates for the above diseases as all-listed diagnosis for ambulatory care visits were about 1.5–3 times higher than those for first-listed diagnosis
[a]Number in thousands
[b]Rate per 100,000

Table 6.4 Rates of hospital discharges (first-listed diagnosis) for common gastrointestinal disorders in the United States, 2004

Disorder	Number of visits[a] (all age groups)	Rate[b]	Number of visits[a] (over age 65 years)	Rate[b]
Peptic ulcer disease	181	62	104	285
Liver disease	185	63	47	129
Gallstones	352	120	124	341
Pancreatitis	277	94	72	197
Abdominal wall hernia	163	55	69	189
Appendicitis	298	101	21	59
Diverticular disease	313	107	173	477
Crohn's disease	57	19	7	18
Ulcerative colitis	35	12	8	23

Data presented is adapted from [2]. Data in this publication was compiled from various government sources
Number and rates for the above diseases as all-listed diagnosis for hospital discharges were about 1.5–3 times higher than those for first-listed diagnosis
[a]Number in thousands
[b]Rate per 100,000

the old [12]. The gastric mucosa undergoes changes with age, most specifically in quantity of gastric acid secretion, predisposing to the common occurrence of *Helicobacter pylori* (*H. pylori*) infection, although the testing for it is infrequently undertaken [13]. Additionally, eradicating *H. pylori* with the standard triple therapy to decrease the risk of ulcer recurrence is a challenge in the elderly due to the undesirable side effects of the medications including *Clostridium difficile*-associated diarrhea, aspiration pneumonia, hip fractures, nutrient deficiencies, and others [14].

As in the young, more than half of all cases of acute upper gastrointestinal bleeding in patients over age 60 are caused by peptic ulcer disease [15]. However, multiple risk factors for GI bleeding often correlate to older age. In a study of 5,888 noninstitutionalized men and women aged 65 years and older in four US communities enrolled in the Cardiovascular Health Study, factors associated with GI bleeding requiring hospitalization included advanced age, male sex, unmarried status, cardiovascular disease, difficulty with activities of daily living, and use of multiple medications including oral anticoagulants [16]. Additionally, the combination of peptic ulcer disease with esophagitis and gastritis accounts for 70–91% of hospital admissions for upper gastrointestinal bleeding in the elderly [17].

Table 6.5 Rates of death (primary cause) due to common gastrointestinal disorders in the United States, 2004

Disorder	Total deaths (all age groups)	Rate[a]	Total deaths[a] (over age 65 years)	Rate[a]
Peptic ulcer disease	3,692	1.3	2,921	8.0
Liver disease	36,090	12.3	13,620	37.5
Gallstones	1,092	0.4	924	2.5
Pancreatitis	3,480	1.2	1,953	5.4
Abdominal wall hernia	1,172	0.4	922	2.5
Appendicitis	453	0.2	304	0.8
Diverticular disease	3,372	1.1	3,027	8.3
Crohn's disease	622	0.2	356	1.0
Ulcerative colitis	311	0.1	238	0.7

Data presented is adapted from [2]. Data in this publication was compiled from various government sources
Mortality rates as primary or secondary cause of death for the above diseases were about 1.5–3 times higher in the over 65 year group compared to the primary cause of death in all age groups
[a]Per 100,000 population

Gastroparesis and delayed gastric emptying are considerably more common in the elderly due, in large part, to the high prevalence of type II diabetes mellitus and its characteristic autonomic neuropathy [18, 19]. Chronic kidney disease, depression, and hypothyroidism also contribute to slower rates of GI transit and impaired gastric emptying [20]. Nutritional anemias need to be addressed in the aged, because their underlying causes, more often related to malabsorption than to dietary intake, require individualized evaluation [21]. Iron-deficiency anemia is frequently caused by iron losses accompanying chronic bleeding, from gastric pathologies, intestinal parasites, or malabsorption in older individuals. Colorectal cancer may present as iron-deficiency anemia, although it is important to remember that the prevalence of colorectal carcinoma in the elderly is high in symptomatic patients (e.g., hematochezia, change in bowel habits, etc.) irrespective of the presence of anemia [22]. Vitamin B12 (cobalamin) deficiency can occur at all ages, with a slight predilection for the geriatric cohort; it most commonly results from food-cobalamin malabsorption, and not always related to deficiency of intrinsic factor, characteristic of pernicious anemia [21].

Pancreatitis

The incidence and mortality from acute pancreatitis increase with age. In older adults, gallstone and idiopathic etiologies predominate, whereas alcohol is a more common cause of acute pancreatitis in the 35–64-year age group. In a US study, the mortality from acute pancreatitis was twofold higher in the 65–74-year group, and fivefold higher in the 75 plus group compared to the 55–64 age group [23]. The corresponding mortality differences for the older groups would be much higher compared to the below-55-year group, since death rates for these groups are significantly lower than those aged 55–64 years [23]. Similar to acute pancreatitis, the etiologic profile and symptomatology for chronic pancreatitis in older adults differ from those in individuals below 65 years of age. Idiopathic chronic pancreatitis is the most common form of the disease in the elderly, and is less symptomatic compared with alcoholic chronic pancreatitis [24].

Abdominal Hernia, Celiac Disease, and Inflammatory Bowel Disease

Abdominal wall hernias are particularly prevalent in older individuals due to decreased muscle mass and decreased tensile strength of connective tissue. Abdominal hernias often go unnoticed and untreated in older cohorts due to vague or misleading signs and symptoms, but emergency surgery for incarceration is associated with increased morbidity in the aged [25]. A prospective US study of abdominal hernia repair suggested that independent risk factors for wound infection and longer hospital stay included COPD, low preoperative serum albumin, coronary artery disease, and steroid use [26].

While often considered a disease entity of the young, 20% of all cases of celiac disease are diagnosed in people aged 60 or older [27]; anemia and symptoms of malabsorption should warrant antibody testing for celiac because accurate diagnosis in this age group is often significantly delayed [28]. Of similar clinical relevance, 15% of all cases of inflammatory bowel disease (IBD) are diagnosed in the over-65-year group [29]. Patients of advanced age may present with classic IBD symptoms but carry a broader differential diagnosis. Older adults with Crohn's disease were less likely to have cramps and abdominal pain than younger patients in one study, but they had notably decreased lag time in diagnosis due to earlier presentation to their general practitioner and more rapid referral to a specialist [30]. Medical and surgical treatment options for IBD are the same, regardless of age. Osteoporosis is a frequent side effect of corticosteroid treatment for IBD, prompting bone mineral density monitoring in the elderly, who are already at a heightened risk for declining bone mass [29].

Gastrointestinal Infections

Bacterial overgrowth and *C. difficile* infection are two common and potentially life-threatening disorders in the old due to their greater rates of hospitalization and immobilization. Institutionalized elderly are particularly prone to gastrointestinal infections, but the manifestations may not be overt [31].

C. difficile infection in the geriatric age group results from multiple factors, including changes in fecal microbiota, immune senescence, prolonged antibiotic use, and nasogastric or parenteral feedings [32]. Most patients with *C. difficile* colitis recover spontaneously, although *C. difficile*-associated diarrhea can be serious and debilitating with a mortality rate as high as 25% in the frail old [33, 34]. Increased admissions and virulence for *C. difficile* are reflected in rising mortality rates over the past decade, especially in the "older" old [35–37].

Diverticular Disease

While 5% or fewer of individuals under 40 have diverticular disease, 65% or more older adults likely experience it, the majority asymptomatic, until a complication occurs [38]. In Western countries, diverticular disease mainly affects the left colon, and is associated with alterations in colonic wall resistance, disordered colonic motility, and diminished dietary fiber consumption [38, 39]. Endoscopic, radiologic, and surgical advances have enhanced therapy for diverticular diseases [40]; while most patients admitted with acute diverticulitis respond to conservative treatment, 15–30% require surgery [38]. In addition to age, predictive factors for severe diverticulitis include gender, obesity, and immunodeficiency [38]. Mortality rates due to diverticular disease are over seven times greater in the elderly compared to the general population due in large part to co-morbidities in the surgical setting and medical complications including stricture, obstruction, abscess formation, and free perforation which may result in life-threatening peritonitis [39, 41].

Gastrointestinal Cancers

Malignant neoplasms occur with greater frequency with advancing age. Phenomena such as the accumulation of DNA damage and dysfunctional proteins are common to the aging process and cancer. Carcinogenesis and aging similarly involve alterations in metabolism and immunosenescence, hypermethylation of promoters, and telomere shortening [42]. A significant duration of chronic inflammation underlies many GI cancers, for instance chronic hepatitis B or C and hepatocellular carcinoma or chronic pancreatitis and pancreatic cancer [43, 44]. In addressing the treatment strategy of a gastrointestinal malignancy, age should not be the only parameter assessed, with management decisions following the same principles as in the young. Older adults must undergo a meticulous medical evaluation to define patient risks and to optimize surgical, chemotherapeutic, and palliative outcomes [45]. Importantly, recovery and progress of older patients treated as in-patients can be complicated by psychological co-morbidities, including delirium and depression, as well as by poor nutrition, deterioration in physical strength, and adverse drug reactions [15].

Table 6.6 Cancer incidence rates per 100,000 US population in 2007, based on SEER data

	<65 years of age	65+ years of age	Overall age-adjusted incidence
Esophagus	1.69	22.68	4.5
Stomach	2.95	39.29	7.8
Liver/intrahepatic bile duct	3.94	29.69	6.9
Gallbladder	0.36	6.91	
Pancreas	3.85	65.59	11.7
Small intestine	0.90	8.62	1.9
Colon	18.00	235.67	47.9

Data derived from [46]

Table 6.7 The US rates (in %) for digestive tract cancer incidence by organ, SEER data 2003–2007

	<65 years of age	65+ years of age
Esophagus	36.9	63.1
Stomach	36.4	63.6
Liver/intrahepatic bile duct	52.0	48.0
Pancreas	32.0	68.0
Small intestine	45.1	54.9
Colon	36.6	63.4
Anus	59.2	40.8

Data derived from [47]

Table 6.8 Median age at diagnosis of cancer and median age at death, SEER data 2003–2007

	Median age at diagnosis	Median age at death
Esophagus	68	69
Stomach	70	73
Liver/intrahepatic bile duct	64	69
Pancreas	72	73
Small intestine	66	71
Colon and rectum	70	75
Anus	60	65

Data derived from [47]

Tables 6.6 and 6.7 provide age-comparative information regarding GI cancers based on recent Surveillance Epidemiology and End Results Data (SEER). Table 6.8 shows the median age of diagnosis and death for common GI cancers, which is highly skewed towards the aged.

Esophageal cancer in the United States presents in two major forms—adenocarcinoma and squamous cell carcinoma. Rates of esophageal adenocarcinoma have risen in recent years due to their association with GERD and Barrett's esophagus, with the increased prevalence of overweight and obesity driving the elevated incidence [48–50]. Squamous cell

carcinoma is predominantly related to older age, male gender, cigarette smoking, and heavy alcohol consumption.

A recent pooled analysis of eight first-line trials including a total 367 patients investigated whether older adults with metastatic esophageal, gastroesophageal, and gastric cancer respond to chemotherapy as well as their younger counterparts [51]. Although rates of neutropenia, fatigue, infection, and stomatitis were significantly higher among older compared to younger patients, overall survival, progression-free survival, and duration of chemotherapy were comparable. Other data indicate that the elderly with gastric cancer experience the same advantages and toxicities of chemotherapy as the young [45]. While taking into account comorbidity, fit older adults should be candidates for standard surgical resection and perioperative chemotherapy or postoperative chemoradiotherapy for locally advanced disease.

Pancreatic adenocarcinoma is characteristically a disease of older individuals and younger age at onset often is a harbinger of a hereditary cause for this cancer [52]. The 5-year survival rate of pancreatic cancer is an abysmal 5%, with the majority of individuals diagnosed with locally or regionally metastatic disease [53]. Unfortunately, patients who undergo surgery are often not healthy enough to receive adjuvant treatment, which can prolong overall and disease-free survival [54]. Similar to pancreatic cancer, rates of colorectal cancer are higher among men than women and greatest among blacks compared to whites and other racial or ethnic groups. Use of NSAIDs is known to decrease the incidence of colonic polyps [55], but the side effects, including upper gastrointestinal bleeding and serious cardiovascular events such as myocardial infarction, heart failure, hemorrhagic stroke, and renal disease, render their use particularly risky in the geriatric population with preexisting heart or kidney disease; furthermore, these patients may also be on anticoagulants [56].

Advancing age is the strongest determinant of the prevalence of adenomatous colonic polyps [57] and colon polyps have been found in 33% of completely asymptomatic patients who are aged 65–75 years at screening colonoscopy [58]. The age at which to stop screening for colorectal cancer has not met with consensus opinion, although physicians may consider clinical factors, such as age, life expectancy, co-morbidities, and functional status, as well as individual factors, such as personality, previous screening behavior, family support, and their relationship with the patient, in their screening recommendations [59]. Treatment recommendations for older colon cancer patients have been evolving to incorporate the same standards of treatment as for younger patients. For instance, recent evidence indicates that elderly patients may benefit from similar postsurgical chemotherapy with 5-FU without a significant increase in toxicity compared with their younger counterparts [60].

Key Points

- Neurologic, endocrine, neuropsychiatric, cardiac, musculoskeletal, renal, and pulmonary diseases have significant deleterious effects on the gastrointestinal system of older adults.
- *C. difficile* infection in the geriatric age group is a growing problem, often a consequence of altered fecal microbiota, immune senescence, prolonged antibiotic use, and nasogastric or parenteral feedings; mortality rates are particularly high in the debilitated aged.
- About 15% of all cases of IBD are diagnosed in people aged 65 and over and, while they may have fewer presenting symptoms, treatment options are similar to the young.
- Alcohol is a less common etiology of pancreatitis in older adults compared to the young.
- The majority of older adults have asymptomatic diverticular disease; gender, obesity, and immunodeficiency all predict a more severe disease course.
- Malignant neoplasms of the gastrointestinal tract are significantly more likely to occur in older age; management decisions follow the same principles as in the young to optimize surgical, chemotherapeutic, and palliative outcomes.

References

1. US Census. The 65 years and over population: 2000. Census 2000 Brief.
2. Everhart JE, editor. The burden of digestive diseases in the United States. US Department of Health and Human Services, Public Health Service, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. Washington, DC: US Government Printing Office; 2008. NIH Publication No. 09-6443.
3. Erwin WG. Common gastrointestinal diseases in the elderly. Geriatrics. 1988;43(Suppl):75–82.
4. Salles N. Basic mechanisms of the aging gastrointestinal tract. Dig Dis. 2007;25:112–7.
5. Harding SM, Richter JE. The role of gastroesophageal reflux in chronic cough and asthma. Chest. 1997;111:1389–402.
6. Richter JE. Extraesophageal presentations of gastroesophageal reflux disease: the case for aggressive diagnosis and treatment. Cleve Clin J Med. 1997;64:37–45.
7. Richter JE, Hicks DM. Unresolved issues in gastroesophageal reflux-related ear, nose, and throat problems. Am J Gastroenterol. 1997;92:2143–4.
8. Heidelbaugh JJ, Gill AS, Van Harrison R, et al. Atypical presentations of gastroesophageal reflux disease. Am Fam Physician. 2008;78:483–8.
9. Collen MJ, Abdulian JD, Chen YK. Gastroesophageal reflux disease in the elderly: more severe disease that requires aggressive therapy. Am J Gastroenterol. 1995;90:1053–7.
10. Brunt LM, Quasebarth MA, Dunnegan DL, et al. Is laparoscopic antireflux surgery for gastroesophageal reflux disease in the elderly safe and effective? Surg Endosc. 1999;13:838–42.
11. Watanabe T, Chiba T, Watanabe T, et al. [Peptic ulcer in the elderly]. Nippon Rinsho Jpn J Clin Med. 2002;60 Suppl 2:603–7.
12. Khaghan N, Holt PR. Peptic disease in elderly patients. Can J Gastroenterol. 2000;14:922–8.

13. Ofman JJ, Etchason J, Alexander W, et al. The quality of care for Medicare patients with peptic ulcer disease. Am J Gastroenterol. 2000;95:106–13.
14. Cullen DJ, Hawkey GM, Greenwood DC, et al. Peptic ulcer bleeding in the elderly: relative roles of *Helicobacter pylori* and non-steroidal anti-inflammatory drugs. Gut. 1997;41:459–62.
15. Farrell JJ, Friedman LS. Gastrointestinal bleeding in the elderly. Gastroenterol Clin North Am. 1981;30:377–407.
16. Kaplan RC, Heckbert SR, Koepsell TD, et al. Risk factors for hospitalized gastrointestinal bleeding among older persons. Cardiovascular Health Study Investigators. J Am Geriatr Soc. 2001;49:126–33.
17. Antler AS, Pitchumoni CS, Thomas E, et al. Gastrointestinal bleeding in the elderly. Morbidity, mortality and cause. Am J Surg. 1981;142:271–3.
18. Kong MF, Horowitz M. Gastric emptying in diabetes mellitus: relationship to blood-glucose control. Clin Geriatr Med. 1999;15:321–38.
19. Chaudhuri TK, Fink S. Prognostic implication of gastroparesis in patients with diabetes mellitus. Clin Auton Res. 1992;2:221–4.
20. O'Mahony D, O'Leary P, Quigley EM, et al. Aging and intestinal motility: a review of factors that affect intestinal motility in the aged. Drugs Aging. 2002;19:515–27.
21. Carmel R. Nutritional anemias and the elderly. Semin Hematol. 2008;45(4):225–34.
22. Joosten E, Meeuwissen J, Vandewinckele H, et al. Iron status and colorectal cancer in symptomatic elderly patients. Am J Med. 2008;121(12):1072–7.
23. Frey CF, Zhou H, Harvey DJ, et al. The incidence and case-fatality rates of acute biliary, alcoholic, and idiopathic pancreatitis in California, 1994–2001. Pancreas. 2006;33:336–44.
24. Yadav D. Recent advances in the epidemiology of alcoholic pancreatitis. Curr Gastroenterol Rep. 2011;13(2):157–65.
25. Rosenthal RA. Small-bowel disorders and abdominal wall hernia in the elderly patient. Surg Clin North Am. 1994;74:261–91.
26. Dunne JR, Malone DL, Tracy JK, et al. Abdominal wall hernias: risk factors for infection and resource utilization. J Surg Res. 2003;111:78–84.
27. Casellas F, Sardi J, de Torres I, et al. Hydrogen breath test with D-xylose for celiac disease screening is as useful in the elderly as in other age groups. Dig Dis Sci. 2001;46:2201–5.
28. Gasbarrini G, Ciccocioppo R, De Vitis I, et al. Coeliac disease in the elderly. A multicentre Italian study. Gerontology. 2001;47:306–10.
29. Robertson DJ, Grimm IS. Inflammatory bowel disease in the elderly. Gastroenterol Clin North Am. 2001;30:409–26.
30. Wagtmans MJ, Verspaget HW, Lamers CB, et al. Crohn's disease in the elderly: a comparison with young adults. J Clin Gastroenterol. 1998;27:129–33.
31. Holt PR. Diarrhea and malabsorption in the elderly. Gastroenterol Clin North Am. 2001;30:427–44.
32. Taslim H, Taslim H. *Clostridium difficile* infection in the elderly. Acta Med Indones. 2009;41:148–51.
33. Kelly CP, LaMont JT, Kelly C, et al. *Clostridium difficile*–more difficult than ever. N Eng J Med. 2008;359:1932–40.
34. Sailhamer EA, Carson K, Chang Y, et al. Fulminant *Clostridium difficile* colitis: patterns of care and predictors of mortality. Arch Surg 2009;144:433–9; discussion 439–40.
35. Cober ED, Malani PN, Cober ED, et al. *Clostridium difficile* infection in the "oldest" old: clinical outcomes in patients aged 80 and older. J Am Geriatr Soc. 2009;57:659–62.
36. Jaber MR, Olafsson S, Fung WL, et al. Clinical review of the management of fulminant *Clostridium difficile* infection. Am J Gastroenterol. 2008;103:3195–203.
37. Zilberberg MD, Shorr AF, Micek ST, et al. *Clostridium difficile*-associated disease and mortality among the elderly critically ill. Crit Care Med. 2009;37:2583–9.
38. Comparato G, Pilotto A, Franz A, et al. Diverticular disease in the elderly. Dig Dis. 2007;25:151–9.
39. Kang JY, Melville D, Maxwell JD, et al. Epidemiology and management of diverticular disease of the colon. Drugs Aging. 2004;21:211–28.
40. Farrell RJ, Farrell JJ, Morrin MM. Diverticular disease in the elderly. Gastroenterol Clin North Am. 2001;30:475–96.
41. Pfeifer J. Diverticulitis. Acta Chir Iugosl. 2008;55:97–102.
42. Arai T, Kasahara I, Sawabe M, et al. Role of methylation of the hMLH1 gene promoter in the development of gastric and colorectal carcinoma in the elderly. Geriatr Gerontol Int. 2010;10 Suppl 1:S207–12.
43. McMahon BJ. Natural history of chronic hepatitis B. Clin Liver Dis. 2010;14:381–96.
44. Lowenfels AB, Maisonneuve P, Cavallini G, et al. Pancreatitis and the risk of pancreatic cancer. International Pancreatitis Study Group. N Eng J Med. 1993;328:1433–7.
45. Saif MW, Makrilia N, Zalonis A, et al. Gastric cancer in the elderly: an overview. Eur J Surg Oncol. 2010;36:709–17.
46. SEER 17 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, San Jose-Monterey, Los Angeles, Alaska Native Registry, Rural Georgia, California excluding SF/SJM/LA, Kentucky, Louisiana and New Jersey). Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups—Census P25-1130). The modeled rates are the point estimates for the regression lines calculated by the Jointpoint Regression Program (Version 3.4.3, April 2010, National Cancer Institute)
47. Altekruse SF, Kosary CL, Krapcho M, et al. editors. SEER cancer statistics review, 1975–2007 (based on November 2009 SEER data submission, posted to the SEER web site). Bethesda, MD: National Cancer Institute; 2010. http://seer.cancer.gov/csr/1975_2007/.
48. Balbuena L, Casson AG, Balbuena L, et al. Physical activity, obesity and risk for esophageal adenocarcinoma. Future Oncol. 2009;5:1051–63.
49. Vial M, Grande L, Pera M. Epidemiology of adenocarcinoma of the esophagus, gastric cardia, and upper gastric third. Recent Results Cancer Res. 2010;182:1–17.
50. Bechade D, Blondon H, Sekkach Y, et al. Review of the association between obesity and gastroesophageal reflux and its complications. Gastroenterol Clin Biol. 2009;33:155–66.
51. Jatoi A, Foster NR, Egner JR, et al. Older versus younger patients with metastatic adenocarcinoma of the esophagus, gastroesophageal junction, and stomach: a pooled analysis of eight consecutive North Central Cancer Treatment Group (NCCTG) trials. Int J Oncol. 2010;36:601–6.
52. Klein AP, Brune KA, Petersen GM, et al. Prospective risk of pancreatic cancer in familial pancreatic cancer kindreds. Cancer Res. 2004;64:2634–8.
53. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2009. CA Cancer J Clin. 2009;59:225–49.
54. Simons JP, Ng SC, McDade TP, et al. Progress for resectable cancer?: a population-based assessment of US practices. Cancer. 2010;116:1681–90.
55. Arber N, Eagle CJ, Spicak J, et al. Celecoxib for the prevention of colorectal adenomatous polyps. N Eng J Med. 2006;355:885–95.
56. Solomon SD, Pfeffer MA, McMurray JJ, et al. Effect of celecoxib on cardiovascular events and blood pressure in two trials for the prevention of colorectal adenomas. Circulation. 2006;114:1028–35.
57. Rex DK, Lehman GA, Ulbright TM, et al. Colonic neoplasia in asymptomatic persons with negative fecal occult blood tests: influence of age, gender, and family history. Am J Gastroenterol. 1993;88:825–31.
58. Khullar SK, DiSario JA. Colon cancer screening. Sigmoidoscopy or colonoscopy. Gastrointest Endosc Clin N Am. 1997;7:365–86.
59. Lewis CL, Griffith J, Pignone MP, et al. Physicians' decisions about continuing or stopping colon cancer screening in the elderly: a qualitative study. J Gen Intern Med. 2009;24:816–21.
60. Fata F, Mirza A, Craig G, et al. Efficacy and toxicity of adjuvant chemotherapy in elderly patients with colon carcinoma: a 10-year experience of the Geisinger Medical Center. Cancer. 2002;94:1931–8.

Comprehensive Geriatric Assessment

7

T.S. Dharmarajan

Comorbidities and medical complexities are common in older adults. Many in the geriatric age group receive suboptimal care at high health care costs; nowhere is the inadequacy of health care more evident than in this age group [1, 2]. Ideally, the health needs of geriatric patients must be addressed both comprehensively and efficiently, and patients must be encouraged to be active partners in their own care [1–3]. Efforts continue to prepare physicians to care for the growing elderly, with the American Geriatrics Society (AGS), the American Medical Association, and the Council for Medical Specialty Societies addressing the need to understand elder care, as the number of geriatricians are inadequate to meet demands [4]. The American Gastroenterological Association Future Trends Committee Report suggests the need for greater awareness on the part of gastroenterologists about issues unique to the older adult [5].

The Concept of Comprehensive Geriatric Assessment

Comprehensive geriatric assessment (CGA) refers to a team-based approach to the older patient that is feasible in multiple settings. Over 15 successful CGA models have been described that supplement primary care or add to ambulatory care, long-term care, day care, home care or even inpatient and transitional care [2, 6, 7]. The efficiency and applicability of CGA has been demonstrated in the emergency department [6], orthopedic unit [8], oncology setting [9], and in older patients with chronic kidney disease [10]. Key components of care in these settings have included health assessment, disease management, preventive care, case management, pharmaceutical care, rehabilitation, caregiver support, transitional care, and interdisciplinary care [3]. Many models can improve outcomes and have been adopted widely in clinical practice with good patient acceptability [2, 11]. The concept and utility of CGA has been addressed by the AGS and in several reviews [12–22].

CGA Is a Team Approach

CGA uses a team approach, the process being described interchangeably as either "interdisciplinary" or "multidisciplinary," although the two descriptions are not truly the same. A *multidisciplinary approach* utilizes a group of health care workers of different disciplines with complementary skills to meet the individual's specific objectives in a coordinated manner. These professionals work independently and interact informally; assessments are performed separately [23]. Multidisciplinary teams may meet in the absence of the patient. The *interdisciplinary approach* involves the integration of separate disciplines with the goal of working interdependently and formally in the same setting. Here a group of health care professionals performs separate assessments, but shares patient information in a systematic but explicitly collaborative manner [23]. The *interdisciplinary* patient-centered approach may provide an advantage over the *multidisciplinary* approach.

The team members for CGA are tailored to the patient's needs and setting. In general, the team is led by the primary care physician or geriatrician, with the core comprised of a physiatrist, nurse, and psychosocial worker. Extended team members may include specialists such as the gastroenterologist, nephrologist, rheumatologist, psychiatrist, neurologist, pharmacist, and others. Effective communication between the primary care physician and the specialists is required to improve care coordination [23, 24] (Table 7.1).

Consultations can be provided in any setting including the hospital [25] and the community. Benefits of CGA include

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identification and treatment of common and frequently ignored conditions in the geriatric patient, including incontinence, gait imbalance, falls, cognitive impairment, and sensory impairment. Although several drugs may be discontinued to minimize polypharmacy, newly diagnosed entities may result in the use of additional medications [26].

Table 7.1 Comprehensive geriatric assessment (CGA): the multidisciplinary team members[a]

Physician (or geriatrician)
Psychosocial worker
Physiatrist
Physical therapist
Occupational therapist
Specialist based on indication
Gastroenterologist, nephrologist, orthopedist, physiatrist, cardiologist, etc.
Nurse
Nutritionist
Geropsychiatrist
Consultant pharmacist
Pastoral or spiritual care representative
Extended care disciplines based on individual need
Podiatrist
Speech and swallow specialist
Dentist
Psychologist
Audiologist
Legal representative (for directives)

[a]Team members differ based on setting and patient profile

Elements of Assessment

The goals of CGA are to promote function, independence, and most importantly improved quality of life. Broad domains addressed are physical, cognitive, and psychosocial. A major thrust is towards prevention (primary, secondary, and tertiary); screening principles are consistent with guidelines; meticulous examination is likely to detect disease, both overt and that not readily apparent [18, 19]. The theme of CGA is patient-centered. The elements of CGA are depicted in Fig. 7.1 and the domains detailed in Table 7.2.

The approach in CGA includes an understanding of overall life expectancy to incorporate the appropriate evidence-based care as applicable. Short-term issues attempt restoration of previous state of health; midrange issues provide preventive care and identify geriatric syndromes; long-term issues require planning for eventual decline and end of life care [27].

History and Evaluation

The value of the periodic health examination is justified in clinical practice; it improves delivery of recommended services and lessens patient worry [28]. The initial history and examination may be time consuming and cumbersome to the geriatric patient. It may be therefore reasonable and appropriate to spread the evaluation over two or more visits. The history may be obtained from the patient, caregiver or both;

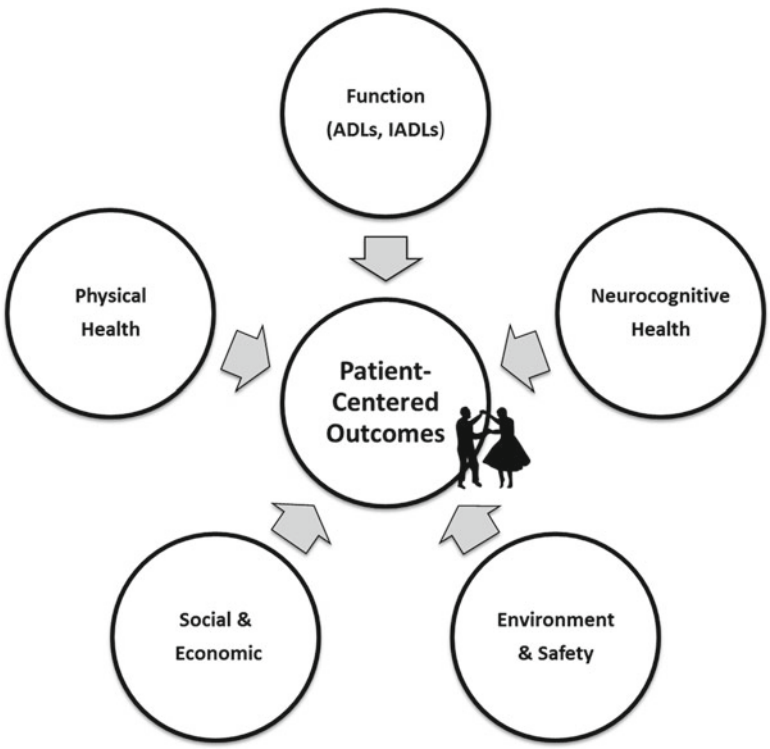

Fig. 7.1 Elements of comprehensive geriatric assessment

Table 7.2 Multidisciplinary competencies in the care of older adults

Domain 1: health promotion and safety
Promote physical and mental health, nutrition, function, safety, independence, and quality of life
Advocate for screening, immunizations, and health promotion
Assess risks and barriers including falls, elder abuse, and mistreatment
Recognize the appropriate use of medications
Understand the indications, contraindications, risks of physical, and pharmacological restraints
Domain 2: evaluation and assessment
Define the purpose and components of interdisciplinary CGA
Understand physical, cognitive, psychological, and social changes
Learn the use of valid tools to assess cognition, mood, physical function, nutrition, and pain
Demonstrate knowledge of signs and symptoms of delirium
Develop communication strategies to overcome limitations in the old
Domain 3: care planning and coordination
Understand the care across the spectrum including end-of-life care
Make recommendations based on best evidence, modify to patient preferences
Develop advance care plans based on patient preferences
Domain 4: interdisciplinary and team care
Communicate and collaborate with older adults, caregivers, and healthcare professionals to use disease-specific information towards the goal of positive outcomes
Domain 5: caregiver support
Assess caregiver knowledge and expectations; assist as needed
Evaluate continued appropriateness of care plans and services
Domain 6: healthcare systems and benefits
Serve as an advocate for older adults and caregivers
Provide knowledge of healthcare programs such as Medicare and Medicaid, and continuum of care services and support in the relevant setting: community, nursing home, hospital, assisted living, and hospice

Source: Partnership for Health in Aging (PHA) and American Geriatrics Society (AGS), March 2010

in the presence of cognitive impairment, the discussion with the caregiver may take place separately to correlate the story. In addition to the standard medical examination, one must review the medications, comment on activities of daily living (ADL) and instrumental activities of daily living (IADL), assess for neglect or mistreatment, determine immunization history, assess mobility, determine cognition, and look for signs of depression or anxiety.

In the United States, Medicare beneficiaries (typically aged 65 or more) have the opportunity for a one-time "Initial Preventive Physical Examination" (also termed the Welcome to Medicare visit) within 12 months of receiving Medicare benefits [29]. Thereafter, patients are entitled to an Annual Wellness Visit to focus on preventive services [30].

Attention to communication strategies is important when interacting with older adults. The basics require use of a well-lit examination area with minimal glare and avoidance of extraneous noise, as sensory deficits are common in older people. Conversation must be nonhurried, clear, and appropriate in volume. Speakers must take care to avoid covering the face, as the hearing impaired tend to comprehend speech by reading lip movements. One may need to write questions; repeat remarks should utilize distinctly different words, sentences, and expressions to improve patient understanding [12].

Contrary to common belief, older persons under-report illness and do not complain perhaps as much as they should. Under-reporting is a result of several factors, including decreased awareness, denial, depression and fear of consequences including costs, institutionalization, or hospitalization. The beliefs that problems are inevitable with aging or that nothing can be done are often contributory.

Medication Review and Reconciliation

Following the history and examination, a review of prescribed and over-the-counter medications is indicated at the initial visit. Medications require reconciliation in all relevant settings including follow-up visits, hospital admission, hospital discharge, and at transfers to and between facilities or physician offices. Reconciliation can reduce inappropriate medication use, polypharmacy and the potential for adverse drug events [31, 32]. The Beers criteria provide a list of potentially inappropriate medications for older adults [33]. Medication adherence can be improved by use of systematic monitoring and follow-up, patient education, and use of care teams [34]. Over-the-counter medications, herbals, supplements, and mega-vitamins contribute to interactions and adverse events. The United States Preventive Services Task Force (USPSTF) has concluded that evidence is insufficient to recommend for or against use of routine vitamins A, C, E, folic acid, and antioxidants to prevent cancer or cardiovascular disease and recommends against the use of beta-carotene supplements.

Psychosocial Assessment

The social assessment includes ethnic, cultural, and social elements, including evaluation of caregiver status and burden, home environment, and economic well-being [12]. Detection of clues for unmet needs or neglect, judging visiting nurse requirements, and assessment of home safety are considerations in this category [12]. These interventions can also identify the available social resources for the patient; those socially isolated are not surprisingly at risk for poor health outcomes.

Quality of life is given importance in geriatric patients; their preferences are given priority in determining health care and goals. Older adults' (and perhaps caregiver) beliefs

differ markedly when chronological age and physiological age or function in a given individual are taken into account; added to this is the impact from religious beliefs, cultural background, education, and social factors. Following the patient's wishes enhances adherence to management and the overall quality of life [12].

Advance Directives

Advance care planning must be routinely offered to patients by health care providers. Although a large number of deaths occur in hospitals, currently only about a third of patients who enter hospitals have advance directives (ADs). Barriers to implementing ADs include attitudes towards "end of life" discussions and "time constraints;" culture, race, education and religious beliefs are also influential. Regulations demand that we document information on patient preferences. ADs include a living will or a Health Care Proxy; the latter preferred. ADs are invaluable resources to a health care professional when confronted by a life-threatening situation, end of life care, or when a decision regarding a surgical procedure or endoscopy has to be made [35, 36]. Assessment of the patient's capacity is always the first step. In the absence of capacity and an available AD, the Family Health Care Decisions Act may be invoked, to enable decision making by a relative or friend.

End of Life Care

Most patients prefer to die at home rather than at the hospital. In general, it is widely assumed that more medical care through tests and procedures translates into better outcomes, but evidence suggests otherwise. It is not age or cognitive function that must determine whether to provide comfort care or aggressive care, but rather the individual patient's articulated goals following a meaningful discussion of prognosis, risks, benefits, and alternatives, including impact on quality of life [37]. Health care must be consistent with the patient's wishes.

Prevention Is Effective

Preventive approaches are generally effective and are recommended for all age groups. However, measures are individualized, taking into account the benefits, harms, and costs of interventions [38]. Recommendations have also been subject to biases; and multiple guidelines on the same topic may carry different recommendations [39].

Primary prevention refers to interventions in asymptomatic persons who lack clinical evidence of target conditions and are designed to prevent occurrence of disease [18]. *Secondary prevention* includes screening tests for the early detection of disease in the preclinical or asymptomatic state and is designed to prevent significant morbidity [19]. *Tertiary prevention* aims to reduce the negative impact of established disease through restoration of function and reduction of additional complications. While all forms of prevention apply to the geriatric population, each form of prevention has a greater impact in certain age groups. Examples of broad preventive categories are listed in Table 7.3.

Table 7.3 Preventive health care: broad categories

Primary prevention
Immunization
Pneumococcal vaccination
Influenza vaccination
Herpes zoster vaccination
Tetanus, diphtheria, pertussis vaccines
Counseling
Diet
Dental health
Physical activity
Prevention of falls and fractures
Tobacco use
Alcohol and drug use
Behavior counseling for skin cancer
Activity
Exercise: aerobic, resistance, balance
Chemoprophylaxis
Aspirin therapy for prevention of coronary artery disease
Oseltamivir for the prevention of influenza
Safety-related
Falls and unintentional injuries
Water heater temperature
Smoke detectors
Driving (or bicycle)-related safety
Secondary prevention: Use of measure or screen for
Aspirin (for secondary prevention of stroke and coronary artery disease)
Cognitive impairment
Depression and anxiety
Visual disorders
Hearing impairment
Diabetes mellitus
Hyperlipidemia
Peripheral arterial disease
Abdominal aortic aneurysm
Osteoporosis
Elder abuse and self-neglect
Tuberculosis
Cancer: colorectal, breast, cervix, skin
Tertiary prevention: examples, applicable to
Post hip fracture surgery
Post stroke rehabilitation
Parkinson's disease
Following lower extremity amputation

Counseling

Counseling, as a physician competency for prescribing life style medicine is effective in all stages of health [40]; it is an effective strategy to prevent as well as manage several disorders in the geriatric population. Leading causes of death in the U.S. are related to lifestyle and include tobacco use, poor diet, physical inactivity, and excessive alcohol use [40]. Lifestyle counseling competencies for primary physicians include knowledge, assessment skills, management skills, and the use of community support to provide additional leverage [40].

Imparting advice pertinent to *dietary components* and a healthy balanced diet must relate to the 2010 dietary guidelines [41]. Recent recommendations have cut down the daily sodium intake to 1,500 mg from the previous threshold of 2,300 mg/day for adults aged 51 and over, and for those with diabetes, hypertension, or chronic kidney disease [41]. Much of the ingested salt originates from processed food. In a recent study of over 500,000 U.S. adults aged 50–71 years, followed for a mean 9 years, dietary fiber appeared to reduce the risk of death from infections, cardiovascular, and respiratory disease [42]. The Mediterranean and DASH (Dietary Approach to Stop Hypertension) diets have been favorably perceived in promoting health.

Similarly, *maintaining physical activity* in conjunction with diet and other life style factors produces favorable results [43, 44]. Physical function declines with age; physical activity improves outcomes for almost every category of illness, including cardiovascular disease, dementia, depression, diabetes, hyperlipidemia, obesity, deep vein thrombosis, osteoporosis, deconditioning, and others. The exercise prescription must be tailored to the individual; medical evaluation may be indicated prior to beginning an exercise program. Warning signs during activity such as lightheadedness, palpitation, and chest pain must be taken seriously and addressed [43]. Walking is a commonly accepted and safe form of exercise, although patients are encouraged to participate in the activity of their liking. A little activity is always better than none, and more is better than less. Moving more and sitting a little less are complementary in optimizing health and function in future years and can even delay age-associated cognitive decline [45].

The 2008 Federal guidelines recommend adults to perform 150 min a week of moderate intensity (or 75 min of vigorous intensity) aerobic physical activity, preferably spread throughout the week and in at least 10 min episodes [46]. In those with limitations, exercise can be broken down into a few minutes of activity (e.g., walking) several times a day. Moderate intensity activity includes brisk walking, cycling, dancing, and gardening; one should be able to talk but not sing during the activity. Exercises may be aerobic, balance, or resistance type, based on indication and should be performed in safe walking areas, using proper apparel and shoes. Lack of time, lack of facilities, lack of knowledge, and most importantly lack of motivation are common barriers that need to be overcome strategically [47]. A recent meta-analysis, in fact, the first study to provide quantitative data supporting the 2008 guidelines, showed that 150 min of moderately intense physical activity lowers coronary heart disease risk by 14% and 300 min by 20% [48]. The risks were modestly lower at higher exercise levels. The study confirms that some physical activity is better than none and additional benefits occur with more physical activity, with the "biggest bang for the buck" at the lower end with very modest physical activity [48].

Contraindications to exercise include recent myocardial infarction or unstable angina, unstable cardiac arrhythmias, uncontrolled hypertension, tight aortic stenosis, decompensated heart failure, uncontrolled metabolic disorders (e.g., diabetes, some abnormal thyroid function states), and other serious illness. A combination of weight loss through dietary intervention and exercise provides greater improvement in physical function than either intervention alone [49].

Controlled trials suggest counseling for the increased use of *sun-protective behavior* and sunscreens that may help prevent skin cancer [50].

In addition, counseling includes enquiry about *tobacco and alcohol use*. Smoking cessation counseling must be offered to all smokers and include information on the consequences of smoking and strategies to stop the behavior. The message must be brief, unambiguous, and informative and include follow-up [18, 51]. Benefits are noted even if one quits after age 70. Currently available first-line treatments include nicotine replacement, bupropion, and varenicline [52]. Alcoholism is not uncommon in the elderly. It causes systems disease, negatively impacts judgment and driving skills, and contributes to injuries and deaths. Chronic alcoholism is a significant cause of gastrointestinal bleeding and liver disease [18]. Patients should be made aware of the consequences of alcoholism and limits must be set on amounts used.

Dental health must be addressed, as decayed or missing teeth are common in older age. A significant number of the elderly are edentulous (see Chap. 45 on oral health).

Falls prevention is currently a performance improvement measure in hospitals and institutions [53]. Falls can be reduced by exercise and physical therapy interventions (13%), vitamin D (17%), and a multifactorial risk assessment (11%) [53]. Medications may be contributory and must be reviewed. Falls are often multifactorial in basis. Use of a fall prevention tool kit reduced rate of falls in acute care hospitals [54]. Clinical practice guidelines for falls prevention introduced recently by the American and British Geriatrics Societies have stressed the importance of routinely questioning every patient about falls in the past year; if the history suggests that a fall occurred, gait

Table 7.4 An approach to the patient with falls (adapted from refs. [53–56])

Falls are not a consequence solely from aging
Incident rates higher in nursing home and hospital compared to community
Most falls are multifactorial in origin
Verify if the patient sustained a fall in the past year; if "yes"
Ask about frequency and circumstances of the fall
Evaluate gait and balance
If gait or balance is abnormal or if there are multiple falls, the patient requires a multifactorial fall risk assessment
Focused history in relation to fall must include
Circumstances, frequency, associated symptoms, consequences
Medication review: prescribed and over-the-counter
Relevant risk factors: acute and chronic disorder
Gait and balance evaluation
Get up and go test
Functional reach test
Nudge on the sternum or back
Romberg's sign
Tandem walking
Physical examination for
Neurological function
Musculoskeletal examination, including strength of lower limbs
Cardiovascular status
Visual acuity
Feet examination (including footwear)
Determine the possible cause of fall from
Intrinsic factors: disorders in the patient
Medications and their impact
Environmental factors at the site of fall
A combination of the above
Interventions may involve multiple disciplines
Address illness, medications, environment
Involve specialists and other disciplines as indicated
Neurologist, physiatrist, ophthalmologist, etc.
Occupational or physical therapist, homecare nurse, pharmacist

and balance evaluation is indicated with further multifactorial assessment as needed [55]. The occurrence of two or more falls with presence of gait imbalance suggests the need for further assessment. The evaluation also seeks to verify the distance a patient can walk, if safely and whether assistance is needed [56]. The most common risk factors include medications (especially anti-psychotics and sedative hypnotics), visual impairment, musculoskeletal disorders, vitamin D deficiency, and environmental disorders (Table 7.4).

Unintentional injuries are common in the old and negatively impact confidence and quality of life. Injuries, falls, and motor vehicle accidents are leading causes of death. Use of a safe temperature for water heaters (120°F) and working smoke detectors in homes and the use of using safety belts or helmets are recommended [18].

Table 7.5 The older driver (adapted from refs. [12, 18, 57])

Issue of safety
Number of crashes and injury in older adults is higher than any age group except 16–24-year-olds
Risk factors for driving accidents
Older age (especially over 85 years)
Reduced vision: maximum sensory input for driving is visual
Cognitive impairment
Impaired hearing
Impaired musculoskeletal function
Depression
High-risk medications
Sedative hynotics, muscle relaxants, narcotics, etc.
Alcohol
Responsibility
Discuss risk with patient and caregiver
Reduce risk by minimizing driving at night, during rush hour, and during bad weather
Refer for appropriate evaluation, based on impairment
If at high risk, consider recommendation to cease driving
Provider responsibility guided by state laws and local DMV

Assessment of *driving skills* and counseling where indicated is considered a preventive measure Driving is a means of maintaining independence; however, verifying that the older adult is a safe driver is relevant if risk is posed to safety of the patient or those around. Where necessary, the help of a motor vehicles rehabilitation specialist may be sought for thorough driving assessment [57]. State laws vary and some states require physicians to report unsafe drivers to the motor vehicles department. Table 7.5 provides a synopsis.

Immunizations

The adult i*mmunization schedule* endorsed by the American College of Physicians (ACP) applies to persons 19 years and older. Influenza is common in older adults and associated with morbidity, hospitalizations, and mortality. The recommendation schedule has been now expanded to annual administration of the seasonal inactivated vaccine with 3 viruses, including 2 Type A and 1 Type B (15 μg/dose) for all adults. A high-dose vaccine introduced in 2010 containing the same three strains but with four times the antigen (60 μg/dose) to boost immune response has not clearly demonstrated increased efficacy in older adults. Disadvantages include local reactions and increased cost [58, 59]. The revaccination strategy for pneumococcal vaccine has been clarified to include persons below age 65 with high-risk conditions, if 5 years have elapsed since the last dose. The vaccine is safe, with little to no reactions; the 23 valent vaccine covers

Table 7.6 Immunizations in older adults (adapted from refs. [58, 59])

Influenza vaccine
Seasonal vaccine indicated for all adults, once a year
Is a trivalent, inactivated vaccine (15 μg)
High-dose vaccine (60 μg) licensed in 2010 for those >65 years
Intranasal form not indicated for those over age 49 years
Intradermal vaccine (9 μg) introduced in 2011
Protection begins in about 2 weeks
Contraindication: anaphylaxis to egg protein or thimerosal
Pneumococcal vaccine
Single dose protects against 23 types of *Streptococcus pneumoniae*
Contraindications: practically none
Indicated in all adults: single dose after age 65 years
Revaccinate one time, if first dose provided before age 65 and 5 years have elapsed
Indicated before age 65 if there is evidence of any of the following: chronic lung or heart disease, diabetes, chronic liver disease, alcoholism, functional or anatomic asplenia, prior to elective splenectomy, nephrotic syndrome, immune-suppressed states
Herpes zoster vaccine
Single-dose zoster vaccine for adults aged 60 and older
Recommended regardless of prior history of herpes zoster
Contraindicated in immune-suppressed persons
Decreases likelihood for herpes zoster and postherpetic neuralgia
Tetanus, diphtheria, and acellular pertussis (Tdap) vaccine
Single dose of Tdap, followed by Td booster every 10 years
Adults >65 in contact with infants, who have not received prior Tdap, must be vaccinated, regardless of interval of last tetanus or Td vaccine
If uncertain history, complete a three vaccine series (over 6–12 months)
Other vaccines
Varicella: all adults who lack evidence of immunity receive two doses
Hepatitis A and B: indication based on risk factors hepatitis B vaccine recommended in diabetics 60 and older based on physician discretion
Meningococcal vaccine: if risk factors present

Table 7.7 The importance of assessing cognition in older adults (adapted from refs. [62–64])

Cognitive impairment is common in older adults
Patient is unlikely to volunteer, and in fact, may deny the problem
Dementia often escapes attention and is under-recognized
To distinguish age-related mild cognitive decline from dementia
To distinguish dementia from depression and delirium
Implications of under-recognition
Affects decision making: relates to capacity and competence
May lead to nonadherence to recommendations
Dementia increases caregiver burden
Safety of patient and others may be jeopardized
Victimization may be an issue
Suggest screening in certain situations
Older age, especially >75 years
History of delirium, depression, diabetes mellitus, Parkinson's disease, unexplained loss of function
Preoperative or preprocedure evaluation, to assess capacity and obtain informed consent
Screening tests for cognition are not diagnostic by themselves and are an adjunct to clinical assessment and judgment

75–90% of all pneumococcal disease cases. Tetanus, diphtheria, pertussis (Tdap) is termed a "family affair" as house hold members transmit the majority of infections to infants; persons over age 65 in contact with young children should receive a single dose of Tdap [58]. Other adults over age 65 may also receive Tdap boosters; Td booster is offered every 10 years [59] (Table 7.6).

A goal in prevention is to emphatically encourage immunization, a theme that holds true not only for older adults but also for health care workers [58]. While the strength of the immune response may be suboptimal in the old, vaccines do help to lower the intensity of illness, hospitalization, and mortality.

Hormone replacement therapy with estrogen and progestin is now considered to be more harmful than beneficial, as noted in the Women's Health Initiative Trial in 2002. The benefits for reducing risk of fracture are outweighed by the increased risk for venous thromboembolism, arterial thrombosis, breast cancer, and cholecystitis [60]. Unopposed estrogen and combination hormone therapy appears carcinogenic; while there may be a role for short-term use of estrogen for menopausal symptoms, questions remain regarding safety [61].

Secondary Prevention

Screening to recognize a variety of diseases in their subclinical state is the principle in secondary prevention. Several common disorders such as chronic obstructive lung disease, lung cancer, and ovarian cancer do not demonstrate benefit from screening in the elderly. Furthermore, not all societies agree on screening approaches, as noted with colon, breast and prostate cancer. The chapter will offer guidelines recommended by the USPSTF and other societies where applicable. As not every guideline is presented here, the reader is encouraged to obtain additional information of interest.

Screening for dementia is generally recommended on the grounds that cognitive impairment is often unrecognized by health providers until it is clearly advanced and that dementia poses risks to patient, caregiver, and others [62] (Table 7.7). A firm diagnosis of dementia offers an opportunity to explain to the patient and caregiver the anticipated alteration in function (ADL, IADL, intellectual functioning) and future care plans [62]. The status also helps plan and implement advance directives, current medical options, and end of life

care [63, 64]. Understanding cognitive status is vital in also planning feeding and nutritional support including the placement of a feeding tube, as well as also other surgical or gastrointestinal procedures, and to assess capacity and obtain informed consent. An intermediate state of cognitive function between that associated with aging and dementia is termed mild cognitive impairment (MCI); the estimated prevalence of MCI is 10–20% in the over 65-year group [65].

Most providers use at least one instrument for cognitive screening, with the Folstein Mini-Mental State Examination (MMSE) the most commonly used [66]. The MMSE tests five sections including orientation, registration, attention and calculation, recall, and language for a total of 30 points, but does have limitations in that the score is affected by education, culture, and sensory impairments [66]. The test correlates well with the easier to administer Mini-Cog [67] which combines a three-item delayed word recall test and the Clock Drawing Test [68] and widely captures cognitive dysfunction. The sensitivity and specificity for the MMSE are 76% and 89% vs. 79% and 88% for the Mini-Cog, respectively; the latter is less biased by low literacy [69]. The Montreal Cognitive Assessment is gaining credibility due to improvement in sensitivity and lesser bias from cultural and educational factors [63] (Table 7.8).

Depression is common in the old and may be attributable to circumstances; primary care physicians are encouraged to routinely screen for depression utilizing simple questions such as: "Are you basically satisfied with your life? Are you happy most of the time? Do you often feel sad or depressed?" Unexplained weight loss or anorexia may be a clue. The Geriatric Depression Scale short form offers a 15-question tool with yes/no answers, with a score over 5 suggesting depression [70, 71]. Affective domains also requiring evaluation include anxiety and hostility [71].

Visual impairment is also common in the geriatric age group and account for many unintentional injuries, falls, and poor quality of life. The most prevalent disorders beside refractory errors include glaucoma, macular degeneration, and diabetic retinopathy [72] (Table 7.9).

Hearing impairment increases in prevalence to over 80% in those aged 80 years and older. Older adults often fail to perceive their impairment and do not bother to rectify the problem, with only few wearing hearing aids. Age-related hearing loss is bilateral, gradual, and progressive. Hearing impairment is a cause of impaired quality of life, with many older adults falsely judged to have cognitive impairment. The USPSTF, in 1996, recommended screening for hearing loss in those 50 and older, but now seeks additional evidence to justify its universal application to this age group. Clear links to improved health outcomes are lacking at this time [73].

*Osteoporosis i*s a bone disorder that increases with age; it is a silent disease, until fractures arise, resulting in much morbidity. While current screening guidelines stated by the USPSTF have differed and are listed in Table 7.10 [74]. In general, groups for whom screening appears indicated include all women over age 65 and men over 70 regardless of risk factors, and women aged 50–69 at greater than average risk [75]. The World Health Organization has made available a computer-based fracture risk assessment tool (FRAX) to estimate the 10-year probability of major osteoporotic fractures in the 40–90 year age group. Items include age, sex, height, weight, ethnicity, femoral neck bone mineral density (optional), in addition to history of previous fracture, parent with hip fracture, smoking, alcohol use, steroid use, and rheumatoid arthritis [75]. The frequency with which to follow patients with repeat studies such as dual energy x'ray absorptiometry and the duration of therapy of osteoporosis with bisphosphonates are topics of much discussion today, with clear data driven directions pending.

Diabetes: screening recommendations endorsed by the USPSTF [76] and American Diabetes Association (ADA) [77] differ. The ADA now promotes hemoglobin A1c as a screening test, with a cut-off point of 6.5%; prediabetes is defined as 5.7–6.4% and denotes increased risk for developing

Table 7.8 Instruments to screen for dementia (adapted from refs. [63–69, 95, 96])

Mini-Mental State Examination (MMSE) [66]
Widely used, administered in about 10 min
Score below 24 (out of 30) abnormal
Range: <21 increases and >25 decreases odds of dementia
In advanced dementia, patient may be difficult to test
Scores influenced by education, culture, language, and impairments
Score must be taken in conjunction with clinical assessment
Three-item recall
Recall three items (for e.g., apple, pony, quarter)
3 Points score negative for dementia; 0 points suggest dementia
Clock drawing test [68]
Draw a clock, place the numbers correctly and the hands of the clock at a suggested time (e.g., 10 past 10)
Maximum score 5 points, normal score 4–5 points
Mini-Cog test [67]
Combines three item recall and clock drawing test
Less affected by ethnicity
Montreal Cognitive Assessment (MoCA) [95]
May be superior in sensitivity and specificity to MMSE
Designed to be sensitive for mild cognitive impairment; takes 10 min to administer
In primary care, threshold of 26 appears optimal
Covers eight cognitive domains (visuo-spatial, naming, memory, attention, recall, language, abstraction, orientation)
The Sweet 16 [96]
Simple, quick to administer
Scores <14 correlates with MMSE <24
Demonstrates sensitivity of 80% and specificity of 70%
Does not include items that may be biased against low education

Table 7.9 Visual loss in older adults (adapted from ref. [72])

Risk factors for impaired vision
Older age
Exposure to sunlight, radiation
Smoking and alcohol
Diabetes mellitus
Use of corticosteroids
Common disorders of vision
Diabetic retinopathy: proliferative and nonproliferative
Cataracts: among the most common reasons for surgery
Macular degeneration
Loss of central vision
More in Caucasians
Glaucoma
Loss of peripheral vision
Predisposition: blacks, hypertension, steroid use, myopia, diabetes
Refractory errors
Visual impairment predisposes to
Safety impairment
Driving accidents
Falls
Impaired quality of life
Screen
Screening questions are not as accurate as visual acuity testing
Annual screen for visual acuity (C21)
Office testing
Snellen chart (normal 6/6 or 20/20)
Jaeger card: held 14 in. from eye
Diabetics require annual evaluation and more often in presence of retinopathy

Table 7.10 Screening in older adults: the noncancerous disorders

Hearing loss [73]
Uncertain whether screening of asymptomatic adults aged 50 and older will lead to better health outcomes
Osteoporosis [74, 75]
Screening test: dual energy X-ray absorptiometry of hip and lumbar spine
Women
Age ≥65 years without prior fractures or secondary osteoporosis
Age <65 years with 10-year-old fracture risk equal to or greater than a 65-year-old White woman with average risk
Men
Current evidence insufficient to assess the balance of benefits and harms of screening
Men without previous known fractures or secondary causes of osteoporosis: no recommendation (insufficient evidence)
Diabetes [76, 77]
Diabetes: defined as A1c level 6.5% or higher (American Diabetes Association) [77]
Prediabetes (increased risk for diabetes): defined as A1c 5.7–6.4% [77]
Target goal for HbA1c <7% for most adults; <8% for frail old (AGS)
The USPSTF recommends screening for diabetes in asymptomatic adults with blood pressure >135/80 mmHg; balance of benefits and harms for screening are unclear in those with BP <135/80 mmHg [76]
Hypertension [79]
Screen for high blood pressure in adults age 18 or older
Screen every 2 years if <120/80 mmHg; screen annually if higher
Thyroid disease
USPSTF guidelines being updated; recommendations vary with society
Because of low costs of tests and common occurrence of hyper and hypothyroidism, may screen with serum thyrotropin assay every 2–5 years
Depression [70]
Consider screening annually
Instrument: Geriatric Depression Scale (short form: normal score 0–5)
Abdominal aortic aneurysm [78]
Ultrasonography for screening and follow-up for change in size of aneurysm
Indicated one time, in male ever smokers, between 65 and 75 years age
Urinary abnormalities (USPSTF)
Periodic screening for hematuria and proteinuria prudent
Screening not recommended for asymptomatic bacteriuria or diabetes
Elder mistreatment and neglect [80, 81]
May be physical, neglect, financial, sexual, or verbal
Risk factors and presentation may be suggestive; screening is debated
Chronic obstructive pulmonary disease [82]
Spirometry may be obtained to diagnose airflow obstruction
Screening not recommended in those without respiratory symptoms
Hyperlipidemia
Fasting lipid profile in adults over age 20 and thereafter every 5 years
Moderate evidence supports screening adults over 65 years

diabetes [77]. The A1c test measures average blood glucose levels for a period of up to 3 months, and in the past was used only to monitor diabetes control. Most guidelines agree on the target HbA1c goal of <7%, with the AGS recommending a target <8% for the frail old. The USPSTF guidelines are more restrictive and do not support screening for diabetes in normotensives [76].

Screening for *dyslipidemia* is generally recommended in adults over age 20 and moderate evidence supports screening the older adult over 65 years; the USPSTF recommends screening men >35 and women >45 years with increased risk for coronary artery disease.

Abdominal aortic aneurysms (AAAs) are associated with significant mortality when the aneurysms rupture, although most do not. The most important reversible risk factor is smoking, with cigarette smoking accounting for the majority of aneurysms larger than 4 cm in diameter. AAAs are more common in men than women and increase with age. The USPSTF recommends one-time screening using abdominal ultrasonography in male "ever smokers," aged 65–75 years [78]. Details are provided in chapter 68.

Screening for *hypertension* in adults is worthwhile. Hypertension coexists with common disorders in the elderly

such as diabetes, coronary artery disease, and hyperlipidemia. Screening is suggested every 2 years if the blood pressure is below 120/80 mmHg and annually if levels are higher [79].

It is important that older adults be screened for *elder mistreatment*, a common but under-recognized condition, especially in those who are frail. Mistreatment encompasses a range of behaviors including financial, physical, emotional, fiduciary and sexual abuse, and self-neglect [80, 81]. Elder abuse exists in community and other settings and is associated with increased morbidity and mortality. Health care professionals should take steps to report the matter to Adult Protective Services when reasonable suspicion arises; failure to report can lead to legal consequences [80]. Reasons for under-reporting include lack of knowledge, losing patient rapport, patient denial, and doubts about the intervention. The question of screening is debated. While the USPSTF has not endorsed screening for elder abuse, the World Health Organization encourages primary providers to discuss the matter with patients.

Lung disease: While spirometry is used to diagnose airflow obstruction in those with respiratory symptoms, it is not used to screen for airflow obstruction in those without respiratory symptoms [82] (Table 7.10).

Screening for Cancer

The optimal frequency and timing for *breast cancer* screening has become controversial in recent years [83]. A recent study suggested that mammography screening be personalized based on a woman's age, breast density, history of positive breast biopsy, family history, and personal beliefs with regards to screening and treatment [84]. The USPSTF suggested that there is moderate certainty that the net benefit is small for women in their 40s and false positives were higher than if screening were initiated at 50 years [85]. Screening may be concluded between 69 and 79 years for women of average health. Biennial screening averts 80% deaths averted by annual screening [85]. The benefits and potential harms of mammographic screening, frequency of screening, and the continuation of screening after age 74 continue to be debated; and recommendations are inconsistent between organizations [86]. However, it is clear that the value of clinical breast examination is less than ultrasound or MRI [87]. Some societies do not recommend self-examination at all. Risk factors must be given consideration in decision making and include genetic factors, family history, therapeutic radiation, hormonal factors, smoking and alcohol consumption, postmenopausal obesity, white race, and breast density [88].

Screening for *cervical cancer* may be discontinued after age 65, if three previous Pap smears have been negative and the patient is not otherwise at higher risk due to medical history. In practice, many older women do not recollect their past experience with screening for cervical cancer and may require screening if they have an intact uterus [72].

While the value of *colorectal cancer* screening in preventive health care is well established [89], the age at which to discontinue or not offer screening is controversial; CRC screening is detailed in chapter 58. There is no evidence at present to recommend screening for *ovarian cancer* through the use of imaging or tumor markers such as CA-125.

Screening for *prostate cancer* is not recommended above age 75 years. In 2008, the USPSTF determined that there is insufficient evidence for routine screening in the below 75 age group as well, based on the USPSTF recommendations [72, 90]. These recommendations have been endorsed by the AGS and ACP. However, recently, the USPSTF updated their recommendations and have stated that prostate-specific antigen (PSA)-based screening results in small or no reduction in prostate cancer-specific morality and is associated with harm related to subsequent evaluations and treatments [91]. The recommendation against routine PSA screening is now extended to all men and carries a D rating, denoting no benefits or more harm than benefits [91]. If screening is offered, it must follow a frank discussion with the patient on risks, benefits, and alternatives. Other organizations differ in their recommendations with the American Cancer Society and American Urological Association recommending annual PSA measurements and digital rectal examination in men after the age of 50.

The value of low-dose CT scan and chest radiography in screening for lung cancer has not been substantiated specifically in the elderly. The recent National Lung Screening Trial (NLST) involving 53,454 current and former smokers aged 66–74 years showed a 20% reduction in lung cancer-specific deaths in the low-dose CT group (vs. chest radiography group [92]). Low-dose CT screening in select high-risk individuals 55–74 years appears beneficial (International Early Lung Cancer Action Program). Although encouraging, the recommendation to adopt lung cancer screening in practice is not clear [93] (Table 7.11).

Other Common Disorders

Urinalysis for presence of protein and blood is prudent periodically. Urine screen for asymptomatic bacteriuria is not recommended, nor is periodic urine culture for surveillance in a person with an indwelling catheter. Screening for *anemia*, *B12 deficiency*, *and thyroid disorders* may be performed based on clinical judgment and prudence; these conditions are common in older adults, and testing is easy. Recommendations vary by organization.

Ultimately, care should be balanced. Quality indicators in the future need to factor life expectancy and encourage more appropriate care, rather than just more care. Older adults are

Table 7.11 Screening for cancer in older adults

Colorectal cancer [89]
CRC screening includes cancer prevention and detection (American College of Gastroenterology Guidelines, 2008)
Preferred prevention test: colonoscopy every 10 years, beginning at age 50, and at age 45 in African Americans
Alternative prevention: flexible sigmoidoscopy and CT colonography every 5–10 years
Cancer detection: preferred test is annual FOBT
The USPSTF recommends against ever screening those aged over 85 years and against routine screening of those >75 years [72]
Prostate cancer [72, 90, 91]
Insufficient evidence for or against routine screening through use of prostate-specific antigen in men <75 years (USPSTF) [90]
Recommend against routine PSA screening in men (USPSTF) [91]
Most likely to benefit: men 50–70 years and men >45 with increased risk (black Americans and family history) (American Urological Association)
Men with life expectancy <10 years are unlikely to benefit
Breast cancer [72, 83–88]
Consider personalized risk-based screening
USPSTF recommends that women in the 40–49 years make individualized decisions for screening as more false positives occur in this population vs. beginning at age 50. No recommendation for those 75 and older. Decision to screen should be based on patient values regarding benefits and harms
Screening may conclude between 69 and 79, in women of average health
Biennial screening averts 80% of deaths averted by annual screening
The ACP and American Academy of Family Physicians concur with above
The AGS recommends screening every 1–2 years; cost effective <age 80 years; not recommended in the frail old with <5 years life expectancy
American College of Obstetricians and Gynecologists: 40–49 years every 1–2 years; age ≥50 years, annually
American Cancer Society and American College of Radiology: age ≥40 years, annually
National Cancer Institute: age ≥40 years, every 1–2 years
National Health Service, UK: age 47–73 years, every 3 years
Cervical cancer [72]
May discontinue screening after age 65, if previously screened with three negative Pap smears, and not otherwise at higher risk
Older women who were never screened require screening and two negative Pap smears 1 year apart
Ovarian cancer
No screening recommended through use of CA 125 or ultrasound
Lung cancer
Evidence insufficient for or against screening through use of low-dose CT or chest radiography in older adults
Low-dose CT screening in select high-risk individuals (55–74 years) appears encouraging [92, 93]

the highest consumers of health care, but providers must prevent unintended harm [94].

Table 7.12 provides a means to document relevant information pertinent to CGA.

Caregiver Support and Burden

The caregiver is often forgotten. The question is: "who will care for the caregiver?" Providers must work closely with the caregiver and provide the necessary education to understand the disease, management options, strategies to care for the demented or frail old, and decision making in difficult situations, as for example, in severe Alzheimer's dementia. Caregiver stress and burden are problematic and real; caregivers have a higher likelihood of suffering from depression, musculoskeletal disorders, and hypertension. Discussions in a timely manner should include the anticipated course of illness to provide time for arrangements such as long-term care placement or death. Support groups, counseling services, and respite care are helpful options that may be provided.

Key Points

- Comprehensive geriatric assessment (CGA) encompasses multiple domains including physical, psychosocial, and functional areas.
- Health assessment encompasses evaluation for common disorders in geriatrics, including but not limited to visual and hearing impairment, musculoskeletal disorders, falls, cognitive impairment, depression, elder abuse, osteoporosis, incontinence, impaired gait and balance, and cardiac, renal, pulmonary, and gastrointestinal disease.
- Primary providers must offer a variety of preventive health services including timely immunizations and must develop competence in counseling patients with regard to life style interventions.
- Medication review, reconciliation, and minimizing polypharmacy help improve outcomes.
- The approach should be to assess life expectancy, implement advance directives, and target health care pertinent to health status, stage of life, and patient preferences.
- Psychosocial assessment including ethnic, cultural, and spiritual aspects must not be forgotten.
- Utilizing clinical practice guidelines is suggested; however, recommendations are not consistent and often need to be tailored to particular patients and situations.
- Successful CGA is dependent on utilizing several members of a multi or interdisciplinary team.
- Improvement of function and quality of life are the paramount goals in most geriatric patients.
- Caregiver stress and burden are common; and must not be ignored.

Table 7.12 A record of comprehensive geriatrics assessment

Name: DOB: Pertinent info: ☐Hospital ☐Clinic ☐NH ☐Home	**Allergies**: **Medications reviewed:** ☐ Yes ☐ No
Caregiver information:	**Advance directives:** ☐Yes ☐No ☐Living will ☐Health Care Proxy ☐DNR/DNI
Visual impairment: ☐Yes ☐ No Eyeglasses: ☐Yes ☐ No	**Hearing impairment:** ☐Yes ☐No Hearing aid: ☐Yes ☐ No
Smoking: ☐No ☐ Yes _____ pack yrs Quit: ☐Yes _____ years ago ☐No Counseled: ☐Yes ☐No	**Alcohol:** ☐No ☐Yes Qty /yrs _____ Quit: ☐Yes _____ years ago ☐No Counseled: ☐Yes ☐ No
Immunizations:	**Mobility:** Walks Independently: ☐Yes ☐ No Assist device: ☐ Cane ☐Walker ☐ Wheelchair
Pneumococcal vaccine: ☐Yes ☐ Date: ☐No	
Influenza vaccine	**Falls:** ☐ No ☐ Yes Frequency:
Tetanus/Diphtheria/ Pertussis Vaccine	**Incontinence:** Bladder ☐ Yes ☐ No Bowel ☐ Yes ☐ No
Herpes zoster: Date:	

Function	Comments:
ADL	☐Independent ☐Partially dependent ☐Dependent
IADL	☐Independent ☐Partially dependent ☐Dependent

Dates					
Weight (lbs / kgs)					
GFR / Cr. Clearance					

Screening	**Dates**				
MMSE					
GDS					
Breast exam					
Mammogram					
PAP smear					
FOBT					
Colonoscopy					
DEXA					
PPD					
Hearing exam					
Eye exam					
Podiatry exam					
Other (e.g. x'ray, EKG etc):					

Lab test	**Dates**				
Hgb / Hct					
WBC					
BUN					
Creatinine					
T. protein					
T. albumin					
Cholesterol					
LDL					
HDL					
Vit B12					
Folic acid					
TSH					
HbA1C					
PSA					
Vitamin D					

*Individualize to indication MD: _____ Date:_____

References

1. Reuben DB. Better ways to care for older persons: is anybody listening? J Am Geriatr Soc. 2009;57:2348–9.
2. Boult C, Green AF, Boult LB, et al. Successful models of comprehensive care for older adults with chronic conditions: evidence for the Institute of Medicine's "Retooling for an Aging America" report. J Am Geriatr Soc. 2009;57:2328–37.
3. Bloom HG. Preventive medicine, when to screen for older patients. Geriatrics. 2001;56:41–5.
4. Kuehn BM. Effort under way to prepare physicians to care for growing elderly population. JAMA. 2009;302:727–8.
5. Hall KE, Proctor DD, Fisher L, et al. American Gastroenterological Association Future Trends Committee Report: effect of aging of the population on gastroenterology practice, education and research. Gastroenterology. 2005;129:1305–38.
6. Graf CE, Zekry D, Giannelli S, et al. Efficiency and applicability of the comprehensive geriatric assessment in the emergency department: a systematic review. Aging Clin Exp Res. 2011;23(4):244–54.
7. Bilotta C, Bowling A, Nicolini P, et al. Older people's quality of life (OPQOL) scores and adverse outcomes at a one year follow up. A prospective cohort study on older outpatients living in the community in Italy. Health Qual Life Outcomes. 2011;9:72.
8. Pioli G, Davoli M, Pellicciotti F, et al. Comprehensive care. Eur J Phys Rehabil Med. 2011;47(2):265–79.
9. Horgan AM, Leighl NB, Coate L, et al. Impact and feasibility of a comprehensive geriatric assessment in the oncology setting: a pilot study. Am J Clin Oncol. 2011; ahead of print.
10. Pilotto A, Sancario D, Franceschi M, et al. A multidimensional approach to the geriatric patient with chronic kidney disease. J Nephrol. 2010;23 Suppl 15:S5–10.
11. Lucchetti G, Granero AL. Use of comprehensive geriatric assessment in general practice: results from the 'Senta Pua' project in Brazil. Eur J Gen Pract. 2011;17(1):20–7.
12. Gill TM. Approach to the patient: assessment. In: Pacala JT, Sullivan GM, editors. Geriatrics review syllabus: a core curriculum in geriatric medicine. 7th ed. New York: American Geriatric Society; 2010. p. 50–6.
13. Palmer RM. Geriatric assessment. Med Clin North Am. 1999;83:1503–23.
14. Elon R, Philips C, Leome JF, et al. General issues and comprehensive approach to assessment of elders. In: Osterweill D, Brummel-Smkith K, Beck JC, editors. Comprehensive geriatric assessment. New York: McGraw Hill; 2000. p. 1–39.
15. Dharmarajan TS, Ahmed S, Adapa SR. Comprehensive geriatric assessment. In: Dharmarajan TS, Norman RA, editors. Clinical geriatrics. Boca Raton: CRC Press; 2003. p. 23–35.
16. Koretz BK, Moore AA. Assessment of the geriatric patient: a practical approach. J Clin Outcomes Manage. 2001;8:35–40.
17. Solomon D, Consensus Development Panel. National Institute of Health Consensus Development Conference Statement. Geriatric assessment methods for clinical decision-making. J Am Geriatr Soc. 1988;36:342–7.
18. Woolf SH, Kamerow DB, Lawrence RS, et al. The periodic health examination of older adults: the recommendations of the US Preventive Services Task Force. Part I: counseling, immunizations and chemoprophylaxis. J Am Geriatr Soc. 1990;38:817–23.
19. Woolf SH, Kamerow DB, Lawrence RS, et al. The periodic health examination of older adults: the recommendations of the US Preventive Services Task Force. Part II: screening tests. J Am Geriatr Soc. 1990;38:933–42.
20. Zubenstein LZ. Comprehensive geriatric assessment: from miracle to reality. J Gerontol. 2004;59A(5):473–7.
21. Kane RL. What can improve chronic disease care? J Am Geriatr Soc. 2009;57:2338–45.
22. Schimid R, Eschen A, Ruegger-Frey B, Martin M. Instruments for comprehensive needs assessment in individuals with cognitive complaints, cognitive impairment or dementia, a systematic review. Int J Geriatr Pscyiatry. 2012;27(4):329–41.
23. Campbell LJ, Cole KD. Geriatric assessment teams. Clin Geriatr Med. 1987;3(1):99–110.
24. O'Malley AS, Reschovsky JD. Referral and consultation communication between primary care and specialist physicians. Arch Intern Med. 2011;171(1):56–65.
25. Winograd CH. Inpatient geriatric consultation. Clin Geriatr Med. 1987;3(1):193–202.
26. Tulner LR, van Campen JP, Frankfort SV, et al. Changes in undertreatment after comprehensive geriatric assessment: an observational study. Drugs Aging. 2010;27(10):831–43.
27. Reuben DB. Medical care for the final years of life. "When you're 83, it is not going to be 20 years". JAMA. 2009;302:2686–94.
28. Boulware LE, Marinopoulos S, Phillips KA, et al. Systematic review: the value of the periodic health evaluation. Ann Intern Med. 2007;146:289–300.
29. Initial Preventive Physical Examination (IPPE). Centers for Medicare andMedicaidServices.2011.http://www.cms.gov/MLNMattersArticles/downloads/MM3638.pdf. Accessed 21 May 2011.
30. The ABCs of providing the annual wellness visit. Centers for Medicare and Medicaid Services. Quick reference information. 2011. http://www.cms.gov/MLNProducts/download/AWV/Chart_ICN905706.pdf. Accessed 10 June 2011.
31. Serg G, De Rui M, Sarti S, Manzato E. Polypharmacy in the elderly: can comprehensive geriatric assessment reduce inappropriate medication use? Drugs Aging. 2011;28(7):509–19.
32. George CJ, Jacobs LG. Geriatrics medication management rounds: a novel approach to teaching rational prescribing with the use of the medication screening questionnaire. J Am Geriatr Soc. 2011;59(1):138–42.
33. Fick D, Semla T, Beizer J et al. American geriatrics society updated beers criteria for potentially in appropriate medication use in older adults. The American Geriatrics Society 2012 Beers Criteria Update Expert Panel. J Am Geriatr Soc. 2012;60:616–31.
34. Epstein RS. Medication adherence: hope for improvement? Mayo Clin Proc. 2011;86(4):268–70.
35. Lanier WL. Medical interventions at the end of life: what is appropriate and who is responsible? Mayo Clin Proc. 2005;80(11):1411–3.
36. Cohen NH. Advance directives: know what you want, get what you need. Mayo Clin Proc. 2007;82(12):1460–2.
37. Grudzen C, Grady D. Improving care at the end of life. Arch Intern Med. 2011;171(13):1202.
38. Owens DK, Qaseem A, Chou R, Shekelle P. High-value, cost-conscious health care: concepts for clinicians to evaluate the benefits, harms and costs of medical interventions. Ann Intern Med. 2011;154:174–80.
39. Powers JH. Practice guidelines. Belief, criticism and probability. Arch Intern Med. 2011;171(1):15–7.
40. Lianov L, Johnson M. Physician competencies for prescribing lifestyle medicine. JAMA. 2010;304:202–3.
41. Dietary Guidelines for Americans: Report of the Dietary Guidelines Advisory Committee on the Dietary Guidelines for Americans. 2010. http://www.cnpp.usda.gov/dgas2010-dgacreport.htm. Accessed 1 Feb 2011.
42. Park Y, Subar AF, Hollenbeck A, Schatzkin A. Dietary fiber intake and mortality in the NIH-AARP diet and health study. Arch Intern Med. 2011;171(12):1061–8.
43. Nakasato YR, Carnes BA. Health promotion in older adults. Promoting successful aging in primary care settings. Geriatrics. 2006;61(4):27–31.

44. Kendig H, Browning C, Pedlow R, et al. Health, social and lifestyle factors in entry to residential aged care: an Australian longitudinal analysis. Age Ageing. 2010;39(3):342–9.
45. King AC, Guralnik JM. Maximizing the potential of an aging population. JAMA. 2010;304:1944–5.
46. Office of Disease Prevention and Health Promotion. 2008 Physical activity guidelines for Americans. Washington, DC: U.S. Department of Health and Human Services; 2008. Publication No. U0036.
47. Firdaus M, Mathew MK, Wright J. Health promotion in older adults: the role of lifestyle in the metabolic syndrome. Geriatrics. 2006;61(2):18–25.
48. Sattelmair J, Pertman J, Ding El, et al. Dose response between physical activity and risk of coronary artery disease. Circulation. 2011;124:789–95.
49. Villareal DT, Choide S, Parimi N, et al. Weight loss, exercise or both and physical function in obese older adults. N Eng J Med. 2011;364:1218–29.
50. Lin JS, Eder M, Weinmann S. Behavior counseling to prevent skin cancer: a systematic review for the U.S. Preventive Task Force. Ann Intern Med. 2011;154:190–201.
51. Abdullah ASM, Simon JL. Health promotion in older adults. Evidence-based smoking cessation programs for use in primary care settings. Geriatrics. 2006;61(3):30–5.
52. Mui C, Sherman SE. New and emerging treatments in smoking cessation. J Clin Outcomes Manage. 2008;15(11):545–52.
53. Tinneti ME. Making prevention recommendations relevant for an aging population. Ann Intern Med. 2010;153:843–4.
54. Dykes PC, Carroll DL, Hurley A, et al. Fall prevention in acute care hospitals. A randomized trial. JAMA. 2010;304(17): 1912–8.
55. Kenny RAM, Rubenstein LZ, Tinetti ME, et al. Summary of the updated American Geriatrics Society/British Geriatrics Society Clinical Practice guidelines for prevention of falls in older persons. J Am Geriatr Soc. 2011;59:148–57.
56. Berg K, Norman KE. Functional assessment of balance and gait. Clin Geriatr Med. 1996;12(4):705–23.
57. Murden RA, Unroe K. Assessing older drivers. A primary protocol to evaluate driving risk. Geriatrics. 2005;60(8):20–4.
58. Fryhofer SA. Immunization 2011: expanding coverage, enhancing protection. Ann Intern Med. 2011;154:204–6.
59. Advisory Committee on Immunization Practices. Recommended adult immunization schedule: United States, 2012. Ann Intern Med. 2012;156:211–7.
60. Calonge N, Allan JD, Berg AO, et al. Hormone therapy for the prevention of chronic conditions in postmenopausal women: recommendations from the U.S. Preventive Services Task Force. Ann Intern Med. 2005;142:855–60.
61. Junegheim ES, Colditz GA. Short term use of unopposed estrogen. A balance of inferred risks and benefits. JAMA. 2011;305:1354–5.
62. Ravdin LD, Mattis PJ, Lachs MS. Assessment of cognition in primary care. Neuropsychological evaluation of the geriatric patient. Geriatrics. 2004;59(2):37–44.
63. Ismail Z, Rajji TK, Shulman KI. Brief cognitive screening instruments: an update. Int J Geriatr Psychiatry. 2010;25:111–20.
64. Milne E, Culverwell A, Guss R, et al. Screening for dementia in primary care: a review of the use, efficacy and quality of measures. Int Psychogeriatr. 2008;20:911–26.
65. Peterson RC. Mild cognitive impairment. N Eng J Med. 2011; 364:2227–34.
66. Folstein MF, Folstein SE, McHugh PR. Mini-mental state: a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12:189–98.
67. Borson S, Scanlan JM, Chen P, Ganguli M. The Mini-Cog as a screen for dementia: validation in a population-based sample. J Am Geriatr Soc. 2003;51(10):1451–4.
68. Schulman KI. Clock drawing: is it the ideal cognitive screening test? Int J Geriatr Psychiatry. 2000;15(6):548–61.
69. Borson S, Scanlan JM, Watnabe J, et al. Simplifying detection of cognitive impairment: comparison of the Mini-Cog and Mini-Mental State Examination in a multiethnic sample. J Am Geriatr Soc. 2005;53(5):871–4.
70. Sheikh JL, Yesavage JA. Geriatric depression scale: a recent evidence and development of a shorter version. Clin Gerontol. 1986;5:165–72.
71. Gallagher D. Assessing affect in the elderly. Clin Geriatr Med. 1987;3(1):65–85.
72. Schonberg MA. Prevention. In: Pacala JT, Sullivan GM, editors. Geriatrics review syllabus: a core curriculum in geriatric medicine. 7th ed. New York: American Geriatrics Society; 2010. p. 70–81.
73. Chou R, Dana T, Bougatsos BS, et al. Screening adults aged 50 years or older for hearing loss: a review of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med. 2011;154:347–55.
74. Calonge N, Bibbins-Domingo K, Cantu AG, et al. Screening for osteoporosis: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med. 2011;154:356–64.
75. Cotton D, Taichman D, Williams S. In the clinic: osteoporosis. Ann Intern Med. 2011;155:ITC1-1–16.
76. Helfand M, Whitlock E, Nygren P, et al. Screening for type 2 diabetes mellitus in adults: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med. 2008;148:846–54.
77. American Diabetes Association. Executive summary: standards of medical care in diabetes—2010. Diabetes Care. 2010;33:S4–10.
78. Fleming C, Whitlock EP, Bell TL, et al. Screening for abdominal aortic aneurysm: a best evidence systematic review for the US Preventive Services Task Force. Ann Intern Med. 2005; 142:203–11.
79. Wolff T, Miller T. Evidence for the reaffirmation of the U.S. Preventive Services Task Force Recommendation on screening for high blood pressure. Ann Intern Med. 2007;147:787–91.
80. Mosqueda L, Dong X. Elder abuse and self-neglect. "I don't care anything about going to the doctor to be honest…". JAMA. 2011;306:532–40.
81. Lachs MS, Pillemar KA. Elder abuse. Lancet. 2004;304:1236–72.
82. Qaseem A, Wilt TJ, Weinberger SE, et al. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. Ann Intern Med. 2011;155:179–91.
83. Mandelblatt JS, Stout N, Trentham-Dietz A. To screen or not to screen women in their 40's for breast cancer: is personalized risk-based screening the answer? Ann Intern Med. 2011;155:58–60.
84. Schousboe JT, Kerlikowske K, Loh A, Cummings SR. Personalizing mammography by breast density and other risk factors for breast cancer: analysis of health benefits and cost-effectiveness. Ann Intern Med. 2011;155:10–20.
85. U.S. Preventive Services Task Force. Screening for breast cancer: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med. 2009;151(10):716–26.
86. Turner B, Williams S, Taichman D. In the clinic: breast cancer screening and prevention. Ann Intern Med. 2010;152:ITC4-1–16.
87. Berg WA. Benefits of screening mammography. JAMA. 2010; 303:168–9.
88. Warner E. Breast-cancer screening. N Eng J Med. 2011;365:1025–32.
89. Rex D, Johnson D, Anderson J, et al. American college of gastroenterology guidelines for colorectal cancer screening 2008. Am J Gastroenterol. 2009;104:739–50.
90. Lin K, Lipsitz R, Miller T, Janakiraman S. Benefits and harms of prostate-specific antigen screening for prostate cancer: an evidence update for the U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med. 2008;149(3):192–9.

91. Chou R, Croswell JM, Dana T, et al. Screening for prostate cancer: a review of the evidence for the U.S. Preventive Services Task Force. 2011. http://www.annals.org/content/early/2011/10/070003. Accessed 14 Oct 2011.
92. Aberle DR, Adams AM, Berg CD, et al. National Lung Screening Trial Research Team. Reduced lung cancer mortality with low-dose computed tomographic screening. N Eng J Med. 2011;365: 395–409.
93. Silvestri GA. Screening for lung cancer: it works, but does it really work? Ann Intern Med. 2011;155:537–8.
94. Lee SJ, Walter LC. Quality indicators for older adults: preventing unintended harms. JAMA. 2011;306:1481–2.
95. Damian AM, Jacobson SA, Hentz JG, et al. The Montreal Cognitive Assessment and the Mini-Mental State Examination as screening instruments for cognitive impairment: item analyses and threshold scores. Dement Geriatr Cogn Disord. 2011;31(2):126–31.
96. Fong TG, Jones RN, Rudolph JL, et al. Development and validation of a brief cognitive assessment tool. Arch Intern Med. 2011;171(5):432–7.

Part III

Pharmacology

Drug Effects on the Gastrointestinal Tract

8

Vishal Jain, T.S. Dharmarajan, and C.S. Pitchumoni

Introduction

In the United States, four billion or more prescriptions are dispensed each year to manage health disorders. Several medications are associated with adverse drug events (ADEs), many being iatrogenic, with the Gastro Intestinal (GI) tract a frequent site of affliction [1]. According to the Food and Drug Administration report of 1995, 10% of the drug-induced adverse effects relate to the GI tract. "Older adults," defined as persons aged 65 or older, typically use multiple medications; an average of 5 or more medications per patient are not unusual [2]. An adverse drug reaction (ADR) is defined as a response to a drug that is noxious and unintended, occurring with doses normally used in prophylaxis, diagnosis, or therapy; ADRs are harm caused by the drug at normal doses, during normal use. An ADE is harm caused by use of a drug, including harm from inappropriate use of the drug (such as ADRs and overdoses). ADEs may result from medication error, but most do not. The broad interests of the patient safety movement have adopted the term ADE over ADR. The Institute of Medicine defines ADE as "injury resulting from medical intervention related to a drug [3]." The term side effect refers to a predictable dose-dependent drug effect that may be desirable, undesirable, or inconsequential; this term is discouraged. Studies have suggested that ADRs increase in occurrence with advancing age [4].

The top five ranked classes of medications causing most GI symptoms include central nervous system agents, hormones, cardiovascular drugs, anti-infective agents, and antineoplastic agents [1]. GI disorders in older adults may manifest with atypical presentations. Complaints can be vague and seldom accurately described by the patient or caregiver. The range of side effects is wide from nausea, vomiting, dyspepsia, abdominal cramps, diarrhea, or constipation, occur without identifiable pathology, some transient and resolve shortly after drug discontinuation, to major adverse effects including bleeding, perforated viscous, and lasting adverse effects (mucosal ulceration, stricture, or increased susceptibility to pseudomembranous colitis) [5]. It is not unusual for the adverse effects to be worse than the illness for which the drug was prescribed. A group of drug-related medical problems has been termed the "prescribing cascade" [6]. The cascade develops when an ADE is mistaken to be a new medical problem; an additional drug is prescribed, placing the patient at further risk for yet another drug-related problem from the new therapy (Fig. 8.1). The classic examples are development of constipation while taking an anticholinergic antidepressant such as amitryptiline or a calcium channel blocker for hypertension, leading to dependency on laxatives.

A description of drug effects on the GI tract follows based on site of effect.

Mouth

Local Effects

An erythematous or ulcerative reaction in the buccal mucosa may follow repeated contact with several substances including antibiotics, mouthwashes, cosmetics, topical anesthetics, and antiseptic lozenges [7]. Oral ulceration may follow use of aspirin,

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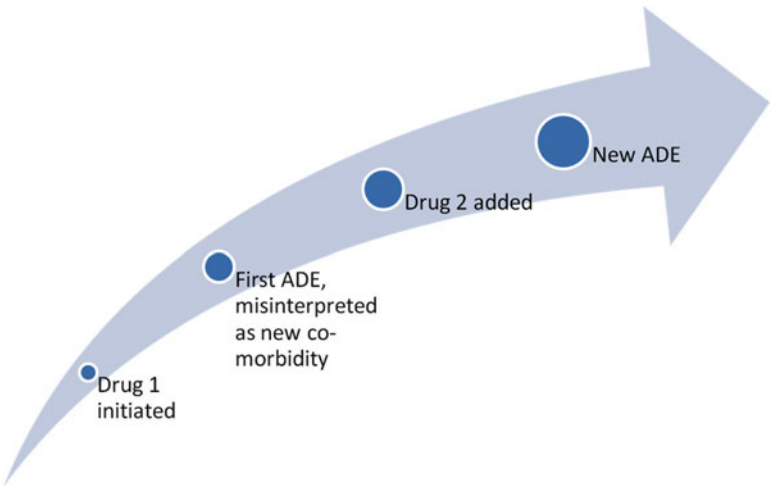

Fig. 8.1 Prescribing cascade and adverse drug events (ADEs)

potassium preparations, and anticholinergic medications particularly if they are retained in the mouth during dissolution.

Systemic Effects

Mouth lesions may be the initial manifestation of drug-induced bone marrow suppression. This severe complication of drug therapy should be considered in all patients with petechial hemorrhage, buccal ulceration, or signs of oral infection. A serious oral complication of drug therapy is Steven–Johnson syndrome, a severe form of erythema multiforme, manifest as extensive ulceration of buccal mucosa and lips, along with involvement of the conjunctivae and skin. Sulphonamides, barbiturates, nonsteroidal anti-inflammatory drugs (NSAIDs), and penicillin are implicated agents [8].

Miscellaneous Effects

Xerostomia or dryness of the mouth is a frequently encountered side effect of over 400 medications including but not restricted to parasymptholytic drugs such as atropine, tricyclic antidepressants, antiparkinsonian drugs, and phenothiazines. Drugs usually do not cause permanent damage to the salivary glands; drug-induced xerostomia is potentially reversible A decrease in saliva may result in difficulty in speaking (dysphonia), taste impairment (ageusia), and impaired chewing and swallowing abilities (dysphagia). Related changes in the oral microflora may increase susceptibility to oral candidiasis.

Ageusia or dysgeusia (altered taste) are commonly reported in association with ACE inhibitors [9] and other drugs such as griseofulvin, lithium, and tetracycline. Gingival hyperplasia is a recognized complication of phenytoin therapy and seen with cyclosporine and calcium channel blockers (e.g., nifedipine). Besides drug withdrawal, plaque removal and good oral hygiene help recovery and limit severity of lesions, though it may not completely resolve [7]. Tetracycline can produce a black hairy tongue, mostly benign due to hyperplasia of the filiform papillae.

Esophagus

Local Effects (Pill Esophagitis)

Nonchewable tablets or capsules usually pass quickly through the esophagus and release their contents in the stomach or intestines. Occasionally, these pills are lodged within the esophagus, dissolve, and release concentrated contents, causing direct mucosal damage (Table 8.1). A warning sign may be dull, aching pain in the chest or shoulder after drug consumption. Dysphagia resulting from neurological disorders, motility disorder, esophagitis, esophageal stricture, or insufficient liquid consumption to swallow the pills increases the risk of pill esophagitis. However, most patients with pill-induced esophagitis do not have underlying esophageal disorders. The pills frequently get stuck in areas of anatomical narrowing of the esophagus, especially the tracheal bifurcation, where the left atrium presses on the lower end of esophagus [10].

The severity of drug-induced esophageal damage ranges from mild, asymptomatic inflammatory changes to severe ulceration and stricture formation. The acute forms are most common, self-limited, and do not lead to serious consequences. Aspirin, tetracycline, doxycycline, quinidine, potassium chloride, vitamin C, and iron all cause esophageal ulcers [11]. In a recent large series, one third of cases were due to aspirin or NSAIDs [12]. Bisphosphonates, popularly used to treat and prevent osteoporosis, causes esophagitis, including severe ulcerations. Patients should take bisphosphantes with at least 240 mL of water on an empty stomach and remain in an upright position for at least 30 min to prevent esophagitis.

Table 8.1 Drug commonly implicated in causing pill esophagitis

Aspirin
Doxicycline
Potassium chloride
Bisphosphonate
NSAIDs
Vitamin C
Quinidine
Ferrous sulfate
Theophylline
Captopril

Table 8.2 Precautions suggested to prevent pill esophagitis

Swallow several sips of water to lubricate the throat before consuming a tablet or capsule
Swallow tablets or capsules with at least 8 oz of liquid
Swallow tablets or capsules while in an upright or sitting position
Do not lie down immediately after taking a tablet or capsule to ensure that the solid dosage forms pass through the esophagus and into the stomach
If swallowing continues to be painful or if the tablets or capsules continue to stick in the throat, the primary care physician must be informed and endoscopy may be needed

The presenting complaint, often dysphagia or chest pain, warrants esophagoscopy to demonstrate esophageal mucosal injury. In a patient on multiple medications, it may be difficult to pinpoint the offending drug. However, knowledge of the side effects of medications will help identify a causative agent. Capsules in general are more likely to get stuck in the esophagus than tablets [13]. The best approach to this disorder is prevention (see Table 8.2 for precautions), while the treatment for drug-induced esophageal damage is withdrawal of the offending medication.

Systemic Effects

The prevalence of gastro esophageal reflux disease (GERD) increases with age and is multifactorial in its pathogenesis. Defects in esophagogastric motility (transient lower esophageal sphincter (LES) relaxations, LES incompetence, poor esophageal clearance, and delayed gastric emptying) are central to the pathogenesis of GERD [14]. Normally, the LES, with a pressure zone 15–35 mmHg, prevents the gastric contents from entering the esophagus. Some drugs (e.g., theophylline, morphine, diazepam, sildenafil, calcium channel blockers, ethanol, and nitrates) cause gastroesophageal reflux by inappropriately relaxing the LES [14]. Progesterone, cholinergic agonists, and tricyclic antidepressants also reduce LES pressure [14]. It is well recognized that the severity of symptoms does not correlate with the degree of mucosal injury [15]. Unrecognized mucosal injury may lead to stricture formation. When an older adult complains of heart burn or regurgitation, a careful review of prescriptions and esophagogastroduodenoscopy (EGD) are warranted. Although medications may exacerbate these symptoms, it may be one side effect that is frequently "treated" rather than withdrawal of the offending medications. Treatment of drug-induced GERD includes reducing the dosage or discontinuing the offending drug and initiating standard measures to manage GERD, including lifestyle changes.

Stomach

As a slow transit organ, wherein ingested substances remain for minutes to hours, the stomach should be eminently vulnerable to drug-induced injury. Yet, a highly efficient mucosal protection system ensures that most oral medications either dissolve or navigate through the stomach without inducing damage. Both local and systemic factors influence the pathogenesis of gastric mucosal injury. NSAID injury has been well studied [16, 17]. NSAIDs and COX 2 receptor antagonists' use progressively increase with advancing age, more in women than in men [18]. NSAIDs constitute one of the most widely used classes of drugs, with more than 70 million prescriptions and more than 30 billion over-the-counter tablets sold annually in the United States [16].

Local

The pathogenesis of NSAID-induced gastroduodenal mucosal injury is complex. The dual-injury hypothesis suggests that NSAIDs have direct toxic effects on the gastroduodenal mucosa and indirect effects through active hepatic metabolites and decreases in mucosal prostaglandins to induce gastric damage [18, 20]. When NSAIDs irritate the gastric mucosa, they weaken the resistance to acid, causing gastritis, ulcers, bleeding, or perforation. The damage ranges from superficial injury to single or multiple ulcers, any of which may bleed. The clinical signs and symptoms of NSAID-induced gastropathy include dyspepsia, diarrhea, nausea, and vomiting. As the symptoms do not always correlate with the severity of the mucosal damage, patients need to understand the prudent use of NSAIDs to prevent serious complications. Older adult patients are especially at risk for NSAID-induced gastroduodenal mucosal injury; risk factors are listed in Table 8.3.

The various NSAIDs differ with regard to their risk of inducing upper GI bleeding and/or perforation. Commonly prescribed NSAIDs such as ibuprofen and diclofenac have the lowest relative risk [19]. Sulindac, aspirin, naproxen, and indomethacin have an intermediate relative risk, while

Table 8.3 Factors that increase the risk of GI complications from non-steroidal anti-inflammatory drugs (NSAIDs)

Age over 65 (risk increases linearly with age)
Polypharmacy
Comorbid conditions: cardiac, renal, pulmonary, etc.
First month of use
Prior history of peptic ulcer disease
High doses
Concomitant use of more than one NSAID
Concomitant use of anticoagulants or corticosteroids
Helicobacter pylori infection

piroxicam and ketorolac have the highest relative risk [19, 20]. The reason for these differences is not clear. NSAID-induced peptic ulcer disease in the elderly is often painless and associated with severe anemia. Indomethacin has been listed in the Beers criteria among the potentially inappropriate medications for older adults [21].

Systemic

Nausea and vomiting, common adverse effects of drugs, usually occur early in the course of pharmacologic therapy. Often, symptoms disappear with continued use. In some instances, concurrent administration of antiemetics may help prevent dehydration and electrolyte imbalance. Nausea and vomiting are not necessarily minor adverse effects; either may signify a more serious situation. Nausea and vomiting associated with digoxin or theophylline use may be a sign of drug toxicity. In the older adult, failure to recognize nausea/vomiting as an adverse drug effect may lead to unnecessary diagnostic studies.

The vomiting center receives neural impulses from different sites in the body such as the chemoreceptor trigger zone and GI tract. Chemotherapy-induced vomiting is multifactorial in origin. Each drug has a specific minimal, moderate or high emetogenic potential. Cisplatin has a high emetogenic potential, while vinblastine has minimal emetogenic potential. Depending on the chemotherapeutic drug, the emetogenic potential can increase with escalating dose. The emetogenic potential of cyclophosphamide can be moderate or high depending upon the dose. When chemotherapeutic drugs such as cyclophosphamide and doxorubicin are coadministered, the emetogenic potential is greater than that of either drug alone. Chemotherapy-induced vomiting is more common in females and younger patients.

Small Bowel

The incidence of drug-induced damage to the small bowel has long been underestimated because manifestations are often mild and nonspecific. Further, the jejunum and most of ileum have, until recently, remained largely inaccessible to endoscopic examination. Video capsule endoscopy, now widely available, is becoming the test of choice to diagnose drug-induced enteropathy.

Local Effects

Intraluminal drug concentrations decrease considerably when the medication reaches the small bowel and concentrations continue to fall through its length. However, local tissue damage can still occur with enteric-coated tablets or acid-resistant capsules. NSAIDs are the primary cause of drug-induced ulcers of the small intestine [22]. The older adult and those on long-term NSAIDs are at the highest risk [23]. The advent of Wireless Capsule Endoscopy has helped investigate small bowel lesions secondary to NSAID use. In contrast to the stomach, direct contact of NSAIDs with intestinal mucosa has a major role in the pathogenesis of the NSAID small bowel toxicity.

NSAIDs cause a clinical entity of diffuse intestinal inflammation and increased intestinal mucosal permeability. The so-called NSAID enteropathy is characterized clinically by occult blood loss, iron deficiency anemia, malabsorption, and protein-losing enteropathy, with blood loss the most significant. Many on NSAIDs chronically present with fecal occult blood loss and iron deficiency anemia, with no endoscopically identifiable source of bleeding in the upper gastrointestinal tract or colon that is an adequate explanation. In such patients, NSAID enteropathy should be considered and video capsule endoscopy may be indicated. Capsule retention is quite rare; however, caution is warranted as NSAID enteropathy was the most common cause of retention in a single experience of 1,000 capsule endoscopies by Li et al. [24].

Frequent coprescription of medications caused detrimental reactions in elderly chronic NSAID users in a study of nearly one million people, prescribed for hypertension and heart failure (59.5%), antithombotics (35.1%), glucocorticoids (12.9%), SSRIs (8.3%), and warfarin (4.8%) [25]. In a large cohort of 644,183 elderly, among users of proton pump inhibitors (PPIs), the combination of traditional NSAID and acetaminophen increased the risk of GI bleeding and hospitalization compared to the reference drug acetaminophen alone; even among nonusers of PPIs, the risk of GI hospitalization was highest with the combination [26].

"Diaphragm" disease is a rare form of NSAID enteropathy characterized by the presence of numerous, thin, web-like septa that protrude into the lumen and may cause strictures. The mid small intestinal and ileum are preferentially involved, but lesions have been described in the right colon and duodenum of patients on prolonged high-dose aspirin therapy [27]. Subacute bowel obstruction, diarrhea,

and weight loss are the most common symptoms of diaphragm disease.

Jejunal diverticula may increase the risk of local complications, with diverticular perforation reported from local iron toxicity [28]. Drug-induced malabsorption is an adverse effect of nonabsorbable antibiotics such as neomycin. Like cholestyramine, neomycin binds bile salts in the gut and thus reduces their availability for micelle formation, with resultant fat and fat-soluble vitamin malabsorption. Tetracycline chelates calcium, mineral oil reduces absorption of carotene and fat-soluble vitamins, thiazides impair ileal transport of sodium, and aluminum/magnesium hydroxide precipitates calcium and phosphate ions. Colchicine, neomycin, methotrexate, methyldopa, and allopurinol interfere with absorption of nutrients by causing mucosal damage. Fat and mineral bioavailability appears unaltered by PPI therapy [29]. However, absorption of protein-bound vitamin B12 level can be impaired by long-term PPI therapy, with profound acid suppression leading to B12 deficiency in some [30]. Absorption-related adverse effects are generally reversible following discontinuation of the medication.

Systemic

Small intestinal motor activity is less likely to be affected by drugs compared to that of the colon. Anticholinergics as pre-medication can delay the return of bowel sounds following surgery, and in large doses, may precipitate paralytic ileus. Antiparkinsonian drugs, tricyclic antidepressants, phenothiazines, loperamide, calcium channel blockers, and opiods all reduce small bowel motility. Intestinal motility usually returns shortly after discontinuation of the drug.

A noninfective hemorrhagic enterocolitis may result from immunosuppresive drugs which affect all rapidly dividing cells, including the GI tract. Vinblastine, methotrexate, and cyclophosphamide may induce this condition, which may progress to perforation, but usually responds to supportive therapy along with withdrawal of the offending drug. The clinical features include pain, bleeding, vomiting, ileus, and diarrhea.

Several drugs may cause small bowel ischemia; these include hormonal preparations, digoxin, and cocaine. Digitalis may compromise small intestinal blood flow by diminishing splanchnic flow, primarily in older adults with heart failure. A symptom complex of abdominal pain, vomiting, and distension with diarrhea or melena has been observed along with other features of digitalis toxicity. Various diuretics and antihypertensive medications may lead to bowel ischemia through their hypovolemic or hypotensive effects.

Colon

Local

Broad-spectrum antibiotics, particularly tetracycline and ampicillin, are the most common offenders in drug-induced diarrhea. With ampicillin, the effect is independent of dose and route of administration. Hence, in patients who develop diarrhea on an oral preparation, the antibiotic should be changed rather than the mode of administration. The pathogenesis for antibiotic-induced diarrhea is unclear. Although an alteration in intestinal flora may be contributory, this cannot be the only mechanism, as drugs with similar spectrum of activity produce widely differing incidences of diarrhea. Other drugs that induce diarrhea include systemic anti-inflammatory agents and salts of iron, potassium, and calcium. Magnesium-containing antacids cause diarrhea; the salts are poorly absorbed and increase gut luminal fluid volume through osmotic action.

NSAIDs may cause colitis or exacerbate a preexisting colonic disease, but the mechanism (local or systemic) is unclear [23]. NSAID-induced lesions can develop in the healthy colon or at sites of preexisting disease, such as diverticular disease or chronic inflammatory bowel disease (IBD). The most common pattern of NSAID-associated colonic damage is a nonspecific colitis, and NSAIDs can induce de novo nonspecific colorectal lesions that clinically and pathologically mimic IBD and are difficult to distinguish from IBD early in its natural history. Presentation is typically bloody diarrhea and abdominal pain, with a history of NSAID use (for days, months, or years). Colonic ulcers are described in patients taking NSAIDs [31]. Diaphragm-like strictures of the colon, similar to those in the small bowel and duodenum, have been reported with long-term NSAID therapy [32]. Abdominal pain, alteration in bowel habits, and weight loss are common manifestations.

Systemic

Ischemic colitis, the most common form of ischemic injury of the GI tract, encompasses the clinical spectrum of reversible colopathy, transient colitis, chronic colitis, colonic stricture, gangrene, and fulminant universal colitis [33]. Colonic ischemia results from compromised systemic circulation as well as mesenteric circulation causing local injury. Ischemic colitis occurs in individuals predisposed to ischemic heart disease, hypertension, peripheral vascular disease, and vasculitis. Pharmacological agents may predispose to ischemic colitis as a vascular adverse effect or worsen a compromised blood supply in the presence of preexisting disease. A focused medication history may help identify a probable drug that predisposes to colonic ischemia.

A consequence of antibiotic therapy is *Clostridium difficile*-associated diarrhea (CDAD). CDAD occurs because the antibiotic allows the overgrowth of *C. difficile*, which does not typically colonize the colon of a healthy adult. Although most antibiotics can cause CDAD, the antibiotics most commonly associated with CDAD are fluoroquinolones, clindamycin, ampicillin, amoxicillin, and the cephalosporins [34]. Other antibiotics associated with CDAD, but less frequently, include erythromycin, other penicillins, and trimethoprim-sulfamethoxazole. Multiple courses or repeated antibiotic therapy increase risk of infection. CDAD may result from both oral and parenteral antibiotic use. The role of PPIs predisposing to CDAD is recognized in epidemiological studies [35, 36]. Data also suggest that PPI use during incident *C. difficile* infection is associated with a 42% increased risk of recurrence [37].

The epidemiology of CDAD has changed in recent years, with the incidence and severity increasing considerably. North America and Europe are in the midst of an epidemic of severe CDAD associated with the emergence in 2002 of a hypervirulent strain of *C. difficile* known as toxinotype III Nap 1 BI, Nap 1, or Nap 1/027. The Canadian province of Quebec has been especially hard hit, with >3,000 nosocomial cases of CDAD diagnosed between August 2004 and March 2005; studies of this epidemic documented the presence of the hypervirulent toxinotype III Nap 1 BI strain, and risk factors for CDAD in this epidemic included older age and use of quinolones [38].

Patients receiving chemotherapy, including cytosine arabinoside, cytarabine, cisplatin, vincristine, adriamycin, 5-fluorouracil, thioguanine, and mercaptopurine are at risk of developing necrotizing enterocolitis or neutropenic colitis [39]. The common feature in all cases is profound drug-induced leucopenia and neutropenia (<100 neutrophils/mm^3) that permits mural bacterial invasion. Risk factors include underlying leukemia and administration of drugs toxic to the gastrointestinal mucosa, such as cytosine arabinoside.

In an aging population, recent practice patterns indicate use of opiates for prolonged treatments of chronic nonmalignant medical conditions. It is well recognized that opiates adversely affect gastrointestinal motility. These effects, known as opioid bowel dysfunction, are manifest as constipation, nausea, bloating, ileus, and sometimes pain. However, when pain is the predominant symptom, the condition is termed narcotic bowel syndrome (NBS). NBS is characterized by chronic or frequently recurring abdominal pain that worsens with continued or escalating dosages of narcotics. There is also marked worsening of pain when the narcotic dose wanes and improvement when narcotics are reinstituted (soar and crash) [40].

Drug-induced diarrhea is common in the older adult because of age-related factors and polypharmacy associated with treatment of acute and chronic diseases. Early diagnosis and treatment of diarrhea in the elderly helps prevent dehydration, loss of electrolytes, and deterioration of nutritional status. Laxative abuse is a consideration in the differential diagnosis of diarrhea. Patients complain of watery diarrhea, weight loss, and hypokalaemia and are often considered to be suffering from a hormone secreting pancreatic neoplasm. Laxatives, particularly the anthraquinones like senna, are associated with pigmentation of the colonic wall (melanosis coli) in patients who consume large doses for years and disappear within months of discontinuing the laxative. Chronic use of stimulant laxatives can lead to fluid and electrolyte imbalance, steatorrhea, protein-losing gastroenteropathy, osteomalacia, and vitamin and mineral deficiencies. When the drug is discontinued, radiographic and functional changes in the colon may only partially return to normal because of drug-induced neuromuscular damage to the colon.

Intestinal obstruction may result from the use of fiber in older adults with inadequate water intake. Drugs known to induce constipation include antacids containing aluminum, together with drugs that alter intestinal motility such as anticholinergics, antiparkinsonian drugs, tricyclic antidepressants, and opiates. Table 8.4 lists some common drugs causing diarrhea and constipation in the older adult. Excessive fiber intake may interfere with absorption of nutrients such as calcium, iron, and magnesium besides medications, a fact relevant in the older adult on multiple drugs [41].

Table 8.4 Common medications implicated in constipation and diarrhea

Constipation
Opiates
Peppermint oil
Aluminum-containing antacids
Gaviscon
Iron
Laxatives (chronic)
Antimuscarinic drugs (atropine, tricyclic antidepressants)
Calcium supplements
Sucralfate
Calcium channel blockers
Anticholinergics
Diarrhea
Antibiotics
Magnesium-containing antacids
Iron
Laxatives (acute)
Metformin
Olsalazine
Misoprostol
Promotility drugs
Nonsteroidal anti-inflammatory agents
Mesoprostol
Cholinesterase inhibitors
Selective serotonin reuptake inhibitors

Anus and Rectum

Anorectal ulcerations have been described in patients who use suppositories containing ergotamine tartrate to excess. The mucosal lesions resemble those observed in "solitary rectal ulcer syndrome." Characteristic features of ergotamine-induced ulcers include the absence of a mucosal prolapse, absent history of constipation, and rapid healing after discontinuation of the drug. Similar anorectal lesions are associated with chronic administration of NSAID suppositories; erosions or ulcers are seen even with short-term NSAID use, with lesions remitting following discontinuation of treatment [42]. Anorectal stenosis, perforation, and recto-vaginal fistulas are reported after prolonged overuse of NSAID suppositories [43]. The uses of kayexalate retention enemas have been associated with mucosal necrotic ulcers.

Pancreas

Medication-induced pancreatitis due to medications is an unusual event and has been estimated to be about 2% of cases of pancreatitis [44]. Many drugs have been implicated as etiologic agents, and the list continues to grow. Table 8.5 lists some medications commonly used in the older adult which can cause pancreatitis. They have been divided into Class Ia, Ib, and II based on the classification used by Badalov et al. [45]. The pathogenesis of drug-induced pancreatitis may be due to an idiosyncratic response in some cases (e.g., 6-mercaptopurine, aminosalicylates, and sulfonamides) or to a direct toxic effect (e.g., diuretics, sulfonamides). Drug-induced pancreatitis has no distinguishing clinical features.

Table 8.5 Drug-induced pancreatitis

Class Ia	Class Ib	Class II
Alpha-methyldopa	Amiodarone	Acetaminophen
Benzafibrate	Azathiprine	Chlorthiazide
Carbimazole	Dexamethasone	DDI
Codeine	Lamivudine	Erythromycin
Enalapril	Losartan	Estrogen
Furosemide	6-MP	Propofol
Isoniazid	Methimazole	Tamoxifen
Mesalamine	Nelfinavir	
Metronidazole	Omeprazole	
Pentamidine	Premarin	
Pravastatin	Sulfamethzole	
Procainamide	Trimethoprim	
Simvastatin		
Sulindac		
Tetracycline		
Valproic acid		

Modified from ref. [45, 46]

A high index of suspicion and careful drug history are therefore essential for making the diagnosis. Proving the association with a particular drug may not always be straightforward, even in suspected cases. Thus, patients restarted on their medications should be closely monitored and the drug promptly discontinued if symptoms recur. The prognosis of drug-induced pancreatitis is generally excellent [46].

Special Problems in the Older Adult

With regard to drug effects on the GI system, the geriatric patient differs in many ways. Drug absorption is generally not affected, but drug effects vary through interactions with other medications, nutrients, and comorbidity; with the background of polypharmacy and impaired cognition, dysphagia, and impaired musculoskeletal function, all common in the old, drug interactions are common, compounded by errors in drug administration. Cholinesterase inhibitors are typically prescribed to help cognition in dementia; the first drug (tacrine) lost favor predominantly due to ADEs manifesting as hepatitis and diarrhea; in a study of 773 reports among 75–84 year olds, with 65% women, serious ADRs occurred in 57% of cholinesterase inhibitor use, raising questions whether the ADE is worse than the disease [47]. In an era of polypharmacy, the safety of analgesic use (opioids and NSAIDs) in the elderly raises concerns; nonselective NSAIDs are among the most common OTC medications used, with ibuprofen being the third in US adults [48].

Extrapolation of data from trials in the younger adults does not provide adequate risk-benefit estimates for the old, stressing the need to understand drug kinetics and dynamics; the elderly appear underrepresented in clinical trials [49]. Strategies in future should focus on prevention of GI complications from commonly used drugs. Examples include prevention of aspirin-induced injury from mucosal prostaglandin depletion [50]; drug interactions and complications from PPIs, such as on mineral metabolism and fractures or *C. difficile* infection [51]; GI adverse effects from newer anticoagulants such as dabigatran, which requires dosage adjustment for renal function and should bleeding occur, there is no antidote [52]; and others. It may be prudent at times to not prescribe or even withdraw a medication for a new manifestation, rather than add yet another.

Key Points

- Polypharmacy in the elderly is frequent, prompting clinicians to be aware of the increasing number of drugs with adverse GI effects and their presentation.
- Unrecognized GI side effects of medications lead to frequent and unwanted endoscopies, biopsies, and increased costs and risks to the patient.

- A new manifestation in an older adult should prompt consideration for an adverse drug event (ADE), prompting attention to revision of the medication regimen, rather than the immediate addition of yet another medication.
- Prevention of ADEs is partly dependent on adequate understanding of altered drug kinetics and dynamics with aging.
- While health care professionals can usually do little to alter the pharmacokinetics or dynamics of individual patients, the decision to prescribe a drug, the choice of drug, and the manner in which it is to be used are all factors under the control of the prescriber.

References

1. FDA. Annual adverse drug report 1995. 1995. http://www.fda.gov/cder/reports/annrep95.pdf.
2. Jorgensen T, Johansson S, Kennerfalk A, et al. Prescription drug use, diagnoses, and healthcare utilization among the elderly. Ann Pharmacother. 2001;35(9):1004–9.
3. Nebeker JR, Barach P, Samore MH. Clarifying adverse drug events: a clinician's guide to terminology, documentation, and reporting. Ann Intern Med. 2004;140(10):795–801.
4. Nolan L, O'Malley K. Prescribing for the elderly. Part I: sensitivity of the elderly to adverse drug reactions. J Am Geriatr Soc. 1988;36(2):142–9.
5. Jain V, Pitchumoni CS. Gastrointestinal side effects of prescription medications in the older adult. J Clin Gastroenterol. 2009;43(2):103–10.
6. Rochon PA, Gurwitz JH. Optimising drug treatment for elderly people: the prescribing cascade. BMJ. 1997;315(7115):1096–9.
7. Abdollahi M, Radfar M. A review of drug-induced oral reactions. J Contemp Dent Pract. 2003;4(1):10–31.
8. Roujeau JC, Kelly JP, Naldi L, et al. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. N Engl J Med. 1995;333(24):1600–7.
9. Unnikrishnan D, Murakonda P, Dharmarajan TS. If it is not cough, it must be dysgeusia: differing adverse effects of angiotensin-converting enzyme inhibitors in the same individual. J Am Med Dir Assoc. 2004;5(2):107–10.
10. Taybos G. Oral changes associated with tobacco use. Am J Med Sci. 2003;326(4):179–82.
11. Carlborg B, Densert O. Esophageal lesions caused by orally administered drugs. An experimental study in the cat. Eur Surg Res. 1980;12(4):270–82.
12. Abid S, Mumtaz K, Jafri W, et al. Pill-induced esophageal injury: endoscopic features and clinical outcomes. Endoscopy. 2005;37(8):740–4.
13. O'Neill JL, Remington TL. Drug-induced esophageal injuries and dysphagia. Ann Pharmacother. 2003;37(11):1675–84.
14. Castell DO, Murray JA, Tutuian R, et al. The pathophysiology of gastro-oesophageal reflux disease—oesophageal manifestations. Aliment Pharmacol Ther. 2004;20 Suppl 9:14–25.
15. Shaker R. Gastroesophageal reflux disease: beyond mucosal injury. J Clin Gastroenterol. 2007;41 Suppl 2:S160–2.
16. Lichtenstein DR, Syngal S, Wolfe MM. Nonsteroidal antiinflammatory drugs and the gastrointestinal tract. The double-edged sword. Arthritis Rheum. 1995;38(1):5–18.
17. Schoen RT, Vender RJ. Mechanisms of nonsteroidal anti-inflammatory drug-induced gastric damage. Am J Med. 1989;86(4):449–58.
18. Dominick KL, Ahern FM, Gold CH, Heller DA. Gender differences in NSAID use among older adults with osteoarthritis. Ann Pharmacother. 2003;37(11):1566–71.
19. Garcia Rodriguez LA, Cattaruzzi C, Troncon MG, Agostinis L. Risk of hospitalization for upper gastrointestinal tract bleeding associated with ketorolac, other nonsteroidal anti-inflammatory drugs, calcium antagonists, and other antihypertensive drugs. Arch Intern Med. 1998;158(1):33–9.
20. Griffin MR, Piper JM, Daugherty JR, et al. Nonsteroidal anti-inflammatory drug use and increased risk for peptic ulcer disease in elderly persons. Ann Intern Med. 1991;114(4):257–63.
21. Fick DM, Cooper JW, Wade WE, et al. Updating the Beers criteria for potentially inappropriate medication use in older adults: results of a US consensus panel of experts. Arch Intern Med. 2003;163(22):2716–24.
22. Allison MC, Howatson AG, Torrance CJ, et al. Gastrointestinal damage associated with the use of nonsteroidal antiinflammatory drugs. N Engl J Med. 1992;327(11):749–54.
23. Gibson GR, Whitacre EB, Ricotti CA. Colitis induced by nonsteroidal anti-inflammatory drugs. Report of four cases and review of the literature. Arch Intern Med. 1992;152(3):625–32.
24. Li F, Gurudu SR, De Petris G, Sharma VK, et al. Retention of the capsule endoscope: a single-center experience of 1000 capsule endoscopy procedures. Gastrointest Endosc. 2008;68(1):174–80.
25. Vandraas KF, Spigset O, Mahic M, Slordal L. Non-steroidal anti-inflammatory drugs: use and co-treatment with potentially interacting medications in the elderly. Eur J Clin Pharmacol. 2010;66(8):823–9.
26. Rahme E, Barkun A, Nedjar H, et al. Hospitalizations for upper and lower GI events associated with traditional NSAIDs and acetaminophen among the elderly in Quebec, Canada. Am J Gastroenterol. 2008;103(4):872–82.
27. Pusztaszeri MP, Genta RM, Cryer BL. Drug-induced injury in the gastrointestinal tract: clinical and pathologic considerations. Nat Clin Pract Gastroenterol Hepatol. 2007;4(8):442–53.
28. Ingoldby CJ. Perforated jejunal diverticulum due to local iron toxicity. BMJ. 1977;1(6066):949–50.
29. Saltzman JR, Kowdley KV, Pedrosa MC, et al. Bacterial overgrowth without clinical malabsorption in elderly hypochlorhydric subjects. Gastroenterology. 1994;106(3):615–23.
30. Dharmarajan TS, Kanagala MR, Murakonda P, et al. Do acid-lowering agents affect vitamin B12 status in older adults? J Am Med Dir Assoc. 2008;9(3):162–7.
31. Stamm C, Burkhalter CE, Pearce W, et al. Benign colonic ulcers associated with nonsteroidal antiinflammatory drug ingestion. Am J Gastroenterol. 1994;89(12):2230–3.
32. Halter F, Weber B, Huber T, et al. Diaphragm disease of the ascending colon. Association with sustained-release diclofenac. J Clin Gastroenterol. 1993;16(1):74–80.
33. Brandt LJ, Boley SJ. Colonic ischemia. Surg Clin North Am. 1992;72(1):203–29.
34. Cappell MS. Colonic toxicity of administered drugs and chemicals. Am J Gastroenterol. 2004;99(6):1175–90.
35. Dial S, Delaney JA, Schneider V, Suissa S. Proton pump inhibitor use and risk of community-acquired *Clostridium difficile*-associated disease defined by prescription for oral vancomycin therapy. CMAJ. 2006;175(7):745–8.
36. Al-Tureihi FI, Hassoun A, Wolf-Klein G, Isenberg H. Albumin, length of stay, and proton pump inhibitors: key factors in *Clostridium difficile*-associated disease in nursing home patients. J Am Med Dir Assoc. 2005;6(2):105–8.
37. Linsky A, Gupta K, Lawler EV, et al. Proton pump inhibitors and risk for recurrent *Clostridium difficile* infection. Arch Intern Med. 2010;170(9):772–8.
38. Muto CA, Pokrywka M, Shutt K, et al. A large outbreak of *Clostridium difficile*-associated disease with an unexpected proportion of deaths and colectomies at a teaching hospital following increased fluoroquinolone use. Infect Control Hosp Epidemiol. 2005;26(3):273–80.

39. Petruzzelli GJ, Johnson JT, de Vries EJ. Neutropenic enterocolitis. A new complication of head and neck cancer chemotherapy. Arch Otolaryngol Head Neck Surg. 1990;116(2):209–11.
40. Grunkemeier DM, Cassara JE, Dalton CB, Drossman DA. The narcotic bowel syndrome: clinical features, pathophysiology, and management. Clin Gastroenterol Hepatol. 2007;5(10):1126–39; quiz 1121–2.
41. Dharmarajan TS, Kumar A, Pitchumoni CS. Drug-nutrient interactions in older adults. Pract Gastroenterol. 2002;26(9):37–55.
42. Gizzi G, Villani V, Brandi G, et al. Ano-rectal lesions in patients taking suppositories containing non-steroidal anti-inflammatory drugs (NSAIDs). Endoscopy. 1990;22(3):146–8.
43. de Parades V, Sultan S, Bauer P. Ano-rectal and colonic complications of suppositories and enemas. Gastroenterol Clin Biol. 1996;20(5):446–52.
44. Lankisch PG, Droge M, Gottesleben F. Drug induced acute pancreatitis: incidence and severity. Gut. 1995;37(4):565–7.
45. Badalov N, Baradarian R, Iswara K, et al. Drug-induced acute pancreatitis: an evidence-based review. Clin Gastroenterol Hepatol. 2007;5(6):648–61; quiz 4.
46. Trivedi CD, Pitchumoni CS. Drug-induced pancreatitis: an update. J Clin Gastroenterol. 2005;39(8):709–16.
47. Pariente A, Sanctussy DJ, Miremont-Salame G, et al. Factors associated with serious adverse reactions to cholinesterase inhibitors: a study of spontaneous reporting. CNS Drugs. 2010;24(1): 55–63.
48. Becker WC, O'Connor PG. The safety of opioid analgesics in the elderly: new data raise new concerns: comment on "the comparative safety of opioids for nonmalignant pain in older adults". Arch Intern Med. 2010;170(22):1986–8.
49. Cho S, Lau SWJ, Tandon V, et al. Geriatric drug evaluation. Where are we now and where should we be in the future? Arch Intern Med. 2011;171(10):937–40.
50. Hiraishi H, Maeda M, Sasai T, et al. Strategy to manage low dose aspirian-induced gastrointestinal injury. Nippon Rinsho. 2011;69(2):369–75.
51. Laria A, Zoli A, Gremese E, Ferraccioli GF. Proton pump inhibitors in rheumatic diseases; clinical practice, drug interactions, bone fractures and risk of infections. Reumatismo. 2011; 63(1):5–10.
52. Schulman S, Majeed A. A benefit-risk assessment of dabigatran in the prevention of venous thromboembolism in orthopaedic surgery. Drug Saf. 2011;3496:449–63.

Pharmacokinetics of Aging

9

Ryan J. Haumschild

Background

Aging is an important factor in the biotransformation of drugs with respect to their therapeutic efficacy and safety. Changing demographics indicate an aging population with a longer life expectancy. The geriatric age group is the most medicated segment of the population, with the average older person taking three times more drugs compared to the young. Further, 80% of older adults manifest one or more chronic disease states. Significant changes resulting from aging physiology of many systems alter the pharmacokinetics and pharmacodynamics of drugs (Table 9.1).

Alteration in aging physiology is partially contributory to an increase in adverse drug events (ADEs), further compounded by polypharmacy, common in the elderly. In fact, 10% of hospital admissions among older adults relate to drug interactions. Pharmacotherapy is a challenge for providers of health care because of the need to adjust dosage appropriately to account for the age-related changes in older adults [1]. A patient's age is often the strongest predictor of being prescribed a large number of medications due to the increase in comorbidities and decline in overall function [2].

Besides physiological changes, aging is associated with impaired system and organ functions due to disease, leading to susceptibility to adverse effects of drugs. One must differentiate between the "fit" and the "frail" elderly; the frail now represent an older subpopulation in whom multiple disease states, not age, account for pharmacokinetic and pharmacodynamic effects [3]. ADEs are the most common medication-related outcomes in a nursing home setting, with an incidence rate from 1.19 to 7.26 per 100 resident-months, with more than half preventable with surveillance systems to detect and minimize consequences of ADEs. Biomedical informatics can reach the goal of therapeutic medication monitoring to guide dosing in the elderly when there is a narrow therapeutic range and the medication level is not readily predictable from the dosage prescribed [4].

Pharmacokinetics

Pharmacokinetics refers to the absorption, distribution, metabolism, and excretion of drugs in the body [5]. Although the clinical significance continues to evolve, pharmacokinetic changes clearly occur with aging. With age, there is a decline in total body water (females more than males), with a change in the volume of distribution [6]. The relative proportion of lean muscle mass to total body fat is also reduced; the decline in muscle mass (referred to as sarcopenia) is accompanied with an increase in body fat, again more pronounced in females. Fat-soluble drugs tend to accumulate in adipose tissues with chronic dosing. Prolonged effects occur as the elimination of these drugs from fatty tissue is slow and decreased, ultimately leading to potential toxic side effects [7].

All drugs enter the systemic circulation regardless of route of administration, and most irreversibly bind to plasma proteins. The higher fraction of protein-bound drugs exists in a reversible state of equilibrium, with the smaller "free-floating" unbound fraction, called the free fraction. Much of the free-fraction drug is able to cross the blood–brain barrier into the central nervous system and bind to other organs of the body; it is the free-fraction drug that exerts a pharmacological therapeutic effect or causes adverse events. Only the free fraction undergoes metabolism in the liver or clearance through the kidneys. Although albumin levels do not decline solely from age, in the older debilitated or undernourished adult, there may be a decrease in serum albumin with a greater proportion of drug now existing as free fraction. Taking multiple drugs that bind to the same plasma protein may lead to displacement of the protein-bound fraction to result in more adverse events, through higher concentrations of the free fraction [7, p. 16].

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Table 9.1 Pharmacokinetics: age-related changes [3]

Increased	Decreased
Concentration of water-soluble drugs	Water compartment of the body
Fat compartment of the body	Free drug fraction, if albumin levels rise
Volume of lipophilic drugs	Renal function from age or disease
Half-life of lipophilic drugs	Hepatic blood flow and first-pass metabolism

Following administration, a drug is distributed to its site of action where it may have a beneficial or undesired effect. Pharmacodynamics refers to the pharmacological mechanism of action of a drug at its particular targets. This includes therapeutic effects as well as the adverse effects. Various enzymes, transporters, and receptors are psychotropic drug targets that regulate the synthesis, transmission, and degradation of different chemical neurotransmitters in the central nervous system [7]. How a drug affects a patient depends on the net effect of its intended therapeutic use, together with any unintended effect on organ systems in the body. Older patients are more sensitive to the pharmacological effects of medications due to pharmacodynamic changes associated with aging [8].

Absorption

Since aging affects pharmacokinetics and pharmacodynamics, there are implications for the use of psychotropic medications in the elderly. The absorption of orally administered medications may be impaired or delayed, most drugs have an altered volume of distribution, and there may be a gradual accumulation of drug in the fat stores. Some changes have been observed in the gastrointestinal tract with age, but for most drugs absorption by passive diffusion remains unchanged [9]. Presystemic elimination by the intestinal mucosal and the first pass through the liver must be taken into account when evaluating oral bioavailability. Plasma concentrations of highly cleared medications, such as propranolol and labetalol, may be higher as liver mass and hepatic perfusion decline with aging. Yet, there is no difference between young and old patients with other high-clearance drugs, such as verapamil and propafenone [3]. The dosage regimen for the elderly needs to be based on age-related changes in pharmacokinetics [6]. This may be difficult as dosing for safety and efficacy is guided by few clinical trials in the geriatric population.

Age-related pharmacokinetic changes result from reduced renal and hepatic clearance, and prolonged elimination half-life, with increased sensitivity to drug classes such as anticoagulants, psychotropic, and cardiovascular drugs. Most drugs are absorbed from the gastrointestinal tract and pass through the liver. Liver blood flow declines with age causing impaired biotransformation. Advancing age is often associated with a decline in kidney function through diminished renal blood flow, glomerular filtration rate (GFR), and tubular secretion, all influential in drug elimination [10]. Unfortunately, there is no endogenous marker for hepatic clearance that can help guide drug dosing to predict kinetic behavior in liver disease [11].

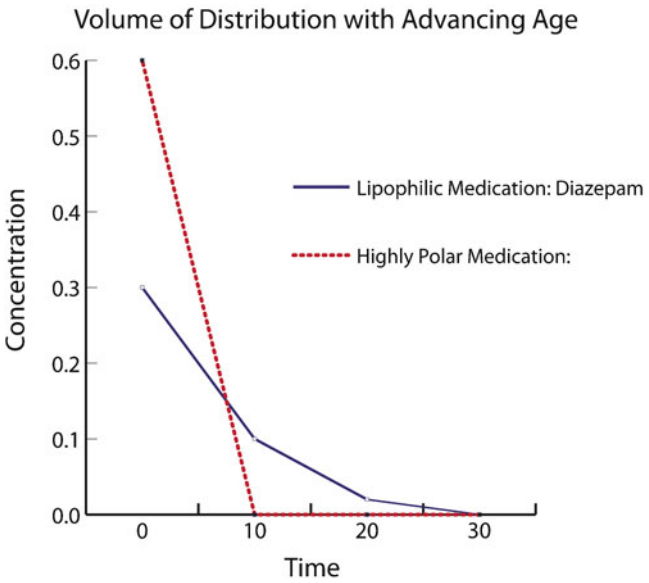

Fig. 9.1 Pharmacokinetics and aging. *Data source*: Klotz [3]

Distribution

As stated earlier, advancing age leads to changes in body composition. With the increase in body fat compared to a decline in muscle mass and a larger decline in total body water, the volume of distribution of highly polar (water soluble) medications such as digoxin and lithium will decrease while that of lipophilic agents (diazepam, lorazepam) will increase with advancing age. Drugs such as warfarin, digoxin, and phenytoin are protein bound, adding complexities to age-related kinetics from protein binding [3] (Fig. 9.1).

Elimination

There is a gradual decline in the number of functioning glomeruli between the age of 30 and 80 years. Based on longitudinal studies, creatinine clearance may even increase in a small subpopulation, remain about the same in a third, and decline by about 1% per year in the rest from the age of around 30 years. The causes for this are complex, with both age and disease components such as hypertension and diabetes

Table 9.2 Hepatic influences on high- and low-extraction drugs [3]

	High-extraction drug			Low-extraction drug		
Scenarios	Clearance	Bioavailability	Half-life	Clearance	Bioavailability	Half-life
Increase in liver blood flow	↑	↑	↓	↔	↔	↔
Decrease in liver enzyme activity	↔	↑	↔	↓	↔	↑

possible. GFR may be approximated from the creatinine clearance using the Cockcroft–Gault formula, or estimated using the "modification of diet in renal disease" (MDRD) equation [12].

Further a measure of GFR in the very old may differ based on the choice of formula used [12]. Based on the high prevalence of chronic kidney disease in older adults, drug dosing in the elderly requires caution, as there is risk for renal injury from ischemia as well as medications with nephrotoxic effects [13]. The principles of drug prescribing apply to drugs used for gastrointestinal or any other illness. Traditionally, the Cockcroft–Gault equation is most often used to estimate creatinine clearance for appropriate dosage adjustments for maintenance doses of renally excreted drugs with a narrow therapeutic window such as aminoglycosides, digoxin, and injectable anticoagulants [14]. As a general rule, evaluation of eGFR is essential before administration of any drug to an older adult [15].

Metabolism

Most medications need to be biotransformed to more polar metabolites by several cytochrome P450 (CYP)-dependent phase I and phase II pathways such as acetylation, glucuronidation, or sulfonation, before their final excretion. Drug metabolism takes place primarily in the liver, although the small bowel may also be a site. Hepatic blood flow and mass generally decline with age; therefore, high-extraction drugs may be affected by these changes (Table 9.2).

Routine liver function tests do not alter with age [3]. Phase 1 hepatic metabolism is reduced and variable in the elderly, with a 30–50% reduction in clearance of drugs through phase I. This is secondary to age-related changes in hepatic blood flow, liver mass, and the hepatic epithelium rather than aging changes in drug-metabolizing enzymes or their expression [16].

There are few if any changes in hepatic microsomal protein content, nor in the activities of CYP450 enzymes with age in the range of 10–85 years, based on in vitro data. In another study the influence of the age of the donor was investigated on various activities (e.g., IA2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4, and 4A11). The age group 20–60 years was compared with the group above 60, and no differences were visible [3, p. 71]. Population pharmacokinetics (POP) can provide PK data from the "real clinical world" as, by its means, drug disposition can be described for populations (including the elderly) in which drugs are actually used [17]. This approach has recently been successfully applied for olanzapine (probe of CYP1A2) and paroxetine (probe of CYP2D6). Based on 1,527 plasma levels from 117 patients with Alzheimer's disease and 406 with schizophrenia, clearance of olanzapine varied from 6.7 to 68.0 L/h in the age range 18–103 years. This demonstrates significant variation in renal clearance from the young to the elderly adult. Smoking status, sex, and race accounted for 26, 12, and 7% of the variability, respectively ($P<0.0001$). However, height, weight, and age had no effect on the clearance of olanzapine [3, p. 72].

Acid-related disorders are common in the elderly [18]. Although as a class proton pump inhibitors (PPIs) are highly effective, differences in their pharmacokinetics, such as bioavailability, elimination, half-life, and metabolism, may translate into different clinical outcomes. Most PPIs have short elimination half-lives. Tenatoprazole has a five- to sevenfold longer half-life, which could be useful for gastroesophageal reflux disease. Omeprazole allows rapid absorption, which may promote better nocturnal gastric acid control compared to delayed-release medications [19].

Omeprazole represents the best probe for CYP2C19 among the widely used PPIs. This PPI was studied in Japanese volunteers who were given a single intravenous dose to examine the effect of aging and the pharmacokinetics of the three CYP2C19 phenotypes, poor metabolizer (PM), intermediate metabolizer (IM), and extensive metabolizer (EM). This resulted in some genotype and age-related differences in drug exposure. The AUC was more pronounced (about twofold) in the elderly EMs and IMs but not in elderly PMs. As a result, when studying the age effects for the CYP2C19 substrates, all subjects have to be differentiated according to their defined genotype, which therefore has more impact than age. CYP2C9 is another polymorphically expressed enzyme that is involved in the metabolism of important drugs such as warfarin, anticonvulsants, or NSAIDs. Whether intestinal metabolism and inducibility of metabolism are affected by aging has not been extensively studied [3]. Various PPIs differ in their pharmacokinetic properties and concomitant intake of food or antacids may alter absorption rates and bioavailability [20]. In one study,

mosapride was found to be effective in older adults with abnormal gastric motility, compared with younger patients with normal gastric motility [21]. In another study, researchers found that mosapride significantly influenced pharmacokinetics and coadministration could have favorable effect in PPI-based therapy [22].

Impact of Aging

Frailty is an emerging syndrome perceived as undesirable and associated with health risks, predisposed by advancing age in combination with physiological decline, loss of muscle and bone mass, and deterioration of functional abilities [23]. Frailty is a confounding factor when considering the impact of aging on drug disposition. Future clinical trials may require a more comprehensive characterization of genetic and biochemical markers in older adults to account for age and other confounding effects on pharmacokinetics, in particular, drug metabolism. In healthy older people, Phase II metabolism appears to be maintained, but reduced with frailty. In the clinical development of any drug, it is important to assess possible deleterious effects, especially on cognitive function in the old, who are sensitive to such effects [24].

ADEs have been increasingly evident over the last decade, and rates of hospital admissions for drug reactions in the elderly have followed. It is becoming clear that age-related altered pharmacokinetics and dynamics contribute to the risk of ADEs, an important consideration when managing various disease states and their appropriate medication therapy [14].

Another area is that of prophylactic prescriptions and drug treatment of chronic diseases, both common over age 65. Geriatric patients receive a disproportionate number of drugs, accounting for 45% of total prescriptions in the UK. While older adults benefit from prophylactic agents, each additional drug brings in the risk of an ADE (e.g., aspirin); prescribers must use knowledge of pharmacology to weigh the conflicting pressures and engage in good prescribing decisions [25].

In the future, we may consider additional factors that influence pharmacokinetics in geriatric populations. The effect of obesity and kinetics of PPIs or H_2 receptor antagonists in GERD or erosive esophagitis will be relevant to determine dosing in overweight older adults; as the severity of GERD is influenced by body mass index, the dose must be individualized for pharmacokinetic profiles and weight [26]. As adults encounter an increase in percentage of body fat with age, their volume of distribution may be even more significant in the older obese individuals. This increase in distribution directly alters the solubility and absorption of medications in the gastrointestinal tract [27]. Individualization to age, body mass index, and specific comorbid processes will be crucial to optimize treatment and improve health outcomes [28].

Key Points

- Aging is an important factor in the biotransformation of drugs with respect to their therapeutic efficacy and safety; additional impaired systems and organ function lead to increased susceptibility to ADEs.
- Pharmacokinetics refer to the absorption, distribution, metabolism, and excretion of drugs in the body, and are altered with age.
- Only the free-fraction drug undergoes metabolism in the liver or clearance through the kidneys. The free fraction may be altered in debilitated or undernourished patients in whom plasma proteins tend to be lower. Higher concentrations of free fraction can lead to more ADEs.
- Age-related pharmacokinetic changes result from reduced renal and hepatic clearance, prolonging the half-life of drugs.
- Altered pharmacodynamics include sensitivity to several drugs such as anticoagulants, psychotropic, and cardiovascular drugs.

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References

1. Wauthier V, Verbeeck RK, Calderon PB. The effect of ageing on cytochrome P450 enzymes: consequences for drug biotransformation in the elderly. Curr Med Chem. 2007;14:745–57.
2. Modig S, Kristensson J, Ekwall AK, et al. Frail elderly patients in primary care—their medication knowledge and beliefs about prescribed medicines. Eur J Clin Pharmacol. 2009;65:151–5.
3. Klotz U. Pharmacokinetics and drug metabolism in the elderly. Drug Metab Rev. 2009;41:67–76.
4. Handler SM, Hanlon JT, Perera S, et al. Consensus list of signals to detect potential adverse drug reactions in nursing homes. J Am Geriatr Soc. 2008;56:805–15.
5. DiPiro JT, Spruill WJ, Wade WE, et al. Concepts in clinical pharmacokinetics. 5th ed. Bethesda: American Society of Health-System Pharmacists; 2010.
6. Rivera R, Antognini J. Perioperative drug therapy in elderly patients. Anesthesiology. 2009;110:1176–81.
7. Howland R. Effects of aging on pharmacokinetic and pharmacodynamic drug processes. J Psychosoc Nurs Ment Health Serv. 2009;47:15–8.
8. Delafuente JC. Pharmacokinetic and pharmacodynamic alternation in the geriatric patient. Consult Pharm. 2008;23:324–34.
9. Sostress C, Gargallo C, Lanas A. Drug-related damage of the ageing gastrointestinal tract. Best Pract Res Clin Gastroenterol. 2009;23:849–60.
10. Rosenthal T, Nussinovitch N. Managing hypertension in the elderly in light of the changes during aging. Blood Press. 2008;17:186–94.
11. Delco F, Tchambaz L, Schlienger R, et al. Dose adjustment in patients with liver disease. Drug Saf. 2005;28:529–45.

12. Carnevale V, Pastore L, Camaioni M, et al. Estimate of renal function in oldest old inpatients by MDRD study equation, Mayo Clinic equation and creatinine clearance. J Nephrol. 2010;23(3): 306–13.
13. Olyaei AJ, Bennett WM. Drug dosing in the elderly patients with chronic kidney disease. Clin Geriatr Med. 2009;25(3):459–527.
14. Hilmer SN. Clinical pharmacology in the geriatric patient. Fundam Clin Pharmacol. 2007;21:217–30.
15. Merle M, Laroche ML, Dantoine T, Charmes JP. Predicting and preventing adverse drug reactions in the very old. Drugs Aging. 2005;22:375–92.
16. Couteur DG. The aging liver. Drug clearance and an oxygen diffusion barrier hypothesis. Clin Pharmacokinet. 1998;34:359–73.
17. Edholm M. Regulatory aspects of pharmacokinetic profiling in special populations: a European perspective. Clin Pharmacokinet. 2008;47:693–701.
18. Ali T, Roberts DN, Tiernay WM. Long-term safety concerns with proton pump inhibitors. Am J Med. 2009;122:896–903.
19. Fock KM, Ang TL, Bee LC, Lee EJ. Proton pump inhibitors: Do differences in pharmacokinetics translate into differences in clinical outcomes? Clinical Pharmacokinet. 2008;47:1–6.
20. Qasim A, O'Morain CA, O'Connor HJ. *Helicobacter pylori* eradication: role of individual therapy constituents and therapy duration. Fundam Clin Pharmacol. 2009;23:43–52.
21. Kamiya T, Adachi H, Hirako M, et al. Impaired gastric motility and its relationship to reflux symptoms in patients with nonerosive gastroesophageal reflux disease. J Gastroenterol. 2009;44:183–9.
22. Arai K, Takeuchi Y, Watanabe H, et al. Prokinetics influence the pharmacokinetics of rabeprazole. Digestion. 2008;78:67–71.
23. Pel-Little RE, Schuurmans MJ, Emmelot-Vonk MH, et al. Frailty: defining and measuring of a concept. J Nutr Health Aging. 2009;13(4):390–4.
24. Patat A, Parks V, Raje S, et al. Safety, tolerability, pharmacokinetics and pharmacodynamics of ascending single and multiple doses of lecozotan in healthy young and elderly subjects. Br J Clin Pharmacol. 2009;67:299–308.
25. Wynne HA, Blagburn J. Drug treatment in an ageing population: practical implications. Maturitas. 2010;66(3):246–50.
26. Scholl S, Dellon E, Shaheen N. Treatment of GERD and proton pump inhibitor use in the elderly: practical approaches and frequently asked questions. Am J Gastroenterol. 2011;106:386–92.
27. Fass R, Johnson D, Orr W, et al. The effect of dexlansoprazole MR on nocturnal heartburn and GERD-related sleep disturbances in patients with symptomatic GERD. Am J Gastroenterol. 2011;106: 421–31.
28. Cho S, Lau S, Tandon V, et al. Geriatric drug evaluation: where are we now and where should we be in the future? Arch Intern Med. 2011;171(10):937–40.

Drug–Nutrient Interactions

10

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Introduction

Drug interactions may be broadly classified into three categories: drug–drug, drug–disease, and drug–nutrient interactions (DNI). Interactions involve pharmacokinetics and pharmacodynamics, resulting in amplification or nullification of the drug or nutrient effect. DNI is defined as an alteration of pharmacokinetic or pharmacodynamic properties of a drug or a nutrient [1], which leads to compromise in nutritional status or complications [2] or treatment failures [3]. Commonly consumed items such as leafy vegetables, ginger, garlic, caffeine, and grapefruit juice (GPJ) have potential for interactions. This review focuses on the burden imposed by DNIs, types of DNIs, responsible factors, special situations such as tube feeding and parenteral nutrition, and their presentation (Table 10.1).

Up to 40–55% of older adults are subjected to polypharmacy (for the purpose of this discussion, refers to five or more medications), providing health providers opportunity for prevention [11, 12]. Elder patient prescriptions exceed 30% of prescribed drugs [12]. Besides polypharmacy, several factors render older adults prone to DNIs: comorbidities, age-related changes in pharmacokinetics and pharmacodynamics, malnutrition, individual variability, and reduced homeostatic reserves with age [12, 13]. With aging, alteration in pharmacokinetics and dynamics result by virtue of differences in body fat (increases), lean body mass (decreases), body water (decreases), and associated decline in renal and hepatic functions [11]. The Joint Commission which accredits hospitals expects every patient to be counseled on potential DNIs at the time of discharge from the hospital [14]. DNIs are common, with the potential for over 300 medications capable of interacting with food [15].

Relevant Aging Changes That may be Contributory

Alterations in oral protective reflexes, thickening of the smooth muscle layer of esophagus, reduced contraction velocity and duration, and decreased enteric plexus neurons [16] may affect esophageal emptying. Gastric emptying is not significantly altered by age, but can be in the presence of disease or through medication effect. Older adults may have varying degrees of acid suppression, either from gastric disease (such as gastric atrophy) or from the use of acid-neutralizing agents. Alterations in gut motility from diseases such as scleroderma or diabetes and decreased splanchnic blood flow (common with age) can alter bioavailability of drugs [17]. Passive intestinal permeability is probably unchanged in older age. Active transport of calcium [18] and vitamin B12 [19] may be impaired [11]. High permeable drugs defined as drugs absorbed immediately, with high dissolution rates, are classified as Class I [highly permeable and highly soluble] according to Biopharmaceutical Classification System [20]. High permeable drugs depend on gastrointestinal blood flow which diminishes with age [11]. Age-related reduction of hepatic blood flow (could be as much as 40%) and hepatocyte mass may contribute to reduced hepatic drug clearance. A decline in hepatic drug clearance and renal function results in increased blood levels of some therapeutic drugs. With aging, there is a decline in phase I hepatic metabolism of drugs, a process dependent on hepatic blood flow, with little change in phase II metabolism. Longitudinal studies suggest a decline in glomerular filtration rate with age of about 1% per year,

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Table 10.1 Categories of drug interactions

Drug–drug interactions
Proton pump inhibitors (PPIs) decrease thyroxine absorption [4]
PPIs may decrease formation of the active metabolite of clopidogrel [5]
Lansoprazole may increase efficacy of warfarin [6]
Angiotensin converting enzyme inhibitors provided with NSAIDs cause hyperkalemia and worsening of hypertension
Warfarin and NSAIDs combination increase likelihood for gastrointestinal bleeding
Synthetic fiber, such as psyllium, decreases the absorption of statins, metformin, and digoxin
Drug–disease interactions
PPIs increase the risk of osteoporosis, hip fracture, and community-acquired pneumonia [7]
Antibiotics increase risk for *Clostridium difficile* associated diarrhea, secretory and inflammatory diarrhea [8]
Phenytoin, ferrous salts, calcium channel blockers, and anticholinergics may cause constipation [8]
Worsening of gastroesophageal reflux disease may occur with bisphosphonates [8]
Long-term heparin and warfarin therapy may cause osteoporosis
Drug–nutrient interactions (DNIs)
PPIs may decrease vitamin B12 absorption [9]
Acid lowering drugs can decrease absorption of calcium, iron, folic acid, and vitamin B12 [10]
Phenytoin increases metabolic breakdown of vitamin D and decreases levels
Cations in milk chelate iron, tetracyclines, and fluoroquinolones, to decrease absorption
Alcohol causes folic acid deficiency through multiple mechanisms

with great variability in individuals; this decline would lead to decreased renal clearance of drugs [21].

In a DNI, a "precipitant agent" causes the interaction and an "object agent" is the one affected; DNIs are of 4 types [1]: Type I, ex vivo bioinactivation, Type II, decreased/increased absorption, Type III, decreased/increased effect, and Type IV, decreased/increased clearance.

Type I—Ex vivo bioinactivation: Here a drug and nutrient interacts chemically or physically altering the bioavailability and absorption of either [1]. Common mechanisms involved are hydrolysis, oxidation, neutralization, and precipitation [22]. This interaction typically occurs with enteral tube feeding. Antacids and tube feeding formulations (TFF) when given together clog the feeding tube [2]. TFF decrease phenytoin absorption by forming protein complexes; TFF decrease warfarin absorption [2]. Fiber (pectin) decreases digoxin, lovastatin, acetaminophen, and penicillin absorption [2]. Zinc, calcium, and magnesium chelate tetracyclines, quinolones, and antacids; iron chelates levodopa; and sucralfate chelates protein components in the diet [2]. Syrups are commonly acidic in pH and when administered with tube feeds, form insoluble complexes [2].

Type II interactions are of three subtypes [22]: Type IIA: precipitant agents alter enzymatic functions, Type IIB: precipitant agents alter transport mechanisms, and Type IIC: complexations, chelation, and/or deactivating process.

Absorption of a nutrient is dependent on the food-calorie content, composition, volume, temperature of diet, amount of fluid ingested, and the fed status [11]. Drugs or nutrients that have the potential to alter gastrointestinal (GI) pH, motility, secretions, flora, and mucosal morphology or function can consequentially be absorbed in higher or lower amounts [2]. Acidic pH facilitates absorption of certain nutrients or drugs such as iron, cyanocobalamin, thiamine, ketoconazole, and isoniazid, while alkaline pH facilitates absorption of ciprofloxacin and omeprazole [2]. Gastrointestinal motility is affected by type and composition of diet, medications, disease processes and surgical interventions. Hyperosmolar diets, such as certain beverages, promote diarrhea through osmotic effects on the mucosa with a negative effect in both nutrient and drug absorption. GI motility affects the rate of absorption rather than the amount of absorption. Bile salts in the GI tract increase absorption of griseofulvin and atovaquone. Mucosal integrity is well known to be altered by nonsteroidal anti-inflammatory drugs (NSAIDs) and aspirin. Black and green teas decrease bioavailability of folates [23]. Calcium-containing foods such as dairy products decrease the bioavailability of ciprofloxacin [24]. Cow's milk contains high levels xanthine oxidase, which can metabolize mercaptopurine, decreasing its bioavailability when given concurrently [25].

Through complex interactions, food increases the bioavailability of several drugs: a partial list includes vitamin D supplements [26], cefuroxime, erythromycin ethylsuccinate, lovastatin, and lithium [22], mefloquine, tacrolimus, itraconazole capsules [27], propranolol, hydrochlorothiazide, and aspirin [17]. Food decreases bioavailability of ampicillin, ciprofloxacin, doxycycline, tetracycline, azithromycin capsules [28], captopril, levothyroxine, indinavir [22], omeprazole, lansoprazole, esomeprazole [29], metformin [17], and etidronate [30]. High-sodium diet decreases lithium absorption; protein in the diet decreases levodopa absorption [17]. Food has no effect on dexlansoprazole [29], udenafil [31], and febuxostat [32] absorption. Metamucil and fiber bind calcium, iron, bile salts, and other drugs, decreasing their bioavailability [33–35].

Type III interactions involve attaining the levels of drug or active metabolite required for action, whereas *Type IV interactions* involve elimination of the drug via hepatic metabolism or renal excretion.

The factors that influence occurrence of DNIs include age, nutritional status, comorbidities, route used for nutrition, composition and calories of diet, the type of drug, and therapeutic index of drug (Table 10.2). High-protein and low-carbohydrate diets decrease, while high-fat diet increases the half-life of theophylline [2]. Drugs that depend on hepatic extraction ratio such as metaprolol, propranolol, and labetalol are dependent on protein and fat in diet; this is because protein and fat increase splanchnic-hepatic blood flow, thereby increasing hepatic extraction ratio, and increased drug bioavailability [2, 36].

Table 10.2 Key factors leading to DNIs [2]

Patient
Age
Nutritional status: obesity and undernutrition
Consumption of herbals or supplements without prescription and health provider awareness
Comorbidity: renal, hepatic or cardiac failure, diabetes mellitus, small intestinal bacterial overgrowth syndromes
Consumption of drug with vehicles other than water
Nutrient
Delivery method of nutrient
Composition of food and state of stomach (fasting or postprandial)
Feeding modality
Feeding tube location: hypertonic or hyperosmolar feeds are better tolerated through gastric feeding versus jejunostomy feeding
Composition of feed: protein (casein) prone to form insoluble complexes in acidic solutions such as syrup
Maintenance protocols, including frequency of tube flushes
Drug
Narrow therapeutic index increases likelihood for DNIs (theophylline, phenytoin, warfarin, digoxin)
Steep dose–response curve: steroids, rifampin, and carbamazepin
Potency, protein binding characteristics: anticoagulants, digoxin, phenytoin

Table 10.3 Nutrient depletion from long-term medication use [10]

Medication or class of medication	Nutrient depleted
Antibiotics	
Penicillins, cephalosporins, macrolides, quinolones, aminoglycosides, tetracyclines.	Vitamins B1, B2, B3, B6, B12, and K; calcium, magnesium, and iron
Neomycin	Vitamins A and B12
Co-trimoxazole	Folic acid
Isoniazid	Vitamins B3, B6, and D
Rifampin, phenytoin	Vitamin D
Antidiabetics	
Metformin	Vitamin B12
Corticosteroids	
Cortisone, dexamethasone	Folic acid
Methylprednisolone	Potassium
Triamcinalone	Zinc, vitamins C and D
Psychotherapeutic drugs	
Tricyclic antidepressants, phenothiazines	Coenzyme Q10 and vitamin B2
Haloperidol	Coenzyme Q10
Anti-inflammatory/analgesics	
Nonsteroidal anti-inflammatory drugs	Iron and folic acid
Salicylates	Iron, folic acid, potassium, sodium, and vitamin C
Cardiovascular drugs	
Angiotensin converting enzyme inhibitors	Zinc
Digoxin	Magnesium, potassium
Chlorthalidone, hydrochlorothiazide	Zinc, potassium, B vitamins
Loop diuretics	Calcium, magnesium, potassium, zinc, vitamins B1, B6
Hydralazine	Vitamin B6 and coenzyme Q10
Anticonvulsants	
Barbiturates	Calcium, folic acid, vitamin D and K
Phenytoin	Calcium, folic acid, vitamins B1, B2, and D
Carbamazepine	Folic acid, and vitamin D
Miscellaneous	
Mineral oil	Calcium, beta-carotene, vitamins A, D, and E
H2 receptor antagonists, PPIs	Calcium, iron, folic acid, zinc, vitamin B12
Cholestyramine, colestipol	Calcium, iron, magnesium, zinc, folic acid, vitamins A, B12, D, E, and K
Sulfasalazine	Folic acid

Corticosteroids influence glucose and protein metabolism; cyclosporine affects lipid metabolism. Antituberculosis drugs are typically used for several months with opportunity for nutrient depletion; isoniazid depletes vitamins B6, B3, and D; rifampin, a powerful CYP inducer, depletes vitamin D by inducing its metabolism through the CYP mechanism; ethambutol depletes zinc and copper [37]. Phenytoin causes vitamin D deficiency by inactivating the vitamin in the liver through CYP 450 induction; chronic use also causes folate deficiency, whereas folic acid supplementation leads to decline in phenytoin levels [1]. High doses of pyridoxine may decrease drug effect; pyridoxine enhances peripheral conversion of levodopa, decreasing its efficiency [38], and increases phenytoin metabolism, leading to subtherapeutic levels [15]. Valproic acid induces carnitine deficiency and may cause encephalopathy [3]. Corticosteroids and salicylates deplete vitamin C levels [15]. Most antibiotics deplete the B vitamins, and may deplete calcium, iron, and magnesium [37]. Table 10.3 provides examples of DNIs leading to nutrient deficiencies [10].

Most drugs are cleared by renal or hepatic metabolism. In older adults, drugs with high hepatic extraction have decreased clearance compared to drugs with low hepatic extraction [21]. Examples of drugs characterized by decreased hepatic clearance include theophylline, amiodarone, cyclosporine, diltiazem, naproxen, warfarin, verapamil, and morphine [21]. Long-term use of loop diuretics as in ascites or heart failure increases excretion of thiamine, riboflavin, pyridoxine, zinc, calcium, magnesium, and potassium, seldom recognized in management [2]. Low-protein diets raise urinary pH; an alkaline urinary pH enhances renal reabsorption of quinidine and allopurinol, but increases excretion of nitrofurantoin. High-protein diets decreases urinary pH, and increase excretion of amitriptylline, an antidepressant associated with side effects. Medications provided as solutions with sorbitol-based elixirs via feeding tubes may cause osmotic diarrhea [39].

Select Common Drug–Nutrient Interactions

Warfarin: Is a drug commonly used in the old and associated with serious adverse drug events (ADEs) because of drug–drug interactions or DNIs; geriatric patients are commonly on warfarin for thromboembolic prophylaxis. DNIs may cause potentiation of drug effect and adverse events, typically bleeding, or a decrease in anticoagulant effect, with higher likelihood for thromboembolism. Warfarin kinetics and dynamics are influenced by several drugs, herbs, and dietary components. Foods with high vitamin K such as cruciferous vegetables, spinach, avocado, asparagus, green teas, canola oil, soy oils, and liver tend to decrease the INR (International Normalized Ratio), while warfarin effect is potentiated by 3G's, garlic, ginger, and ginkgo [40]. Ginseng is reported to blunt warfarin action and increase thrombotic effect [41]. Decrease in plasma levels of warfarin and anticoagulant effect is noted with St. John's wort (SJW). Saw palmetto, a berry extract used for treatment of benign prostatic hyperplasia, potentiates anticoagulant effect of warfarin and bleeding from NSAIDs [42]. Although several studies fail to confirm an interaction between warfarin and cranberry juice, case reports suggest an increase in the INR in those on warfarin ingesting cranberry juice [43–45]. Patients tend to use herbals on their own and do not necessarily inform the doctor; it is essential to counsel patients on warfarin about the potential for DNIs as a safety goal [46]. Patients are allowed to consume green leafy vegetables, but need to keep their dietary habits regular and avoid periodic excesses or major diet alterations [46].

Alcohol: While alcohol is not a drug, at-risk alcohol intake (>7 standard drinks per week or >3 drinks per occasion for women and >14 per week or >4 drinks per occasion) is noted on average 2–3% for women and 9–10% for men aged over 65 years [47]. Excessive alcohol intake leads to malabsorption of several nutrients; for example alcohol decreases folate binding at the enterocyte [48] and possibly interferes with the enterohepatic circulation, causing folic acid deficiency [49]. Alcohol also increases renal excretion of folate and has an overall negative impact on folate status.

Caffeine: Caffeine is a white crystalline xanthine alkaloid that tastes bitter. Per capita consumption in the USA is approximately 300 mg per day per individual, three times the global average [50]. Caffeine amount varies widely from 71 to 220 mg per 150 mL of coffee, 32–42 mg per 150 mL of tea, and 32–70 mg per 330 mL of cola [50, 51]. Caffeine is metabolized by cytochrome P450 system and competitively interacts with substrates. Caffeine intake greater than 300 mg per day increases bone loss by inhibiting osteoblast formation and decreasing vitamin D receptor expression, an observation in lean postmenopausal women [52, 53]. The caffeine induced urinary calcium loss from coffee is not sustained over 24 h and can be somewhat countered by consuming a glass of milk for each serving of coffee ingested [54]. Caffeine potentiates antimigraine medications [55] and decreases efficacy of antiseizure medications [56] and sedatives [57]. Although tea also contains caffeine, its other components such as flavonoids may favorably influence BMD to protect against osteoporosis; the effect of habitual tea drinking on bone density is small as shown in studies and does not significantly alter fracture risk in postmenopausal women [58–60]. Table 10.4 provides caffeine-related interactions.

Table 10.4 Caffeine-related drug interactions [61–63]

Drug/nutrient/disease	Effect of caffeine
Minor	
Aspirin	Increased aspirin levels
Dipyridamole	Decreased effect of dipyridamole
Melatonin	Increased serum concentrations
Cimetidine	Caffeine effects may be increased
Nicotine	Decreased caffeine activity
Diazepam [61]	Decreased serum levels
Grapefruit juice (GPJ)	Increases the effect of caffeine
Moderate	
Adenosine	Decreased efficacy of adenosine
Theophylline	Increased serum concentrations
Atazanavir	Increased serum concentrations
Ciprofloxacin	Caffeine effects may be increased
Lithium	Increased renal lithium excretion
Fluvoxamine [63]	Increased caffeine concentrations
Methotrexate (MTX)	Decreased efficacy of MTX [>180 mg caffeine/day]
High blood pressure [62]	Increase in systemic vascular resistance
Gastroesophageal reflux disease	Caffeine relaxes LES and worsens GERD
Major	
Tizanidine	Increased levels of tizanidine
Peptic ulcer	Caffeine stimulates gastric acid secretion

Smoking: It decreases the levels of caffeine, theophylline, propranolol, heparin, and warfarin [64]. Smoking slows insulin absorption after subcutaneous administration [65], while it increases peak levels and total absorption of inhaled insulin [66]. It also decreases efficacy of inhaled steroids [66], sedatives, and opioid analgesics [65].

Vitamin D: Phenytoin, carbamazepine, levetiracetam, isoniazid, and rifampin increase metabolism of vitamin D and decrease the levels. Valproic acid interferes with hydroxylation of vitamin D in liver, thereby decreasing the effective form of vitamin D level. Calcium channel blockers, cimetidine, and statins decrease endogenous production of vitamin D. Fibrates, mineral oil, cholestyramine, colestipol, and orlistat

decrease absorption of vitamin D. Gabapentin interferes with vitamin D physiology at all levels such as absorption, production, and function; adequate vitamin D status reduces side-effects of gabapentin. On the other hand, vitamin D optimizes the efficacy of NSAIDs. Hydroxychloroquine blocks the formation of active complex of vitamin D. Oral steroids decrease the absorption of vitamin D. Vitamin D amplifies digoxin effects and toxicity by increasing calcium absorption [67].

Vitamin B12: Vitamin B12 is commonly prescribed or consumed by older adults. Although gastric acidity and intrinsic factor are required for vitamin B12 absorption, the literature has conflicting results in demonstrating the influence of a decline in acidity through proton pump inhibitors (PPI) and H2 blockers on B12 absorption and levels [9, 68, 69]. Our studies suggest that H2 receptor blockers had no effect on vitamin B12 status but long-term PPI use for years caused a decline in B12 status [9]. The difference between H2 blockers and PPIs on B12 status may relate to the more potent and prolonged acid suppression achieved by PPIs [9]. However, absorption of crystalline B12 supplements is not affected by gastric acidity [70]. Long-term metformin therapy is now known to affect vitamin B12 status by decreasing uptake of B12 via calcium-dependent ileal cell membrane receptors [71]. This can be overcome with calcium supplementation [71]. Cholestyramine and colchicine can decrease vitamin B12 absorption [10].

Bisphosphonates: Oral bioavailability of most bisphosphonates is very low at 1–5%, being the reason to administer the drug only with water [72–74]. Food decreases the rate of absorption but not the extent of the absorption [75]. Milk, coffee, and orange juice decrease oral bioavailability [74]. Acid suppressants such as H2 receptor blockers increased bioavailability of bisphosphonates [74].

Unique Situations in Geriatrics

Tube feeding: Many elderly in long-term care are dependent on enteral tube feeding and receive medications through the same tube, typically a gastrostomy. Medications need to be administered with at least 30 mL of free water, and the tube must be flushed with free water before and after medication administration to minimize interactions and enhance bioavailability. Immediate release formulations or tablets are pulverized and mixed with free water before administration; they should never be mixed in the bag containing TFF [76]. Liquid formulations are preferred for jejunostomy tubes which are small bored tubes, to minimize occlusion [76]. Enteric coated and extended release formulations will lose bioavailability characteristics if crushed and therefore cannot be administered via enteral tubes [77]. PPIs are best provided with acidic fruit juices via gastrostomy, but with milk or sodium bicarbonate slurry via jejunostomy [78]. Warfarin binds to enteral tubes irreversibly at variable rates, with decline in bioavailability; therefore, concentrated warfarin is administered rapidly with free water flushes before and after the administration [79]. Compatibility of liquid formulations of psychotropic medications is detailed in Table 10.5. DNIs, including enteral feeding recommendations, are listed in Table 10.6.

Table 10.5 Psychotropic liquid formulations and interactions [80]

Medication	Compatible with	Incompatible with
Risperidone	Water, coffee, orange juice, low-fat milk	Cola or tea
Fluphenazine	Tomato juice, milk	Caffeine, tannins, apple juice
Thioridazine	Acidic juices	Water, milk, caffeine, tea
Doxepin	Ensure, TwoCal HN, milk, juices	Carbonated beverages

Table 10.6 Drug-enteral nutrition interaction and recommendations[a] [81]

Acyclovir, valacyclovir (Grade 2C): No medication administration changes required
Aminophylline (Grade 1A): High-protein and carbohydrate-diets decreases absorption
Amiodarone (Grade 2C): No medication administration changes required. Drug is administered with meals, as food increases the rate and amount of absorption
Amoxycillin-clavulanic acid (Grade 2C): No medication administration changes required; fasting decreases the absorption rate
Azithromycin (Grade 2C): For tablet form, no administration changes required
Carbamazepine (Grade 2B): Suspension must be diluted with equal amounts of water; when provided with tube feeding formulations, bioavailability is significantly reduced
Cimetidine and ranitidine (Grade 2B): No administration changes required
Ciprofloxacin (Grade 2B) and levofloxacin (Grade 2C): are not be administered via feeding tubes; food is provided an hour before or 2 h after ciprofloxacin
Clindamycin (Grade 2C): No medication administration changes required
Cyclosporine (Grade 2C): No medication administration changes required
Diazepam (Grade 2B): Solution form not to be given via enteral feeding tubes; tablets preferred
Diltiazem (Grade 2C): No medication administration changes are needed
Fluconazole (Grade 1A): No medication administration changes required
Hydralazine (Grade 2B): No medication administration changes required
Lansoprazole, pantoprzaole, and omeprazole (Grade 2B): Separate from food intake by an hour before and after medication. For tube feeds lansoprazole in granules can be given either with acidic juices (apple or orange) or alkaline solutions (sodium bicarbonate) depending on the diameter of the enteral tube. (For small tubes prefer alkaline, for large, prefer acidic juices)

(continued)

Table 10.6 (continued)

Levothyroxine (Grade 2B): Separate food from drug by an hour before or after administration
Linezolid (Grade 1A): No medication administration requirements
Lorazepam (Grade 2C): No medication administration requirements
Metoprolol (Grade 2C): No medication administration requirements
Metronidazole (Grade 2C): No medication administration requirements
Penicillin V (Grade 2B): must be separated from food intake by an hour before and 2 h
Phenytoin (Grade 2B): must be separated from food intake by an hour before and 2 h
Tacrolimus (Grade 1B): No medication administration requirements
Theophylline (Grade 2B): Separate food from drug by an hour before and after administration
Valproic acid (Grade 2C): No medication administration requirements
Warfarin (Grade 2B): Separate food from medication by an hour before and after administration. Caution with use of ginger, garlic, ginkgo, and soy protein containing formulations

[a]Recommendations may be:
Grade 1A: Strong recommendations with high quality of evidence
Grade 1B: Strong recommendations with moderate quality of evidence
Grade 1C: Strong recommendations with low quality of evidence
Grade 2A: Weak recommendations with high quality of evidence
Grade 2B: Weak recommendations with moderate quality of evidence
Grade 2C: Weak recommendations with low quality of evidence

Table 10.7 Drug incompatibility with parenteral nutrition [82]

Aminoacids and carbohydrates in solution
Penicillins, cefazolin, metoclopromide, midazolam, phenytoin, sodium and potassium phosphate, sodium bicarbonate, cyclosporine, furosemide, cisplatin, cytarabine, methotrexate, doxorubicin, fluorouracil, amphotericin B, acyclovir, gancyclovir, and immune globulins
Aminoacids, carbohydrates and fat emulsions
Ondansetron, erythromycin, haloperidol, lorazepam, midazolam, phenytoin, hydromorphone, morphine (high concentrations), cyclosporine, dopamine, doxorubicin, fluorouracil, acyclovir, gancyclovir, heparin, and immune globulins

Parenteral nutrition and interactions: Although this feeding route is an uncommon mode of nutrition in geriatric patients, it is worthwhile reviewing the compatibility of various medications with parenteral nutritional formulations. Intravenous lipid formulations derived from phytosterols (safflower and soybean oil) contain vitamin K, a factor that lowers the INR of patients on warfarin [78]. Drug compatibility with parenteral nutrition is listed in Table 10.7.

Herbs, Fruits, Vegetables, Supplements and Drug Interactions

Herbs are of plant origin, including any part from root to flowers or seeds. Herbal medications are used by 20–49% of the US population for a variety of reasons. In the USA, herbs are regarded as dietary supplement; they are easily available over the counter, but unlike drugs are not tightly regulated by the FDA with regards to accuracy of ingredients and safety [15, 83]. The most commonly used herbals, based on sales in the USA. are Echinacea, garlic, *Ginkgo biloba*, saw palmetto, ginseng, grape seed extract, green tea, SJW, bilberry, and aloe; systematic reviews suggest few are likely to be effective [84]. Herbs contain potent bioactive substances that may benefit from more stringent regulation, as with prescribed drugs [84]. Table 10.8 lists documented, inconclusive, and anticipated interactions of herbal medicines with food and involvement of the cytochrome isoenzymes in humans [85].

Table 10.8 Level of evidence for interactions of select foods and herbs with CYP system [85]

Well documented
Food: GPJ, pomelo juice, bitter oranges, red wine, white wine
Medicinal herbs: St. John's wort (SJW), herbal teas, goldenseal
Inconclusive evidence
Food: Coffee, garlic, pepper, cranberry juice, tangerine
Medicinal herbs: Ginkgo, ginseng, milk-thistle, saw-palmetto, echinacea, black cohosh, valerian
Anticipated risk of interactions (in-vitro evidence)
Food: Soy protein, pomegranate juice, fish oil
Medicinal herbs: Kava, feverfew, cat's claw, frankincense, dong quai, phellodendron, evening primerose

GPJ is popular, with the USA being the largest supplier and consumer of grapefruit; it provides B and C vitamins, as also potassium and magnesium. GPJ inhibits intestinal cytochrome P450 isoenzymes, 11B-hydroxysteroid dehydrogenase, OATP-A transporter protein, and *P*-glycoprotein efflux transporter protein [86], thereby increasing bioavailability of nicardipine, nimodipine, felodipine [87], cyclosporine [3], diazepam, midazolam, erythromycin, lovastatin, simvastatin, sildenafil, buspirone, tacrolimus [88], atorvastatin, and sertraline [22]. GPJ inhibits OATP-A and B transporters decreasing bioavailability of fexofenadine and aliskiren [89]. Whole grapefruit does not have similar interactions [78]. Interestingly, GPJ does not affect levels of fluvastatin, pravastatin, and rosuvastatin, as they are not metabolized by CYP 3A4 intestinal enzyme. The inhibition does not affect enzymes in the liver. By inhibiting the metabolism of drugs, there is an increase in plasma drug concentration and area under the concentration time curve (AUC). GPJ increases the systemic bioavailability and cardiac repolarization of terfenadine in poor metabolizers of the drug, and does not reduce the oral bioavailability of desloratadine [86]. Patients must not be forbidden from consuming GPJ, which is consumed by nearly half the US population; instead, they are told to consume juice in reasonable amounts maintaining regularity in habits for both the juice and medications [88]. The inhibitory effect on CYP3A4 is reversible, with the GPJ effect lasting approximately 24 h and so medications do not

Table 10.9 Commonly used herbs, dietary supplements and drug interactions [2, 15, 43, 44, 94–100]

Herb	Effect
Ginkgo [101]	Increase in serum concentrations of acetaminophen, diazepam, tramadol, simvastatin, amitriptyline, aspirin, losartan
Kava [94]	Increases effects of anxiolytics and alcohol
Glucosamine [101]	Decreases analgesic effect of acetaminophen
	Potentiates hypoglycemic effect of glyburide
CoenzymeQ10 [101]	Enhances effects of thiazides, fosinopril, metformin, and glipizide.
Olive oil [95]	Increases hypolipidemic action of statins
Echinacea [101]	Increases the drug level of simvastatin, lansoprazole, and losartan
Garlic [101]	Increases effects of simvastatin, warfarin, ibuprofen, and antihypertensive medications
Saw palmetto, flaxseed oil [101]	Increase bleeding complications of aspirin and warfarin
Brussels sprouts and cruciferous vegetables [96]	Increase the metabolic clearance of warfarin
Pummelo juice [98]	Decreases bioavailability of sildenafil by 40%
Green tea, black tea, seaweed (wakame), carotenoids [99]	Potentiate antihypertensive medications
Cranberry juice [43, 44]	Uncertain effect on warfarin and diclofenac
Fish oils and vitamin E [2]	Increase the effects of anticoagulation
Tomatoes, egg plants, potatoes [15]	Delay recovery from anesthesia by inhibiting cholinesterases
Licorice [101]	Decreases the effects of antihypertensives
Soybeans, broccoli, cauliflower [15]	Predispose for hypothyroidism and goiter
Guar gum [15]	Decreases absorption of metformin
Black pepper, piperine [93]	Short term: increases bioavailability of phenytoin, propranolol, theophylline, nevirapine, rifampin, and coenzyme Q10

have to be taken separately from the juice. Those on affected medications may preferably consume less than 250 mL of GPJ daily as larger amounts may inhibit CYP 3A4 intestinal enzyme for 24–72 h. Naringenin, a flavonoid component of citrus juices (grape and orange), interacts with amiodarone, quinidine, dofetilide, thereby increasing risk for arrhythmias [90]. Interestingly, GPJ appears to have no effect on warfarin kinetics, while it does increase the absorption of sildenafil.

SJW is a commonly used herbal supplement; it is a potent inducer of CYP450 enzymes and *P*-glycoprotein leading to interactions with several drugs. SJW decreases the levels of cyclosporine, simvastatin, midazolam, nifedipine, theophylline, warfarin, amitriptyline, HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors, phenytoin, phenobarbitone, warfarin, digoxin, and tacrolimus; it potentiates sumatriptan and selective serotonin re-uptake inhibitors [38, 91, 92]. Piperine, an active ingredient of black pepper may alter the bioavailability of drugs via these mechanisms: inhibiting CYP450 family of enzymes, to increase bioavailability of phenytoin, propranolol, cyclosporine A and digoxin [93]. For other herbals, dietary supplements, and drug interactions see Table 10.9.

The Goal: Minimize Occurrence of DNIs

Minimizing the occurrence of DNIs should be a goal for healthcare providers who care for older adults in any setting. Factors that limit understanding and limit provider efforts include time constraints, shorter hospital stays, inadequate understanding of the vast drug formularies and interactions, and inadequate efforts directed at medication reconciliation and diet history. Nutritionists, nurses, pharmacists, and physicians must utilize multidisciplinary efforts and a coordinated approach to benefit the patients and prevent adverse outcomes. Standard drug administration schedules, education of healthcare providers and involved staff, proper labeling, computerized drug interaction screening and warning software along with patient counseling are helpful in minimizing the occurrence of DNIs [28].

Key Points

- DNIs are common in the geriatric population, predisposed by polypharmacy and age-related physiological changes or diseases.
- Commonly used drugs involved in DNIs include warfarin, phenytoin, bisphosphonates, PPIs, antimicrobials, and cardiac drugs.
- Foods may nullify, potentiate, delay, or accelerate medication effects.
- Long-term medication adverse effects include nutrient depletion, typically vitamins and minerals.
- Garlic, ginger, ginseng, gingko, Echinacea, SJW and saw palmetto, and other herbs may contribute to life-threatening drug interactions.
- Providers need awareness of drug interactions with common dietary items such as GPJ, green leafy vegetables, dairy products, and caffeine in view of their everyday use.

- As a general rule, to minimize DNIs, medications are best administered with water for optimal absorption; water should be adequate in quantity to ensure easy passage through the esophagus.
- Prevention includes a periodic, meticulous medication history in every older adult; the history should undoubtedly include enquiry about herbal and nutritional supplement intake.

References

1. Chan LN. Drug nutrient interactions in clinical nutrition. Curr Opin Clin Nutr Metab Care. 2002;5:327–32.
2. Lourenco R. Enteral feeding: drug/nutrient interaction. Clin Nutr. 2001;20(2):187–93.
3. Chan LN. Drug-nutrient interactions in transplant recipients. J Parenter Enteral Nutr. 2001;25(3):132–41.
4. Ward LS. The difficult patient: drug interactions and the influence of concomitant diseases on the treatment of hypothyroidism. Arq Bras Endocrinol Metabol. 2010;54(5):435–42.
5. Ogawa R, Echizen H. Drug-drug interaction profiles of proton pump inhibitors. Clin Pharmacokinet. 2010;49(8):509–33.
6. Hata M, Hayasaka M, Sezai A, et al. Proton pump inhibitors may increase the risk of delayed bleeding complications after open heart surgery if used concomitantly with warfarin. Thorac Cardiovasc Surg. 2008;56(05):274–7.
7. Johnstone J, Nerenberg K, Loeb M. Meta-analysis: proton pump inhibitor use and the risk of community-acquired pneumonia. Aliment Pharmacol Ther. 2010;31(11):1165–77.
8. Zarowitz BJ. Pharmacologic consideration of commonly used gastrointestinal drugs in the elderly. Gastroenterol Clin North Am. 2009;38(3):547–62.
9. Dharmarajan TS, Kanagala MR, Murakonda P, Lebelt AS, Norkus EP. Do acid-lowering agents affect vitamin B12 status in older adults? J Am Med Dir Assoc. 2008;9(3):162–7.
10. http://www.chiro.org/nutrition/ABSTRACTS/Nutrient_Depletion.shtml. Accessed 3 Jan 2011.
11. McLean AJ. Aging biology and geriatric clinical pharmacology. Pharmacol Rev. 2004;56(2):163–84.
12. McCabe BJ. Prevention of food-drug interactions with special emphasis on older adults. Curr Opin Clin Nutr Metab Care. 2004;7:21–6.
13. Mallet L, Spinewine A, Huang A. The challenge of managing drug interactions in elderly people. Lancet. 2007;370(9582):185–91.
14. Utermohlen V. Nutrient–drug interactions. *Encyclopedia of Food and Culture*. 2003. http://www.encyclopedia.com/doc/1G2-3403400440.html. Accessed 23 Jan 2011.
15. Sorenson JM. Herb-drug, food-drug, nutrient-drug and drug-drug interactions: mechanisms involved and their medical implications. J Altern Complement Med. 2002;8(3):293–308.
16. Dharmarajan TS, Pitchumoni CS, Kokkat AJ. The aging gut. Pract Gastroenterol. 2001;25:15–27.
17. Akamine D, Filho MK, Peres CM. Drug nutrient interactions in elderly people. Curr Opin Clin Nutr Metab Care. 2007;10:304–10.
18. Armbrecht HJ, Boltz MA, Kumar VB. Intestinal plasma membrane calcium pump protein and its induction by 1,25 (OH)2D3 decrease with age. Am J Physiol Gastrointest Liver Physiol. 1999;277:G41–7.
19. Toyoshima M, Inada M, Kameyama M. Effects of aging on intracellular transport of vitamin B12 (B12) in rat enterocytes. J Nutr Sci Vitaminol (Tokyo). 1983;29(1):1–10.
20. Custodio J, Wu C, Benet L. Predicting drug disposition, absorption/elimination/transporter interplay and the role of food on drug absorption. Adv Drug Deliv Rev. 2008;60(6):717–33.
21. Turnheim K. When drug therapy gets old: pharmacokinetics and pharmacodynamics in the elderly. Exp Gerontol. 2003;38(8):843–53.
22. Genser D. Food and drug interaction: consequences for the nutrition/health status. Ann Nutr Metab. 2008;52(1):29–32.
23. Alemdaroglu NC, Dietz U, Wolffram S, Spahn-Langguth H, Langguth P. Influence of green and black tea on folic acid pharmacokinetics in healthy volunteers: potential risk of diminished folic acid bioavailability. Biopharm Drug Dispos. 2008;29(6):335–48.
24. Simon Z. The effect of milk components, especially of casein, on the bioavailability of ciprofloxacin tablets cannot be evaluated by dissolution testing. J Pharm Biomed Anal. 2010;53(3):819.
25. De Lemos ML, Hamata L, Jennings S, Leduc T. Interaction between mercaptopurine and milk. J Oncol Pharm Pract. 2007;13(4):237–40.
26. Mulligan GB, Licata A. Taking vitamin D with the largest meal improves absorption and results in higher serum levels of 25-hydroxyvitamin D. J Bone Miner Res. 2010;25(4):928–30.
27. Schmidt LE, Dalhoff K. Food-drug interactions. Drugs. 2002;62(10):1481–502.
28. Gauthier I, Malone M. Drug-food interactions in hospitalised patients. Methods of prevention. Drug Saf. 1998;18(6):383–93.
29. Lee RD, Vakily M, Mulford D, Wu J, Atkinson SN. Clinical trial: the effect and timing of food on the pharmacokinetics and pharmacodynamics of dexlansoprazole MR, a novel Dual Delayed Release formulation of a proton pump inhibitor–evidence for dosing flexibility. Aliment Pharmacol Ther. 2009;29(8):824–33.
30. Gregory C. Drug and enteral feed interactions. J Hum Nutr Diet. 2006;19(3):237–9.
31. Kim T-E, Kim B-H, Kim J-R, et al. Effect of food on the pharmacokinetics of the oral phosphodiesterase 5 inhibitor udenafil for the treatment of erectile dysfunction. Br J Clin Pharmacol. 2009;68(1):43–6.
32. Khosravan R, Grabowski B, Wu J-T, Joseph-Ridge N, Vernillet L. Effect of food or antacid on pharmacokinetics and pharmacodynamics of febuxostat in healthy subjects. Br J Clin Pharmacol. 2008;65(3):355–63.
33. Fernandez R, Phillips SF. Components of fiber bind iron in vitro. Am J Clin Nutr. 1982;35(1):100–6.
34. Floren CH, Nilsson A. Binding of bile salts to fibre-enriched wheat fibre. Scand J Gastroenterol Suppl. 1987;129:192–9.
35. Heaney RP, Weaver CM. Effect of psyllium on absorption of co-ingested calcium. J Am Geriatr Soc. 1995;43(3):261–3.
36. Lentz KA. Current methods for predicting human food effect. AAPS J. 2008;10(2):282–8.
37. Pelton R, LaValle JB, Hawkins EB, Krinsky DL. Drug-induced nutrient depletion handbook: 1999–2000. Hudson: Lexi-comp; 1999.
38. Mason P. Important drug–nutrient interactions. Proc Nutr Soc. 2010;69(04):551–7.
39. Henley E. Sorbitol-based elixirs, diarrhea and enteral tube feeding. Am Fam Physician. 1997;55(6):2084; 2086.
40. Abad MJ, Bedoya LM, Bermejo P. An update on drug interactions with the herbal medicine Ginkgo biloba. Curr Drug Metab. 2010;11(2):171–81.
41. Bressler R. Herb-drug interactions: interactions between ginseng and prescription medications. Geriatrics. 2005;60(8):16–7.
42. Bressler R. Herb-drug interactions. Interactions between saw palmetto and prescription medications. Geriatrics. 2005;60(11):32; 34.
43. Wittkowsky AK. Dietary supplements, herbs and oral anticoagulants: the nature of the evidence. J Thromb Thrombolysis. 2008;25(1):72–7.

44. Ansell J, McDonough M, Zhao Y, Harmatz JS, Greenblatt DJ. The absence of an interaction between warfarin and cranberry juice: a randomized, double-blind trial. J Clin Pharmacol. 2009;49(7):824–30.
45. Hamann GL, Campbell JD, George CM. Warfarin-cranberry juice interaction. Ann Pharmacother. 2011;45(3):e17.
46. Dharmarajan L, Dharmarajan TS. Prescribing warfarin appropriately to meet Patient Safety Goals. Am Health Drug Benefits. 2008;1(6):26–32.
47. Moore AA, Blow FC, Hoffing M, et al. Primary care-based intervention to reduce at-risk drinking in older adults: a randomized controlled trial. Addiction. 2011;106(1):111–20.
48. Hamid A, Kaur J. Long-term alcohol ingestion alters the folate-binding kinetics in intestinal brush border membrane in experimental alcoholism. Alcohol. 2007;41(6):441–6.
49. Hamid A, Wani NA, Kaur J. New perspectives on folate transport in relation to alcoholism-induced folate malabsorption - association with epigenome stability and cancer development. FEBS J. 2009;276(8):2175–91.
50. Gilbert RM. Caffeine consumption. Prog Clin Biol Res. 1984;158:185–213.
51. Nehlig A. Are we dependent upon coffee and caffeine a review on human and animal data. Neurosci Biobehav Rev. 1999;23:563–76.
52. Rapuri P, Gallagher J, Nawaz Z. Caffeine decreases vitamin D receptor protein expression and 1,25(OH)2D3 stimulated alkaline phosphatase activity in human osteoblast cells. J Steroid Biochem Mol Biol. 2007;103(3–5):368–71.
53. Korpelainen R, Korpelainen J, Heikkinen J, et al. Lifestyle factors are associated with osteoporosis in lean women but not in normal and overweight women: a population-based cohort study of 1222 women. Osteoporos Int. 2003;14(1):34–43.
54. Hallström H, Wolk A, Glynn A, Michaëlsson K. Coffee, tea and caffeine consumption in relation to osteoporotic fracture risk in a cohort of Swedish women. Osteoporos Int. 2006;17(7):1055–64.
55. Eadie MJ. Clinically significant drug interactions with agents specific for migraine attacks. CNS Drugs. 2001;15(2):105–18.
56. Jankiewicz K, Chroscinska-Krawczyk M, Blaszczyk B, Czuczwar SJ. Caffeine and antiepileptic drugs: experimental and clinical data. Przegl Lek. 2007;64(11):965–7.
57. Cysneiros RM, Farkas D, Harmatz JS, von Moltke LL, Greenblatt DJ. Pharmacokinetic and pharmacodynamic interactions between zolpidem and caffeine. Clin Pharmacol Ther. 2007;82(1):54–62.
58. Hegarty VM, May HM, Khaw K. Tea drinking and bone mineral density in older women. Am J Clin Nutr. 2000;71:1003–7.
59. Chen Z. Habitual tea consumption and risk of osteoporosis: a prospective study in the women's health initiative observational cohort. Am J Epidemiol. 2003;158(8):772–81.
60. Devine A, Hodgson JM, Dick IM, Prince RL. Tea drinking is associated with benefits on bone density in older women. Am J Clin Nutr. 2007;86:1243–7.
61. Cooper M, Safran M, Eberhardt M. Caffeine consumption among adults on benzodiazepine therapy: United States 1988–1994. Psychol Rep. 2004;95(1):183–91.
62. Houston MC. Nutrition and nutraceutical supplements in the treatment of hypertension. Expert Rev Cardiovasc Ther. 2010;8(6):821–33.
63. Brosen K. Differences in interactions of SSRIs. Int Clin Psychopharmacol. 1998;13 Suppl 5:S45–7.
64. Nathisuwan S, Dilokthornsakul P, Chaiyakunapruk N, et al. Assessing evidence of interaction between smoking and warfarin: a systematic review and meta-analysis. Chest. 2011;139(5):1130–9.
65. Zevin S, Benowitz NL. Drug interactions with tobacco smoking. An update. Clin Pharmacokinet. 1999;36(6):425–38.
66. Kroon LA. Drug interactions with smoking. Am J Health Syst Pharm. 2007;64(18):1917–21.
67. Vitamin D. 2010. http://www.nlm.nih.gov/medlineplus/druginfo/natural/929.html. Accessed 27 Jan 2011.
68. Dharmarajan TS, Norkus EP. Does long-term PPI use result in vitamin B12 deficiency in elderly individuals? Nat Clin Pract Gastroenterol Hepatol. 2008;5(11):604–5.
69. Ito T, Jensen RT. Association of long-term proton pump inhibitor therapy with bone fractures and effects on absorption of calcium, vitamin B12, iron, and magnesium. Curr Gastroenterol Rep. 2010;12(6):448–57.
70. Stover PJ. Vitamin B12 and older adults. Curr Opin Clin Nutr Metab Care. 2010;13(1):24–7.
71. Liu KW. Metformin-related vitamin B12 deficiency. Age Ageing. 2006;35(2):200–1.
72. Ezra A, Hoffman A, Breuer E, et al. A peptide prodrug approach for improving bisphosphonate oral absorption. J Med Chem. 2000;43:3641–52.
73. Mitchell DY, Eusebio RA, Sacco-Gibson NA. Dose-proportional pharmacokinetics of risedronate on single-dose oral administration to healthy volunteers. J Clin Pharmacol. 2000;40(3):258–65.
74. Gertz BJ, Holland SD, Kline WF. Studies of the oral bioavailability of alendronate. Clin Pharmacol Ther. 1995;58(3):288–98.
75. Umland EM, Boyce EG. Risedronate a new oral bisphosphonate. Clin Ther. 2001;24(5):835–6.
76. Williams NT. Medication administration through enteral feeding tubes. Am J Health Syst Pharm. 2008;65(24):2347–57.
77. Beckwith MC, Feddema SS, Barton RG, Graves C. A guide to drug therapy in patients with enteral feeding tubes: dosage form selection and administration methods. Hosp Pharm. 2004;39(3):225–37.
78. Brown RO, Dickerson RN. Drug nutrient interactions. Am J Manag Care. 2000;5(3):345–55.
79. Klang M, Graham D, McLymont V. Warfarin bioavailability with feeding tubes and enteral formula. J Parenter Enteral Nutr. 2010;34(3):300–4.
80. Muramatsu RS, Litzinger MHJ, Fisher E, Takeshita J. Alternative formulations, delivery methods, and administration options for psychotropic medications in elderly patients with behavioral and psychological symptoms of dementia. Am J Geriatr Pharmacother. 2010;8(2):98–114.
81. Wohlt PD, Zheng L, Gunderson S, et al. Recommendations for the use of medications with continuous enteral nutrition. Am J Health Syst Pharm. 2009;66(16):1458–67.
82. Mirtallo JM. Complications associated with drug and nutrient interactions. J Infus Nurs. 2004;27(1):19–24.
83. Gardiner P, Graham R, Legedza ATR, et al. Factors associated with herbal therapy use by adults in the USA. Altern Ther Health Med. 2007;13:22–9.
84. Bent S. Commonly used herbal medicines in the United States: a review. Am J Med. 2004;116(7):478–85.
85. Nowack R. Cytochrome P450 enzyme, and transport protein mediated herb–drug interactions in renal transplant patients: grapefruit juice, St John's wort—and beyond! (review article). Nephrology. 2008;13(4):337–47.
86. Boobis A, Watelet J-B, Whomsley R, et al. Drug interactions. Drug Metab Rev. 2009;41(3):486–527.
87. Sica D. Interaction of grapefruit juice and calcium channel blockers. Am J Hypertens. 2006;19(7):768–73.
88. Dharmarajan TS, Pitchumoni CS. Drug-nutrient interactions in older adults. Pract Gastroenterol. 2002;26(4):37–55.
89. Tapaninen T, Neuvonen PJ, Niemi M. Grapefruit juice greatly reduces the plasma concentrations of the OATP2B1 and CYP3A4 substrate aliskiren. Clin Pharmacol Ther. 2010;88(3):339–42.

90. Lin C, Ke X, Ranade V, Somberg J. The additive effects of the active component of grapefruit juice (naringenin) and antiarrhythmic drugs on HERG inhibition. Cardiology. 2008; 110(3):145–52.
91. Hammerness P, Basch E, Ulbricht C, et al. St John's wort a systematic review of adverse effects and drug interactions for the consultation psychiatrist. Psychosomatics. 2003;44:271–82.
92. Henderson L, Yue QY, Bergquist C, Gerden B, Arlett P. St John's wort (hypericum perforatum) drug interactions and clinical outcomes. Br J Clin Pharmacol. 2002;54:349–56.
93. Han H-K. The effects of black pepper on the intestinal absorption and hepatic metabolism of drugs. Expert Opin Drug Metab Toxicol. 2011;7(6):721–9.
94. Ernst E. The risk-benefit profile of commonly used herbal therapies: Ginkgo, St. John's wort, ginseng, Echinacea, Saw Palmetto, and Kava. Ann Intern Med. 2002;136:42–53.
95. Sanchez-Muniz FJ, Bastida S, Gutierrez-Garcia O, Carbajal A. Olive oil-diet improves the simvastatin effects with respect to sunflower oil-diet in men with increased cardiovascular risk: a preliminary study. Nutr Hosp. 2009;24(3):333–9.
96. Ovesen L, Lyduch S, Idorn ML. The effect of a diet rich in brussels sprouts on warfarin pharmacokinetics. Eur J Clin Pharmacol. 1988;33:521–3.
97. Deferme S, Mols R, Van Driessche W, Augustijns P. Apricot extract inhibits the P-gp-mediated efflux of talinolol. J Pharm Sci. 2002;91(12):2539–48.
98. Al-Ghazawi MA, Tutunji MS, AbuRuz SM. The effects of pummelo juice on pharmacokinetics of sildenafil in healthy adult male Jordanian volunteers. Eur J Clin Pharmacol. 2010; 66(2):159–63.
99. Houston MC. The role of cellular micronutrient analysis, nutraceuticals, vitamins, antioxidants and minerals in the prevention and treatment of hypertension and cardiovascular disease. Ther Adv Cardiovasc Dis. 2010;4(3):165–83.
100. Pae C, Lim H, Han C, Neena A, Lee C, Patkar A. Selegiline transdermal system: current awareness and promise. Prog Neuropsychopharmacol Biol Psychiatry. 2007;31(6):1153–63.
101. Bush TM, Rayburn KS, HoUoway SW, et al. Adverse interactions between herbal and dietary substances and prescription medications a clinical survey. Altern Ther Health Med. 2007;13(2): 30–5.
102. Vaes LPJ, Chyka PA. Interactions of warfarin with garlic, ginger, ginkgo, or ginseng: nature of the evidence. Ann Pharmacother. 2000;34:1478–82.

Probiotics

11

Martin H. Floch

Introduction

The Food and Agriculture Organization (FAO) of the United Nations defines probiotics as "live microorganisms which, when administered in adequate amounts, confer a health benefit on the host" [1]. This definition does not clearly identify the organisms coming from humans. Most authorities in probiotics do define probiotic microorganisms as human bacteria and most originate from the anaerobic flora. Although important probiotics such as *Escherichia coli* Nissle strain and *Saccharomyces boulardii* are exceptions that do not come from anaerobes, most of the probiotics do belong to the genus *Lactobacillus* or *Bifidobacteria* [2]. Probiotics are organisms that are fed in supplements and are classified as nutritional supplements. They may be fed in foods such as yogurts or in capsules and powders where they are usually freeze-dried. When fed, they become part of the microflora of the gastrointestinal tract. Once in the microflora, they can readily be recovered from the stool [3, 4].

The Microflora in the Human Life Cycle

The microflora of the gastrointestinal tract varies greatly in the life cycle of humans. The tract is sterile before birth, and following a natural childbirth, the flora is initially colonized and becomes complex reflecting the maternal flora [5]. Common lactic acid-producing organisms, usually probiotics from the genus of both *Bifidobacterium* and *Lactobacillus* colonize early after normal childbirth, but when the birth is cesarean, these species are often delayed up to 30 days [5]. In breast-fed infants, *Bifidobacterium* is the primary organism with *Lactobacillus* and *Streptococcus* being minor components [5]. In formula fed infants, *Bacteroides* and *Bifidobacteria* are the major organisms, with minor components of more pathologic species such as *Staphylococcus*, *E. coli*, and *Clostridia* [5]. Once infants and children are fed regular foods, the flora reaches a content as is found in adults where the organisms in the colon are primarily anaerobic and 100–1,000 times more common than the aerobes [6]. There are approximately 500 species and numerous more strains, but the most common still belong to the anaerobic species of *Bacteroides*, *Bifidobacteria*, and *Lactobacilli* [6]. When humans reach maturity, the mouth contains its own rich anaerobic flora. The stomach is relatively sterile due to its high acid output. Growth in the duodenum and proximal jejunum is approximately 10^2 to 10^5 of colony forming units (CFU)/mL content. In the small bowel, the counts increase reaching 10^8–10^{10} in the distal ileum and anywhere from 10^{13} to 10^{14} in the colon. These extremely high counts establish that there are more bacterial cells in the colon than cells within the human body [6, 7].

In the ecosystem of microecology, foods and, hence, culture will affect the content significantly. As demonstrated by Finegold's initial identifications, high fiber, high vegetable foods will result in a dramatically different flora compared to humans eating more protein or animal foods [8]. Most of the data identifying these relationships were collected with standard biochemical delusion techniques. With the new rRNA polymerase identifications, there is a greater ability to identify more genera, but it is still difficult to identify a great number of species [9].

New techniques have found that there are four main families of bacteria: Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria [10]. In addition, it is also now known from several studies through rRNA techniques that a common organism in normal controls is *Faecalibacterium prausnitzii* and that this organism appears decreased in gastrointestinal diseases such as Inflammatory Bowel Disease (IBD) [11]. In adulthood, the microflora appears to be stable in a given individual [8, 12, 13]. Alterations induced by antibiotics, drugs, food binging, or supplements appear temporary,

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and the flora remains stable in a given individual. Investigators have noted that *Bifidobacteria* seem to decline with age, while *Clostridia*, *Lactobacilli*, *Coliforms*, and *Enterococci* tend to increase [12, 14]. Tiihonen et al. studied this subject but concluded that there is no simple marked change in the fecal microbiota composition [12]. He observed that geography plays a role in that the changes vary in different countries as noted in studies from France, Italy, Germany, and Sweden.

Using sophisticated human intestinal tract chip and quantitative PCR of 165 rRNA genes, Biagi et al. found age related differences in the gastrointestinal tract microbiota. Studying adults, elderly, and centenarians, they found that the flora of adults and elderly are similar, but those of centenarians differed significantly [15]. They found a rearrangement in the Firmicutes, an increase in facultative anaerobes, and a marked decrease in *F. prausnitzii*. The conclusions were that aging at the level of centenarians affects the structure of the human gut microbiota. In so doing, it also probably affects the host's immune response system. This is only one observation, yet it was also one using new and sophisticated identification techniques. Future research will have to verify these findings and determine their significance.

Woodmansey also stressed that the colonic microbiota is relatively stable throughout adult life but there are changes in the elderly and recorded a decrease in the number of facultative anaerobes, particularly of the *Bacteroides* group anaerobic *Lactobacilli* and *Bifidobacteria*. These shifts may occur because of diseases of the gastrointestinal tract in the elderly or dietary changes [16]. The exact reasons are uncertain.

Metabolic Effects of Transit Time and Probiotics in the Elderly

A stimulant of colonic motility (e.g., senna) or a deterrent to colonic motility (codeine or loperamide) affects the microflora. When the transit time was increased by the slowing agents, the excreted mass decreased, and the bacterial mass also significantly decreased [17]. Conversely, when the colon motility was stimulated, the transit time decreased, but the fecal excretion increased and the bacteria mass significantly increased. This experiment clearly indicated that the transit time is inversely related to the microflora. Much of the geriatric population has problems with defecation with increasing constipation [18], and it can be assumed there is decreased transit time. With this decreased transit time, there is an associated change in the microflora [17]. With change in the bacterial flora, there is increased protein fermentation with the putrefactive process producing more ammonia and amines [19]. Therefore, it is postulated that constipation, a decrease in fecal mass, and a change in the microflora could result in deleterious metabolic effects which may be corrected by either stimulating the bowel, i.e., introducing prebiotics that would stimulate a beneficial change in the microflora, or adding probiotics that would give the same results [20]. These effects are discussed under treatment of constipation with prebiotics or probiotics.

Since there is a change in the microflora and apparent associated delay in transit time, these observations correlate with the change in the metabolic effects of the flora [16–20]. Metchnikoff in his Noble-Prize-winning thesis postulated that aging was related to increased putrefaction in the gut [21]. In a randomized, double-blind, placebo controlled human dietary study, it was shown that reconstituted skim milk containing *Bifidobacteria lactis* HN019 resulted in an increased number of resident *Bifidobacteria*, reduced the *Enterobacteria* counts as well as increased the *Enterococci* and *Lactobacilli*. The conclusion was that this food could produce desirable changes in the intestinal microflora of the elderly [22]. These results are reinforced by the work of Lahtinen et al. who showed that a fermented oat drink could modulate the *Bifidobacteria* microflora in elderly subjects [23]. They did both quantitative PCR and plate counting after feeding the fermented oat drink that contained *Bifidobacterium longum* 46 and *B. longum* 2C for 6 months. Specifically, the *Bifidobacterium catenulatum*, *Bifidobacterium bifidum*, and *Bifidobacterium breve* were all enhanced [23]. The conclusions were reinforced by the work of Matsumoto et al. who showed that *Bifidobacterium animalis* subspecies *lactis* LKM512 when fed to a hospitalized elderly population resulted in a dramatic increase in the probiotic fed as a yogurt [24]. It should be kept in mind that the positive effects of feeding probiotics in pills or foods to change the microflora in the elderly can be enhanced by the use of prebiotics [25]. Both *oligofructose* and inulin effectively increase the growth of *Bifidobacteria* in the intestine, and their use in conjunction with probiotics is helpful in altering the flora [25].

In a careful study on age of the metabolic characteristics of the fecal microflora in humans, the authors divided 50 subjects into three groups: those averaging 77 years, those averaging 39 years, and 14 children averaging 8 years. They found that all of the metabolic functions were the same in all three groups, but there were significant variations within the elderly group. In the elderly, there were great variations, but, as a whole, they had a higher dextro to levo ratio and higher concentrations of metabolites resulting from protein fermentation such as ammonia, valerate, isobutyrate, and isovalerate. The mean enzymatic activities and the concentrations of the major short chain fatty acids did not differ significantly suggesting that the major metabolic characteristics of the fecal microflora were not greatly altered by the aging process, although there were significant differences in the elderly [26].

Immunity in the Elderly

There is concern that elderly humans have decreased immunity and, hence, are susceptible to increased infections [27]. There is increasing evidence that probiotics and prebiotics can enhance immune function. In a study involving 25 healthy elderly volunteers with a mean age of 69 years, 12 controlled subjects consumed 180 mL of low-fat, low-lactose milk twice daily, while 13 test subjects consumed the same milk product but with *B. lactis* (HN019) added in significant amounts. Interferon production and polymorphonuclear cell phagocytic activities were measured and increased in those taking the probiotics supplemented milk [28]. In a study performed in New Zealand, 30 healthy elderly volunteers with a mean age of 69 years participated in a three-stage dietary supplemented trial lasting 9 weeks. Milk supplemented with *B. lactis* HN019 clearly was able to increase levels of CD4 helper cells and activate CD25 T lymphocytes. They concluded that *B. lactis* HN019 is an effective probiotic to enhance some aspects of cellular immunity in the elderly [29]. Ouwehand et al. reported on a 6-month study of 55 institutionalized elderly subjects. They performed a complex double blind, placebo-controlled study and concluded that modulation of the fecal *Bifidobacteria* may produce a means of influencing inflammatory responses. They showed that *Bifidobacteria* (characterized by genus-and species-specific PCR) negative correlations were observed between the levels of *Bifidobacteria* species and the proinflammatory cytokine TNF-α and the regulatory cytokine IL-10. The presence of fecal *B. longum* and *Bifidobacterium animalis* correlated with reduced serum IL-10. The anti-inflammatory TGF-β1 levels were increased over time in all three groups, and the presence of *B. breve* correlated with higher serum TGF-β1 levels [30]. This points out the importance of strains having a specific effect as the various strains of *Bifidobacteria* do have different effects on the immune response.

In two different vaccination studies, a fermented dairy drink proved to be effective. Two randomized multicenter, double-blind, controlled studies were conducted during two vaccinated seasons in 2005–2006 and again in 2006–2007. Eighty-six subjects were in the first pilot study, and 222 elderly volunteers in the second study. The fermented dairy drink contained the probiotic strain *Lactobacillus casei* DN-114001 and yogurt ferments (Actamel®). A nonfermented controlled dairy product was used for the control group. In the pilot study, the influenza specific antibody titers increased after vaccination, being consistently higher in the probiotic group as compared to the control group. In the robust confirmatory study with a larger number of patients, there were significant differences in seroconversion between the groups, noticed 5 months after vaccination. These two studies indicated that the probiotic product increased relevant specific antibody responses to influenza vaccination in elderly subjects [31]. Using the same product, another group reported on a multicentric, double-blind, controlled study involving 1,072 volunteers with a median age of 76 years that were randomized for consumption of the product or a control product without the *L. casei* DN-11400, the same organism that was used by Boge et al. [31]. They administered the probiotic drink for 3 months and followed the patients for an additional month, and found an increase in *L. casei* species in stools throughout the period of consumption. Clinically they noted that considering all common infectious diseases of the airways and the gastrointestinal tract, those taking the fermented products had a significantly reduced average duration per episode of infection and the cumulative duration of infections. They concluded that the fermented product was safe, well tolerated and its consumption was associated with decreased duration of infection in comparison with the control group, but the incidence of infection was the same [32].

In a randomized controlled trial studying *Candida* oral infections using *Lactobacillus rhamnosus* GG, *L. rhamnosus* LC705, and *Propionibacterium freudenreichii*, the group that had the probiotic cheese had significantly lower counts of oral *Candida* [33]. This is only one study, yet it involved 304 patients and indicates that other studies are warranted. Although this is a limited literature with great variations, it does indicate that the immune response in the elderly is different and is affected by the administration of probiotics. Much more research and larger studies are needed to indicate which specific strains are most effective and for specific diseases.

Diarrhea in the Elderly

The causes of diarrhea are clearly delineated for most adults and are the same for the elderly [34]. The Yale University Workshops on Recommendations for Probiotic Use were outlined in 2008 [35]. Treatments of most diarrhea due to gastroenteritis are standard [34], and the recommendations for the use of probiotics in selective incidences are outlined [35]. These studies have largely been successful in children but also have been done in adults. The literature is less robust for adults and does not exist for elderly. Nevertheless, since probiotics have relatively no risk, they may be used early and can be helpful in institutions where they may cut down the time of incapacitating diarrhea [35]. It also should be pointed out that studies employing a probiotic in nursing homes have resulted in normalizing bowel movements in the elderly. When *Bifidobacteria* are used according to one study, either the *longum* strain or BB12 strain has regulated bowel movements when they have been associated with either diarrhea or constipation [36].

In antibiotic-associated diarrhea (AAD) not due to *Clostridium difficile*, it is recommended that a probiotic may be started at the onset of the diarrhea. The literature reveals that *Lactobacillus* GG, *S. boulardii*, or a combination as outlined in the references maybe helpful and shorten the period of infectious diarrhea [35].

In elderly subjects in whom *C. difficile* diarrhea is more common, the usual treatment is embarked upon. On average a third of these will relapse and may become resistant. In these cases, both *S. boulardii* and *Lactobacillus* GG have been helpful in the treatment as adjuvant therapy and in many reports also helpful in prevention. Since the risk of *C. difficile* is greatest in the elderly in the hospital or in an ICU, it behooves the clinician to consider using one of these probiotics to prevent the onset of life-threatening *C. difficile* diarrhea [35].

All of the recommendations for the use of probiotics in conditions causing diarrhea are the same for subjects that have either diarrhea or constipation. The study reported from a geriatric institution in Helsinki reveals either *B. longum* or *B. lactis* BB12 help regulate the bowel pattern. This was effective for both the nursing home residences that had diarrhea or constipation. It was a robust study and the statistics were meaningful. The fermented oat drink was fed daily and well tolerated by the home residents [36].

Constipation and the Irritable Bowel Syndrome in Elderly Patients

Constipation is defined in the literature as less than three bowel movements per weeks, but it is also usually associated with hard stools. According to the Rome II criteria, it is considered a functional disorder. When it is without associated abdominal pain, it is a functional disorder, but when it is characterized as associated with abdominal pain or bloating it then falls into the category of the Irritable Bowel Syndrome (IBS) [37]. The incidence of constipation or IBS in the elderly is difficult to evaluate. Some studies have it as high as 15%, others as high as 20%, and nursing home evaluations are as high as 25–30% [38, 39].

The cause of constipation in the elderly is certainly multifactorial. Not only are they the group with dysmotility and an inertia of the bowel (see explanation under metabolic effects) [37, 40], but there are also those that suffer from comorbidities requiring medications whose adverse effect is constipation [37]. Probiotics can be helpful in the treatment of constipation and IBS in the elderly.

Within the elderly nursing home patients it is important in constipation to first make the necessary dietary changes. This may be difficult depending on the support services. However, it is clear that dietary changes do help regulate the bowel pattern. Substances that are considered both prebiotics as well as dietary fiber should be included in these dietary changes. The elderly should be encouraged to have a normal intake of fruits, vegetables, and grains as tolerated. This is often difficult but can be accomplished in nursing home settings or where food is purchased for the old or where the elderly can purchase their own food. However, when there is difficulty, supplements can be helpful. Guar, which can be obtained in drinks or powder (Benefiber®), or inulin, which can be prescribed and obtained as a medication, will help increase the number of bowel movements and help regulate bowel pattern [3]. When the dietary approach is not successful and constipation persists, probiotics have been shown to be helpful as reported in the study using *Bifidobacteria* supplements [36].

When abdominal pain occurs with constipation, consideration should be given to treat the patient as an individual with IBS. In a robust study *Bifidobacteria infantis* was helpful when administered in a dose of at least 10^8. Although the study was not specific for older adults, probiotics may be used in this age group [41]. Although the industry may report benefits in this regard from probiotics, there is inadequate data to support the claims. The literature does exist on the use of food supplements such as yogurts and drinks to regulate the bowel pattern. One study has shown that *B. animalis* may be helpful [42], and another suggests that *Lactobacillus plantarum* holds promise [43, 44]. Nevertheless, these products hold promise and may be tried following the same treatment as used in the referenced articles. Furthermore, there has been some work done with VSL#3 in adults and in children that hold promise but there is no selective work in the elderly. Probiotics may hold promise since it is employed in many clinical situations [45, 46].

Although the data is limited on the use of probiotics in the elderly, there is enough to indicate there is a dysbiosis in some elderly and that probiotics may be helpful in selective clinical situations (see Table 11.1). It must be stressed that these recommendations include using the strain used in the quoted references in Table 11.1.

Key Points

- There is a change in the microflora in the elderly, with significant alterations found in centenarians.
- The immune process is supported by the addition of probiotics.
- Probiotic therapy promotes nonimmunologic gut defense barrier by normalization of increased intestinal permeability and alerted gut microbiology.
- Probiotics can help alleviate intestinal inflammation, normalize gut mucosal dysfunction and downregulate hypersensitivity reactions.
- Regulation of bowel movements may be helped by probiotics in the older adult.

Table 11.1 Probiotic use in health

Conditions	Probiotic	Products	References
Acute diarrhea	*Lactobacillus* GG	Culturelle	[35]
	Saccharomyces boulardii	Florastor	
Antibiotic-associated diarrhea (AAD) and *Clostridium difficile* prevention and recurrence	*Lactobacillus acidophilus* CL1285 plus *Lactobacillus casei* Lbc80r	BioK+CL1285 (fermented milk, capsule)	[47, 48]
	L. casei DN-114001 (Immunitas)	DanActive (fermented milk)	[49]
	Multiple *Lactobacilli*	DanActive (fermented milk)	[47]
	Lactobacillus rhamnosus GG (LGG)	Culturelle (capsule), Danimals (drinkable yogurt)	[35]
	Streptococcus cerevisiae (S. boulardii)	Florastor (powder)	[35]
Support immunity	*Bifidobacterium lactis* BB12	Yo-Plus (yogurt)	[24]
	B. lactis HN019	Ingredient for dairy and supplement products	[22, 28, 29]
	L. casei DN-114001 (Immunitas)	DanActive (fermented milk)	[31, 32]
	L. casei Shirota	Yakult (daily dose drink)	[48]
	Lactobacillus reuteri ATCC 55730	BioGaia Chewable Gut Health Tablets and Probiotic Straws	[50]
	LGG	Culturelle (capsule), Danimals (drinkable yogurt)	[35]
Constipation	*Bifidobacterium longum*	Fermented Drink (only reported from Finland)	[36]
	B. lactis BB12		
Irritable bowel syndrome (IBS)	*Bifidobacterium infantis* 35624	Align	[41]
	VSL#3	VSL #3	[45, 46]
	Lactobacillus plantarum		[43, 44]

References

1. Floch MH. Introduction. In: Floch MH, Kim AS, editors. Probiotics: a clinical guide. Thorofare: Slack; 2010. p. xix.
2. Montrose D, Floch MH. Probiotics used in human studies. J Clin Gastroenterol. 2005;39:469–84.
3. Floch MH. Prebiotics, probiotics and dietary fiber. In: Buchman AL, editor. Clinical nutrition in gastrointestinal disease. Thorofare: Slack; 2006. p. 123–39.
4. Collins MD, Gibson GR. Probiotics, prebiotics, and synbiotics: approaches for modulating the microbial ecology of the gut. Am J Clin Nutr. 1999;69:1052S–7.
5. Claud EC, Walker WA. Bacterial colonization, probiotics, and necrotizing enterocolitis. J Clin Gastroenterol. 2008;42:S46–52.
6. Simon GL, Gorbach SL. Intestinal flora in health and disease. Gastroenterology. 1984;86:174–93.
7. Neish AS. Microbes in gastrointestinal health and disease. Gastroenterology. 2009;136:65–80.
8. Finegold SM, Attebery HR, Sutter VL. Effect of diet on human fecal flora: comparison of Japanese and American diets. Am J Clin Nutr. 1974;27:1456–69.
9. Carroll IM, Ringel-Kulka T, Ringel Y. Quantification and identification of probiotic organisms in humans. In: Floch MH, Kim AS, editors. Probiotics: a clinical guide. Thorofare: Slack; 2010. p. 55–70.
10. Ojetti V, Gigante G, Ainora ME, et al. Microflora imbalance and gastrointestinal diseases. Dig Liver Dis. 2009;2 Suppl 3:35–9.
11. Sokol H, Seksik P, Furet JP, et al. Low counts of *Faecalibacterium prausnitzii* in colitis microbiota. Inflamm Bowel Dis. 2009;15:1183–9.
12. Tiihonen K, Ouwehand AC, Rautonen N. Human intestinal microbiota and healthy ageing. Ageing Res Rev. 2010;9:107–16.
13. Moore WC, Holdeman LV. Human fecal flora: the normal flora of 20 Japanese-Hawaiians. Appl Microbiol. 1974;27:961–79.
14. Mitsuoka T. *Bifidobacteria* and their role in human health. J Ind Microbiol. 1990;6:263–7.
15. Biagi E, Nylund L, Candela M, et al. Through ageing, and beyond: gut microbiota and inflammatory status in seniors and centenarians. PLoS One. 2010;5(5):e10667.
16. Woodmansey EJ. Intestinal bacteria and ageing. J Appl Microbiol. 2007;102:1178–86.
17. Stephen AM, Wiggins HS, Cummings JH. Effect of changing transit time on colonic microbial metabolism in man. Gut. 1987;28:601–9.
18. Murray FE, Bliss CM. Geriatric constipation: a brief update on a common problem. Geriatrics. 1991;46:64–8.
19. Macfarlane GT, Cummings JH, Macfarlane S, Gibson GR. Influence of retention time on degradation of pancreatic enzymes by human colonic bacteria grown in a 3-stage continuous culture system. J Appl Bacteriol. 1989;67:520–7.
20. Hamilton-Miller J. Probiotics and prebiotics in the elderly. Postgrad Med J. 2004;80:447–51.
21. Metchnikoff E. The prolongation of life. Optimistic studies. London: Butterworth-Heinemann; 1907.
22. Ahmed M, Prasad J, Gill H, et al. Impact of consumption of different levels of *Bifidobacterium lactis* HN019 on the intestinal microflora of elderly human subjects. J Nutr Health Aging. 2007;11:26–31.
23. Lahtinen SJ, Tammela L, Korpela J, et al. Probiotics modulate the *Bifidobacterium* microbiota of elderly nursing home residents. Age (Dordr). 2009;31:59–66.
24. Matsumoto M, Sakamoto M, Benno Y. Dynamics of fecal microbiota in hospitalized elderly fed probiotic LKM512 yogurt. Microbiol Immunol. 2009;53:421–32.
25. Gibson GR. Dietary modulation of the human gut microflora using the prebiotics *oligofructose* and inulin. J Nutr. 1999;129:1438S–41.
26. Andrieux C, Membre JM, Cayuela C, Antoine JM. Metabolic characteristics of the faecal microflora in humans from three age groups. Scand J Gastroenterol. 2002;37:792–8.

27. Goodwin JS. Decreased immunity and increased morbidity in the elderly. Nutr Rev. 1995;53:S41–51.
28. Arunachalam K, Gill HS, Chandra RK. Enhancement of natural immune function by dietary consumption of *Bifidobacterium lactis* (HN019). Eur J Clin Nutr. 2000;54:263–7.
29. Gill HS, Rutherfurd KJ, Cross ML, Gopal PK. Enhancement of immunity in the elderly by dietary supplementation with the probiotic *Bifidobacterium lactis* HN019. Am J Clin Nutr. 2001;74: 833–9.
30. Ouwehand AC, Bergsma N, Parhiala R, et al. *Bifidobacterium* microbiota and parameters of immune function in elderly subjects. FEMS Immunol Med Microbiol. 2008;53:18–25.
31. Boge T, Remigy M, Vaudaine S, et al. A probiotic fermented dairy drink improves antibody response to influenza vaccination in the elderly in two randomized controlled trials. Vaccine. 2009;27:5677–84.
32. Guillemard E, Tondu F, Lacoin F, Schrezenmeir J. Consumption of a fermented dairy product containing the probiotic *Lactobacillus casei* DN-114001 reduces the duration of respiratory infections in the elderly in a randomized controlled trial. Br J Nutr. 2010;103:58–68.
33. Hatakka K, Ahola AJ, Yli-Knuuttila H, et al. Probiotics reduce the prevalence of oral *Candida* in the elderly-a randomized controlled trial. J Dent Res. 2007;86:125–30.
34. Floch MH. Diarrhea. In: Floch MH, editor. Netter's gastroenterology. 2nd ed. Philadelphia: Saunders Elsevier; 2010. p. 286–8.
35. Floch MH, Walker WA, Guandalini S, et al. Recommendations for probiotic use-2008. J Clin Gastroenterol. 2008;42(3 Suppl):S104–8.
36. Pitkala KH, Strandberg TE, Finne Soveri UH, et al. Fermented cereal with specific *Bifidobacteria* normalizes bowel movements in elderly nursing home residents. A randomized, controlled trial. J Nutr Health Aging. 2007;11:305–11.
37. Floch MH. Irritable bowel syndrome and functional gastrointestinal disorders, and constipation. In: Floch MH, editor. Netter's gastroenterology. 2nd ed. Philadelphia: Saunders Elsevier; 2010. p. 277–9, 360–2.
38. Choung RS, Locke GR, Schleck CD, et al. Cumulative incidence of chronic constipation: a population-based study 1988–2003. Aliment Pharmacol Ther. 2007;26:1521–8.
39. McCrea GL, Miaskowski C, Stotts NA, et al. Pathophysiology of constipation in the older adult. World J Gastroenterol. 2008;14: 2631–8.
40. Bharucha AE, Wald A, Erick P, Rao S. Functional anorectal disorders. Gastroenterology. 2006;130:1510–8.
41. O'Mahoney L, McCarthy J, Kelly P, et al. *Lactobacillus* and *Bifidobacterium* in irritable bowel syndrome: symptom responses and relationship to cytokine profiles. Gastroenterology. 2005;128: 541–51.
42. Guyonnet D, Chassany O, Ducrotte P, et al. Effect of a fermented milk containing *Bifidobacterium animalis* DN-173 010 on the health-related quality of life and symptoms in irritable bowel syndrome in adults in primary care: a multicentre, randomized, double-blind, controlled trial. Aliment Pharmacol Ther. 2007;26:475–86.
43. Niedzielin K, Kordecki H, Birkenfield B. A controlled, double-blind, randomized study on the efficacy of *Lactobacillus plantarum* 299V in patients with irritable bowel syndrome. Eur J Gastroenterol Hepatol. 2001;13:1143–7.
44. Nobaek S, Johansson M-L, Molin G, et al. Alteration of intestinal microflora is associated with reduction in abdominal bloating and pain in patients with irritable bowel syndrome. Am J Gastroenterol. 2000;95:1231–8.
45. Kim HJ, Camilleri M, McKinzie S, et al. A randomized controlled trial of a probiotic, VSL#3, on gut transit and symptoms in diarrhoea-predominant irritable bowel syndrome. Aliment Pharmacol Ther. 2003;17:895–904.
46. Guarditini S, Magazzu G, Chiaro A, et al. VSL#3 improves symptoms in children with irritable bowel syndrome: a multicenter, randomized, placebo-controlled, double-blind, crossover study. J Pediatr Gastroenterol Nutr. 2010;51:24–30.
47. Beausoleil M, Fortier N, Guenette S, et al. Effect of a fermented milk combining *Lactobacillus acidophilus* LC 1285 and *Lactobacillus casei* in the prevention of antibiotic-associated diarrhea. A randomized, double-blind, placebo-controlled trial. Can J Gastroenterol. 2007;21:732–6.
48. Takeda K, Okumura K. Effects of a fermented milk drink containing *Lactobacillus casei* strain Shirota on the human NK-cell activity. J Nutr. 2007;137:791S–3.
49. Hickson M, D'Souza AL, Muthu N, et al. Use of probiotic *Lactobacillus* preparation to prevent diarrhoea associated with antibiotics: randomized double blind placebo controlled trial. BMJ. 2007;335:80.
50. Gao XW, Mubasher M, Fang CY, et al. Dose-response efficacy of a proprietary probiotic formula of *Lactobacillus acidophilus* CL1285 and *Lactobacillus casei* LBC80R for antibiotic-associated diarrhea and *Clostridium difficile*-associated diarrhea prophylaxis in adult patients. Am J Gastroenterol. 2010;105(7):1636–41.

Part IV

Nutrition

Geriatric Nutritional Assessment

12

Kumar Dharmarajan and Kenneth L. Minaker

The historical focus of geriatric nutrition has been on identifying and treating undernutrition, a common and highly morbid condition in older populations. Almost 20% of older adults in the US consume less than 1,000 kcal/day and 50% do not meet requirements for vitamin and mineral intake [1, 2]. These individuals are more likely to experience functional decline, morbidity, and mortality [3–6]. Reassuringly, both prevention and treatment of undernutrition in older persons are possible [7–9].

This chapter begins by highlighting the epidemiology and consequences of undernutrition among elders in diverse settings including the community, hospital, and skilled nursing facilities (SNFs). They are followed by a description of the unique causes of undernutrition in older adults and validated strategies for the ascertainment of nutritional status. Specific attention is paid to the topic of decision-making in the elderly. The final section discusses an issue of increasing importance in the Western world, that of overnutrition and obesity in older adults. Nutrition related to the intake of water, electrolytes, fiber, and specific vitamins, minerals, and trace elements are discussed in subsequent chapters.

Epidemiology of Undernutrition in Older Persons

Among community dwelling elderly, 10% of men and 20% of women have intakes of protein below the US Recommended Daily Allowance (RDA) of 0.8 g/kg, and one-third consume fewer calories than the RDA [2]. Vitamin deficiency is also common, especially for water-soluble vitamins that lack large body stores [10, 11]. These deficiencies increase with age, especially in populations at higher risk, such as those who are institutionalized [12]. Undernutrition also becomes increasingly prevalent in the months prior to hospitalization [13].

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Inadequate nutritional intake often continues throughout the hospital admission and subsequent postacute care [14]. In a study of general medicine patients, almost one-third became malnourished when hospitalized. These patients were more likely to have baseline cognitive and functional impairments [15]. Hypothesized reasons for iatrogenic malnutrition within the hospital include poor recognition and monitoring of nutritional status as well as forced periods of inadequate nutritional intake [16–18]. Triceps skinfold thickness and mid-arm circumference often decrease even in those not predicted to be at high nutritional risk on hospital admission [19]. Nutritional parameters are often suboptimal in the over one million elderly residing in skilled nursing facilities. Up to 90% of older persons newly admitted to a SNF following hospitalization are undernourished or at high risk of developing nutritional deficiencies [20]. Similarly, undernutrition is prevalent in over 50% of older persons newly admitted for long-term care [21]. Indices of protein-energy nutrition including body weight, mid-arm muscle circumference, and visceral protein levels have been found to be low in the majority of nursing home patients [22, 23].

Adverse Effects of Undernutrition in Older Persons

Undernutrition has been convincingly shown to be associated with adverse health outcomes in diverse populations of older persons. In community dwelling elderly, a body mass index (BMI) less than 22 has been associated with excess risk of 1-year mortality as well as impaired functional status; mortality increases linearly with reductions in BMI [6, 24]. Additional hazard has also been found in older persons who lose weight [25]. For example, community dwelling women with some baseline disability are prone to a twofold increase in adjusted lower extremity disability with weight loss in excess of 5% of body weight [5]. This relationship between weight loss and both disability and death is especially pronounced among frail older patients who are already homebound [26].

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Similarly, older patients who are undernourished experience both in-hospital and posthospital complications at a higher rate. Older patients with a BMI less than 20 are more likely to die while in the hospital; those who survive to discharge are more likely to die in the following year [27]. These relationships hold true despite adjustment for illness severity and functional status and are also seen in seriously ill patients admitted to the intensive care unit [28, 29]. Undernourished older adults are also more likely to experience serious in-hospital complications [30]. Studies of albumin and other biomarkers also demonstrate clear links with both in-hospital and postdischarge mortality [31, 32].

Data from older persons in SNFs are consistent with those from both community dwelling and hospitalized elderly. Patients in SNFs for short-term rehabilitation are more likely to have serious complications if they have a low BMI or have experienced significant weight loss in the preceding year [33]. Those of very low weight in this short stay group are more likely to die at 5 years [34]. In residents of long-term care, including those with advanced dementia, a 5% loss of body weight in 1 month or 10% loss in 6 months are both associated with increased short-term mortality [35, 36].

A particular concern pertinent to frail elderly in both hospitals and SNFs is that of skin breakdown. Undernutrition has been associated with this complication in both settings. Among elderly inpatients, those with undernutrition defined using an index of biochemical and anthropometric variables were twice as likely to develop a pressure ulcer [37]. Similarly, those newly admitted to long-term care who were most severely undernourished were much more likely to develop skin breakdown [38]. Given that most trials of nutritional intervention to treat pressure ulcers have been disappointing, successful strategies regarding skin breakdown must emphasize prevention [39].

Etiologic Factors of Undernutrition in Older Adults

Older persons are predisposed to undernutrition, as there is an almost universal decrease in caloric intake with aging without a concomitant decrease in nutritional requirements [40]. A number of physiologic changes may contribute to this state including reduction in taste, salivation, and smell with aging, as well as earlier satiety from a combination of factors including hormonal changes, reductions in gastric emptying times, and possible increased sensitivity to gastric distention [41–44]. However, the key change may be that of dysregulation; older persons are less capable of reducing food intake after a period of overfeeding and are less able to increase intake after a period of underfeeding [45]. This predisposition to undernutrition may also be a response to the reduction in total energy expenditure that occurs with aging due to reductions in both resting metabolic rate and physical energy expenditure [46, 47].

Table 12.1 "Malnourished," a mnemonic for causes of weight loss in older persons

*M*edications, malignancy, malabsorption
*A*lcohol (substance) abuse, appetite changes
*L*ack of resources
*N*eglect, normal aging (physiologic changes)
*O*ral health and dysphagia
*U*remia (metabolic abnormalities)
*R*estricted diets
*I*nfection, inflammation, immobility
*S*ocial factors, sarcopenia
*H*yperthyroidism, HIV/AIDS
*E*lder abuse
*D*ementia, depression, drug effects

In addition to these physiologic changes that accompany aging, older persons experience a number of pathologic conditions that place them at further risk of undernutrition. These conditions are often present simultaneously and can be summarized using the mnemonic, "Malnourished" (Table 12.1) [48]. Several of these etiologic factors are of importance in older persons because of their high prevalence; they include polypharmacy, dementia and cognitive impairment, depression, oral health problems, and social factors.

Polypharmacy is frequent in older persons and places them at increased risk of adverse drug events not only due to cumulative drug exposure, but also due to aging changes that impact both pharmacokinetics and pharmacodynamics. Within this context, certain drugs are well known to impact nutritional intake and absorption. For example, acetylcholinesterase inhibitors, digoxin, angiotensin-converting enzyme inhibitors, anti-depressants, neuroleptics, and metformin can cause nausea, anorexia, or dysguesia, as can calcium channel blockers, opioids, anti-cholinergics, diuretics, certain antacids, and calcium itself by inducing constipation. Proton pump inhibitors, histamine receptor antagonists, bile acid sequestrants, and laxatives can impair nutrient absorption through effects on gastric pH, direct binding of micronutrients, and promotion of rapid intestinal transit [49].

Dementia is a common geriatric syndrome that often results in nutritional impairment regardless of underlying cause. Those with mild-to-moderate dementia may become undernourished as they withdraw from friends and family who provide assistance with meal planning and grocery shopping. As memory further declines, cooking and feeding become impaired and disorganized, leading to nutritionally inadequate meals [49]. In contrast with SNFs that are subject to numerous federal regulations designed to improve feeding and nutrition among the cognitively impaired, assisted living facilities may not adequately address these needs. This concern will become more important, as assisted living is becoming an increasingly popular residential environment, even among those with significant functional and cognitive impairments [50, 51]. With advanced dementia, loss of weight is one of

the features used to consider hospice referral. Patients at end-of-life may have little or no desire to eat. Neuromuscular impairments in the swallowing mechanism commonly lead to dysphagia, recurrent aspiration, and pneumonia. Unfortunately, despite the natural instinct to feed these individuals via artificial enteral methods, mortality, morbidity, and functional status fail to improve with tube feeding [52].

As with the young, depression is common in the elderly, but may present atypically as multiple somatic complaints, cognitive impairment, or weight loss [53]. It is perhaps the most common cause of reversible weight loss in older persons [54]. Depression increases the release of hypothalamic corticotrophin-releasing factor, a potent anorectic agent. In addition, depression often impairs the motivation to obtain, prepare, and consume nutritionally adequate food [49]. Therefore, every older adult with weight loss should be screened for depression. Ideally, a validated screening tool for depression in older patients such as the Geriatric Depression Scale (GDS short form) should be used [55].

Oral health is an important but often neglected area by physicians; poor oral health can limit food intake by older persons [56]. Pain and burning from dental caries, oral candidiasis, and denture stomatitis can cause discomfort with eating. Edentulous states and weakness of the masticatory muscles are common with aging and impair the ability to chew nutrient dense foods including meat and vegetables [57]. Nearly 25% of individuals over 65 are completely edentulous [58]. Even mild reductions in salivary flow due to medication use or disease can impair taste or alter the oral antimicrobial environment with resultant increases in dental caries and oral candidiasis [59].

Ultimately, social support plays a critical role in the prevention of malnutrition among those who are most frail and functionally impaired, who often rely heavily, if not exclusively, on others for nutritional support [60]. Help may be needed with transportation to and from the grocery store, meal preparation, feeding, and cleaning up afterwards. Financial support may be needed to purchase food in the first place. Social factors and caregiving resources should always be explored while determining the etiologies of undernutrition and opportunities for remediation.

Assessment of Nutritional Status in Older Persons

A careful history of body weight should be obtained from all older patients. As described earlier, weight loss in excess of 5% in 1 month or 10% in the previous 6 months should be considered an indicator of a serious nutritional problem unless weight fluctuations are intentional or ascribed to changes in fluid balance [61]. In contrast to simple history and weight measurement, alternative screening approaches tend to be more cumbersome or nonspecific. For example, anthropomorphic testing including skinfold and arm circumference measurements require specialized equipment and training to be performed in a reliable manner. Similarly, biochemical markers such as serum albumin, prealbumin, transferrin, and lipids are more difficult to interpret with advancing age, as the effects of natural aging, chronic disease, and acute illness become harder to disentangle. While albumin, prealbumin, and transferrin do not change with healthy aging, all are negative acute phase reactants that decline after just 8 h of bed rest [62, 63].

A separate but important task is the identification of those at risk for nutritional impairment. A number of validated screening tools have been created for community, inpatient, and nursing facility settings. For the outpatient setting, one can use the Simplified Nutritional Appetite Questionnaire (SNAQ), a short four-item scale that can be administered by nonmedical personnel (Table 12.2) [64].

Table 12.2 Simplified Nutritional Appetite Questionnaire (SNAQ)

Name: _____
Sex (circle): Male Female
Age: _____ Weight: _____
Height: _____
Date: _____
Administration Instructions: Ask the subject to complete the questionnaire by circling the correct answers and then tally the results based upon the following numerical scale: a = 1, b = 2, c = 3, d = 4, e = 5. The sum of the scores for the individual items constitutes the SNAQ score. SNAQ score ≤14 indicates significant risk of at least 5% weight loss within six months
1. My appetite is a. very poor b. poor c. average d. good e. very good
2. When I eat a. I feel full after eating only a few mouthfuls b. I feel full after eating about a third of a meal c. I feel full after eating over half a meal d. I feel full after eating most of the meal e. I hardly ever feel full
3. Food tastes a. very bad b. bad c. average d. good e. very good
4. Normally, I eat a. less than one meal a day b. one meal a day c. two meals a day d. three meals a day e. more than three meals a day

Reproduced with permission from [64]

The SNAQ recognizes that impaired appetite often precedes and is a key component of weight loss. It identifies older persons with reduced appetite and prospectively predicts those who will have greater than 5 or 10% weight loss in the next 6 months. This tool has also been validated in nursing home residents.

For both inpatient and long-term care settings, one can use the Mini Nutritional Assessment (MNA), a screening tool with dietary questions, global assessment questions for domains including functional and cognitive status, and anthropomorphic measures (Fig. 12.1) [65–67]. The tool was initially tested and validated in long-term care populations where it was compared to a battery of anthropomorphical and biochemical indices including calf and mid-arm circumferences, triceps and scapular skinfolds, total energy intake, acute phase reactants including albumin, prealbumin, and transferrin, and serum levels of multiple vitamins, minerals, and trace elements. Correlations were favorable. Additional cross-validation studies of hospitalized patients have shown that approximately 75% of older adults are correctly classified as either adequately nourished (MNA score ≥ 24) or undernourished (MNA score < 17) without use of additional biochemical data. Those in the intermediate zone (MNA score of 17–23.5) are considered at risk for malnutrition and may benefit from further case by case analysis [4, 68]. The main drawback to the MNA is that it is fairly time-consuming to administer and requires some anthropomorphic testing.

The long-term care setting also uses a number of "automatic" triggers for in-depth nutritional assessment and intervention. These include familiar items such as involuntary weight loss of greater than 5% in 30 days or 10% in 180 days, as well as others including leaving behind more than 25% of food in the past 7 days or a BMI less than or equal to 19. These parameters were included in the 1987 Omnibus Budget Reconciliation Act (OBRA) that provided markedly increased regulation and oversight of SNFs [69].

Management of Undernutrition in Older Adults

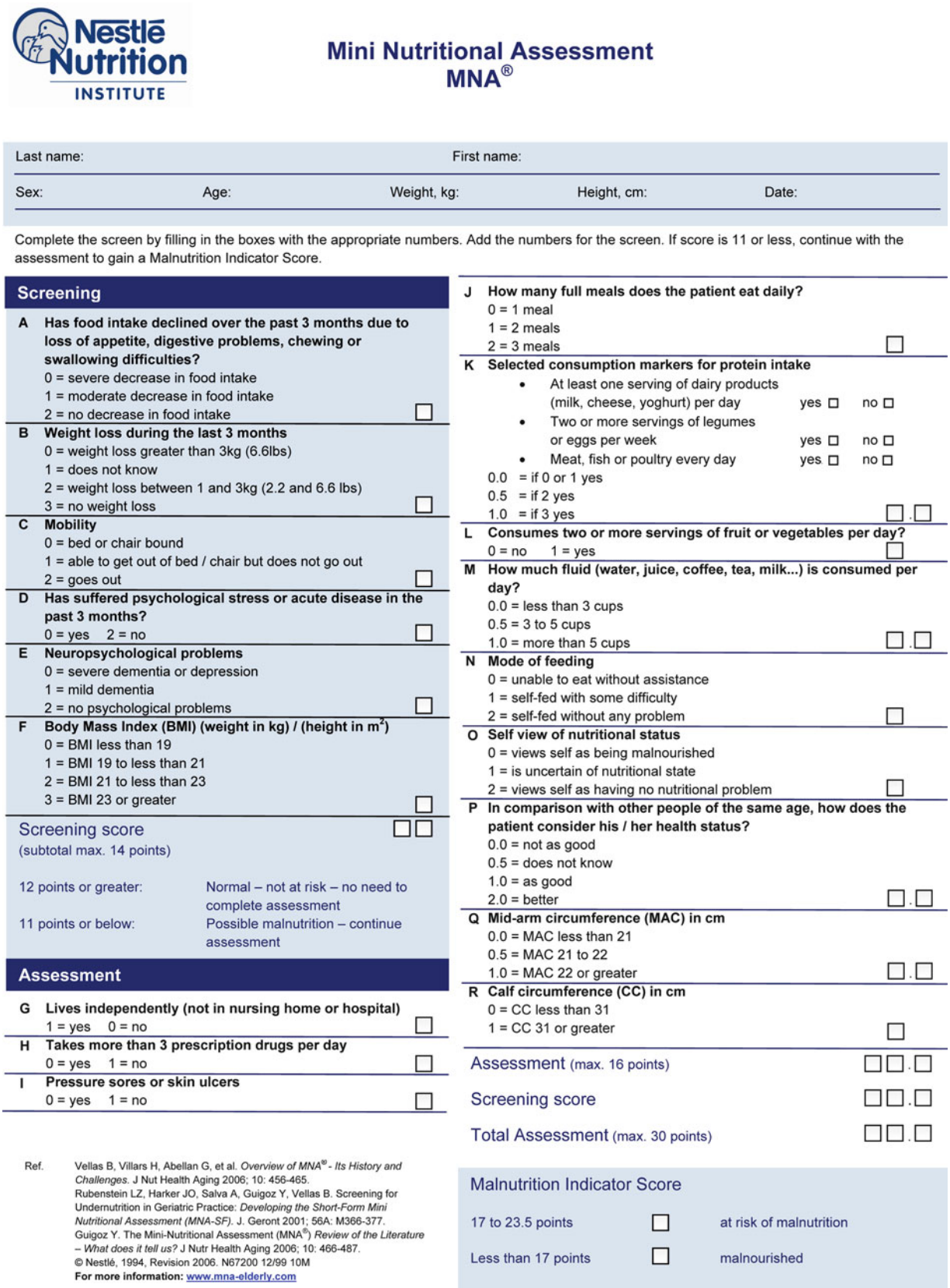
Once the diagnosis of undernutrition has been made, the critical issue becomes its management. Importantly, none of the screening tools above provide clear guidance as to who will and will not respond to nutritional intervention. Treatment outcomes can be predicted with greater accuracy by grouping causes of undernutrition and weight loss into three categories: starvation, sarcopenia, and cachexia. The starvation phenotype occurs when an older person takes in insufficient nutrition and calories to maintain weight due to lack of access to food, inability to consume adequate calories because of mechanical limitations, or inability to absorb ingested nutrients. These include many etiologies including polypharmacy, oral disease, and lack of social support to overcome functional, cognitive, and psychiatric impairments. Treatment addresses rectification of the underlying cause and nutritional supplementation.

In contrast, both sarcopenia and cachexia are significantly more resistant to nutritional intervention. Sarcopenia is defined as the loss of muscle mass, quality, and function that accompanies advancing age. It is technically defined as a lean body mass more than two standard deviations below the young normal mean. Overall, approximately 13% of 60-year-olds and 50% of 80-year-olds have this condition [70]. Both resistance exercise and spontaneous physical activity are the critical components of management, not nutritional intervention [71].

Cachexia involves significant loss of both muscle and adipose tissue. It is usually associated with anorexia and a number of chronic illnesses including cancer, AIDS, tuberculosis, chronic kidney disease, advanced heart failure, severe obstructive pulmonary disease, and rheumatologic conditions. Almost universal is the presence of proinflammatory cytokines, increased metabolic rate, and up-regulation of the ubiquitin-proteasome system leading to muscle atrophy [72, 73]. Unfortunately, without amelioration of the underlying cause, supplemental nutritional intervention rarely, if ever, yields significant benefits.

Therefore, the most fruitful interventions will be those that increase food intake in persons with a starvation phenotype. In addition to addressing the underlying cause of the nutritional deficit, the practitioner should always encourage common-sense nonpharmacologic methods to increase eating. These include meeting food preferences, avoiding diets that are overly restricted for salt, cholesterol, saturated fat, or glucose, ensuring proper serving temperature, providing favorite high-calorie foods, altering food consistency if needed, and providing intermeal snacks [74–76]. Dieticians may aid greatly in these efforts [77]. In addition, residents with dementia in SNFs may benefit from having their family members help with mealtime assistance and feeding [78]. Facilities should provide food in well-lit, well-decorated, unhurried, and "appetizing" environments [79]. Food intake has been shown to increase in the presence of company, emphasizing the importance of social factors. Ambient music may be helpful in this setting [80].

There may be a role for oral nutritional supplements. A recent meta-analysis showed that these supplements can cause a small but significant gain in weight across all care settings including the home, hospital, and SNF. Unfortunately, mortality reductions were only demonstrated in the most undernourished inpatients, not in those residing in the community or nursing home [8]. Similarly, there have been no consistently demonstrated improvements in either functional status or cognition with supplementation [81]. However, given its impacts on weight gain, oral nutritional supplementation including use of a therapeutic multivitamin is a reasonable measure. The following table describes commonly used oral preparations. All are lactose-free (Table 12.3).



Nestlé Nutrition INSTITUTE

Mini Nutritional Assessment MNA®

Last name: First name:

Sex: Age: Weight, kg: Height, cm: Date:

Complete the screen by filling in the boxes with the appropriate numbers. Add the numbers for the screen. If score is 11 or less, continue with the assessment to gain a Malnutrition Indicator Score.

Screening

A Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?
0 = severe decrease in food intake
1 = moderate decrease in food intake
2 = no decrease in food intake ☐

B Weight loss during the last 3 months
0 = weight loss greater than 3kg (6.6lbs)
1 = does not know
2 = weight loss between 1 and 3kg (2.2 and 6.6 lbs)
3 = no weight loss ☐

C Mobility
0 = bed or chair bound
1 = able to get out of bed / chair but does not go out
2 = goes out ☐

D Has suffered psychological stress or acute disease in the past 3 months?
0 = yes 2 = no ☐

E Neuropsychological problems
0 = severe dementia or depression
1 = mild dementia
2 = no psychological problems ☐

F Body Mass Index (BMI) (weight in kg) / (height in m^2)
0 = BMI less than 19
1 = BMI 19 to less than 21
2 = BMI 21 to less than 23
3 = BMI 23 or greater ☐

Screening score ☐☐
(subtotal max. 14 points)

12 points or greater: Normal – not at risk – no need to complete assessment
11 points or below: Possible malnutrition – continue assessment

Assessment

G Lives independently (not in nursing home or hospital)
1 = yes 0 = no ☐

H Takes more than 3 prescription drugs per day
0 = yes 1 = no ☐

I Pressure sores or skin ulcers
0 = yes 1 = no ☐

J How many full meals does the patient eat daily?
0 = 1 meal
1 = 2 meals
2 = 3 meals ☐

K Selected consumption markers for protein intake
- At least one serving of dairy products (milk, cheese, yoghurt) per day yes ☐ no ☐
- Two or more servings of legumes or eggs per week yes ☐ no ☐
- Meat, fish or poultry every day yes ☐ no ☐

0.0 = if 0 or 1 yes
0.5 = if 2 yes
1.0 = if 3 yes ☐.☐

L Consumes two or more servings of fruit or vegetables per day?
0 = no 1 = yes ☐

M How much fluid (water, juice, coffee, tea, milk...) is consumed per day?
0.0 = less than 3 cups
0.5 = 3 to 5 cups
1.0 = more than 5 cups ☐.☐

N Mode of feeding
0 = unable to eat without assistance
1 = self-fed with some difficulty
2 = self-fed without any problem ☐

O Self view of nutritional status
0 = views self as being malnourished
1 = is uncertain of nutritional state
2 = views self as having no nutritional problem ☐

P In comparison with other people of the same age, how does the patient consider his / her health status?
0.0 = not as good
0.5 = does not know
1.0 = as good
2.0 = better ☐.☐

Q Mid-arm circumference (MAC) in cm
0.0 = MAC less than 21
0.5 = MAC 21 to 22
1.0 = MAC 22 or greater ☐.☐

R Calf circumference (CC) in cm
0 = CC less than 31
1 = CC 31 or greater ☐

Assessment (max. 16 points) ☐☐.☐

Screening score ☐☐.☐

Total Assessment (max. 30 points) ☐☐.☐

Malnutrition Indicator Score

17 to 23.5 points ☐ at risk of malnutrition

Less than 17 points ☐ malnourished

Ref. Vellas B, Villars H, Abellan G, et al. *Overview of MNA® - Its History and Challenges.* J Nut Health Aging 2006; 10: 456-465.
Rubenstein LZ, Harker JO, Salva A, Guigoz Y, Vellas B. Screening for Undernutrition in Geriatric Practice: *Developing the Short-Form Mini Nutritional Assessment (MNA-SF).* J. Geront 2001; 56A: M366-377.
Guigoz Y. The Mini-Nutritional Assessment (MNA®) *Review of the Literature – What does it tell us?* J Nutr Health Aging 2006; 10: 466-487.

For more information: www.mna-elderly.com

Fig. 12.1 Mini Nutritional Assessment (MNA) (reprinted with permission from Nestle Nutrition Institute)

Table 12.3 Examples[a] of lactose-free and gluten-free oral nutritional supplements with *nutrients per serving*

Product	Flavor	kcals/ml	mOsm/ kg water	Protein (g)	Carbohydrates (g)	Fat (g)	Na (mg)	K (mg)	Fiber (g)	Free Water (%)
Boost	*V, Ch, S	1.0	625	10	41	4	130	400	0	85
Boost glucose control	*V, Ch, S	1.06	400	14	20	12	260	260	3.5	85
Boost Hi Protein	*V	1.0	650	15	33	6	170	380	0	85
Boost Pudding	*V, Ch, B	240/5 oz		7	33	9	125	250	0	62
Carnation Instant Breakfast	*V, Ch	1.0	480(V) 490(C)	8.75	33.1	9.2	220	312		85
Diabeti Source AC	uniflavor	1.2	450	15	25.2	14.7	265	430	3.8	82
Fiber Source HN	uniflavor	1.2	490	13.4	39.3	9.84	300	500	2.5	81
Nepro	*V, BP, MB	1.8	559	19.1	39.4	22.7	250	250	3.7	68
Ensure	*V, Ch, S, Co, BP	1.06	590	9	40	6	200	370	0	80
Ensure Fiber	*V, Ch	1.06	500	8.8	42	6.1	200	370	2.8	78
Ensure Hi Protein	*V, Ch, WB	0.97	610	12	31	6	290	500	0	81
Ensure Plus	*V, Ch, S BP, S, Co	1.5	680	13	50	11	220	420	3	72
Ensure Pudding	*V, Ch, B	170/4 oz		4	30	5	3.7	110	3	
Glucerna	*V, U	1.0	355	9.9	22.3	12.0	220	370	3.4	80

**V* vanilla; *Ch* chocolate; *S* strawberry; *B* butterscotch; *BP* butter pecan; *U* unflavored; *Co* coffee; *MB* mixed berry; *WB* wild berry

[a]Source of information: Abbot Nutrition Pocket Guide 2009; Nestle Nutrition Health Care Products 2010

Whenever possible, supplements should be provided between meals, rather than with them, in order to prevent compensatory reductions in mealtime food intake.

In contrast, orexigenic drugs have not been consistently shown to have significant benefits in older persons, in whom they have been relatively poorly studied. The best data showing drug benefit come from trials of younger persons with cachexia due to the acquired immunodeficiency syndrome or cancer [82, 83]. Even here, weight gain was not universally associated with improved quality of life, functional status, or mortality. Fat mass was gained preferentially to muscle. If use of an orexigenic agent is planned, megestrol acetate is the most common agent of choice. Megestrol acetate has been trialed in long-term care settings and is more effective than another commonly used orexigenic agent, dronabinol, when used in cancer cachexia [9]. Combination therapy was no better than megestrol acetate alone [84]. Potential side effects of megestrol use include fluid retention, glucose intolerance, and venous thromboembolism.

Whenever nutritional intervention is considered for older patients, it is important to consider the degree of malnutrition and its potential reversibility before suggesting aggressive measures. One should realize that the starvation phenotype is more amenable to nutritional treatment than are sarcopenia and causes of cachexia like chronic cardiopulmonary disease, infection, and cancer. Whenever possible, projected illness course should be discussed with patients and caretakers, and advance directives should be in place to guide treatment decisions. Patient preferences regarding long-term enteral and parenteral feeding are particularly important, as these have not been validated to prolong life, improve functional status, decrease pressure ulcers, or increase quality of life. In contrast, careful mouth feeding for comfort can be a reasonable and beneficial strategy even in the context of known aspiration and end-stage dementia. Ultimately, whatever approach is chosen, it is imperative that physicians enlarge the circle of support by involving caregivers in both monitoring and treatment plans.

Overnutrition Among Older Persons

Increasingly, older persons are becoming overweight and obese, the consequences of which include worsening mobility-related disability and loss of independence, reduced quality of life, metabolic disease including glucose intolerance and hyperlipidemia, hypertension, and common geriatric conditions such as urinary incontinence, osteoarthritis, and lower extremity pain [85–91]. These outcomes often correlate better with markers of visceral fat mass such as waist circumference and waist-to-hip ratio than they do with simple BMI [92, 93]. For example, a waist-to-hip ratio greater than 0.83 in women and 0.9 in men has been associated with a threefold increased risk of myocardial infarction [94].

However, the impact of overweight and obesity on mortality among older persons is less pronounced than in younger populations. A meta-analysis found that a BMI of 25–27 is not associated with increased cardiovascular or all-cause mortality in the elderly. Although the higher relative risk for all-cause mortality of a BMI > 28 was noted in this older age group, the additional relative harm was significantly less than in overweight young and middle-aged people [95]. A similar analysis of overweight and obese patients in Germany (age 18–74 years) showed that the excess mortality associated with obesity declined with age and that the lowest mortality risk was observed in patients aged 50–74 years with BMIs of 25–32 [96]. Thus, although standardized mortality rates may increase with increasing BMI, the additional harm decreases with age. This may be because those with higher weight tend to have increased bone mineral density and lean mass, both of which may be protective during periods of acute illness and increased catabolic stress [97].

Given these findings, it is reasonable to recommend weight loss in older persons with metabolic or musculoskeletal morbidities caused or worsened by obesity. Epidemiologic studies suggest that those most likely to benefit from weight loss are those who have gained significant weight from early adulthood or mid life [98]. Ascertainment of prior weights can therefore be of great help in predicting the benefits of weight reduction.

In the majority of cases, the approach to weight loss should rely primarily on increased endurance and resistive training. Endurance training can increase fatty acid oxidation, improve insulin sensitivity, and attenuate the age-related decline in total energy expenditure [99]. Resistance training can improve skeletal muscle function and lower visceral fat [100, 101]. Studies have demonstrated that in self-selected older adults, these physical activities can improve physical performance, functional status, and self-reported quality of life [102]. In contrast, extreme diets such as marked caloric restriction have not been well studied in older adults and should not be routinely recommended as they can worsen sarcopenia and both micro and macronutrient deficiencies. However, recommendation that older persons consume diets low in saturated fat and cholesterol, high in fiber including fresh fruits and vegetables, high in plant proteins, and plentiful in vitamins, minerals, and trace elements is almost always prudent.

Both DASH (Dietary Approaches to Stop Hypertension) and Mediterranean diets are nutritionally rich and calorically efficient options that incorporate these elements and have strong evidence in their favor. The DASH diet was initially studied in the DASH trial. The research demonstrated that a daily diet comprised of four to five servings of fruit, four to five servings of vegetables, two to three servings of low-fat dairy products, mostly plant-based protein including legumes and nuts, and less than 25% of total calories from fat, resulted in a significant decline in blood pressure within 2 weeks [7]. Follow-up studies have shown that a similar diet also reduced

low-density lipoprotein levels and deleterious cardiovascular endpoints [103, 104]. Additional salt restriction to 1.2 g/day provided further benefit in blood pressure reduction [105].

A "Mediterranean diet" has significant overlap with the DASH diet and is also a reasonable starting point. Although there is no single Mediterranean diet, these diets are typically high in fruits, vegetables, whole grains, legumes, and nuts, and predominantly use a monounsaturated oil like olive oil as a source of fat. Fish, poultry, and dairy products are eaten in preference to red meats. As in studies of the DASH diet, trials of Mediterranean diets have typically found improved cardiovascular health in diet adherents [106, 107]. In addition to promoting a balanced diet rich in micro and macronutrients, both Mediterranean and DASH diets typically entail less calorie and saturated fat intake than in the typical Western diet. As a result, these diets can be the cornerstone of healthy eating practices to both prevent incident undernutrition and the development of obesity [108]. Recent dietary recommendations from the United States Department of Agriculture (USDA) similarly endorse the value of substantial fruit and vegetable intake in conjunction with whole grains and lean sources of protein including legumes, seafood high in omega-3 fatty acids, and low-fat dairy products. These guidelines can be found on the USDA website at http://www.choosemyplate.gov and are meant to replace those found in the USDA Food Pyramid.

Key Points

- Undernutrition is common in older persons and is a contributor to significant harm including functional decline and death.
- It is critical that height and weight be measured at every outpatient visit; any unintentional weight loss should prompt evaluation for conditions such as polypharmacy, dementia, depression, oral disease, and poor social support. A suggested diagnostic pathway is described in Table 12.4.
- Treatment recommendations should consider the degree of malnutrition and its potential reversibility. Sarcopenia and cachexia are much less responsive to nutritional supplementation than are situations of impaired food bioavailability due to problems acquiring, preparing, or ingesting food.
- Whenever possible, projected illness course should be discussed with patients and their caregivers, and advanced directives should be implemented to guide treatment decisions.
- Both enteral and parenteral feedings should be generally discouraged as patients approach the end of life; neither has been validated to improve functional status or longevity. In contrast, compassionate oral feedings by family members and unrestricted diets can improve caregiver satisfaction and patient quality of life.
- The combination of endurance/resistive exercises and prudent eating can safely combat obesity in older persons [109].

Table 12.4 Geriatric Nutritional Assessment Summary

Step 1: Screen for malnutrition
Community dwelling elderly
≥5% Weight loss/6 months
Body mass index (BMI) < 22
BMI ≥ 30
SNAQ score ≤14
Mini Nutritional Assessment (MNA) score <24
Hospitalized elderly
BMI ≤ 20
Albumin <3.5 g/dL, prealbumin <15 ng/dL, transferrin <200 mg/dL
Dietary intake < estimated caloric needs
Absolute lymphocyte count <800/mm^3
Total cholesterol <130 mg/dL
Long-term care
≥5% Weight loss/30 days
≥10% Weight loss/6 months
Dietary intake ≤75% of most meals
Step 2: If screen is concerning for malnutrition, identify etiology using "Malnourished" mnemonic (Table 12.1)
Step 3: Provide prognosis by grouping etiology into one of three general categories of weight loss among older persons (starvation, cachexia, sarcopenia)
Step 4: Address underlying cause of malnutrition, if possible
Step 5: Consider treatment with oral nutritional supplementation. Starvation phenotype most likely to respond favorably
Step 6: If oral supplementation ineffective, consider an orexigenic agent; megestrol acetate preferred to dronabinol
Step 7: Consider interdisciplinary consultation in select cases:
Dentist: oral disease, need for dentures
Physical therapist/occupational therapist: immobility, ADL disability, frailty, sarcopenia
Nutritionist: avoidance of restricted diets
Social worker: lack of resources, elder abuse, self-neglect
Substance abuse counselor/program: alcohol abuse, drug abuse

References

1. Abraham S, Carroll MD, Dresser CM, et al. Dietary intake of persons 1-74 years of age in the United States. Advance data from vital and health statistics of the National Center for Health Statistics No. G. Rockville, MD: Public Health Service; 1977.
2. Ritchie CR, Thomas DR. Aging. In: Heimburger DC, Weinsier RL, editors. Handbook of clinical nutrition. 3rd ed. St Louis, MO: Mosby; 1997.
3. McGandy RB, Barrows Jr CH, Spanias A, et al. Nutrient intake and energy expenditure in men of different ages. J Gerontol. 1966;21:581–7.
4. Thomas DR. Nutritional assessment in older patients. In: Morley JE, Thomas DR, editors. Geriatric nutrition. New York, NY: CRC; 2007. p. 197–216.
5. Launer LJ, Harris LT, Rumpel C, Madans J. Body mass index, weight change, and risk of mobility disability in middle-aged and older women. JAMA. 1994;271:1083–98.
6. Calle EE, Thun MJ, Petrilli JM, et al. Body-mass index and mortality in a prospective cohort of US adults. N Engl J Med. 1999;341:1097–105.

7. Appel LJ, Moore TJ, Obarzanek E, et al. A clinical trial of the effects of dietary patterns on blood pressure. N Engl J Med. 1997;336:1117.
8. Milne AC, Avenell A, Potter J. Meta-analysis: protein and energy supplementation in older people. Ann Intern Med. 2006;144:37–48.
9. Yeh SS, Wu SY, Lee TP, et al. Improvement in quality of life measures and stimulation of weight gain after treatment with megestrol acetate oral suspension in geriatric cachexia: results of a double-blind, placebo-controlled study. J Am Geriatr Soc. 2000;48:485–92.
10. Hajjar RR, Nahhas Z. Vitamin disorders. In: Morley JE, Thomas DR, editors. Geriatric nutrition. New York, NY: CRC; 2007. p. 137–78.
11. McCormack P. Undernutrition in the elderly population living at home in the community: a review of the literature. J Adv Nurs. 1997;26:856–63.
12. Plata-Salaman CR. Anorexia during acute and chronic disease. Nutrition. 1996;12:69–76.
13. Mowe M, Bohmer T, Kindt E. Reduced nutritional status in an elderly population (>70 y) is probable before disease and possibly contributes to the development of disease. Am J Clin Nutr. 1994;59:317–24.
14. Kaiser MJ, Bauer JM, Ramsch C, et al. Frequency of malnutrition in older adults: a multinational perspective using the Mini Nutritional Assessment. J Am Geriatr Soc. 2010;58:1734–8.
15. Incalzi RA, Gemma A, Capparella O, et al. Energy intake and in-hospital starvation. A clinically relevant relationship. Arch Intern Med. 1996;156:425–9.
16. Sullivan DH, Moriarty MS, Chernoff R, et al. Patterns of care: an analysis of the quality of nutritional care routinely provided to elderly hospitalized veterans. JPEN J Parenter Enteral Nutr. 1989;13:249–54.
17. Kamath SK, Lawler M, Smith AE, et al. Hospital malnutrition: a 33-hospital screening study. J Am Diet Assoc. 1986;86:203–6.
18. Tobias AL, Van Itallie TB. Nutritional problems of hospitalized patients. J Am Diet Assoc. 1977;71:253–7.
19. Pinchcofsky GD, Kaminski Jr MV. Increasing malnutrition during hospitalization: documentation by a nutritional screening program. J Am Coll Nutr. 1985;4:471–9.
20. Thomas DR, Zdrowski CD, Wilson MM, et al. Malnutrition in subacute care. Am J Clin Nutr. 2002;75:308–13.
21. Thomas DR, Verdery RB, Gardner L, et al. A prospective study of outcome from protein-energy malnutrition in nursing home residents. JPEN J Parenter Enteral Nutr. 1991;15:400–4.
22. Sliver AJ, Morley JE, Strome LS, et al. Nutritional status in an academic nursing home. J Am Geriatr Soc. 1988;36:487–91.
23. Drinka PJ, Goodwin JS. Prevalence and consequences of vitamin deficiency in the nursing home: a critical review. J Am Geriatr Soc. 1991;39:1008–17.
24. Landi F, Zuccala G, Gambassi G, et al. Body mass index and mortality among older people living in the community. J Am Geriatr Soc. 1999;47:1072–6.
25. Lee CG, Boyko EJ, Nielson CM, et al. Mortality risk in older men associated with changes in weight, lean mass, and fat mass. J Am Geriatr Soc. 2011;59:233–40.
26. Payette H, Coulombe C, Boutier V, Gray-Donald K. Weight loss and mortality among free-living frail elders: a prospective study. J Gerontol A Biol Sci Med Sci. 1999;54:M440–5.
27. Thomas DR, Kamel H, Azharrudin M, et al. The relationship of functional status severity of illness, and nutritional markers to in-hospital mortality and length of stay. J Nutr Health Aging. 2005;9:169–75.
28. Liu L, Bopp MM, Roberson PK, Sullivan DH. Undernutrition and risk of mortality in elderly patients within 1 year of hospital discharge. J Gerontol A Biol Sci Med Sci. 2002;57:M741–6.
29. Galanos AN, Pieper CF, Kussin PS, et al. Relationship of body mass index to subsequent mortality among seriously ill hospitalized patients. SUPPORT Investigators. The Study to Understand Prognoses and Preferences for Outcome and Risks of Treatments. Crit Care Med. 1997;25:1962–8.
30. Sullivan DH, Bopp MM, Roberson PK. Protein-energy undernutrition and life-threatening complications among the hospitalized elderly. J Gen Intern Med. 2002;17:923–32.
31. Herrmann FR, Safran C, Levkoff SE, Minaker KL. Serum albumin level on admission as a predictor of death, length of stay, and readmission. Arch Intern Med. 1992;152:125–30.
32. Sullivan DH, Walls RC, Bopp MM. Protein-energy undernutrition and the risk of mortality within one year of hospital discharge: a follow-up study. J Am Geriatr Soc. 1995;43:507–12.
33. Sullivan DH, Walls RC. The risk of life-threatening complications in a select population of geriatric patients: the impact of nutritional status. J Am Coll Nutr. 1995;14:29–36.
34. Sullivan DH, Walls RC. Protein-energy undernutrition and the risk of mortality within six years of hospital discharge. J Am Coll Nutr. 1998;17:571–8.
35. Murden RA, Ainslie NK. Recent weight loss is related to short-term mortality in nursing homes. J Gen Intern Med. 1994;9:648–50.
36. Sullivan DH, Johnson LE, Bopp MM, Roberson PK. Prognostic significance of monthly weight fluctuations among older nursing home residents. J Gerontol A Biol Sci Med Sci. 2004;59:M633–9.
37. Thomas DR, Goode PS, Tarquine PH, Allman R. Hospital acquired pressure ulcers and risk of death. J Am Geriatr Soc. 1996;44:1435.
38. Pinchcofsky-Devin GD, Kaminski Jr MV. Correlation of pressure sores and nutritional status. J Am Geriatr Soc. 1986;34:435.
39. Langer G, Schloemer G, Knerr A, et al. Nutritional interventions for preventing and treating pressure ulcers. Cochrane Database Syst Rev. 2004;(4):CD003216.
40. Morley JE, Silver AJ. Anorexia in the elderly. Neurobiol Aging. 1988;9:9.
41. Schiffman SS. Chemosensory impairment and appetite commentary on "impaired sensory functioning in elders: the relation with its potential determinants and nutritional intake". J Gerontol A Biol Sci Med Sci. 1999;54:B332.
42. Suzuki Y, Critchley HD, Suckling J, et al. Functional magnetic resonance imaging of odor identification: the effect of aging. J Gerontol A Biol Sci Med Sci. 2001;56:M756.
43. Clarkston WK, Pantano MM, Morley JE, et al. Evidence for the anorexia of aging: gastrointestinal transit and hunger in healthy elderly vs. young adults. Am J Physiol. 1997;272:R243.
44. MacIntosh CG, Morley JE, Wishart J, et al. Effect of exogenous CCK-8 on food intake and plasma CCK, leptin, and insulin concentration in older and young adults: evidence of increased CCK activity as a cause of the anorexia of aging. J Clin Endocrinol Metab. 2001;86:5830.
45. Roberts SB, Fuss P, Heyman MB, et al. Control of food intake in older men. JAMA. 1994;272:1601.
46. Delany JP, Lovejoy JC. Energy expenditure. Endocrinol Metab Clin North Am. 1996;25:831.
47. Blanc S, Schoeller DA, Bauer D, et al. Energy requirements in the eighth decade of life. Am J Clin Nutr. 2004;79:303.
48. Morley JE, Silver AJ. Nutritional issues in nursing home care. Ann Intern Med. 1995;123:850–9.
49. Gammack J. Geriatric assessment and its interaction with nutrition. In: Morley JE, Thomas DR, editors. Geriatric nutrition. New York, NY: CRC; 2007. p. 217–34.
50. Bales CW, Buhr GT, Hawk VH, et al. Providing optimal nutrition in the assisted living environment. In: Morley JE, Thomas DR, editors. Geriatric nutrition. New York, NY: CRC; 2007. p. 341–58.

51. Zimmerman S, et al. Assisted living and nursing homes: apples and oranges. Gerontologist. 2003;43:107.
52. Dharmarajan TS, Unnikrishnan D, Pitchumoni CS. Percutaneous endoscopic gastrostomy and outcome in dementia. Am J Gastroenterol. 2001;96:2556–63.
53. Gebretsadik M, Grossberg GT. Nutrition and depression. In: Morley JE, Thomas DR, editors. Geriatric nutrition. New York, NY: CRC; 2007. p. 373–96.
54. Gallo JJ, Bogner HR, Morales KH, et al. Depression, cardiovascular disease, diabetes, and two-year mortality among older, primary-care patients. Am J Geriatr Psychiatry. 2005;13: 748–55.
55. Sheikh JL, Yesavage JA. Geriatric depression scale: recent evidence and development of a shorter version. Clin Gerontol. 1986;5:165–72.
56. Garcia N, Miley DD. The oral cavity and nutrition. In: Morley JE, Thomas DR, editors. Geriatric nutrition. New York, NY: CRC; 2007. p. 249–65.
57. Krall E, Hayes KC, Garcia R. How dentition status and masticatory function affect nutrient intake. J Am Dent Assoc. 2002;133:1369–79.
58. Bayle R, Gueldner S, Ledikwe J, et al. The oral health of older adults. J Gerontol Nurs. 2005;31:11–7.
59. Ritchie CS. Oral health, taste, and olfaction. Clin Geriatr Med. 2002;18:709–17.
60. Wham CA, Teh RO, Robinson M, et al. What is associated with nutrition risk in very old age? J Nutr Health Aging. 2011;15: 247–51.
61. Sullivan DH, Johnson LE. Nutrition and aging. In: Halter JB, Ouslander JG, Tinetti ME, Studenski S, High KP, Asthana S, editors. Hazzard's geriatric medicine and gerontology. 6th ed. New York, NY: McGraw Hill; 2009. p. 439–57.
62. Schweigert FJ. Inflammation-induced changes in the nutritional biomarkers serum retinol and carotenoids. Curr Opin Clin Nutr Metab Care. 2001;4:477–81.
63. Hyloft PP, Felding P, Horder M, Tryding N. Effects of posture on concentration of serum proteins in healthy adults. Scand J Clin Lab Invest. 1980;40:623–8.
64. Wilson MM, Thomas DR, Rubenstein LZ, et al. Appetite assessment: simple appetite questionnaire predicts weight loss in community-dwelling adults and nursing home residents. Am J Clin Nutr. 2005;82:1074–81.
65. Guigoz Y, Vellas B, Garry PJ. Mini Nutritional Assessment: a practical assessment tool for grading the nutritional state of elderly patients. Facts Res Gerontol. 1994;2S:15–59.
66. Rubenstein LZ, Harker JO, Salva A, et al. Screening for undernutrition in geriatric practice: developing the short-form Mini Nutritional Assessment (MNA-SF). J Gerontol. 2001;56A:M366–77.
67. Morley JE. Assessment of malnutrition in older persons: a focus on the Mini Nutritional Assessment. J Nutr Health Aging. 2011;15:87–90.
68. Guigoz Y. The Mini-Nutritional Assessment (MNA) review of the literature—what does it tell us? J Nutr Health Aging. 2006;10:466–87.
69. Thomas DR. Management of protein-energy undernutrition in older adults. In: Morley JE, Thomas DR, editors. Geriatric nutrition. New York, NY: CRC; 2007. p. 267–90.
70. Morley JE, Baumgarter RN, Roubenoff R, et al. Sarcopenia. J Lab Clin Med. 2001;137:231.
71. Morley JE, Haren MT. Sarcopenia and cachexia. In: Morley JE, Thomas DR, editors. Geriatric nutrition. New York, NY: CRC; 2007. p. 59–68.
72. Morley JE, Thomas DR, Wilson MM. Cachexia: pathophysiology and clinical relevance. Am J Clin Nutr. 2006;83:735.
73. Bodine SC, Latres E, Baumhueter S, et al. Identification of ubiquitin ligases required for skeletal muscle atrophy. Science. 2001;294: 1704–8.
74. Buckler DA, Kelber ST, Goodwin JS. The use of dietary restrictions in malnourished nursing home patients. J Am Geriatr Soc. 1994;42:1100–2.
75. Hotaling DL. Nutritional considerations for the pureed diet texture in dysphagic elderly. Dysphagia. 1992;7:81–5.
76. Chang CC, Roberts BL. Strategies for feeding patients with dementia. Am J Nurs. 2011;111:36–44.
77. Feldblum I, German L, Castel H, et al. Individualized nutritional intervention during and after hospitalization: the nutrition intervention study clinical trial. J Am Geriatr Soc. 2011;59:10–7.
78. Holzapfel SK, Ramirez RF, Layton MS, et al. Feeder position and food and fluid consumed by nursing home residents. J Gerontol Nurs. 1996;22:612.
79. Kayser-Jones J. Mealtime in nursing homes: the importance of individualized care. J Gerontol Nurs. 1996;22:26–31.
80. Ragneskog H, Kihlgren M, Karlsson I, Norberg A. Dinner music for demented patients: analysis of video-recorded observations. Clin Nurs Res. 1996;5:262–77.
81. Lauque S, Arnaud-Battandier F, Gillette S, et al. Improvement of weight and fat-free mass with oral nutritional supplementation in patients with Alzheimer's disease at risk of malnutrition: a prospective randomized study. J Am Geriatr Soc. 2004;52:1702–7.
82. Beal JE, Olson R, Lefkowitz L, et al. Long-term efficacy and safety of dronabinol for acquired immunodeficiency syndrome-associated anorexia. J Pain Symptom Manage. 1997;14:7–14.
83. Pascual LA, Roque FM, Urrutia CG, et al. Systematic review of megestrol acetate in the treatment of anorexia-cachexia syndrome. J Pain Symptom Manage. 2004;27:360–9.
84. Jatoi A, Rowland K, Loprinzi CL, et al. Dronabinol versus megestrol acetate versus combination therapy for cancer-associated anorexia: a North Central Cancer Treatment Group Study. J Clin Oncol. 2002;20:567–73.
85. Visser M, Langlois J, Guralnik JM, et al. High body fatness, but not low fat-free mass, predicts disability in older men and women: the Cardiovascular Health Study. Am J Clin Nutr. 1998;68:584–90.
86. Baumgartner RN, Wayne SJ, Waters DL, et al. Sarcopenic obesity predicts instrumental activities of daily living disability in the elderly. Obes Res. 2004;12:1995–2004.
87. Cassano PA, Rosner B, Vokonas PS, Weiss ST. Obesity and body fat distribution in relation to the incidence of non-insulin-dependent diabetes mellitus. A prospective cohort study of men in the normative aging study. Am J Epidemiol. 1992;136:1474–86.
88. Biggs ML, Mukamal KJ, Luchsinger JA, et al. Association between adiposity in midlife and older age and risk of diabetes in older adults. JAMA. 2010;303:2504–12.
89. Masaki KH, Curb DK, Chiu D, et al. Association of body mass index with blood pressure in elderly Japanese American men. The Honolulu Heart Program. Hypertension. 1997;29:673–7.
90. Melville JL, Katon W, Delaney K, Newton K. Urinary incontinence in US women: a population-based study. Arch Intern Med. 2005;165:537–42.
91. Adamson J, Ebrahim S, Dieppe P, Hunt K. Prevalence and risk factors for joint pain among men and women in the West of Scotland Twenty-07 study. Ann Rheum Dis. 2006;65:52–524.
92. Angleman SB, Harris TB, Melzer D. The role of waist circumference in predicting disability in periretirement age adults. Int J Obes (Lond). 2006;30:364–73.
93. Canoy D, Luben R, Welch A, et al. Fat distribution, body mass index and blood pressure in 22,090 men and women in the Norfolk cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC-Norfolk) study. J Hypertens. 2004;22:2067–74.

94. Yusuf S, Hawken S, Ounpuu S, et al. Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: a case-control study. Lancet. 2005;366:1640–9.
95. Heiat A, Vaccarino V, Krumholz HM. An evidence-based assessment of federal guidelines for overweight and obesity as they apply to elderly persons. Arch Intern Med. 2001;161: 1194–203.
96. Bender R, Jockel KH, Trautner C, et al. Effect of age on excess mortality in obesity. JAMA. 1999;281:1498–504.
97. Harris TB. Weight and age: paradoxes and conundrums. In: Halter JB, Ouslander JG, Tinetti ME, Studenski S, High KP, Asthana S, editors. Hazzard's geriatric medicine and gerontology. 6th ed. New York, NY: McGraw Hill; 2009. p. 459–67.
98. Harris TB, Launer LJ, Madans J, Feldman JJ. Cohort study of effect of being overweight and change in weight on risk of coronary artery disease in old age. BMJ. 1997;314:1791–4.
99. Kim HJ, Lee JS, Kim CK. Effect of exercise training on muscle glucose transporter 4 protein and intramuscular lipid content in elderly men with impaired glucose tolerance. Eur J Appl Physiol. 2004;93:353–8.
100. Ryan AS, Hurlbut DE, Lott ME, et al. Insulin action after resistive training in insulin resistant older men and women. J Am Geriatr Soc. 2001;49:247–53.
101. Hurley BF, Roth SM. Strength training in the elderly: effects on risk factors for age-related diseases. Sports Med. 2000;30: 249–68.
102. Jensen GL, Roy MA, Buchanan AE, Berg MB. Weight loss intervention for obese older women: improvements in performance and function. Obes Res. 2004;12:1814–20.
103. Obarzanek E, Sacks FM, Vollmer WM, et al. Effects on blood lipids of a blood pressure-lowering diet: the Dietary Approaches to Stop Hypertension (DASH) Trial. Am J Clin Nutr. 2001;74:80.
104. Fung TT, Chiuve SE, McCullough ML, et al. Adherence to a DASH-style diet and risk of coronary heart disease and stroke in women. Arch Intern Med. 2008;168:713.
105. Sacks FM, Svetkey LP, Vollmer WM, et al. Effects on blood pressure of reduced dietary sodium and the dietary approaches to stop hypertension (DASH) diet. N Engl J Med. 2001;344:3.
106. de Lorgeril M, Salen P, Martin JL, et al. Effect of a Mediterranean type of diet on the rate of cardiovascular complications in patients with coronary heart disease. Insights into the cardioprotective effect of certain nutriments. J Am Coll Cardiol. 1996;28:1103.
107. Esposito K, Marfella R, Ciotola M, et al. Effect of a Mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. JAMA. 2004;292:1440.
108. Ornish D. The spectrum: a scientifically proven program to feel better, live longer, lose weight, gain health. New York, NY: Ballantine Books; 2007.
109. Villareal DT, Chode S, Parimi N, et al. Weight loss, exercise, or both and physical function in obese older adults. N Engl J Med. 2011;364:1218–29.

Tube Feeding: Techniques and Procedure

13

Amit Sohagia and Hilary I. Hertan

Introduction

Enteral feeding is preferred to parenteral nutrition (total or peripheral) in patients unable to maintain adequate oral intake in spite of having a functional gastrointestinal tract. Enteral nutrition is physiological and prevents mucosal atrophy and gut bacterial translocation, while maintaining intestinal epithelial cell integrity. Besides enteral nutrition, also relevant is gut-associated lymphoid tissue (GALT), referring to immune cells disseminated in intestinal Peyer's patches, mucosa, and lamina propria; GALT supports gastrointestinal functions in a dynamic manner by controlling intestinal permeability, orienting immune response, preventing bacterial translocation, and minimizing nosocomial infection. The enteral approach to nutrition is always less expensive. Malnutrition and dehydration are common in the frail elderly, particularly during hospitalization. Inadequate dietary counseling including the consumption of enteral supplements and appetite stimulants may lead to premature consideration for tube feeding [1, 2].

Nasogastric Tube Feeding

Temporary access is achieved via a nasogastric or nasoenteral feeding tube. Nasogastric tubes are used for 30 days or less; they are easily placed and removed at the bedside. The patient is positioned sitting upright with the neck partially flexed. The nasogastric tube tip is lubricated and gently inserted along the floor of the nose and advanced parallel to the nasal floor until it reaches the back of the nasopharynx. The patient sips water through a straw and begins a swallow. The tube is advanced to 50 cm. Tube placement is verified by auscultating the abdomen for a rush of air into the stomach or by aspirating gastric content. It is best to obtain a chest radiograph to verify correct placement. Nasogastric tubes often fail due to clogging or inadvertent dislodgement and do not provide a secure access route to provide calories, medications, or fluids. Potential nasoenteric tube complications are mentioned in Table 13.1 [3–5].

Percutaneous Endoscopic Gastrostomy

Long-term permanent enteral access is obtained either endoscopically, surgically, or via interventional radiology.

The most common approach utilized to gain gastric access is the percutaneous endoscopic gastrostomy (PEG), accounting for approximately 200,000 procedures annually in the U.S. The technique was first described by Gauderer in 1980. Variations of the technique include the pull (Ponsky), push (Sachs-Vine), introducer (Russell), and Versa (T-fastener) methods. The advent of PEG in 1980 altered the approach to gastric access, largely replacing surgical gastrostomy. Endoscopic gastrostomy is an easy, safe technique compared to open gastrostomy. The size of gastrostomy tubes for adults ranges from 16 to 24 French. Most tubes are constructed of silicone, and some of polyurethane. Newer PEGJ (percutaneous endoscopic gastrojejunostomy) tubes combine gastric and jejunal ports to allow distal feeding and proximal decompression [6–9] (Figs. 13.1 and 13.2).

The Technique of Percutaneous Endoscopic Gastrostomy

PEGs can be placed in several ways. Indications and contraindications for PEG are listed in Table 13.2.

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Table 13.1 Common complications of enteral tube feeding [3–5, 20]

Nasogastric tube	Gastrostomy tube	Jejunostomy tube
Tube dislodgment	Peristomal leakage	Difficult placement
Clogging	Wound infection	Tube clogging
Nasal mucosal ulceration	Tube deterioration	Wound infection
Pulmonary intubation	Bleeding/clogging	Dumping syndrome
Sinusitis	Tube dislodgement	Tube dislodgement
Bleeding	Gastric ulceration	Bleeding
Epistaxsis	Gastric outlet obstruction	Peristomal leakage
Otitis media	Pneumoperitoneum	Intestinal obstruction
Esophagitis	Buried bumper syndrome	Tube migration
Esophageal perforation	Necrotizing fascitis Gastrocolocutaneous fistula PEG-induced pancreatitis	Diarrhea

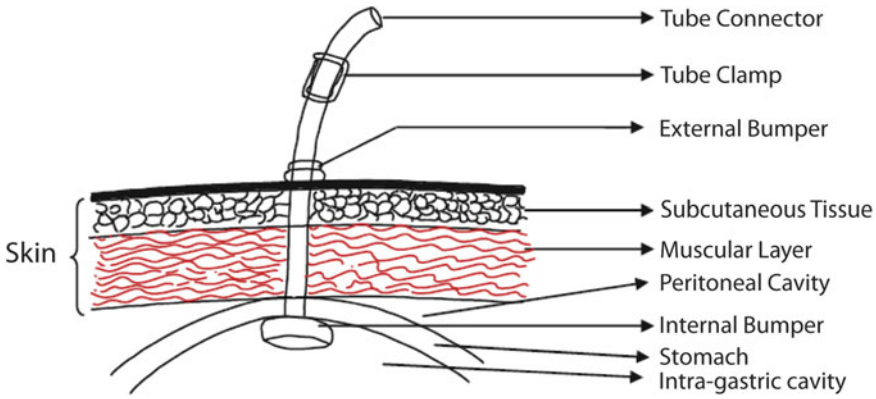

Fig. 13.1 Schematic diagram of a gastrostomy tube

Fig. 13.2 The gastrostomy tube

Table 13.2 Indications and contraindications for percutaneous endoscopic gastrostomy (PEG) [3–5]

Indications
Head and neck cancer
Esophageal cancer
Neurological conditions (most common indication): stroke, multiple sclerosis, brain tumors, amyotrophic lateral sclerosis, advanced dementia (use is common but controversial), and head injury
AIDS enteropathy
Absolute contraindications
Inability to perform an esophagogastroduodenoscopy (EGD)
Uncorrected coagulopathy
Peritonitis
Bowel obstruction (unless PEG is used to provide drainage)
Relative contraindications
Massive ascites
Gastric mucosal abnormalities including large gastric varices
Prior abdominal surgery, including partial gastrectomy, which increases risk of organ interposition between gastric wall and abdominal wall
Morbid obesity, which poses difficulties in locating stomach position by digital indentation of stomach, transillumination, and needle insertion
Gastric wall neoplasm
Abdominal wall infection, which increases risk of infection at PEG site

Push Technique

The patient should be supine, with the head of the bed elevated to a 30° angle to reduce risk of aspiration. The patient is kept NPO for 4 h, preferably longer. A first-generation cephalosporin (e.g., cefazolin 1 g) is administered intravenously to reduce the risk of insertion site infection [10].

Esophagogastroduodenoscopy (EGD) is performed to rule out gastric outlet or duodenual obstruction. The stomach is insufflated and the abdominal wall is transilluminated, visible externally on the abdominal wall. Finger pressure is applied at the point of maximal transillumination, and a focal indentation of the anterior gastric wall is visible endoscopically (Fig. 13.3) and the site marked. The skin is cleansed with povidone-iodine or chlorhexidine, in concentric centrifugal fashion. The site is anesthetized followed by a small horizontal incision (Fig. 13.4). The needle with inner stylet is passed through this incision into the stomach. This maneuver is a rapid poke. The needle is visible inside the stomach cavity at this time. A snare which is passed through the endoscope into the stomach catches the needle (Fig. 13.5). The stylet is removed, leaving the needle in place. A guidewire passed through the needle into the stomach is caught by the snare; the guidewire is pulled out of the mouth along with the endoscope. The tapered end of the PEG tube is passed over the guide wire through the mouth until it comes out at the site of the abdominal wall incision (Fig. 13.6). The internal bumper sits snugly against the gastric mucosa; excessive tension on the tube should be avoided (Fig. 13.7). An external bumper is then passed over the PEG tube and placed 1–2 cm away from the abdominal wall. The excess tube is cut, leaving 6–12 in. of tube behind. A dressing is applied over the external bumper and the tube is looped and taped to the abdominal wall (Fig. 13.8). The PEG can be safely used for feeding 4 h after the procedure [5, 11–13]. An abdominal binder may help inadvertent removal of the tube by demented or agitated patients.

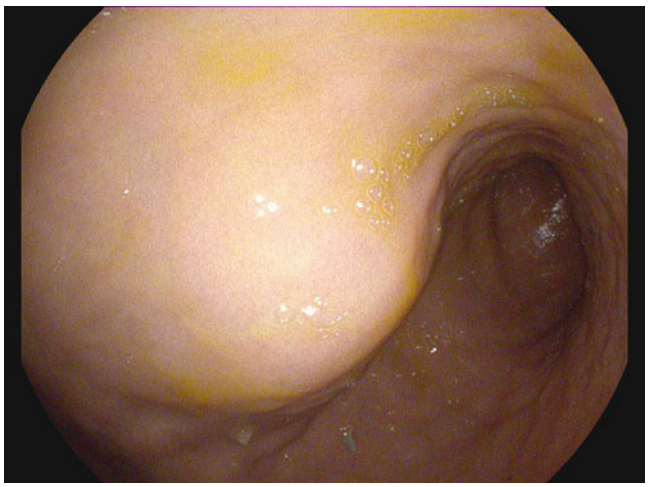

Fig. 13.3 Endoscopic finger impression on the stomach wall

Pull Technique

The Pull technique is similar to the Push method, but instead of a guidewire, a wire loop is placed from outside through the trocar into the stomach; this wire loop is snared through the endoscope and brought out of the mouth along with endoscope. The PEG tube with wire loop at its tapered end

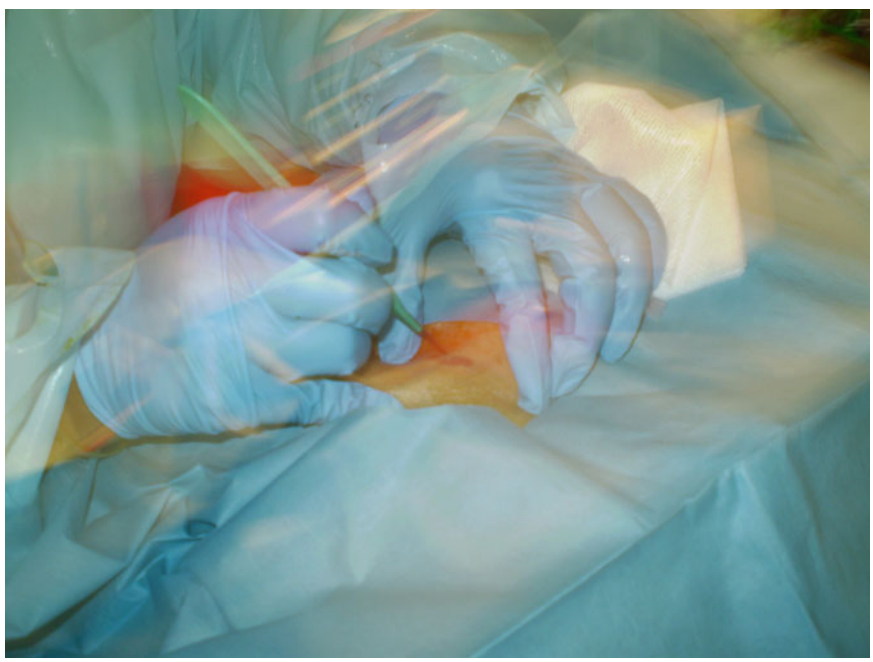

Fig. 13.4 Under sterile conditions after injecting lidocaine, a small horizontal incision is made over the anterior abdominal wall at the site of transillumination

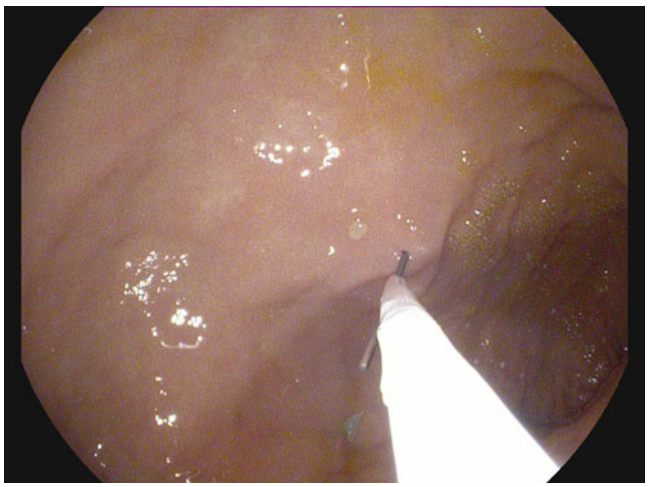

Fig. 13.5 Needle is caught by the snare

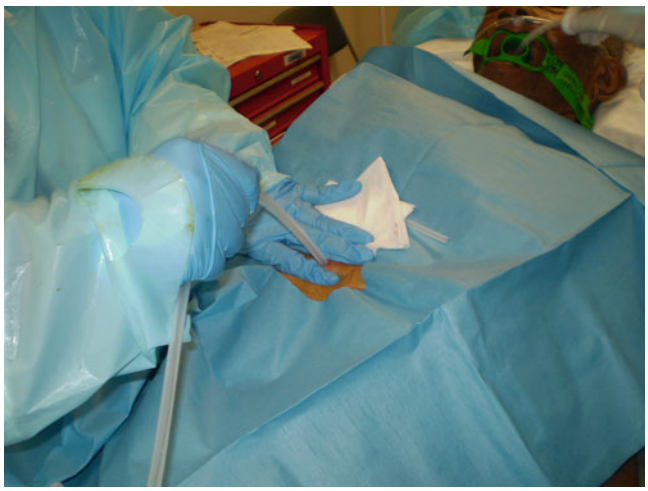

Fig. 13.6 Gastrostomy tube pulled out from incision site on anterior abdominal wall

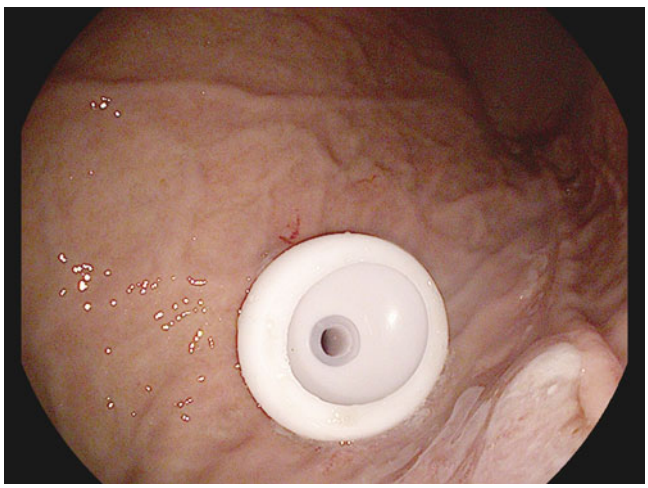

Fig. 13.7 Endoscopic view of internal bumper

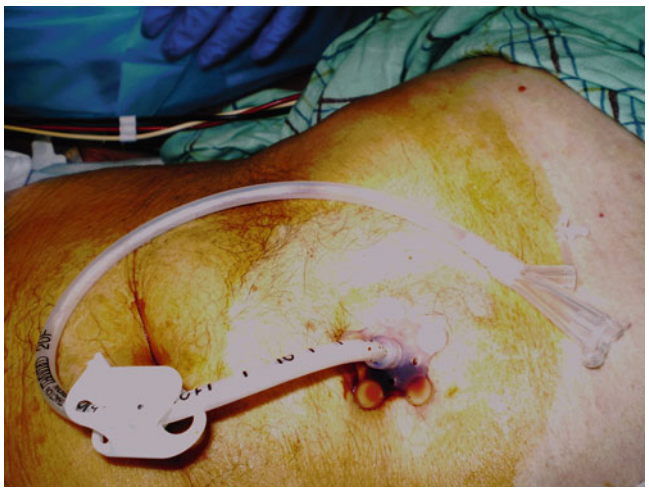

Fig. 13.8 Gastrostomy tube with external bumper, tube clamp, and connector

knots with the other wire to permit the tube to be pulled down the esophagus and out via the gastric wall.

Introducer Method

The third method is the Russell "Introducer Method," similar in principle to the pull technique. An introducer with an outer sheath is passed over guide wire in a twisted motion until the sheath is clearly visible inside the stomach. The introducer is removed leaving the sheath behind. The PEG tube with balloon is advanced through this sheath inside the stomach, the balloon is inflated under direct endoscopic visualization, and then the sheath is pealed away. This technique is useful in the presence of esophageal strictures or tumor [13].

Surgical Gastrostomy is indicated when an endoscopic gastrostomy cannot be performed. Patients with esophageal stricture, atresia, inability to transilluminate the abdominal wall during endoscopy, and patients due for gastric surgery are some indications for surgical gastrostomy.

Fluoroscopic Percutaneous Gastrostomy is an alternative performed by interventional radiologists for patients who are not candidates for endoscopy under conscious sedation.

A comparison of open surgical, endoscopic, and laparoscopic methods for gastrostomy tube placement revealed the following: insertion times were longer in the open technique; insertion complications were noted in the laparoscopic and PEG cohorts; maintenance complications were higher in the laparoscopy cohort; overall complications were significantly lower in the PEG and open groups; feeding start day was delayed most often in the open technique. The conclusion was that PEG should be the procedure of choice, and if contraindicated, the open surgical technique is best [14]. A comparison of endoscopic to radiological methods of tube insertion suggested that both were safe for nutrition delivery [15].

Removal of PEGs

PEGs may be removed under several circumstances: when they are no longer required (following recovery from stroke or head and neck cancer), following a complication such as persistent site infection, failure, breakage, or deterioration of the PEG tube (a new tube can be inserted along the existing track) and "buried bumper syndrome" (internal bumper erodes into the gastric wall and is buried inside the gastric wall because of long-term external traction on the PEG tube).

Old PEG tubes are removed by simple traction on the tube at the bedside since the bumper is collapsible. If this can't be done, the PEG tube can be removed endoscopically. The endoscope is passed following patient sedation and the PEG tube is pushed into the stomach so that part of the tube is visible behind the bumper. A snare is passed through the endoscope to grasp the internal bumper. The external part of the tube is then cut, the tube is withdrawn into the stomach and pulled up into the esophagus and removed through the mouth. The PEG site heals without intervention.

Replacement PEG tubes have inflatable balloons instead of internal bumpers, and once placed, the balloon is inflated with 15 mL of sterile water or normal saline. This GT tube has an additional port for balloon inflation at the adaptor site. A rare complication of replacement tube is migration into the duodenum, causing acute pancreatitis.

Percutaneous Endoscopic Gastrojejunostomy

Endoscopic percutaneous small bowel access is obtained by two methods. With the first method, a PEG is placed in the standard fashion, followed by placement of a jejunal feeding tube through the PEG into the small bowel over a guidewire. Usually, a 9- or 12-French J tube is used. This PEGJ system allows for concurrent gastric decompression and small bowel feeding. Jejunal tubes are smaller in caliber and must be flushed periodically to avoid clogging; reported clogging rates of J tubes are 3.5–35% [13].

Percutaneous Endoscopic Jejunostomy (PEJ): Small bowel endoscopic enteral access is used for patients unable to tolerate gastric feeding because of gastroparesis or gastric outlet obstruction or for those at high risk for aspiration. The insertion technique is more difficult and is not done widely. Direct percutaneous endoscopic jejunostomy (DPEJ) is the most common endoscopic procedure utilized to access the small bowel. An enteroscope or pediatric colonoscope is passed up to the proximal jejunum, and through transillumination, the jejunal loop is located at the abdominal wall. The procedure is similar to PEG.

Jejunostomy tubes can also be placed surgically or fluoroscopically. Surgical placement of a jejunostomy is performed by a needle catheter or by the Witzel technique where a tube is placed through an incision in the anterior abdominal wall and a tunneled incision is made in the jejunal wall. The jejunum is sutured to the anterior abdominal wall for adherence. For patients who are not candidates for surgical or endoscopic procedure, jejunal feeding tubes are placed with radiologic guidance. Here, the stomach and small bowel are insufflated with air via a nasogastric or nasoenteral tube; ultrasound or fluoroscopy helps locate the internal organs. A needle is inserted through abdominal wall into the jejunal lumen and a guide wire is inserted through it. The needle is removed and the tract dilated [16, 17].

In clinical practice, there has been underuse of prophylactic antibiotics and delay in institution of nutritional support after gastrostomy, at times associated with mortality in a Canadian study [18, 19]. Table 13.3 provides advantages and disadvantages of different approaches to tube feeding.

Table 13.3 Nasogastric, PEG, and postpyloric feeding [2, 17]

Nasogastric feeding
Advantages
Easily placed, inexpensive, used short term
Use to provide medication, gastric irrigation, and small bowel decompression
Disadvantages
Patient discomfort, epistaxis, respiratory tract intubation
Easily dislodged and clogged
Can use only temporarily
Gastric feeding
Advantages
More physiological, easy placement, convenient, tolerated, satisfactory approach for caregivers
Low complication rate (less likely to be clogged or dislodged), cost-effective
Disadvantages
Delayed gastric emptying, gastroesophageal reflux, and aspiration
Postpyloric (jejunal) feeding
Indication
Recurrent pulmonary aspiration, severe GERD and esophagitis, recurrent emesis
Gastric and antroduodenal dysmotility
Advantages
Minimizes aspiration risk (vs. PEG), beneficial in acute pancreatitis
Maintains gut-based immunity
Disadvantages
Difficulty with placement and ease of displacement, feeding intolerance (dumping syndrome), small size tube is easily clogged

Complications of Enteral Nutrition

Potential complications of enteral feeding may be: mechanical, such as malposition, blockage, unwanted removal, visceral rupture, fistula, ulceration; metabolic or electrolyte

Table 13.4 Problems with use of enteral tubes: prevention and management [5, 17]

Tube degradation and obstruction
Usually from yeast implantation; flush with warm water, or use pancreatic enzymes mixed in bicarbonate solution
Aspiration
Raise head of bed to 30–45° during and for 1 h after feeding
Peristomal leakage or wound infection
Keep the external bumper of GT tube away from the anterior abdominal wall to avoid tissue compression and wound breakdown. Infection is treated with oral and topical or intravenous antibiotics; remove GT tube if infection worsens or leak persists
Peristomal bleeding
Stops with compression; rarely surgical intervention and tight suturing of stoma required
Pneumoperitoneum
Common after PEG placement, usually no intervention required
Colocutaneous fistula
Tube must be removed; monitor for fistula tract closure. Surgery if not healing
Nausea, vomiting, abdominal distention
Resolves by slowing delivery rate of feeding; withdraw offending medications (e.g., anticholinergics); may need trial of promotility agent
Diarrhea
Exclude *Clostridium difficile* infection, avoid liquid-based medications which may contain sorbitol, avoid hyperosmolar formula

abnormalities; gastrointestinal including diarrhea, constipation, reflux, aspiration secondary to vomiting, drug interaction, and refeeding syndrome. Tables 13.1 and 13.4 list complications associated with different enteral feeding tubes [20]. Complications of the PEG procedure itself include bleeding, infection, perforation, or aspiration. Mortality related to PEG procedure is extremely rare. Recently, the value-computerized tomography in delineating thickness of subcutaneous fat, abdominal wall thickness, and muscle has shown value in minimizing potential complications before PEG placement [21].

The provision of a percutaneous enteral tube feeding service should be within the domain of the hospital nutrition support team, which should help assess and select patients for tube feeds and postprocedure care; ethical considerations may complicate decision making [22, 23]. Finally, it is worth noting that up to a fifth of patients may require PEG only for a short term; a weaning trial should remain a consideration; trial of oral feeding while the PEG is in place is a reasonable option.

Key Points

- Percutaneous endoscopic gastrostomy (PEG) is the preferred method for long-term enteral nutrition; the procedure can be done easily, is safe, and has a low complication rate.
- Prepyloric (gastric) feeding is more physiologic and well tolerated compared to postpyloric feeding through jejunostomy.
- The decision to place a PEG should follow careful patient selection and discussions with caregiver, including pros, cons, and alternatives, without providing unrealistic expectations.
- There is insufficient evidence to suggest that long-term enteral tube feeding is beneficial in patients with advanced dementia. Advanced age, poor nutritional status, and presence of pressure ulcer were predictors of poor outcome.
- Up to a fifth of patients may require their PEG only for a short term.
- Pulmonary aspiration, diarrhea, peristomal wound infection, leakage, and tube obstruction are common, but preventable complications of tube feedings.

References

1. Niv E, Fireman Z, Vaisman N. Post-pyloric feeding. World J Gastroenterol. 2009;15(11):1281–8.
2. Lloyd DA, Powell-Tuck J. Artificial nutrition: principle and practice of enteral feeding. Clin Colon Rectal Surg. 2004;17(2):107–18.
3. Dwolatzky T, Berezovski S, Friedmann R, et al. A prospective comparison of the use of nasogastric and percutaneous endoscopic gastrostomy tubes for long-term enteral feeding in older people. Clin Nutr. 2001;20(6):535–40.
4. Nicholsom FB, Korman MG, Richardson MA. Percutaneous endoscopic gastrostomy: a review of indications, complications and outcome. J Gastroenterol Hepatol. 2000;15(1):21–5.
5. Pearce CB, Duncan HD. Enteral feeding. Nasogastric, nasojejunal, percutaneous endoscopic gastrostomy, or jejunostomy: its indications and limitations. Postgrad Med J. 2007;78:198–204.
6. Wilhelm SM, Ortega KA, Stellato TA. Guidelines for identification and management of outpatient percutaneous endoscopic gastrostomy tube placement. Am J Surg. 2010;199(3):396–400.
7. Lynch CR, Fang JC. Prevention and management of complications of percutaneous endoscopic gastrostomy (PEG) tubes. Pract Gastroenterol. 2004;22:66–76.
8. Disario JA. Endoscopic approaches to enteral nutritional support. Best Pract Res Clin Gastroenterol. 2006;20(3):605–30.

9. Eisen GM, Baron TH, Dominitz JA, et al. Role of endoscopy in enteral feeding—ASGE standards of practice. Gastrointest Endosc. 2002;55:794–7.
10. Sharma VK, Howden CW. Meta-analysis of randomized, controlled trials of antibiotic prophylaxis before percutaneous endoscopic gastrostomy. Am J Gastroenterol. 2000;95:3133–6.
11. Kwon RS, Banerjee S, Desilets D, et al. Enteral nutrition access devices. Gastrointest Endosc. 2010;72(2):236–48.
12. Giordano-Nappi JH, Ishioka S, Maluf-Filho F, et al. A new device for the introducer technique for percutaneous endoscopic gastrostomy placement. Endoscopy. 2007;3:E274–5.
13. Fan AC, Baron TH, Rumalla A, et al. Comparison of direct percutaneous endoscopic jejunostomy and PEG with jejunal extension. Gastrointest Endosc. 2002;56:890–4.
14. Bankhead RR, Fisher CA, Rolandelli RH. Gastrostomy tube placement outcomes: comparison of surgical, endoscopic and laparoscopic methods. Nutr Clin Pract. 2005;20(6):607–12.
15. Galaski A, Peng WW, Ellis M, et al. Gastrostomy tube placement by radiological versus endoscopic methods in an acute care setting: a retrospective review of frequency, indications, complications and outcomes. Can J Gastroenterol. 2009;23(2):109–14.
16. Freeman C, Delegg MH. Small bowel endoscopic enteral access. Curr Opin Gastroenterol. 2009;25(2):155–9.
17. Marik PE, Zaloga G. Gastric versus post-pyloric feeding: a systematic review. Crit Care. 2003;7:R46–51.
18. Pruthi D, Duekksen DR, Singh H. The practice of gastrostomy tube placement across a Canadian regional health authority. Am J Gastroenterol. 2010;105:1541–50.
19. Kuo CH, Hu HM, Tsai PY, et al. A better method for preventing infection of percutaneous endoscopic gastrostomy. J Gastrointest Surg. 2008;12(2):358–63.
20. Potack JZ, Chokhavatia S. Complications of and controversies associated with percutaneous endoscopic gastrostomy: report of a case and literature review. Medscape J Med. 2008;10(6):142.
21. Chang WK, Huang WC, Yu CY, Hsieh TY. Long-term percutaneous endoscopic gastrostomy: characteristic computed tomographic findings. Abdom Imaging. 2011;36(6):684–8.
22. Westaby D, Young A, O'Toole P, et al. The provision of a percutaneously placed enteral tube feeding service. Gut. 2010;59(12):1592–605.
23. Loser C. Clinical aspects of long-term enteral nutrition via percutaneous endoscopic gastrostomy (PEG). J Nutr Health Aging. 2004;1:47–50.

Enteral and Parenteral Nutrition

14

Manie Juneja and Stephen J.D. O'Keefe

Overview

Changes associated with normal aging increase nutritional risk [1–3]. Maintenance of nutrition is an essential component of comprehensive geriatric care, particularly in the acute care setting where the presence of malnutrition is clearly associated with increased complications irrespective of the underlying disease, resulting in reduced function and quality of life [4–6].

Prevalence of Malnutrition

Malnutrition and involuntary weight loss occur in 25–60% of institutionalized patients and 35–65% of hospitalized elderly patients [4, 7, 8]. Ambulatory outpatients are less frequently malnourished with estimates ranging from 1 to 15% [4, 7, 8]. In one study, malnutrition was observed in 29% of new admissions to a long-term care geriatric facility [4].

Pathophysiology of Malnutrition

In general, the causes of weight loss in elderly people can be classified into those due to disease, psychological distress, or socioeconomic factors (Table 14.1). Psychological factors contribute significantly more to weight loss in the geriatric population than the young [9–15]. Under-nutrition may itself contribute to the depression, leading to a vicious cycle [16, 17].

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Dementia is commonly associated with insufficient oral intake, and less often with hyperactivity and enhanced energy requirements [18]. In advanced dementia, dysphagia may exacerbate the situation. Up to one-quarter of all cases of malnutrition in this population have no identifiable cause [10].

Nutritional Screening and Assessment

The American Society of Parenteral and Enteral Nutrition (ASPEN) has provided clinical practice guidelines and rationales for nutrition screening, assessment, and intervention in adults [19]; the summary includes:

1. Screening for nutrition risk is suggested for hospitalized patients, as patients identified at nutrition risk are associated with longer length of hospital stay, complications, and mortality.
2. Nutrition assessment is suggested for all patients who are identified to be at nutrition risk by nutrition screening, as malnourished patients have more complications and longer hospitalizations than do patient with optimal nutrition status.
3. Nutrition support intervention is recommended for patients identified by screening and assessment at risk for malnutrition, as it may improve clinical outcomes.

Indications for Nutritional Support

Countless studies have evidenced the adage "if the gut works, use it" (Fig. 14.1). Mechanical obstruction is the only absolute contraindication to enteral feeding. Severe diarrhea, protracted vomiting, enteric fistula, and intestinal dysmotility may provide special challenges to tube feeding, but are not necessarily contraindications [20]. Nutritional support must be tailored to individual needs. When unable to eat adequately, oral nutritional supplementation (ONS) can increase energy, protein, and micronutrient intake to improve nutritional status and survival [21, 22].

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Because nutrient stores are often depleted in the elderly, enteral nutrition (EN) is begun as soon as possible in ICU patients not expected to eat normally within 5 days [23].

Table 14.1 Common causes of unintentional weight loss in geriatric patients, with a range of occurrence [9–13, 15, 90]

Malignancy (%)	16–36
Psychiatric illness including depression (%)	9–42
Gastrointestinal disorder (%)	6–19
Endocrine disease (e.g., hyperthyroidism) (%)	4–11
Cardiovascular disease (%)	2–9
Nutritional deficiency and alcohol abuse (%)	4–8
Respiratory disease (%)	6
Neurologic disease (%)	2–7
Chronic infections (%)	2–5
Chronic kidney disease (%)	4
Connective tissue disease (%)	2–4
Adverse drug effects or drug-induced weight loss (%)	2
Unknown (%)	10–36

Patients with severe neurological dysphagia are commonly malnourished, and, again, tube feeding to bypass the problem is initiated as soon as possible, accompanied by intensive swallow therapy until safe and sufficient oral intake from a normal diet is possible [24, 25].

The indications for postpyloric feeding include gastroparesis, acute pancreatitis, gastric outlet stenosis, recurrent aspiration, and trachea-esophageal fistula. If the estimate is that resumption of normal eating will take over 2 weeks, early percutaneous endoscopic gastrostomy (PEG) should be considered, since it is associated with less treatment failures and better nutritional status [26]. For patients with terminal dementia (irreversible, immobile, unable to communicate, completely dependent, lack of physical resources) nutritional interventions utilizing tube feeding and PEGs are not recommended [27]. When oral or EN is impossible and has been or is likely to be insufficient for more than 7–10 days, parenteral nutrition (PN) should be instituted in the acutely ill older person. EN should always be the first choice with PN

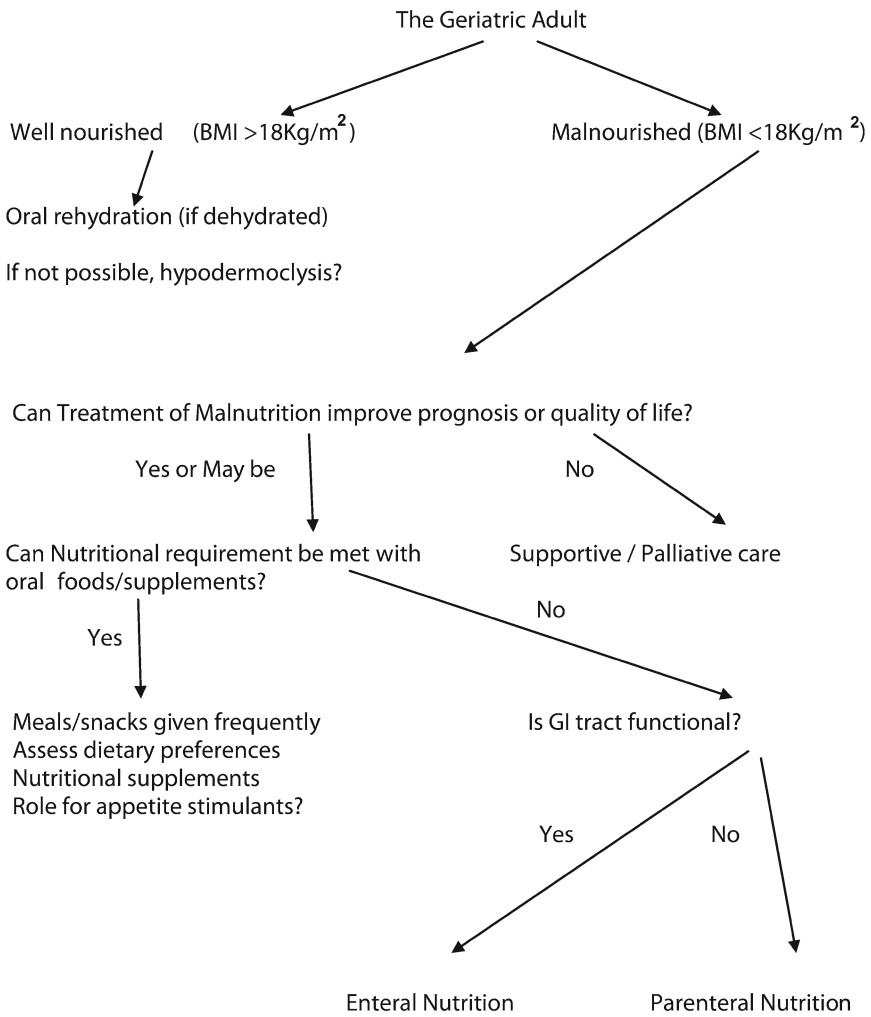

Fig. 14.1 Algorithm for nutritional and fluid management in the aged

less often justified as it is more invasive and associated with serious complications, besides requiring intensive nursing care [28, 29]. PN and parenteral rehydration in this context should be considered medical treatments rather than basic care. Therefore, their use should be balanced against a realistic chance of improvement in the general condition.

For patients unable to fully meet their nutritional requirements through EN, there is accumulating evidence that PN should be used to "top up" in order to meet nutritional goals and prevent progressive energy debt.

Methods of Nutrition Support

Oral Nutritional Supplements

The first approach to the undernourished patient is to improve normal oral food intake. The patient and family should be interviewed in the presence of a dietitian to assess food intake and preferences. Dietary assessment will dictate solutions to poor intake; recommendations on food intake require follow-up within a month to assess the response. If there is no improvement, supplementation of the usual diet with nutrient-dense formula diets is the next step. Supplements are available at drug stores; examples include "Boost," "Carnation Instant Breakfast," and "Ensure," with taste preferences dictating choice. If weight loss continues in a month, it may be appropriate to consider EN or "tube feeding."

Enteral Nutrition

Enteral nutrition (EN) refers to any form of artificial nutrition delivered to the gastrointestinal tract. EN is not only superior to PN in its efficiency of utilization by the body, but also in its ability to maintain mucosal health and suppress systemic inflammatory responses. EN maintains mucosal barrier function and minimizes the risk of overfeeding, infective complications, and hyperglycemia [23, 30, 31]. However, data suggest that nutritional restitution in frail elderly patients with sarcopenia is difficult even with EN compared to younger patients [32, 33].

(A) *Methods of EN*: There are several ways to deliver EN, with the choice dependent on feeding issues [20, 34]. For anorexia, dysphagia, or dementia, placement of a nasogastric (NG) tube is the temporary solution. For gastroparesis, postpyloric placement is more effective and reduces the risk of aspiration. If tube feeding is likely to be required for over a month, placement of a percutaneous gastrostomy is indicated. It is important to assess GI tolerance to additional feeding by initially using an NG tube, before subjecting the patient to the additional surgical risks of PEG for long-term support. This circumvents the issue of anorexia and provides information on whether the inability to eat is due to central causes or mechanical problems, such as subacute obstruction or dysmotility.

(i) *Nasogastric Feeding*: These tubes can be placed at the bedside by virtually any member of the health care team. However, the esophagus may be tortuous (presbyesophagus) in the aged and the tube can get stuck in a fold or diverticulum increasing perforation risk or enter the airways. Placement is best with the patient sitting up, with the nostrils and tube well lubricated. The tube is passed in a simple arc and not bent too acutely. Once in the esophagus, a small sip of water will help propel the tube into the stomach assisted by peristaltic contractions. The end of the tube should be placed in the antro-fundal region for best function. Before feeding, it is imperative to demonstrate that the tube is in the stomach, by injecting 30 cc air down the tube while auscultating the epigastrium. A blast with bubbles is heard; the maneuver is not diagnostic, as the tube tip in the esophagus may sound similar and may be hard to distinguish. If there is any concern, a chest X-ray is performed before commencing feeding, as bronchial displacement can be remarkably asymptomatic in the aged infirm sick patient. Feeding is always begun as a continuous 24-h infusion with monitoring of tolerance as previously described [35]. Nasogastric (NG) tubes are remarkably effective in providing enteral feeding in the ICU setting [36]. If NG feeding is not tolerated because of nausea and vomiting due to high gastric residual volume or delayed gastric emptying (e.g., in diabetics, stroke, critical illness, and as an adverse drug effect), postpyloric feeding may be attempted. Once goal infusion rates are achieved, cyclical feeding is utilized, where infusions are provided primarily at night over 12 h at a faster rate, allowing the tube to be clamped by day to encourage normal activities and eating. Older adults are best encouraged to eat even though enteral feeding is commenced, to minimize withdrawal and social isolation.

(ii) *Postpyloric Feeding*: Feeding tubes can be passed through the stomach and into the duodenum or even further down the jejunum by manual, endoscopic, or radiological techniques. (a) *Manual*: Feeding tubes are easy to place in the stomach, but postpyloric placement is often more difficult because the pylorus is bent back on the body of the stomach. This is even harder with a previous history of peptic ulcer disease or surgery. Prokinetic drugs (e.g., metoclopramide, erythromycin) administered before tube insertion can increase the success of pyloric intubation, as

can maneuvers such as inflating the stomach with 500 cc air and positioning the patient on the right side. Duodenal placement can also be assisted by devices such as the "Cortrak," which uses an external magnet to draw the metal tip of the feeding tube through the pylorus [37]. (b) *Endoscopic*: the development of thin caliber endoscopes (i.e., 5–5.8 mm) has made transnasal endoscopic placement of feeding tubes possible [38]. The technique has the advantage of visibility, minimizing mucosal trauma, misplacement in the airways, and detection of unsuspected upper GI disease. A routine diagnostic endoscopy of the esophagus, stomach, and duodenum is followed by the deployment of a guide wire through the operating channel of the endoscope once in the distal duodenum .When the endoscope is withdrawn, the lubricated feeding tube is fed over the guide wire and pushed into position. (c) *Radiological*: Tubes are manipulated with fluoroscopic guidance through the nose, esophagus, and stomach into the duodenum and jejunum

(iii) *Percutaneous Gastrostomies*: In general, if tube feeding is needed for longer than 2–4 weeks, a gastrostomy should be considered as it is more comfortable for the patient, and easier to use for the caregiver. Gastrostomy, whether by open surgery, endoscopy, or radiology, is a surgical procedure involving willful perforation of the bowel; it is therefore invasive and associated with potentially life-threatening complications particularly in the aged, malnourished, confused patient. While a gastrostomy renders institutional care easier, it deprives the patient of the joy of tasting food, and the individual attention associated with assisted feeding. Consequently, cup-and-spoon feeding should be continued as long as possible, particularly as life draws to a close. Gastroenterologists need to be reminded that PEG placement is easy, but it is invasive, associated with complications that may shorten rather than prolong life. On the other hand, with neurological deficits (e.g., acute stroke with good prognosis) or mechanical esophageal dysfunction (e.g., carcinoma esophagus), PEGs are effective in maintaining nutrition while awaiting recovery.

(B) *Practical guidelines for EN*:

(i) *Nasogastric Feeding*: The risk of aspiration is higher with NG than postpyloric feeding, especially with delayed gastric emptying or dysmotility. The risk is minimized by:

(a) Keeping the head up, body at 45°.

(b) Start at 25 cc/h, increase by 25 cc/h every 12 h until goal feeding rates are achieved at 25 kcal/kg ideal body weight.

(c) Use a regular isotonic polymeric feed unless the patient has pancreatic insufficiency. Check gastric residual volumes every 4–6 h. If volumes are >250 cc try prokinetics (e.g., metoclopramide), and discontinue causative medications such as opiates or anticholinergics. PPIs may reduce endogenous secretions, but long-term use is discouraged due to numerous adverse effects such as aspiration pneumonia, nutrient deficiencies, bacterial overgrowth, hip fracture, and other consequences [39].

(d) Use a pumped continuous feeding rate rather than bolus feeding until good tolerance is shown. After this, bolus feeding can be given to ease administration and institutional care.

(ii) *Postpy*loric Feeding: Use similar precautions as above. The risk of high gastric residual volume is less, as is aspiration. Use a continuous feeding schedule with pump, as bolus feeding is never used in the small intestine, being not physiological. Either add water to the feed or feed at a faster rate and if using a "closed system," piggy-back the hydration requirements into the feeding port. IV infusions for hydration should never be used in patients who have enteral access. Solid medications cause tube occlusion and are ideally never administered via the jejunostomy; the tube should be flushed every 6–8 h with at least 20 cc tap water.

Types of Enteral Formula

Enteral formulas consist of varying mixtures of protein, carbohydrate, and fat and may fall into one of the categories (Table 14.2). Isotonic general-use formulas, based on the composition of normal food, with caloric densities of 1–1.2 kcal/mL, with or without added fiber, are the initial products of choice as they meet most requirements, are well tolerated, and not expensive. Higher caloric density formulas (1.5–2.0 kcal/mL) are useful for short-term use when fluid restriction is crucial.

Disease Specific/Specialty Formula [23, 40–42]

- *Fiber*: Formulas with high fiber content help prevent or decrease tube-feed related diarrhea and constipation. Constipation is more common in the aged, with fiber essential to maintain a normal microbiota to help convert the residues to short chain fatty acids essential for mucosal health, function, and motility [43].
- *Malabsorption, maldigestion, short bowel*: Patients with impaired digestion (e.g., chronic pancreatitis) or mucosal

Table 14.2 Composition of standard and disease-specific enteral nutrition products [87]

Product (examples of brands)	Caloric density (kcal/mL)	Protein (g/L)	Energy (%)		
			Carbohydrates	Fat	Protein
General use: Jevity, Osmolite, Ensure	1.0	35–45	55	30	15
High nitrogen: Promote, Replete, Sustacal	1.0	62	50	25	25
High nitrogen, high calorie: Nutren 1.5, Plus, Ensure Plus, Resource Plus	1.5	60	50	35	15
Very high nitrogen, very high calorie: Magnacal, Nutren 2.0	2.0	70–80	45	40	15
Renal, predialysis: Suplena, Amin-aid	2.0	20–30	50–75	20–45	5
Renal, dialysis: Nepro	2.0	70	43	43	14
Diabetes: Glucerna	1.0	70	33	50	17
Pulmonary disease: Pulmocare, NutriVent	1.5	60–70	27	55	18
Critical care: Alitraq, Impact	1.0	50–70	55–65	15–25	20
Gastrointestinal dysfunction/semielemental: Peptamen	1.0	40	51	33	16

function (the critically ill) will better tolerate formulae that are hydrolyzed to semielemental (e.g., Peptamen, Nestle Nutritionals) or elemental form (Vivonex, Nestle Nutritionals). Such formulae are helpful in acute pancreatitis where pancreatic stimulation is best minimized.

- *Immune-enhancing diets (IED)*: This is a loose term, encompassing all formula that contain enrichments with nutrients known to have an effect on inflammation, e.g., arginine, glutamine, and *n*-3 fatty acids (fish oils). No clinical trials have examined their effectiveness specifically in the elderly; meta-analysis [44] of 22 randomized trials with 2,419 patients comparing immunonutrition to standard enteral nutrition in surgical and critically ill patients revealed that IEDs were associated with lower infection rates, but no difference in mortality. Subgroup analysis suggested that critically ill patients might have a higher mortality with arginine supplementation. In a later meta-analysis of 24 studies (with 3,013 patients), 12 in critical care, 5 involving patients with burns, and 7 concerning trauma victims, data confirmed a reduction in infections but no effect on mortality [45]. In summary, the additional cost of these products is probably unwarranted. It is probably more important to strive to meet nutritional requirements with standard commonly available feeds.
- *Renal failure*: General use formula (Table 14.2) can be used for short-term EN in undernourished patients with chronic kidney disease (CKD) [46] and for patients on dialysis. Disease-specific formulae (protein-restricted formulae containing essential amino acids and ketoanalogues with reduced electrolyte content) are better tolerated in patients with CKD requiring EN greater than 5 days [47]. These products also have a high energy density (1.5–2.0 kcal/mL) to assist in fluid restriction (e.g., Nepro®, Abbott Nutrition, Columbus, OH).
- *Obstructive lung disease*: Studies suggest that the standard formula rich in carbohydrates providing 50–60% calories may predispose to respiratory failure due to a higher respiratory quotient [48, 49]. Patients with obstructive lung diseases may benefit from formulae with higher fat content (e.g., Pulmocare®, Abbott Nutrition, Columbus, OH).
- *Diabetes*: Low glycemic index formulae (e.g., Glucerna SR®, Abbott Nutrition, Columbus, OH) with complex carbohydrates can lead to significantly better 24 h and postprandial glucose profiles than isocaloric standard fiber-containing formulae after bolus administration. This may promote glycemic control in diabetic patients [41].
- *Liver failure*: Hepatic formulae (e.g., Hepatic-Aid II®, Hormel Health Labs, Austin, MN) are high in branched chain amino acids and low in aromatic amino acids. This combination normalizes the disturbed amino acid profile in the bloodstream, reduces encephalopathy, and improves protein synthesis in patients with liver failure [50, 51]. Improvement in nutritional status, survival, and reduction in complications have been noted in cirrhotics with severe malnutrition supplemented with hepatic enteral formula [52, 53].

Parenteral Methods

Hydration

Hypodermoclysis (HDC) is the method of correcting fluid deficits by subcutaneous infusion. Its advantage is that it is simple and less invasive than IV hydration, and can be managed by nursing staff or family members in the home environment or nursing facility, avoiding stressful hospitalization [54]. Near-isotonic fluids are introduced into subcutaneous tissues to correct mild-to-moderate dehydration, especially in chronic care settings where the intravenous route is difficult [55]. The preferred fluid is normal saline, but half-normal saline, dextrose-saline, or 5% dextrose may also be used with additions of potassium chloride up to 40 mEq/L. Typical rates of infusion are 1 mL/min/site or 1.5 L/day/site, by gravity through a 31 or 23 gauge needle, with site changes every 4 days. Needles are inserted at 45–60° angle into sites such as abdomen, upper chest, thigh, and outer upper arm. The addition of hyaluronidase 150 units/L permits higher rates of infusion.

Parenteral Nutrition

Age per se is not a reason to exclude patients from PN [56]. Parenteral nutrition is the sole source of feeding in patients with intestinal failure (total parenteral nutrition) or to supplement malnourished patients inadequately fed by EN. Its use, however, in terminal patients, especially for inoperable or untreatable cancer with limited life expectancy (less than 3 months) should be avoided, as it does not improve quality of life nor survival [57]. This must be firmly explained to the family, as it may be perceived that forced feeding may improve strength and function, when it often has the reverse effect of impairing mobility and worsening outcomes. Pharmacological sedation or physical restraints to make PN possible is not justified. PN is delivered by central vein (e.g., subclavian) if its use is estimated to be >4 weeks, or peripheral vein (PICC) for short term [58], as PICC is easier to place and replace.

In permanent intestinal failure due to massive intestinal loss (short bowel) or inoperable obstruction, long-term PN at home (HPN) is life-saving. In United States, patients over the age of 65 represented a quarter of all HPN patients [59]. With demographic trends suggesting increase in life expectancy, older people will require HPN in the future. Managing TPN at home is difficult, requiring education for the caregiver regarding catheters and infusions, prior to discharge from hospital. Poor management increases the risk of life-threatening septicemias through IV contamination and metabolic derangements [60, 61].

Outcomes Associated with Artificial Feeding in the Elderly

Enteral Nutrition

General: In the elderly with functioning gastrointestinal tracts but eating inadequately, enteral feeding is associated with fewer infections, lower costs, and shorter hospital stays compared to parenteral nutrition support [62]. EN reduces risk of major life-threatening infections and noninfection events, and other adverse events with significant cost reduction; shifting more adults from PN to EN may result in cost savings [63]. Home enteral tube feeding (in the community) is an option that provides several benefits as long as the training and after care is appropriately provided [64].

Orthopedic Surgery: Elderly patients are at greater risk of falls, consequent fractures, and need for orthopedic procedures. Voluntary oral intake may be insufficient to meet the enhanced requirements of energy, protein, and micronutrients following orthopedic surgery. Rapid deterioration in nutritional status impedes recovery and rehabilitation. ONS have a positive impact on the rate of postoperative complications after orthopedic surgery [65, 66].

Pressure Sores: Impaired nutrition may be one of several factors that delays healing of pressure ulcers; ONS with high protein content may favorably impact healing of pressure ulcers in elderly patients [67].

Depression: Anorexia and refusal to eat commonly accompany depression in the aged. If ONS fails, it is appropriate to maintain nutrition by EN while depression is being treated [16, 17].

Dementia: Few studies have shown limited improvement in body weight in patients with dementia on EN [68]. The success of nutritional therapy in dementia is strongly influenced by the severity of disease, comorbidities, and the general condition. Getting an early start with adequate, high-quality nutrition in the early-to-moderate stages of dementia may help sustain a stable condition [69]. While a meta-analysis of 32 randomized controlled trials with 3,017 elderly patients with dementia revealed a lower mortality risk in those supplemented with EN [70], another meta-analysis revealed no effect [71]. The data on functional status in dementia is inconsistent. Gray-Donald et al. [72] observed a significantly lower frequency of falls and higher activity level in patients supplemented with EN as compared to nonsupplemented. On the other hand several studies detected no difference between intervention and control groups with respect to independence in activities in daily living [73, 74].

Dysphagia and Aspiration: Aspiration pneumonia in tube-fed elderly is common; data are inconclusive regarding the reduction in pneumonia risk with nutrition delivered through NG or PEG tubes [75, 76].

PEGs: In comparing PEG with NG tubes in geriatric patients, PEGs are superior in facilitating the administration of greater amounts of energy and nutrients over longer periods, and with less discomfort, helping nutritional status [77, 78]. This may not translate into prolonged survival in all tube-fed patients.

Complications associated with EN have been summarized in Table 14.3.

Parenteral Nutrition

Geriatric patients suffer the same complications as those by the younger, but the frequency is higher [59]. Vitamin and mineral deficiencies are more prevalent in old compared to the young and not always corrected through PN [79]. A study involving 325 patients on PN confirmed that, with a similar nutritional intake, depleted body mass was restored more slowly in older patients; age was a significant independent variable affecting the response to nutritional support [80]. Insulin resistance and the prevalence of diabetes mellitus increase with age, calling for monitoring of glucose tolerance in the elderly on PN [81]. Hyperglycemia in noncritical ill patients receiving PN is a risk factor for increased mortality [82]. Data also suggests that in spite of tight glucose control, PN

Table 14.3 Adverse nonmechanical effects of enteral nutrition and management approaches [91]

Adverse effects	Management
Poor tolerance	Consider
Frequent self-extubation	Percutaneous gastrostomy tubes
Agitation	Parenteral nutrition (if benefits outweigh the risks)
Pulmonary	Elevate head of bed to over 30°
Aspiration	Monitor gastric residuals and rate of feeding Nasointestinal, G-J, J tubes
Gastrointestinal	
Gastric retention	Low-fat formula, metaclopramide
Nausea/vomiting	Nasointestinal, G-J, J-tubes
Diarrhea	Address delivery rate, use of fiber, infectious causes, antidiarrheals
Metabolic complications	
Hyperglycemia	Routine monitoring of glucose, insulin dose, and electrolytes
Fluid and electrolytes	Monitor weight, volume status, free water and electrolyte administration
Refeeding syndrome	Monitor phosphorous, magnesium, potassium
Drug interactions	
Tube feeds and drug bioavailability (e.g., ciprofloxacin, azithromycin)	Hold feedings 15 min before and after medication administration
Frequent medication administration interrupts nutrition	Alternate medication routes may be considered (IV, IM, transdermal)

remains a risk factor for infections in surgical intensive critical care patients [83]. Impaired cardiac and renal functions are common in the old; fluid and sodium infusions require caution, especially during periods of mobilization of extracellular water that has accumulated due to inflammatory processes or during refeeding [84].

Refeeding Syndrome: The refeeding syndrome is common in malnourished elderly. Before commencing EN or PN blood tests must determine metabolic status, with particular attention to phosphate and potassium. Feeding is commenced at 25–50% of estimated daily requirements and advanced as tolerated daily with follow-up laboratory tests. Additional vitamin supplements are advised from start, for example thiamine and water-soluble vitamins, as thiamine deficiency may contribute to the refeeding syndrome, impairing the utilization of infused carbohydrate and protein. Glucose infusion can provoke a rapid drop in plasma phosphate level leading to several acute changes including hypoxia, rhabdomyolysis, hemolysis, and delirium [85]. Thiamine deficiency can be precipitated in the refeeding syndrome causing Wernicke's encephalopathy or Korsakov's syndrome with diplopia, confabulation, confusion, and coma.

Table 14.4 Metabolic and fluid-related complications of TPN and possible corrective strategies [91]

Condition	Prevention/management
Fluid overload	Restrict fluid administration
Hyperglycemia	Carbohydrate delivery (rate, amount)
Hypoglycemia	Avoid sudden cessation of TPN
Refeeding syndrome	First replace vitamin and nutrition deficiencies; Start, titrate TPN slowly
Hypertriglyceridemia	Fat infusion rates and frequency
Metabolic alkalosis	Consider renal or gastrointestinal losses
Metabolic acidosis	Intestinal losses (diarrhea), or sepsis
Respiratory (hypercarbia)	Total calories (proportion) from fat

Table 14.5 Other complications of TPN and potential corrective measures [91]

Condition	Prevention/management
Line related	
Line infection	Single-lumen catheter, dedicated TPN line; infection control practices
Catheter occlusion	Regular flushes; no line blood draws; urokinase
Hepatic	
Steatosis/LFTs	Avoid carbohydrate overfeeding; rule out other causes
Biliary (cholestasis)	Enteral feed if possible

There is some evidence that the elderly on PN may require a formula with higher lipid content, up to 50% of the total energy intake, due to alterations in glucose oxidation, but most important is the need to avoid overfeeding, at over 25 kcal/kg/day [86, 87]. Older age was associated with a higher risk of central catheter vascular erosion in a prospective study of 1,499 patients [88]. Data is inadequate on the effect of PN on quality of life and length of hospital stay in older people [89].

Home TPN can support improvement of functional status, but the margin of improvement is lower than in younger patients [59]. In a study of patients with dysphagia on Home TPN, the elderly had poorer outcome (i.e., lower survival, poorer rehabilitation, and fewer resumed full oral nutrition) than those younger after 1 year of follow-up [59]. The conclusion was that age was a negative prognostic factor, but Home TPN was still reasonably effective.

Complications associated with PN are summarized in Tables 14.4 and 14.5.

Key Points

- Malnutrition is common in geriatric population, and a consideration for some forms of nutritional support.
- As long as the gut is functional, the preferred route for nutrition is oral nutritional supplementation, followed by enteral nutrition.

- Intestinal failure is the only absolute indication for PN, although initial PN supplementation may be necessary in the critically ill depleted patient while awaiting the goals achievable through EN.
- PN is associated with far more complications and costs than EN.
- In the majority of patients, a simple low-cost polymeric formula will meet most nutritional requirements.
- Forced feeding through EN, PN, or PEG tube placement in the terminally ill should be avoided, as these interventions have complications and may actually impair the remaining quality of life.

References

1. Rolls BJ. Do chemosensory changes influence food intake in the elderly? Physiol Behav. 1999;66(2):193–7.
2. Parker BA, Chapman IM. Food intake and ageing—the role of the gut. Mech Ageing Dev. 2004;125(12):859–66.
3. Horowitz M, Maddern GJ, Chatterton BE, et al. Changes in gastric emptying rates with age. Clin Sci (Lond). 1984;67(2):213–8.
4. Silver AJ, Morley JE, Strome LS, et al. Nutritional status in an academic nursing home. J Am Geriatr Soc. 1988;36(6):487–91.
5. Bernstein LH, Shaw-Stiffel TA, Schorow M, et al. Financial implications of malnutrition. Clin Lab Med. 1993;13(2):491–507.
6. Ferguson RP, O'Connor P, Crabtree B, et al. Serum albumin and prealbumin as predictors of clinical outcomes of hospitalized elderly nursing home residents. J Am Geriatr Soc. 1993;41(5):545–9.
7. Abbasi AA, Rudman D. Undernutrition in the nursing home: prevalence, consequences, causes and prevention. Nutr Rev. 1994;52(4):113–22.
8. Edington J, Kon P. Prevalence of malnutrition in the community. Nutrition. 1997;13(3):238–40.
9. Marton KI, Sox Jr HC, Krupp JR. Involuntary weight loss: diagnostic and prognostic significance. Ann Intern Med. 1981;95(5):568–74.
10. Rabinovitz M, Pitlik SD, Leifer M, et al. Unintentional weight loss. A retrospective analysis of 154 cases. Arch Intern Med. 1986;146(1):186–7.
11. Bilbao-Garay J, Barba R, Losa-Garcia JE, et al. Assessing clinical probability of organic disease in patients with involuntary weight loss: a simple score. Eur J Intern Med. 2002;13(4):240–5.
12. Thompson MP, Morris LK. Unexplained weight loss in the ambulatory elderly. J Am Geriatr Soc. 1991;39(5):497–500.
13. Lankisch P, Gerzmann M, Gerzmann JF, et al. Unintentional weight loss: diagnosis and prognosis. The first prospective follow-up study from a secondary referral centre. J Intern Med. 2001;249(1):41–6.
14. Huffman GB. Evaluating and treating unintentional weight loss in the elderly. Am Fam Physician. 2002;65(4):640–50.
15. Lin HW, Li CM, Lee YC, et al. Differences in diagnostic approach between family physicians and other specialists in patients with unintentional body weight loss. Fam Pract. 1999;16(6):586–90.
16. Morley JE, Kraenzle D. Causes of weight loss in a community nursing home. J Am Geriatr Soc. 1994;42(6):583–5.
17. Brozek J. Effects of generalized malnutrition on personality. Nutrition. 1990;6(5):389–95.
18. Marcus EL, Berry EM. Refusal to eat in the elderly. Nutr Rev. 1998;56(6):163–71.
19. Mueller C, Compher C, Ellen DM. A.S.P.E.N. clinical guidelines: nutrition screening, assessment, and intervention in adults. JPEN J Parenter Enteral Nutr. 2011;35(1):16–24.
20. Kirby DF, Delegge MH, Fleming CR. American Gastroenterological Association technical review on tube feeding for enteral nutrition. Gastroenterology. 1995;108(4):1282–301.
21. Horton WL, Colwell DL, Burlon DT. Experience with percutaneous endoscopic gastrotomy in a community hospital. Am J Gastroenterol. 1991;86(2):168–70.
22. Finucane P, Aslan SM, Duncan D. Percutaneous endoscopic gastrostomy in elderly patients. Postgrad Med J. 1991;67(786):371–3.
23. Debaveye Y, Van den Berghe G. Risks and benefits of nutritional support during critical illness. Annu Rev Nutr. 2006;26:513–38.
24. Nyswonger GD, Helmchen RH. Early enteral nutrition and length of stay in stroke patients. J Neurosci Nurs. 1992;24(4):220–3.
25. Broadley S, Croser D, Cottrell J, et al. Predictors of prolonged dysphagia following acute stroke. J Clin Neurosci. 2003; 10(3):300–5.
26. Angus F, Burakoff R. The percutaneous endoscopic gastrostomy tube. Medical and ethical issues in placement. Am J Gastroenterol. 2003;98(2):272–7.
27. Sanders DS, Carter MJ, D'Silva J, et al. Survival analysis in percutaneous endoscopic gastrostomy feeding: a worse outcome in patients with dementia. Am J Gastroenterol. 2000;95(6):1472–5.
28. Braunschweig CL, Levy P, Sheean PM, et al. Enteral compared with parenteral nutrition: a meta-analysis. Am J Clin Nutr. 2001;74(4):534–42.
29. Heyland DK, MacDonald S, Keefe L, et al. Total parenteral nutrition in the critically ill patient: a meta-analysis. JAMA. 1998; 280(23):2013–9.
30. Jeejeebhoy KN. Enteral nutrition versus parenteral nutrition—the risks and benefits. Nat Clin Pract Gastroenterol Hepatol. 2007; 4(5):260–5.
31. Zaloga GP. Parenteral nutrition in adult inpatients with functioning gastrointestinal tracts: assessment of outcomes. Lancet. 2006; 367(9516):1101–11.
32. Hebuterne X, Schneider S, Peroux JL, et al. Effects of refeeding by cyclic enteral nutrition on body composition: comparative study of elderly and younger patients. Clin Nutr. 1997;16(6):283–9.
33. Schneider SM, Al-Jaouni R, Pivot X, et al. Lack of adaptation to severe malnutrition in elderly patients. Clin Nutr. 2002;21(6): 499–504.
34. American Gastroenterological Association medical position statement: guidelines for the use of enteral nutrition. Gastroenterology. 1995;108(4):1280–1.
35. O'Keefe SJ. A guide to enteral access procedures and enteral nutrition. Nat Rev Gastroenterol Hepatol. 2009;6(4):207–15.
36. Marik PE, Zaloga GP. Early enteral nutrition in acutely ill patients: a systematic review. Crit Care Med. 2001;29(12):2264–70.
37. Gray R, Tynan C, Reed L, et al. Bedside electromagnetic-guided feeding tube placement: an improvement over traditional placement technique? Nutr Clin Pract. 2007;22(4):436–44.
38. O'Keefe SJ, Foody W, Gill S. Transnasal endoscopic placement of feeding tubes in the intensive care unit. JPEN J Parenter Enteral Nutr. 2003;27(5):349–54.
39. Lewis SJ, Franco S, Young G, et al. Altered bowel function and duodenal bacterial overgrowth in patients treated with omeprazole. Aliment Pharmacol Ther. 1996;10(4):557–61.
40. Malone AM. Specialized enteral formulas in acute and chronic pulmonary disease. Nutr Clin Pract. 2009;24(6):666–74.
41. Ceriello A, Lansink M, Rouws CH, et al. Administration of a new diabetes-specific enteral formula results in an improved 24 h glucose profile in type 2 diabetic patients. Diabetes Res Clin Pract. 2009;84(3):259–66.
42. Rushdi TA, Pichard C, Khater YH. Control of diarrhea by fiber-enriched diet in ICU patients on enteral nutrition: a prospective randomized controlled trial. Clin Nutr. 2004;23(6):1344–52.
43. Lewis S, Burmeister S, Brazier J. Effect of the prebiotic oligofructose on relapse of *Clostridium difficile*-associated diarrhea: a randomized, controlled study. Clin Gastroenterol Hepatol. 2005;3(5):442–8.
44. Heyland DK, Novak F, Drover JW, et al. Should immunonutrition become routine in critically ill patients? A systematic review of the evidence. JAMA. 2001;286(8):944–53.

45. Marik PE, Zaloga GP. Immunonutrition in critically ill patients: a systematic review and analysis of the literature. Intensive Care Med. 2008;34(11):1980–90.
46. Druml W, Mitch W. Enteral and tube feeding. Philadelphia: WB Saunders; 1997.
47. Abras E, Walser M. Nitrogen utilization in uremic patients fed by continuous nasogastric infusion. Kidney Int. 1982;22(4):392–7.
48. Frankfort JD, Fischer CE, Stansbury DW, et al. Effects of high- and low-carbohydrate meals on maximum exercise performance in chronic airflow obstruction. Chest. 1991;100(3):792–5.
49. Vermeeren MA, Wouters EF, Nelissen LH, et al. Acute effects of different nutritional supplements on symptoms and functional capacity in patients with chronic obstructive pulmonary disease. Am J Clin Nutr. 2001;73(2):295–301.
50. O'Keefe SJ, Ogden J, Ramjee G, et al. Short-term effects of an intravenous infusion of a nutrient solution containing amino acids, glucose and insulin on leucine turnover and amino acid metabolism in patients with liver failure. J Hepatol. 1988;6(1):101–8.
51. Blackburn GL, O'Keefe SJ. Nutrition in liver failure. Gastroenterology. 1989;97(4):1049–51.
52. Le Cornu KA, McKiernan FJ, Kapadia SA, et al. A prospective randomized study of preoperative nutritional supplementation in patients awaiting elective orthotopic liver transplantation. Transplantation. 2000;69(7):1364–9.
53. Kearns PJ, Young H, Garcia G, et al. Accelerated improvement of alcoholic liver disease with enteral nutrition. Gastroenterology. 1992;102(1):200–5.
54. Dasgupta M, Binns MA, Rochon PA. Subcutaneous fluid infusion in a long-term care setting. J Am Geriatr Soc. 2000;48(7):795–9.
55. Remington R, Hultman T. Hypodermoclysis to treat dehydration: a review of the evidence. J Am Geriatr Soc. 2007;55(12):2051–5.
56. Hearnshaw SA, Thompson NP. Use of parenteral nutrition in hospitals in the North of England. J Hum Nutr Diet. 2007;20(1):14–23; quiz 24–6.
57. American Gastroenterological Association medical position statement: parenterul nutrition. Gastroenterology. 2001;121(4):966–9.
58. Anderson AD, Palmer D, MacFie J. Peripheral parenteral nutrition. Br J Surg. 2003;90(9):1048–54.
59. Howard L, Malone M. Clinical outcome of geriatric patients in the United States receiving home parenteral and enteral nutrition. Am J Clin Nutr. 1997;66(6):1364–70.
60. O'Keefe SJ, Burnes JU, Thompson RL. Recurrent sepsis in home parenteral nutrition patients: an analysis of risk factors. JPEN J Parenter Enteral Nutr. 1994;18(3):256–63.
61. Burnes JU, O'Keefe SJ, Fleming CR, et al. Home parenteral nutrition—a 3-year analysis of clinical and laboratory monitoring. JPEN J Parenter Enteral Nutr. 1992;16(4):327–32.
62. Heyland DK, Dhaliwal R, Drover JW, et al. Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. JPEN J Parenter Enteral Nutr. 2003;27(5):355–73.
63. Cangelosi MJ, Auerbach HR, Cohen JT. A clinical and economic evaluation of enteral nutrition. Curr Med Res Opin. 2011;27(2):413–22.
64. Hitchings H, Best C, Steed I. Home enteral tube feeding in older people: consideration of the issues. Br J Nurs. 2010;19(18):1150–4.
65. Tkatch L, Rapin CH, Rizzoli R, et al. Benefits of oral protein supplementation in elderly patients with fracture of the proximal femur. J Am Coll Nutr. 1992;11(5):519–25.
66. Lawson RM, Doshi MK, Barton JR, et al. The effect of unselected postoperative nutritional supplementation on nutritional status and clinical outcome of orthopaedic patients. Clin Nutr. 2003;22(1):39–46.
67. Stratton RJ, Ek AC, Engfer M, et al. Enteral nutritional support in prevention and treatment of pressure ulcers: a systematic review and meta-analysis. Ageing Res Rev. 2005;4(3):422–50.
68. Wouters-Wesseling W, Van Hooijdonk C, Wagenaar L, et al. The effect of a liquid nutrition supplement on body composition and physical functioning in elderly people. Clin Nutr. 2003;22(4):371–7.
69. Faxen-Irving G, Andren-Olsson B, af Geijerstam A, et al. The effect of nutritional intervention in elderly subjects residing in group-living for the demented. Eur J Clin Nutr. 2002;56(3):221–7.
70. Milne AC, Potter J, Avenell A. Protein and energy supplementation in elderly people at risk from malnutrition. Cochrane Database Syst Rev. 2005;(2):CD003288.
71. Avenell A, Handoll HH. Nutritional supplementation for hip fracture aftercare in older people. Cochrane Database Syst Rev. 2005;(2):CD001880.
72. Gray-Donald K, Payette H, Boutier V. Randomized clinical trial of nutritional supplementation shows little effect on functional status among free-living frail elderly. J Nutr. 1995;125(12):2965–71.
73. Wouters-Wesseling W, Wouters AE, Kleijer CN, et al. Study of the effect of a liquid nutrition supplement on the nutritional status of psycho-geriatric nursing home patients. Eur J Clin Nutr. 2002;56(3):245–51.
74. Espaulella J, Guyer H, Diaz-Escriu F, et al. Nutritional supplementation of elderly hip fracture patients. A randomized, double-blind, placebo-controlled trial. Age Ageing. 2000;29(5):425–31.
75. Patel PH, Thomas E. Risk factors for pneumonia after percutaneous endoscopic gastrostomy. J Clin Gastroenterol. 1990;12(4):389–92.
76. Abitbol V, Selinger-Leneman H, Gallais Y, et al. [Percutaneous endoscopic gastrostomy in elderly patients. A prospective study in a geriatric hospital]. Gastroenterol Clin Biol. 2002;26(5):448–53.
77. Norton B, Homer-Ward M, Donnelly MT, et al. A randomised prospective comparison of percutaneous endoscopic gastrostomy and nasogastric tube feeding after acute dysphagic stroke. BMJ. 1996;312(7022):13–6.
78. Dwolatzky T, Berezovski S, Friedmann R, et al. A prospective comparison of the use of nasogastric and percutaneous endoscopic gastrostomy tubes for long-term enteral feeding in older people. Clin Nutr. 2001;20(6):535–40.
79. Lee JS, Frongillo Jr EA. Nutritional and health consequences are associated with food insecurity among U.S. elderly persons. J Nutr. 2001;131(5):1503–9.
80. Shizgal HM, Martin MF, Gimmon Z. The effect of age on the caloric requirement of malnourished individuals. Am J Clin Nutr. 1992;55(4):783–9.
81. Morley JE. Nutrition in the elderly. Curr Opin Gastroenterol. 2002;18(2):240–5.
82. Sarkisian S, Fenton TR, Shaheen AA, et al. Parenteral nutrition-associated hyperglycemia in noncritically ill inpatients is associated with higher mortality. Can J Gastroenterol. 2010;24(7):453–7.
83. Matsushima K, Cook A, Tyner T, et al. Parenteral nutrition: a clear and present danger unabated by tight glucose control. Am J Surg. 2010;200(3):386–90.
84. Allison SP, Lobo DN. Fluid and electrolytes in the elderly. Curr Opin Clin Nutr Metab Care. 2004;7(1):27–33.
85. Kagansky N, Levy S, Koren-Morag N, et al. Hypophosphataemia in old patients is associated with the refeeding syndrome and reduced survival. J Intern Med. 2005;257(5):461–8.
86. Al-Jaouni R, Schneider SM, Rampal P, et al. Effect of age on substrate oxidation during total parenteral nutrition. Nutrition. 2002;18(1):20–5.
87. Aberg W, Thorne A, Olivecrona T, et al. Fat oxidation and plasma removal capacity of an intravenous fat emulsion in elderly and young men. Nutrition. 2006;22(7–8):738–43.
88. Walshe C, Phelan D, Bourke J, et al. Vascular erosion by central venous catheters used for total parenteral nutrition. Intensive Care Med. 2007;33(3):534–7.
89. Oz V, Theilla M, Singer P. Eating habits and quality of life of patients receiving home parenteral nutrition in Israel. Clin Nutr. 2008;27(1):95–9.
90. Huerta G, Viniegra L. [Involuntary weight loss as a clinical problem]. Rev Invest Clin. 1989;41(1):5–9.
91. Bistrian BR, Driscoll DF. Enteral and parenteral nutrition therapy, vol. 17e. New York: McGraw-Hill; 2008.

15 Ethical Aspects, Expectations, and Outcomes Associated with PEG in Dementia

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Background

Percutaneous endoscopic gastrostomy (PEG) has been often used as a means for feeding the elderly with dementia. In a US survey, 34% of 186,835 nursing home residents with advanced cognitive impairment had a feeding tube [1] with the prevalence of PEGs in demented patients varying significantly by race and region [1, 2]. A study that compared ethnic and national differences in end stage dementia in Canada and Israel found that 24% (92/376) of severely demented residents in long-term care (LTC) had either a nasogastric or gastrostomy tube for feeding [3]. A German study found the prevalence of PEG to be 6.6% with 55% of them placed prior to placement in LTC and the rest following placement [4]. The annual per patient cost of tube feeding is around $31,832 ($87.21/day), a significant burden to the health care economy [5]. Annual PEG insertions have increased in the over 65 age group from 15,000 in 1989 to123,000 in 1995 [6]. It is well recognized that the most satisfying mode of feeding is the oral route; yet, PEGs are placed at times prematurely before exploring every alternate option for oral feeding [7]. Ideally, one would expect those with Advance Directives to provide expectations and details regarding preferred feeding options, especially with reference to tube feeding, but in practice this information is often lacking. In such scenarios, decisions should follow meaningful and timely discussions between patient or caregiver and a multidisciplinary team; discussing outcomes, both short-term and long-term without providing undue expectations; aspects to be stressed must include nutritional goals, life expectancy, risk of aspiration, healing of pressure ulcers, and above all quality of life [8–15]. Some institutions have addressed the issue by using quality improvement methodology [16], demonstrating favorable results by involving a hospital enteral feeding service [17]. Addressing reversible or modifiable factors appropriately may even preclude PEG placement [7].

Appropriate Indications for PEG

Although the objective of this chapter is not a discussion on the indications for PEG, one must nevertheless recognize the situations where insertion of PEG is appropriate, well stated by Angus and Burakoff [14]. Gauderer, who developed the procedure, termed PEG, expressed that we address ethical aspects coupled with the "need to demonstrate that our interventions truly benefit the patient" [18]. Appropriate indications for PEG include: esophageal obstruction (e.g., from cancer); dysphagia from neurological disease (e.g., following stroke) without mechanical obstruction; refusal to swallow without evidence of a terminal state (e.g., severe depression); and as supplemental nutrition for those on chemo or radiation therapy [14]. Clinically, one should expect the patient to survive longer than 4 weeks and actually benefit from the procedure; if no physiologic benefit or improvement in quality of life is expected, the provider is not obligated to offer PEG as a means of feeding [14]. Gastroenterologists are expected to evaluate the disease process and ramifications of PEG placement.

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Perceived Reasons for PEGs and Expectations

The concept of PEG feeding is often inadequately understood and assumed to have only benefits, which may be incorrect. The anticipation is that PEGs improve nutritional status, help heal pressure ulcers, reduce aspiration risk, prolong survival, and alleviate discomfort, all considered rationale for placement of a PEG (Table 15.1); the evidence however, does not demonstrate long-term benefits in reducing aspiration risk, healing of pressure ulcers, prolonging survival, or improving quality of life [9, 11, 19–24]. A study of severely demented patients in the Netherlands demonstrated that the level of discomfort (dyspnea, restlessness, and physicians' observations of pain and dehydration, mostly in those awake) was highest only at the time of making the decision not to initiate tube feeding and decreased gradually thereafter [25]. PEGs are perceived to be a problem-free solution to long-term nutritional support, but mechanical problems are common (discussion in another chapter). Decisions are often made hastily, when the patient is ill, and often in the critical care setting; thorough evaluation may reveal modifiable or reversible factors, with change following recovery from acute illness. A study of 302 patients suggested that 15% of cases who received PEG were able to ingest orally after the tube insertion, suggesting that indications for PEG should be carefully considered [26]. A "benign" delay in placing the PEG and placement outside the critical care setting may ultimately prove to be right decision; a study of 200 PEGs inserted over 2 years revealed significant mortality in patients considered for PEGs in the critical care setting, not from the insertion of PEG, but largely related to severe comorbidity in the patient [12]. Hasty decisions to perform PEGs occur because they are perceived to be a less invasive option with fewer complications compared to surgical gastrostomy to provide nutrition [27].

There may also be perceived benefits to long-term care institutions involving convenience, and health care or labor costs. A study compared practices in two nursing homes (NHs), one with a high tube feeding rate (41.8%) for advanced dementia vs. another with a low rate (10.7%). The NH with a high rate had an institution-like environment with poor staffing at mealtimes and less favorable staff attitudes regarding avoidance of aspiration, while the one with a low tube use rate had a home-like environment with better mealtime staffing, better values for hand washing, and advance care planning [28]. Better administrative and nursing support with family member interactions occurred in the NH with fewer tubes [28].

PEG and Outcomes in Dementia

The most frequent reason for PEG insertion appears to be the inability to maintain adequate oral intake in advanced dementia. The current evidence demonstrating benefits or the lack of evidence for assumed benefits are listed in three tables: data on aspiration risk are listed in Table 15.2 [29–32], data on nutritional aspects are listed in Table 15.3 [19, 22, 33–35], and data on short-term and long-term mortality are listed in Table 15.4 [6, 13, 22, 23, 34–39].

Aspiration pneumonia is a serious problem in elderly institutionalized residents, often requiring hospitalization. An observational study found aspiration risk was 38.7% among post-PEG complications [29]. Aspiration is associated with high mortality rate and health care costs. Evidence regarding PEGs and risk of aspiration pneumonia suggests the ineffectiveness of PEGs for this purpose [29–32, 40]. A study from Japan assessed methodology to predict this possibility using clinical factors with an artificial neural network system [41]. Transducer probes connected to PEG tubes have measured intragastric pressure, a possible surrogate for intra-abdominal pressure. While the method may

Table 15.1 Perceptions and reality regarding use of PEG in dementia [9, 11, 19–24]

Perceptions	Reality
Without PEG, the patient may starve to death	No long-term improvement in quality of life or life expectancy
PEGs reduce tendency to aspiration and pneumonia	Aspiration continues to occur and in fact may be more common
Not to feed is a form of euthanasia	Survival not prolonged in advance dementia
PEGs provide comfort care for terminal illness	PEGs are associated with risk of local infections, dislodgement, and injury
Problems with feeding do not exist following use of PEG	Tubes tend to get occluded easily; medications are not easy to administer
PEGs help healing of pressure ulcers through improved nutrition	No decline in occurrence of new pressure ulcers or rapid healing of existing decubiti

Table 15.2 PEG and aspiration pneumonia [29–32]

Advanced dementia; retrospective study, nursing home setting [29]
90 patients, average age 85.7 ± 0.8 years aspiration pneumonia occurred in 38.7%
Long-term outcomes after PEG, retrospective study [30]
35 consecutive patients, over 3 years, most common cause of death aspiration pneumonia
PEG vs. jejunostomy (PEJ), retrospective study, patient with cancer or neurologic deficit.[31]
79 patients; aspiration pneumonia in 11.4%
Aspiration risk not reduced further in those with PEJ
Gastroesophageal reflux and aspiration after PEG, prospective study [32]
5 patients with dysphagic stroke, studied within a week of PEG placement
Manometry and 24-h esophageal pH in patients fed 16 of 24 h
Significant reflux in 4 of 5 patients confirming esophageal sphincter dysfunction, a predictor of poorer outcome

Table 15.3 Nutritional status and PEG [19, 22, 33–35]

Long-term follow-up after PEG, nursing home setting, 1994 [19]
46 nursing home residents, mean age 73.6 years
No changes in cholesterol or albumin in survivors
At 6 months, 30% had increase and 30% decline in albumin
Long-term outcome after PEG in community setting, 2000 [22]
150 patients, mean age 78.9
Over 70% had no improvement in nutritional status
No improvement in weight, BMI, or cholesterol
13.4% of 72 survivors had 1 g improvement in albumin
Albumin as a parameter, prior to PEG [34]
56 patients, levels <2.8 g/dL indicated poor survival at 6 months
Prospective study, University hospital, Sweden, 2005–2009 [35]
484 patients, age >65 years, BMI <18.5
58 (12%) died in 30 days post-PEG
Albumin <3 g/dL, C-reactive protein ≥10, associated with mortality
Patients with combination of low albumin and high CRP had mortality of 20% compared to 2.6% with normal values

Table 15.4 Short-term (≤3 months) and long-term (≥1 year) mortality following PEG placement [6, 13, 22, 23, 34–39]

PEG in hospitalized Medicare beneficiaries aged 65 years or over [6]
15.3% died in hospital
23.9%mortality at 30 days, 63.0% mortality at 1 year
PEG in a mixed population, retrospective cohort study 1990–1992 [13]
7,369 patients, 23.5% died during the hospitalization
Median survival of the full cohort was 7.5 months
PEG in a community setting, 2000 [22]
150 patients, mean age 78.9, 1-year mortality 50%
PEG in two tertiary care centers, 2003–2005 [23]
168 patients, mean age 74 ± 16 years, year mortality 33.9%
PEG in nursing homes, focused ethnographic study [28]
NH with high tube feeding rate for dementia (41%), compared to NH with a low rate (10.7%)
High use NH had poor staffed mealtimes and staff attitudes to minimize aspiration; low use NH had a better home-like environment, better hand washing, and advance care planning
PEG in tertiary hospitals, 2001 [35]
71 patients, mean age 66 years (±17.9 years), range 17–89 year
1-year mortality 39%
PEG in hospitalized patients with advanced dementia [36]
Admitting diagnosis of infection associated with higher mortality with lack of benefit from tube feeding
Six-month median mortality with or without feeding tube was 50%
PEG in nursing home residents with severe dementia [37]
1,386 residents, 65 years and older, no survival benefit with PEG
PEG in acutely ill hospitalized patients, 1995–1996 [38]
39% mortality in NH patients, median survival of 24 months
72% mortality in acutely ill hospitalized patients, median survival 4 months, discouraging use of PEG in the acutely ill
PEG in nursing home residents with advanced dementia, 2009 [39]
64.1% mortality, 1-year post-PEG insertion

help estimate risk for aspiration [42], the transducers and monitors are available only in monitored settings (e.g., critical care) and not applicable to the real world NH settings. Although measures such as holding feeds for a period, using the upright position to feed, measuring the rate of feeds, and correlation with gastric residue have all been utilized, in practice the risk of aspiration remains. Changing the feed consistency to more semisolid forms are claimed to reduce risk of gastric reflux due to better transit from the proximal to distal stomach, compared to liquids in those with PEGs [43]. Other studies have hinted an increased risk of reflux with semisolids [44], suggesting the need for more data. Predictors of risk for aspiration in NH residents include sudden decline in functional status from acute illness in addition to the risk from tube feeding [45]; aspiration is a leading cause of pneumonia, hospitalization, and mortality in tube-fed patients. A prior history of aspiration may indicate that the patient is always at risk for aspiration, with the possible exception with DPEJ (direct percutaneous endoscopic jejunostomy) tubes, which may reduce the incidence of aspiration only because the tube position is more distal compared to that of PEGs. But DPEJs share other complication risks with PEGs [46].

In patients with advanced dementia, dysphagia is common; PEGs are often recommended as a permanent solution. However, underlying modifiable factors are inadequately addressed. With comprehensive and multidisciplinary evaluation, several causes can be discerned, many reversible or modifiable; examples include dysphagia associated with medications, Parkinson's disease, or that occurring only for a transient period following a stroke; in some cases, the patient may tolerate some but not all food consistencies. One of the initial steps should be to ascertain the reason(s) for inability to swallow through a multidisciplinary team approach, including involvement of neurologist, occupation therapist (and speech and swallow specialist), and gastroenterologist [7, 26]. Language barriers should be addressed [7]. Diets should be modified for appropriate consistency and tailored to patient's preferences and quality of life, with provision of help from staff or caregiver.

The frail elderly with advanced or terminal dementia in the NHs are often perceived as not having a terminal condition and candidates for a palliative approach. A significant proportion of this group gets nonpalliative interventions including feeding tubes [47]. Studies consistently demonstrate a lack of benefit for nutrition in this group (Table 15.3). While we recognize that poor nutritional status may delay healing of decubiti and that pressure ulcers may be associated with undernutrition, one should not assume that PEG feeding will facilitate the healing of pressure ulcers. Studies in this regard may be small or not stratified for several variables to draw conclusions; nevertheless, the data do not demonstrate healing of pressure ulcers following PEG feeding. Such patients are also prone to have restraints [48], urinary catheters, and fecal and bladder incontinence to complicate the picture.

PEGs may be erroneously considered as a means to prolong survival (short-term or long-term). The median

survival in a large cohort (7,369 patients) was shown to be 7.5 months; in this study, the in-hospital mortality was 18.9% for those <65, 24.7% for those 65–74, and 27.5% for those over 75 years [13]. Short-term mortality was 72%, with median survival of 4 months in hospitalized patients with acute illness [38]. One-year postinsertion mortality was 64.1% with median survival of 56 days among NH residents [39]. Among Medicare beneficiaries, the 30-day mortality was 23.9%, while the 1-year mortality was 63% in these patients with PEG [6]. PEGs do not lower the mortality risk in dementia; the median survival for patients with dementia and PEG is similar to that in patients without PEG [21]. Comorbidity influences survival following PEG placement; the typical patient who receives a PEG has advanced dementia, malnutrition, is bedbound, and has several systemic disorders. A study correlates poor survival post-PEG insertion if patients are male, of advanced age, have low serum albumin, chronic heart failure, or subtotal gastrectomy [9]. C-reactive protein was found to be predictive of short-term mortality, while Charlson's index (a score that predicts 1-year mortality for several comorbid conditions) was predictive of long-term mortality [23]. This information can be used to counsel families to help anticipate the prognosis [9, 19, 20, 23, 35, 36]. In a population with cancer in three-fourth of the 787 patients, average survival time was 720 days, with the 30, 60, and 90 day and 1,3 and 5-year mortality rates at 6.5%, 9,8%, 13%, 32.1%, 59.3%, and 69.8%, respectively, with predictive factors being higher age, lower BMI, and presence of diabetes mellitus [49]. Finally, when the inpatient mortality and length of hospital stay were compared in patients undergoing PEG and PEGJ, there were no detectable differences in a large study of 187,597 discharges, where 96% underwent PEG placement and 4% had PEGJ tubes [50].

Ethical Aspects and PEG

It is difficult to comment on the impact of ethical aspects including quality of life and functional capacity, especially when the typical patient with PEG is incapable of good communication or make the needs known. An important activity of daily living in humans is the ability to feed, an ability that is often lost last. Oral feeding undoubtedly provides the most satisfaction. When the patient with terminal dementia is deemed to have lost the ability to feed even after extensive evaluation utilizing a multidisciplinary approach, PEGs in reality do not meaningfully improve life expectancy or quality of life. Even sips of water, other liquids, or food may be more appropriate in this setting; on the other hand, patients with PEGs are at risk of being deprived of the pleasure of eating, while suffering the discomfort from the tube itself or frequent repositioning; while some require restraints. In most older adults who have the opportunity to make a decision (when they retain capacity) regarding tube feeding, the reaction is negative [51]. Ice chips and swabs can help a dry mouth; and although thirst sensation may be impaired in dementia, chronic hydration via a PEG tube is not the solution.

The American Medical Association in a policy statement made it clear that artificial nutrition and hydration (ANH) are "life-prolonging treatment"; the view received support from the American Academy of Neurology and the American Nurses Association; a Presidential commission determined that ANH was not required or justifiable in every case [14]. Physicians are not obligated to offer or to continue ANH unless benefits are anticipated; in this regard, ANH is similar to other treatment decisions such as for ventilator support or dialysis [14] and can be withheld when deemed appropriate (as commonly occurs in dialysis patients). This view has received support. But many believe that nutrition and hydration should be provided even after other measures fail, and that failure to provide hydration and nutrition is ethically and morally wrong. In such cases, a nasogastric tube may buy time for a few weeks. The decision may be influenced by cultural or religious beliefs and educational or financial backgrounds. Some states have adopted policies on tube feeding.

If a decision cannot be made, an ethics committee consultation may be requested.

Several tragic cases taught us lessons pertinent to ethical, legal, and medical issues and events that may complicate management [15]. Karen Ann Quinlan (1975) had severe brain damage and extended respiratory failure with requests to withdraw ventilator support, with the court ruling that artificial life-sustaining intervention could be withdrawn; Nancy Cruzon was on artificial nutrition for years after a car accident, till 1990; Terri Schiavo's case went through several rulings and appeals with her tube removed and placed back within days, with the court finally ruling that ANH was comparable to other life-sustaining treatments. The terms "brain dead" and "vegetative state" are used interchangeably and are confusing. While most ethicists believe that one can refuse treatment, decisions to withdraw or withhold treatment are emotionally more difficult to make. Prior to PEG placement, one should consider in-depth discussions with the caregiver regarding the goals: would there be relief of suffering, improvement in health and life expectancy, and importantly, would PEG better the quality of life or would it add to the patient's and caregiver burden [15].

Tube-Related Consequences

The caregiver should be made aware of the potential mechanical complications associated with PEG (dealt with in chapter 13). Tube occlusion (commonly from medications), dislodgement, fistula formation, insertion site infections, diarrhea, electrolyte, and volume imbalance can all occur. It is essential to crush medications and provide them in solution followed by tube flushes with water; long-acting or slow release preparations lose their bioavailability and cannot be administered via the tube. Sorbitol in liquid formulations may predispose to diarrhea. The caregiver should be educated about these possibilities.

Caregiver and Provider Discussions Regarding Outcomes

Opinions and concepts on the meaning of quality of life and suffering at the end of life vary considerably. Ethical aspects and emotions often interfere with and cloud appropriate decision making. The essential initial steps are to determine if the patient has capacity and if an advance directive (AD) has been executed; should an AD be available, it must be reviewed and may facilitate decision making. A meticulous approach must be utilized to evaluate dysphagia, including every attempt at hand feeding. Is the feeding difficulty temporary? Caregiver discussions must include benefits, risks, and alternatives to PEG, without providing undue expectations. A multidisciplinary team approach may include a primary physician (or geriatrician), gastroenterologist, nurse, speech and swallow specialist, psycho-social worker, and others as indicated. A question would be: is the PEG placed to provide medical benefit for the patient or others, as perceived by the surrogate? [14]. Table 15.5 provides an approach that may be utilized for this discussion. The discussion may not be easy; some may view a decision to not offer PEG as a form of euthanasia. Time should be provided for caregiver decision; it is never an emergency. A systematic review of 13 controlled trials over nearly 20 years suggested that high caloric supplements and oral feeds can help people with dementia with feeding problems to gain weight [52]. It is worth remembering that the older adult has few enjoyments left in life; perhaps the most important is enjoyment of food! One should not take away this pleasure without justifiable reason!

In summary, it is important to prepare the family for expectations at the end of life; disappointment arises from unfulfilled expectations. The caregiver/family must be educated about: the lack of evidence to support the benefits of PEG feeding to reduce aspiration risk, improve nutritional status, heal pressure ulcers, improve quality of life and survival, although it may be a convenient means to provide food, water, and medications. A requirement is the need for communication between geriatrician, gastroenterologist, nutritionist, nurse, and other disciplines that the patient will survive at least a few weeks and benefit from tube feeding; in the absence of benefit, there is no obligation to offer the intervention [14]. If a PEG is placed, periodic reevaluation regarding the necessity for PEG and its removal are required. Ultimately, it is a shared decision between patient's values, caregiver, and a multidisciplinary team of gastroenterologist, primary physician, nurse, nutritionist, and occupational therapist.

In the future, we do know whether acute care hospitals influenced by incentives to keep the length of stay short will see changes in the rates of PEG placement. Evidence-based guidelines on tube feeding must be developed and provided to acute care hospitals, along with requirements to monitor quality measures and link the process to incentives [53].

Table 15.5 Suggested discussions prior to PEG placement

Provider pertinent
Discussions must involve primary physician/geriatrician, gastroenterologist, nutritionist, nurse, and other disciplines as necessary
Evaluations must be individualized and multidisciplinary in approach
Health care proxy/caregiver/family member involvement is essential
Evaluate capacity of patient
In dementia, capacity is likely to be impaired to variable extent
Still, if the patient can decide, respect the patient's decision
If patient has no capacity, is an advance directive in place?
If Yes, and a living will has been executed, is there any mention of artificial nutrition and hydration? Abide by the wishes expressed
If Yes, and there is a health care proxy, contact the agent
If No, may contact family member (based on Family Health Care Decisions Act) or seek help though an ethics committee consultation
If patient has no advance directives or caregiver, may opt to contact the ethics committee (*State laws and hospital policies vary and need to be followed*)
Health care agent/caregiver pertinent
Discussions regarding mechanical problems
Immediate complications following PEG insertion
Long-term difficulties encountered, including occlusion, dislodgement
Discuss the impact of PEG on the following measures
Life expectancy
Risk of aspiration and pneumonia
Nutritional status and weight
Healing of wounds
Functional status
Cognition, level of consciousness
Quality of life
Caregiver burden
Address additional concerns, such as
Can patient continue to eat when the PEG is in place?
Is there a possibility that the tube can be removed or reinserted?
Any other concerns?

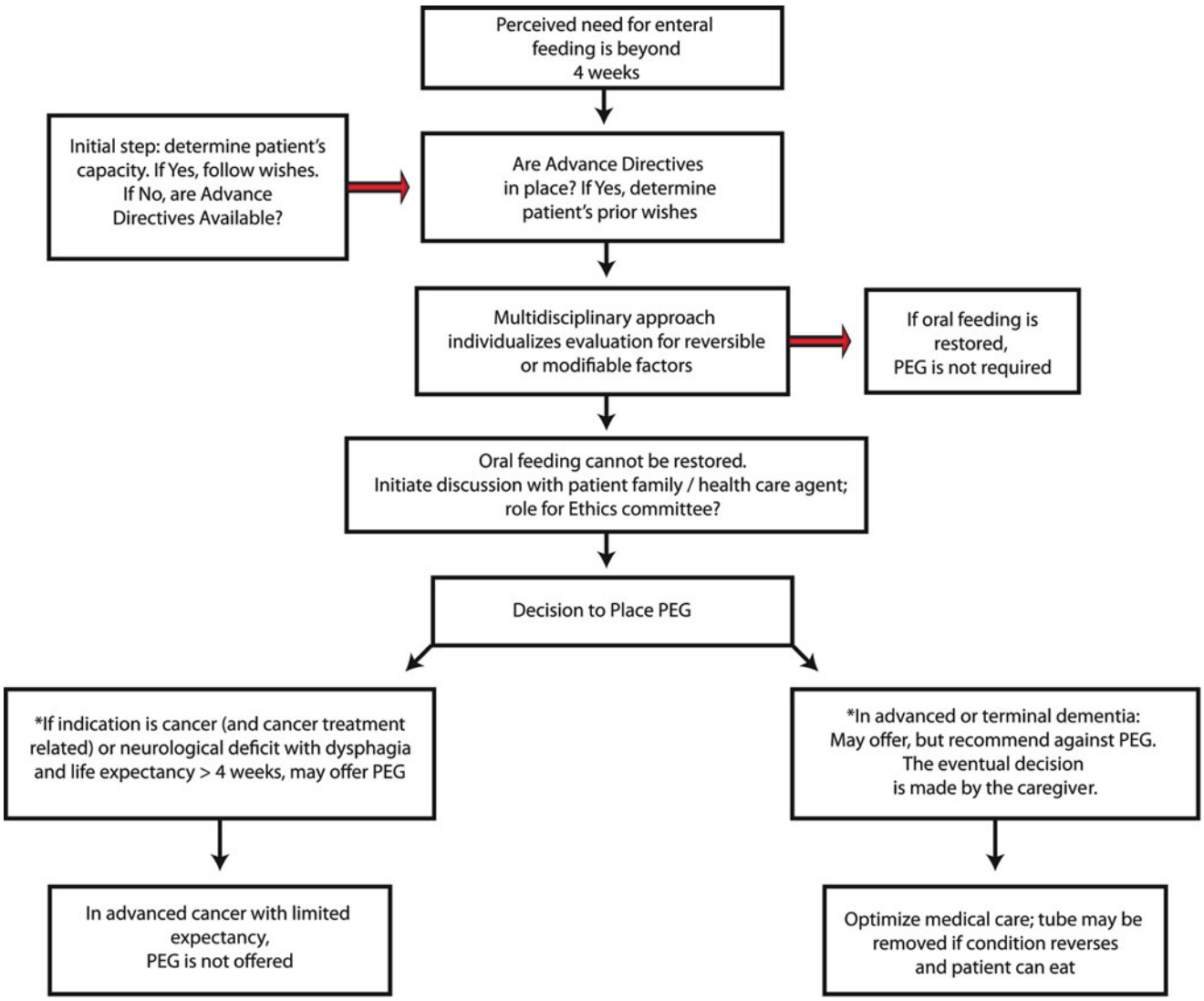

Fig. 15.1 PEG in dementia: an algorithmic approach* [14]

Most patients do not have the mental capacity to provide consent for the procedure [54]. It is hence prudent to inform the patient and caregiver about the disease at an early stage, discuss options for treatment and also implement advance directives, steps that can be helpful [55]. The algorithm shown in Fig. 15.1 is a helpful guide when PEGs are a consideration in advanced dementia.

Key Points

- Nothing is more satisfying than the pleasure of eating normally!
- PEGs provide questionable benefits for long-term nutritional status, reduction of aspiration risk, increase in life expectancy, and improvement in quality of life.
- PEGs must not be placed hastily prior to complete evaluation by a multidisciplinary team for modifiable or reversible factors and alternatives.
- Effort must be taken to involve the caregiver in meaningful discussions regarding benefits, risks, and alternatives to PEG, without providing undue expectations.
- In the absence of anticipated benefit and survival for beyond several weeks, providers are under no obligation to offer the intervention.
- Ethical considerations are common prior to PEG placement; an ethics committee consultation may be required in difficult cases.
- Efforts to restore oral feeding must continue; elective removal of the feeding tube must be attempted when feasible.

References

1. Mitchell SL, Teno JM, Roy J, et al. Clinical and organizational factors associated with feeding tube use among nursing home residents with advanced cognitive impairment. JAMA. 2003;290(1):73–80.
2. Braun UK, Rabeneck L, McCullough LB, et al. Decreasing use of percutaneous endoscopic gastrostomy tube feeding for veterans with dementia-racial differences remain. J Am Geriatr Soc. 2005;53(2):242–8.
3. Clarfield AM, Monette J, Bergman H, et al. Enteral feeding in end-stage dementia: a comparison of religious, ethnic, and national differences in Canada and Israel. J Gerontol. 2006;61A:621–7.
4. Wirth R, Bauer JM, Willschrei HP, et al. Prevalence of percutaneous endoscopic gastrostomy in nursing home residents—a nationwide survey in Germany. Gerontology. 2010;56(4):371–7.
5. Callahan CM, Buchanan NN, Stump TE. Healthcare costs associated with percutaneous endoscopic gastrostomy among older adults in a defined community. J Am Geriatr Soc. 2001;49(11):1525–9.
6. Grant MD, Rudberg MA, Brody JA. Gastrostomy placement and mortality among hospitalized Medicare beneficiaries. JAMA. 1998;279(24):1973–6.
7. Aparanji KP, Dharmarajan TS. Pause before a PEG: a feeding tube may not be necessary in every candidate! J Am Med Dir Assoc. 2010;11(6):453–6.
8. Brotherton A, Abbott J. Clinical decision making and the provision of information in PEG feeding: an exploration of patients and their carers' perceptions. J Hum Nutr Diet. 2009;22(4):302–9.
9. Higaki F, Yokota O, Ohishi M. Factors predictive of survival after percutaneous endoscopic gastrostomy in the elderly: is dementia really a risk factor? Am J Gastroenterol. 2008;103(4):1011–6.
10. Dharmarajan TS, Unnikrishnan D. Tube feeding in the older adult. In: Dharmarajan TS, Norman RA, editors. Clinical Geriatrics. 1st ed. Boca Raton: CRC Press/Parthenon; 2003. p. 105–14.
11. Dharmarajan TS, Unnikrishnan D, Pitchumoni CS. Percutaneous endoscopic gastrostomy and outcome in dementia. Am J Gastroenterol. 2001;96:2556–63.
12. Dharmarajan TS, Mathur S, Hudson A, et al. Percutaneous endoscopic gastrostomy in dementia: Areas for improvement in ethical aspects and documentation prior to the procedure. J Am Med Dir Assoc. 2009;10:B12.
13. Rabeneck L, Wray NP, Petersen NJ. Long-term outcomes of patients receiving percutaneous endoscopic gastrostomy tubes. J Gen Intern Med. 1996;11(5):287–93.
14. Angus F, Burakoff R. The percutaneous endoscopic tube: medical and ethical issues in placement. Am J Gastroenterol. 2003;98:272–7.
15. Wick JY, Zanni GR. Removing the feeding tube: a procedure with a contentious past. Consult Pharm. 2009;24(12):874–83.
16. Monteleoni C, Clark E. Using rapid-cycle quality improvement methodology to reduce feeding tubes in patients with advanced dementia: before and after study. BMJ. 2004;329(7464):491–4.
17. Westaby D, Young A, O'Toole P, et al. The provision of a percutaneously placed enteral tube feeding service. Gut. 2010;59(12):1592–605.
18. Gauderer M. Twenty years of percutaneous endoscopic gastrostomy: origin and evolution of a concept and its expanded applications. Gastrointest Endosc. 1999;50:879–83.
19. Nair S, Hertan H, Pitchumoni CS. Hypoalbuminemia is a poor predictor of survival after percutaneous endoscopic gastrostomy in elderly patients with dementia. Am J Gastroenterol. 2000;95(1):133–6.
20. Shah PM, Sen S, Perlmuter LC, et al. Survival after percutaneous endoscopic gastrostomy: the role of dementia. J Nutr Health Aging. 2005;9(4):255–9.
21. Murphy LM, Lipman TO. Percutaneous endoscopic gastrostomy does not prolong survival in patients with dementia. Arch Intern Med. 2003;163(11):1351–3.
22. Callahan CM, Haag KM, Weinberger M, et al. Outcomes of percutaneous endoscopic gastrostomy among older adults in a community setting. J Am Geriatr Soc. 2000;48(9):1048–54.
23. Figueiredo FA, da Costa MC, Pelosi AD, et al. Predicting outcomes and complications of percutaneous endoscopic gastrostomy. Endoscopy. 2007;39(4):333–8.
24. Smith BM, Perring P, Engoren M, et al. Hospital and long-term outcome after percutaneous endoscopic gastrostomy. Surg Endosc. 2008;22(1):74–80.
25. Pasman HRW, Onwuteaka-Philipsen BD, Kriegsman DMW, et al. Discomfort in nursing home patients with severe dementia in whom artificial nutrition and hydration is forgone. Arch Intern Med. 2005;165:1729–35.
26. Yokohama S, Aoshima M, Koyama S, et al. Possibility of oral feeding after induction of percutaneous endoscopic gastrostomy. J Gastroenterol Hepatol. 2010;26(7):1227–31.
27. Ljungdahl M, Sundbom M. Complication rate lower after percutaneous endoscopic gastrostomy than after surgical gastrostomy: a prospective, randomized trial. Surg Endosc. 2006;20(8):1248–51.
28. Lopez RP, Amella EJ, Strump NE, et al. The influence of nursing home culture on the use of feeding tubes. Arch Intern Med. 2010;170(1):83–8.
29. Kimyagarov S, Levenkron S, Shabi A. Artificial tube feeding of elderly suffering from advanced dementia. Harefuah. 2008;147(6):500–3, 575.
30. Ganga UR, Ryan JJ, Schafer LW. Indications, complications, and long-term results of percutaneous endoscopic gastrostomy: a retrospective study. S D J Med. 1994;47(5):149–52.
31. Kadakia SC, Sullivan HO, Starnes E. Percutaneous endoscopic gastrostomy or jejunostomy and the incidence of aspiration in 79 patients. Am J Surg. 1992;164(2):114–8.
32. Elphick DA, Elphick HL, Smith L, et al. Does gastro-esophageal reflux following PEG placement in stroke patients predict a poorer outcome? Age Ageing. 2006;35(5):545–6.
33. Kaw M, Sekas G. Long-term follow-up of consequences of percutaneous endoscopic gastrostomy (PEG) tubes in nursing home patients. Dig Dis Sci. 1994;39(4):738–43.
34. Bloomberg J, Lagerfren P, Martin L, et al. Albumin and C-reactive protein predict short term mortality after percutaneous endoscopic gastrostomy in a prospective cohort study. Gastrotest Endosc. 2011;73(1):29–36.
35. Verhoef MJ, Van Rosendaal GM. Patient outcomes related to percutaneous endoscopic gastrostomy placement. J Clin Gastroenterol. 2001;32(1):49–53.
36. Meier DE, Ahronheim JC, Morris J, et al. High short-term mortality in hospitalized patients with advanced dementia: Lack of benefit of tube feeding. Arch Intern Med. 2001;161:594–9.
37. Mitchell SL, Kiely DK, Lipsitz LA. The risk factors and impact on survival of feeding tubes placement in nursing home residents with severe cognitive impairment. Arch Intern Med. 1997;157:327–32.
38. Abuksis G, Mor M, Segal N, et al. Percutaneous endoscopic gastronomy: high mortality rates in hospitalized patients. Am J Gastroenterol. 2000;95(1):128–32.
39. Kuo S, Rhodes RL, Mitchell SL, et al. Natural history of feeding-tube use in nursing home residents with advanced dementia. J Am Med Dir Assoc. 2009;10(4):264–70.
40. Finucane TE, Bynum JP. Use of tube feeding to prevent aspiration pneumonia. Lancet. 1996;348:1421–4.
41. Takayama T, Takayama K, Inoue N, et al. Prediction of survival and complications after percutaneous endoscopic gastrostomy in an individual by using clinical factors with an artificial neural network system. Eur J Gastroenterol Hepatol. 2009;21(11):1279–85.
42. Kudo M, Kanai N, Hirasawa T, et al. Prognostic significance of intragastric pressure for the occurrence of aspiration pneumonia in

the patients with percutaneous endoscopic gastrostomy (PEG). Hepatogastroenterology. 2008;55(86–87):1935–8.
43. Nishiwaki S, Araki H, Shirakami Y, et al. Inhibition of gastroesophageal reflux by semi-solid nutrients in patients with percutaneous endoscopic gastrostomy. JPEN J Parenter Enteral Nutr. 2009; 33(5):513–9.
44. Adachi K, Furuta K, Morita T, et al. Half-solidification of nutrient does not decrease gastro-esophageal reflux events in patients fed via percutaneous endoscopic gastrostomy. Clin Nutr. 2009;28(6): 648–51.
45. Langmore SE, Skarupski KA, Park PS, et al. Predictors of aspiration pneumonia in nursing home residents. Dysphagia. 2002;17: 298–307.
46. Panagiotakis PH, DiSario JA, Hilden K, et al. DPEJ tube placement prevents aspiration pneumonia in high-risk patients. Nutr Clin Pract. 2008;23(2):172–5.
47. Mitchell SL, Kiely DK, Hamel MB. Dying with advanced dementia in the nursing home. Arch Intern Med. 2009;164(3):321–6.
48. Finucane TE, Christmas C, Travis K. Tube feeding in patients with advanced dementia: a review of the evidence. JAMA. 1999;282(14): 1365–70.
49. Zopf Y, Maiss J, Konturek P, et al. Predictive factors of mortality after PEG insertion: guidance for clinical practice. JPEN J Parenter Enteral Nutr. 2011;35(1):50–5.
50. Poteet SJ, Holtzman MD, Melvin WV, et al. Inpatient mortality and length of stay comparison of percutaneous endoscopic gastrostomy and percutaneous endoscopic gastrojejunostomy. J Laparpendosc Adv Surg Tech A. 2010;20(7):587–90.
51. Murphy DJ, Santilli S. Elderly patients' preferences for long-term life support. Arch Fam Med. 1998;7(5):484–8.
52. Hanson LC, Ersek M, Gilliam R, Carey TS. Oral feeding options for people with dementia: a systematic review. J Am Geriatr Soc. 2011;59:463–72.
53. Sastry S, Snyder JE. Will the new Medicare rules alter the practice of enteral feeding in patients with advanced dementia? Clin Geriatr. 2011;19(2):27–8.
54. Rahman M, Evans KE, Arif N, Gorard DA. Mental capacity in hospitalized patients undergoing percutaneous endoscopic gastrostomy insertion. Clin Nutr. 2012;31:224–9.
55. Zieschang T, Oster P, Pfisterer M, Schneider N. Palliative care for patients with dementia. Z Gerontol Geriatr. 2012;45(1): 50–4.

Water, Potassium, Sodium, and Chloride in Nutrition

16

Kumar Dharmarajan and Kenneth L. Minaker

Water, potassium, sodium, and chloride play essential roles in human physiology and health. Adequate intake of water helps maintain circulating volume and prevent impairments in cognition and exercise capacity due to dehydration [1, p. 74, 2, 3]. Potassium is needed to maintain electrochemical gradients across cellular membranes; adequate intake from dietary sources can reduce blood pressure, bone demineralization, and formation of kidney stones [1, p. 188, 4–6]. Sodium and chloride also impact membrane potential as principal extracellular ions. When taken in excess, sodium increases blood pressure and cardiovascular risk in salt-sensitive populations such as older persons and African Americans [7].

Dietary reference intakes (DRIs) are a set of reference values created by the Food and Nutrition Board of the Institute of Medicine to guide nutrition education and policy in both the United States and Canada. Terms pertinent to understanding guidelines on water and electrolyte nutrition include the recommended dietary allowance (RDA), adequate intake (AI), and tolerable upper limit (TUL) [8, p. 8]. Each nutrient has a physiologic role, homeostatic balance, and relationship to disease when ingested in inappropriate amounts.

Introduction to the Dietary Reference Intakes

For over 50 years, the US RDAs and Canadian recommended nutritional intakes (RNIs) have been chief components of nutrition policy in their respective countries. They are used to assess dietary adequacy of individuals and populations, provide nutrition education, and guide institutional planning, food labeling, and food fortification [8, p. 1, 9]. Both RDAs and RNIs have been revised multiple times over the years reflecting changes in nutrition science and knowledge.

The DRIs are the successor to the RDAs and RNIs. With the support of the US and Canadian governments, these new reference values were created in 1994 by the Food and Nutrition Board of the National Academies' Institute of Medicine. In addition to denoting states of nutritional deficiency as did the RDAs and RNIs, the DRIs were also intended to identify nutrient overconsumption, reduce chronic degenerative diseases, and improve overall health [8, p. 6, 7]. The DRIs are for apparently healthy people and are not applicable to those with acute or chronic disease, nutritionally deprived states, or conditions characterized by increased nutritional requirements [8, p. 13]. When used for individual nutritional assessment, nutritional intake data should be combined with historical, clinical, and biochemical information as needed to provide a valid assessment of nutritional status.

Reference values included in the DRIs include the RDA, estimated average requirement (EAR), adequate intake (AI), and tolerable upper intake level (UL) [8, pp. 9–12]. The RDA is the average daily dietary nutrient intake level sufficient to meet the nutrient requirements of nearly all (97–98%) healthy individuals in a particular life stage and gender group. In order to calculate the RDA, the EAR must be known. The EAR is the average daily nutrient intake level estimated to meet the requirements of half of the healthy individuals in a particular life stage and group. Calculation of an EAR requires sufficient dose–response data that sensitively relates nutrient intake to one or more clinical or functional endpoints. None of the nutrients described in this chapter had sufficient experimental data to generate an EAR or RDA. Therefore, Adequate Intakes were calculated.

Adequate intake (AI) has been defined as the recommended average daily intake level based on observed or experimentally determined estimates of nutrient intake by a group of apparently healthy people. This nutrient intake is assumed to be adequate. Like the RDA, the AI is expected to meet or exceed the needs of most healthy individuals in a

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specific life stage and group. However, it is based on less data and more judgment than is used in establishing an EAR and RDA [8, p. 11].

The concept of tolerable upper intake level (UL) is also used to generate nutritional recommendations for water and electrolytes. The UL is the highest average daily nutrient intake level that is likely to pose no risk of adverse health effects to almost all individuals in the general population. As intake increases above the UL, potential for adverse effects may increase [1, p. 3]. The need for the UL concept stems from the increased fortification of foods, use of dietary supplements, and increased recognition of the health consequences of excess [1, p. 28]. Its ascertainment includes collection, organization, and evaluation of all information pertaining to the adverse effects of a given nutrient. The UL is ultimately chosen based on the consideration of both sensitive and serious endpoints [1, pp. 54–55]. The UL is not intended to be a recommended level of intake, as there is no clear benefit to nutrient consumption in amounts greater than the RDA or AI.

Data sources used to generate the DRIs include both observational and experimental studies, including the Third National Health and Nutrition Examination Survey (NHANES III) conducted by the US Department of Health and Human Services between 1988 and 1994 and the Continuing Survey of Food Intakes by Individuals (CSFII) conducted by the US Department of Agriculture between 1994 and 1996 [1, pp. 47–48]. Both studies used at least one 24-h diet recall and the food composition database developed by the USDA to calculate nutrient intakes. In addition, experimental data used to generate DRIs for water and electrolytes include basic research in animal models, controlled feeding studies in humans, and randomized clinical trials.

Water in Nutrition

Water comprises approximately 50% of body weight in older persons. In contrast, water comprises approximately 50% of body weight in young adults. Water serves multiple physiologic roles; it is a solvent for biochemical reactions, medium of transport for both nutrients and waste, and regulator of cell metabolism and gene expression via cellular hydration [9]. Approximately two-thirds of total body water is intracellular with the majority of the remainder in the extracellular interstitium. Water exchanges freely between intracellular and extracellular spaces due to osmotic gradients across cell membranes that are freely permeable to water. In contrast, water exchange between interstitial and intravascular spaces largely occurs via capillaries.

Total body water normally exists in a homeostatic balance. It is gained from consumption of liquids and solids as well as via metabolic water production. It is lost via respiratory, urinary, fecal, and insensible routes. Table 16.1 provides an estimate of minimum daily water losses and production [10–13].

Table 16.1 Estimation of minimum daily water losses and production [1]

Reference	Source	Loss (mL/d)	Production (mL/d)
Hoyt and Honing [10]	Respiratory loss	−250 to −350	
Adolph [11]	Urinary loss	−500 to −1000	
Newburgh et al [12]	Fecal loss	−100 to −200	
Kuno [13]	Insensible loss	−450 to −1900	
Hoyt and Honing [10]	Metabolic production		+250 to +350
	Total	−1300 to −3450	+250 to +350
	Net loss	−1050 to −3100	

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Environment, activity level, and diet can impact water balance. For example, climates that are warm or have reduced water vapor pressure can increase insensible and respiratory losses, respectively [14, 15]. Similarly, increased activity level increases not only insensible (sweat) losses, but also respiratory losses from increased minute ventilation [10]. Finally, increased energy intake and expenditure will result in additional metabolic water production from oxidation of hydrogen-containing substrates [16].

Acute reductions in total body water can upset this homeostatic balance and impair both cognition and physical activity. Cognitive impairment affects multiple domains including attention, short term memory, and performance on mathematics problems or other complex tasks [2, 17]. It can impair activities such as the shooting accuracy of expert target shooters [18]. In these cases, even a 2–3% reduction in total body water causes demonstrable impairment, including reductions in maximum aerobic power and physical work capacity [19, 20] Higher levels of dehydration impair physical endurance and can lower cardiac output when combined with heat stress [21, 22].

The current intake of total water (drinking water, beverages, food) in older persons has been reported in NHANES III (see Table 16.2) [23]. Together, drinking water and beverages provide 73–80% of total water consumed, with the remainder derived from foods [23].

Table 16.2 also demonstrates that serum osmolality is virtually identical for markedly different deciles of water intake in each age group. Osmolality is closely controlled by homeostatic mechanisms and is the primary signal used to regulate water balance via hypothalamic/posterior pituitary secretion of arginine vasopressin (ADH). ADH is a potent stimulus for both thirst and renal water conservation. In healthy individuals, serum osmolality rarely varies by more than ±2% and is controlled at a set point of 280–290 mOsmol/kg [24, 25]. Experimental studies have demonstrated that elevated serum osmolality is an accurate marker for

Table 16.2 Selected deciles of daily total water intake and associated mean serum osmolality in men and women, NHANES III, 1988–1994 [1, 23]

		Men		Women	
	Decile of total water	Total water	Mean serum	Total water	Mean serum
Age (years)	Intake	Intake, L/day (mean)	Osmolality (mOsmol/kg)	Intake, L/day (mean)	Osmolality (mOsmol/kg)
19–50	1st	1.69	279	1.25	277
	5th	3.31	280	2.61	277
	10th	7.93	280	6.16	277
51–70	1st	1.64	280	1.32	281
	5th	3.17	283	2.68	281
	10th	7.20	281	5.81	279
71+	1st	1.44	283	1.19	282
	5th	2.71	283	2.38	283
	10th	5.45	281	4.85	282

dehydration [1, p. 94, 26] Therefore, persons in the lowest and highest deciles of water intake in each age group were not systematically dehydrated or hyperhydrated.

NHANES III data does however indicate that persons greater than age 70 have slightly higher serum osmolality concentrations than young adults (see Table 16.2). This finding is not surprising as older persons have impaired renal concentrating (and diluting) abilities and impaired thirst sensation. Maximum urine osmolality, when measured following a short period of dehydration, is inversely related to age [27]. This decline in concentrating ability does not parallel age-related decline in glomerular filtration rate [28]. With regard to thirst, numerous studies confirm an impaired thirst response to experimentally induced hypernatremia in older persons. For example, the osmotic threshold for thirst during hypertonic saline infusion has been found to be much higher in healthy elderly subjects than in their younger counterparts; many healthy elders did not report thirst until serum osmolality exceeded 300 mOsmol/kg [29]. Similarly, in studies of water ingestion after hypertonic saline administration, older persons took in less water and had a marked reduction in the rate of return to baseline plasma osmolality [30].

Given the ability of older persons to maintain serum osmolality at multiple deciles of total water intake and their tendency to undercorrect total body water deficits in settings of water loss, the adequate intake (AI) for total water is derived from the median total water intake of young adults aged 19–30 years old rather than older age groups. This amount is 3.7 L/day for men and 2.7 L/day for women older than age 65. This amount includes total beverages of approximately 3 L/day (13 cups) for older men and 2.2 L/day (9 cups) for older women [1, p. 144]. The AI should compensate for net water losses described in Table 16.1 and maintain serum osmolality in the setting of impaired water conserving and thirst mechanisms associated with aging. This AI is not a requirement. It is a quantity of total water that should meet the nutritional needs of almost all healthy older persons performing moderate physical activity in a temperate climate. Needs may vary markedly based on type of physical activity, climate, and dietary intake.

There is no tolerable upper intake level (UL) for water [1, pp. 164–165]. Although adverse effects of water overconsumption have been reported, these have tended to occur in settings of psychiatric disease (primary polydipsia) or forced water intake scenarios where rapid intake exceeded the maximal renal excretion rate of 0.7–1.0 L/h [31, 32] In the absence of acute large volume hyperhydration, there are no data demonstrating that habitual consumption of large water intakes results in identifiable hazards in apparently healthy persons. There is significant ability to self-regulate water consumption, urine output, and urine concentration. Hyponatremia is generally difficult to achieve [33].

Potassium in Nutrition

Potassium has multiple physiologic effects. As an intracellular cation, potassium influences electrochemical gradients across cells with resultant impacts on vascular tone, neural transmission, and muscle contraction. Dietary potassium, in particular, has a profound effect on acid–base balance via its conjugate anion including citrate and other bicarbonate generating precursors that help neutralize diet-derived acids [34, 35]. Our kidneys often cannot completely excrete acid loads from Western diets high in protein and acid-producing cereals and grains. As a result, basic salts of bone including carbonates and hydroxyapatite are mobilized to counteract the resultant low-grade metabolic acidosis [36]. Bone matrix is thus reduced. Dietary potassium can help reduce this bone demineralization [37].

Potassium balance largely involves dietary intake, cellular shifts, and renal losses. Eighty-five percent of ingested dietary potassium is absorbed [38]. Foods highest in potassium on a calorie basis include leafy greens (1,500 mg/100 kcal) such as

spinach and kale; fruit of vine-based plants (1,200 mg/100 kcal) such as tomatoes, cucumbers, and eggplant; root vegetables (975 mg/100 kcal) including carrots, radishes, and onions; beans and peas (500 mg/100 kcal); tree fruits (430 mg/100 kcal) like apples, oranges, and bananas; and tubers (400 mg/100 kcal) [1, p. 244]. Although dairy products, meat, and cereals do contain potassium, they are low in bicarbonate precursors and are thus net acid producers [39].

The preponderance of dietary potassium is excreted by the kidney, with estimates ranging from 77 to 90% [38]. Fecal and skin losses are normally relatively minor routes of elimination until a decline in renal function occurs [40]. Given that the majority of filtered potassium is reabsorbed in the proximal renal tubule, the majority of urinary potassium losses arise from distal secretion into the cortical collecting duct [1, p. 189]. Importantly, the human premodern diet was rich in uncultivated plant food and vegetables rich in potassium. The human kidney evolved to excrete large potassium and bicarbonate loads and is conversely relatively inefficient at conserving potassium and bicarbonate in the setting of diminished intake, such as the Western diet [35, 41].

This difficulty conserving potassium is unfortunate given its salutary effects on blood pressure, as higher levels of daily potassium intake as measured by urinary potassium excretion are associated with reduced systolic and diastolic blood pressures [42, 43]. Meta-analysis of intervention studies performed on both hypertensive and nonhypertensive individuals shows similar results [4]. The impact of potassium appears strongest in older persons and African Americans with salt sensitivity, a phenomenon of direct blood pressure variation in relation to sodium intake [44, 45]. Salt sensitivity increases cardiovascular risk, even in those without hypertension [46]. A daily potassium intake of 4.7 g/day abolished severe salt sensitivity in a cohort of African Americans without hypertension [44]. White subjects in the same trial achieved similar results at a potassium intake of 2.7 g/day compared to a control group ingesting 1.2 g/day.

Dietary potassium may help reduce bone demineralization and kidney stone formation; a negative association exists with markers of bone turnover such as urinary pyridinoline and deoxypyridinoline and a positive association with bone mineral density [47, 48]. Bone turnover again increases once supplemental potassium is discontinued [5, 34]. Similarly, potassium intake is associated with a reduced incidence of nephrolithiasis [6, 49]. This relationship has biological plausibility given that supplementation with potassium citrate or potassium bicarbonate can reduce hypercalciuria and increase urinary excretion of citrate [50, 51]. Both reduce formation of calcium-containing kidney stones.

The adequate intake (AI) of potassium has been set at 4.7 g/day, a dose sufficient to reduce salt sensitivity in populations at high risk for cardiovascular disease as well as kidney stone formation [6, 44, 49]. This recommended daily intake is significantly less than the US median for persons aged 51–70 and 71+ years old (Table 16.3) [23]. Across all US age groups, less than 10% of men and 1% of women consume potassium in amounts greater than or equal to the AI [1, p. 245]. Canadian intake of potassium is slightly more [52]. It is worth reiterating that the beneficial effects of potassium are maximized when it is naturally occurring and associated with bicarbonate precursors. Vegetables and fruits are excellent sources. In settings of increased potassium loss such as with chronic diuretic use, the AI may be greater than 4.7 g/day. Importantly, the AI does not apply to older adults with medical conditions or on medications that impair potassium excretion (Table 16.4); serious cardiovascular toxicity may occur [1, p. 237].

A tolerable upper intake limit (UL) has not been set for older adults without impairments in urinary potassium excretion. There is no evidence that a high level of dietary potassium has adverse effects in this group. The maximal

Table 16.3 Selected percentiles for usual daily intake of potassium (mg) in older persons in the United States, NHANES III, 1988–1994 [1, 23]

	Percentile					
Sex/age (years)	1st	25th	50th	75th	95th	99th
M, 51–70	1,252	2,547	3,190	3,938	5,323	6,543
M, 71+	1,258	2,321	2,836	3,423	4,459	5,337
F, 51–70	1,120	2,000	2,435	2,932	3,803	4,549
F, 71+	954	1,873	2,343	2,873	3,738	4,420

Table 16.4 Selected clinical conditions that predispose to hyperkalemia [1]

Impaired renal excretion of potassium
Acute kidney injury—acute reduction in glomerular filtration rate (GFR)
Chronic kidney disease in advanced stages
Diabetic nephropathy—hyporeninemic hypoaldosteronism
Use of ACE inhibitors or angiotensin receptor blockers—reversible reduction in GFR
Use of NSAIDs—reduction in GFR with afferent arteriolar constriction
Use of aldosterone receptor antagonists—block tubular response to aldosterone
Use of amiloride or triamterene—inhibitors of distal renal tubular Na^+-K^+ exchange
Impaired cellular accumulation of potassium
Type 1 diabetes mellitus—hypoinsulinemia
Beta adrenergic blockers
Alpha adrenergic agonists
Metabolic acidosis
Excessive cellular release of potassium
Rhabdomyolysis
Tumor lysis syndrome
Excessive intake of non-bicarbonate containing potassium, usually in presence of factors listed in 1 or 2 above
Potassium supplements
Salt substitutes that contain potassium

excretion rate of potassium by normal kidneys after adaptation to high levels of intake has been estimated to be 31.3 g/day for adults, a level very difficult to achieve from food alone [53]. In contrast, non-dietary supplemental potassium can lead to toxicity even in healthy individuals, and chronic excessive consumption of any type of potassium including potassium-containing salt substitutes may cause hyperkalemia in those with impaired potassium balance (Table 16.4) [1, p. 249].

Sodium and Chloride in Nutrition

Both sodium and chloride are important components of extracellular fluid. Sodium is the principal extracellular cation and impacts osmotic function, membrane potential, circulating volume, and vascular tone. Chloride, in contrast, is a major extracellular anion and is a component of gastric juice. Multiple systems and hormones influence sodium and chloride balance including the renin–angiotensin–aldosterone system, sympathetic nervous system, kallikrein–kinin system, atrial natriuretic peptide, and various intrarenal mechanisms [1, pp. 273–274]. Unlike with potassium, normal renal function is associated with a remarkable ability to conserve sodium in the presence of salt depletion or the absence of sodium intake.

Sodium is a ubiquitous part of the Western diet. It is ingested most frequently as sodium chloride, though it is consumed in a variety of other processed forms including monosodium glutamate, sodium phosphate, sodium carbonate, and sodium benzoate [1, p. 274]. Almost all sodium is absorbed in the small intestine and is accompanied by chloride 90% of the time [54]. Importantly, only about 12% of sodium chloride is naturally occurring in foods. Seventy-seven percent of total salt is added during processing, 5% is added while cooking, and 6% is added when eating [54].

Obligatory losses of sodium and chloride are small. In the absence of substantial sweating, only 0.18 g or 8 mmol of sodium is lost per day (Table 16.5) [55]. Chloride losses usually accompany sodium losses, though excess chloride depletion can be seen in vomiting. True chloride deficiency is rarely seen unless special medical products low in chloride constitute almost all caloric intake [56]. Studies of several isolated populations with very low salt ingestion find no evidence of hyponatremia or impaired physical activity despite urinary excretion of less than 0.1 g of sodium per day [57].

Table 16.5 Estimation of daily obligatory sodium losses [1, 55]

Source	g/day	mmol/day
Urine	0.005–0.035	0.2–1.5
Skin (nonsweating)	0.025	1.1
Feces	0.010–0.125	0.4–5.4
Total	0.040–0.185	1.7–8.0

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In contrast, excess sodium chloride has been shown to increase blood pressure and cardiovascular risk in the preponderance of studies. Both cross-sectional and within-population studies have demonstrated direct correlation between increased sodium intake, increased urinary sodium excretion, and both systolic and diastolic blood pressure [42, 58]. These trends amplify with age and have been confirmed by interventional studies such as the Dietary Approaches to Stop Hypertension-Sodium (DASH-Sodium) trial that tested the effects on blood pressure of three levels of sodium intake (1.2, 2.3, 3.5 g/day) as part of a 2,100 kcal diet [59]. The DASH diet is rich in fruits, vegetables, and low fat dairy products and reduced in total and saturated fat. Subjects were randomly assigned to DASH and control diets as well as 1 of 3 levels of sodium intake. The highest level of sodium mirrored typical US consumption. The difference in systolic blood pressure between higher sodium (3.5 g/day) and intermediate sodium (2.3 g/day) diets was 2.1 mmHg, while further lowering of sodium consumption to 1.2 g/day led to an additional systolic blood pressure reduction of 4.6 mmHg. Greater blood pressure reduction was noted among subjects with hypertension, African Americans, and those over 45 years of age. Similar results have been demonstrated in subjects with mildly elevated diastolic blood pressure (83–89 mmHg) and obesity [60–62]. Although a recent study demonstrated possible cardiovascular harm associated with low sodium intake, its results have been questioned by multiple respected authorities and should not be used to guide practice [63–66].

Given the minimal obligate needs for sodium and elevation in blood pressure with increased consumption, the daily adequate intake (AI) for sodium is 1.5 g/2,100 kcal [1, p. 308, 67, 68]. The corresponding daily AI for chloride is 2.3 g/2,100 kcal. This level of intake can provide adequate levels of other nutrients as in the DASH diet and allow for excess sodium loss in sweat by those moderately physically active or unacclimatized to high temperatures. This AI does not apply to highly active individuals such as competitive athletes and workers exposed to substantial heat stress. Importantly, as older persons are more likely to be salt sensitive and consume far less than 2,100 kcal/day, the AI for sodium is 1.3 g/day in persons aged 51–70 years and 1.2 g/day in persons older than 71 (Table 16.6).

The average level of sodium and chloride intake among older persons in the United States is significantly higher than the AI. Based on self-reported data from NHANES III, the estimated mean intake of sodium among older men and women over the age of 70 is approximately 3.2 and 2.4 g/d, respectively [23]. These values are likely underestimates of true sodium consumption as they do not include salt added at the table. Indeed, measurement of 24-h urinary sodium excretion points to slightly higher levels of intake [1], p. 320.

Table 16.6 Adequate intake of sodium and chloride (g/mmol) for older adults [1]

Sex/age (years)	Sodium	Chloride
M, 51–70	1.3 g (55 mmol)/day	2.0 g (55 mmol)/day
M, 71+	1.2 g (50 mmol)/day	1.8 g (50 mmol)/day
F, 51–70	1.3 g (55 mmol)/day	2.0 g (55 mmol)/day
F, 71+	1.2 g (50 mmol)/day	1.8 g (50 mmol)/day

Unlike for water and potassium, sodium has a tolerable upper intake limit (UL) of 2.3 g/day with a corresponding chloride UL of 3.6 g/day. Three trials have shown that when sodium is provided at a level close to its daily AI of 1.5 g/2,100 kcal, blood pressure still rises when sodium intake is raised to 2.3 g/day [59, 69, 70]. Given that there is no apparent threshold below which there is no increased risk of cardiovascular disease across the broad range of blood pressures typically observed in the United States, the additional increase in blood pressure at a sodium intake of 2.3 g/day is likely harmful. Indeed, recent work has documented increased cardiovascular risk even in persons deemed "prehypertensive" with a systolic blood pressure of 120–139 mmHg or diastolic blood pressure of 80–89 mmHg [71]. Ideally, increased salt sensitivity and higher absolute risk of cardiovascular mortality in older persons should lower the tolerable upper intake limit for sodium to a value less than 2.3 g/day. However, data are currently insufficient to precisely define this level in the elderly.

Key Points

- DRIs can help older persons avoid consequences of nutrient deficiency and where applicable, chronic toxicities due to overconsumption. DRIs for water and electrolytes are summarized in Table 16.7.
- DRIs for older persons have been made in the context of specific age-related physiologic and epidemiologic considerations that are summarized in Table 16.8 [28–30, 44, 45, 53, 59, 72].
- DRIs apply to healthy elderly and do not provide adequate nutritional guidance for those who are already malnourished or have specific disease states.
- In the United States, less than 10% of men and 1% of women consume the adequate intake of potassium, and greater than 95% of men and 75% of women consume sodium in excess of the tolerable upper intake limit [23].
- Even small favorable changes in nutrient intake can result in significant benefits, as blood pressure seems more highly correlated with the ratio of sodium:potassium intake than with consumption of either nutrient alone [42, 73]. A reduction in systolic blood pressure by 3 mmHg or diastolic blood pressure by 2 mmHg could reduce cardiovascular mortality by greater than 10% [74–76].

Table 16.7 Summary of dietary reference intakes for water, potassium, sodium, and chloride [1]

Nutrient/age	Adequate intake	Tolerable upper intake level
Men		
Water, 51–70 years	3.7 L/day	–
Water, 71+ years	3.7 L/day	–
Potassium, 51–70 years	4.7 g/day	–
Potassium, 71+ years	4.7 g/day	–
Sodium (chloride), 51–70 years	1.3 g (2.0 g)/day	2.3 g (3.6 g)/day
Sodium (chloride), 71+ years	1.2 g (1.8 g)/day	2.3 g (3.6 g)/day
Women		
Water, 51–70 years	2.7 L/day	–
Water, 71+ years	2.7 L/day	–
Potassium, 51–70 years	4.7 g/day	–
Potassium, 71+ years	4.7 g/day	–
Sodium (chloride), 51–70 years	1.3 g (2.0 g)/day	2.3 g (3.6 g)/day
Sodium (chloride), 71+ years	1.2 g (1.8 g)/day	2.3 g (3.6 g)/day

Table 16.8 Physiologic and epidemiologic factors influencing DRIs for water, potassium, sodium, and chloride in older persons [1]

Water
Impaired thirst sensation including when dehydrated
Impaired ability of kidneys to excrete maximally concentrated urine due to reduced renal concentrating ability with age
Impaired ability of kidneys to maximally dilute urine when challenged with intravenous fluids due to reduced diluting ability with age
Poorer tolerance of dehydration
Use of diuretics
Potassium
Salt sensitivity mitigated by dietary potassium
Low likelihood of developing hyperkalemia from dietary potassium intake in setting of normal renal function
Risk of developing hyperkalemia from excessive supplemental potassium intake in presence of situations predisposing to hyperkalemia (Table 16.4)
Sodium and chloride
Increased salt sensitivity
Reduced ability to excrete sodium loads independent of decline in glomerular filtration rate
Increased prevalence of sodium retaining states including chronic kidney disease and congestive heart failure

References

1. Appel LJ, Baker DH, Bar-Or O, Minaker KL, Morris Jr RC, Resnick LM, Sawka MN, Volpe SL, Weinberger MH, Whelton PK. Panel on Dietary Reference Intakes for Electrolytes and Water. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. Food and Nutrition Board of the Institute of Medicine. Dietary reference intakes for water, potassium, sodium, chloride, and sulfate. Washington, DC: National Academies Press; 2005.

2. Cian C, Koulmann N, Barraud PA, et al. Influence of variations in body hydration on cognitive function: effect of hyperhydration, heat stress, and exercise-induced dehydration. J Psychophysiol. 2000;14:29–36.
3. Fallowfield JL, Williams C, Booth J, et al. Effect of water ingestion on endurance capacity during prolonged running. J Sports Sci. 1996;14:497–502.
4. Whelton PK, He J, Cutler JA, et al. Effects of oral potassium on blood pressure. Meta-analysis of randomized controlled clinical trials. JAMA. 1997;277:1624–32.
5. Pak CY, Peterson RD, Poindexter J. Prevention of spinal bone loss by potassium citrate in cases of calcium urolithiasis. J Urol. 2002;168:31–4.
6. Curhan GC, Willett WC, Rimm ER, Stampfer MJ. A prospective study of dietary calcium and other nutrients and the risk of symptomatic kidney stones. N Engl J Med. 1993;328:833–8.
7. Vollmer WM, Sacks FM, Ard J, et al. Effects of diet and sodium intake on blood pressure: Subgroup analysis of the DASH-sodium trial. Ann Intern Med. 2001;135:1019–28.
8. Otten JJ, Hellwig JP, Meyers LD, editors. Dietary reference intakes: the essential guide to nutrient requirements. Food and Nutrition Board of the Institute of Medicine. Washington, DC: The National Academies Press; 2006.
9. Haussinger D, Lang F, Gerok W. Regulation of cell function by the cellular hydration state. Am J Physiol. 1994;267:E343–55.
10. Hoyt RW, Honig A. Environmental influences on body fluid balance during exercise: altitude. In: Buskirk ER, Puhl SM, editors. Body Fluid Balance: Exercise and Sport. Boca Raton, Fl: CRC Press; 1996. p. 183–96.
11. Adolph EF. Urinary excretion of water and solutes. In: Adolph EF, editor. Physiology of Man in the Desert. New York: Intersciences Publishers; 1947. p. 96–109.
12. Newburgh LH, Woodwell Johnston M, Falcon-Lesses M. Measurement of total water exchange. J Clin Invest. 1930;8:161–96.
13. Kuno Y. Human perspiration. Springfield, IL: Charles C. Thomas; 1956.
14. Mitchell JW, Nadel ER, Stolwijk JAJ. Respiratory weight losses during exercise. J Appl Physiol. 1972;32:474–6.
15. Molnar GW. Man in the tropics compared with man in the desert. In: Adolph EF, editor. Physiology of man in the desert. New York: Intersciences; 1947. p. 315–25.
16. Lloyd LE, McDonald BE, Crampton EW. Water and its metabolism. In: Fundamentals of nutrition. 2nd ed. San Francisco, CA: WH Freeman; 1978, p. 22–35.
17. Gopinathan PM, Pichan G, Sharma VM. Role of dehydration in heat stress-induced variations in mental performance. Arch Environ Health. 1988;43:15–7.
18. Epstein M, Keren G, Moisseiev J, et al. Psychomotor deterioration during exposure to heat. Aviat Space Environ Med. 1980;51:607–10.
19. Below PR, Mora-Rodriguez R, Gonzalez-Alonso J, Coyle EF. Fluid and carbohydrate ingestion independently improve performance during 1 hour of intense exercise. Med Sci Sports Exerc. 1995;27:200–10.
20. Pichan G, Gauttam RK, Tomar OS, Bajaj AC. Effect of primary hypohydration on physical work capacity. Int J Biometeorol. 1988;32:176–80.
21. McConell GK, Burge CM, Skinner SL, Hargreaves M. Influence of ingested fluid volume on physiologic responses during prolonged exercise. Acta Physiol Scand. 1997;160:149–56.
22. Gonzalez-Alonso J, Mora-Rodriguez R, Below PR, Coyle EF. Dehydration markedly impairs cardiovascular function in hyperthermic endurance athletes during exercise. J Appl Physiol. 1997;82:1229–36.
23. US Department of Health and Human Services, National Center for Health Statistics. Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994. Atlanta, GA: US Department of Health and Human Services, National Center for Health Statistics; 1994.
24. Andreoli TE, Reeves WB, Bichet DG. Endocrine control of water balance. In: Fray JCS, Goodman HM, editors. Handbook of Physiology, Section 7, Volume III: Endocrine Regulation of Water and Electrolyte Balance. New York: Oxford University Press; 2000. p. 530–69.
25. Knepper MA, Valtin H, Sands JM. Renal actions of vasopressin. In: Fray JCS, Goodman HM, editors. Handbook of Physiology, Section 7, Volume III: Endocrine Regulation of Water and Electrolyte Balance. New York: Oxford University Press; 2000. p. 496–529.
26. Senay Jr LC, Christensen ML. Changes in blood plasma during progressive dehydration. J Appl Physiol. 1965;20:1136–40.
27. Lindeman RD, Lee Jr TD, Yiengst MJ, Shock NW. Influence of age, renal disease, hypertension, diuretics, and calcium on the antidiuretic responses to suboptimal infusions of vasopressin. J Lab Clin Med. 1966;68:206–23.
28. Rowe JW, Shock NW, DeFronzo RA. The influence of age on the renal response to water deprivation in man. Nephron. 1976;17:270–8.
29. Fish LC, Minaker KL, Rowe JW. Altered thirst threshold during hypertonic stress in aging men. Gerontologist. 1985;25:A118–9.
30. Murphy DJ, Minaker KL, Fish LC, Rowe JW. Impaired osmostimulation of water ingestion delays recovery from hyperosmolarity in normal elderly. Gerontologist. 1988;28:A141.
31. Gardner JW, Gutmann FD. Fatal water intoxication of an Army trainee during urine drug test. Mil Med. 2002;167:435–7.
32. Arieff AI, Kronlund BA. Fatal child abuse by forced water intoxication. Pediatrics. 1999;103:1292–5.
33. Freund BJ, Montain SJ, Young AJ, et al. Glycerol hyperhydration: Hormonal, renal, and vascular fluid responses. J Appl Physiol. 1995;79:2069–77.
34. Sebastian A, Harris ST, Ottaway JH, et al. Improved mineral balance and skeletal metabolism in postmenopausal women treated with potassium bicarbonate. N Engl J Med. 1994;330:1776–81.
35. Sebastian A, Frassetto LA, Sellmeyer DE, et al. Estimation of the net acid load of the diet ancestral preagricultural Homo sapiens and their hominid ancestors. Am J Clin Nutr. 2002;76:1308–16.
36. Barzel US. The skeleton as an ion exchange system: Implications for the role of acid-base imbalance in the genesis of osteoporosis. J Bone Miner Res. 1995;10:1431–6.
37. New SA, Robins SP, Campbell MK, et al. Dietary influences on bone mass and bone metabolism: Further evidence of a positive link between fruit and vegetable consumption and bone health. Am J Clin Nutr. 2000;71:142–51.
38. Holbrook JT, Patterson KY, Bodner JE, et al. Sodium and potassium intake and balance in adults consuming self-selected diets. Am J Clin Nutr. 1984;40:786–93.
39. Lemann J, Bushinsky DA, Hamm LL. Bone buffering of acid and base in humans. Am J Physiol. 2003;285:F811–32.
40. Agarwal R, Afzalpurkur R, Fordtran JS. Pathophysiology of potassium absorption and secretion by the human intestine. Gastroenterology. 1994;107:548–71.
41. Eaton SB, Eaton SBI, Konner MJ. Paleolithic nutrition revisited. In: Trevathan WR, Smith EO, McKenna JJ, editors. Evolutionary Medicine. New York: Oxford University Press; 1999. p. 313–32.
42. Rose G, Stamler J, Stamler R, et al. Intersalt: an international study of electrolyte excretion and blood pressure. Results for 24 hour urinary sodium and potassium excretion. BMJ. 1988;297:319–28.
43. Dyer AR, Elliott P, Shipley M. Urinary electrolyte excretion in 24 hours and blood pressure in the Intersalt study. II. Estimates of electrolyte blood pressure associations corrected for regression dilution bias. Am J Epidemiol. 1994;139:941–51.
44. Morris Jr RC, Sebastian A, Forman A, et al. Normotensive salt-sensitivity: effects of race and dietary potassium. Hypertension. 1999;33:18–23.
45. Weinberger MH. Salt sensitivity of blood pressure in humans. Hypertension. 1996;27:481–90.

46. Weinberger MH, Fineberg NS, Fineberg SE, Weinberger M. Salt sensitivity, pulse pressure, and death in normal and hypertensive humans. Hypertension. 2001;37:429–32.
47. New SA, Bolton-Smith C, Grubb DA, Reid DM. Nutritional influences on bone mineral density: a cross-sectional study in premenopausal women. Am J Clin Nutr. 1997;65:1831–9.
48. Tucker KL, Hannan MT, Chen H, et al. Potassium, magnesium, and fruit and vegetable intakes are associated with greater bone mineral density in elderly men and women. Am J Clin Nutr. 1999;69: 727–36.
49. Curhan GC, Willett WC, Speizer FE, et al. Comparison of dietary calcium with supplemental calcium and other nutrients as factors affecting the risk of kidney stones in women. Ann Intern Med. 1997;126:497–504.
50. Pak CY. Citrate and renal calculi. Miner Electrolyte Metab. 1987;13:257–66.
51. Lemann J, Pleuss JA, Gray RW. Potassium bicarbonate, but not sodium bicarbonate, reduces urinary calcium excretion and improves calcium balances in healthy men. Kidney Int. 1989;35:688–95.
52. Health and Welfare Canada, Wright JD, Ervin B, Briefel RR, editors. Consensus workshop on dietary assessment: nutrition monitoring and tracking the year 2000 objectives. Hyattsville, MD: US Department of Health and Human Services; 1994.
53. Berliner RW. Renal mechanisms for potassium excretion. In: Harvey Lectures Series 55. New York: Academic; 1961, p. 141–71.
54. Mattes RD, Donnelly D. Relative contributions of dietary sodium sources. J Am Coll Nutr. 1991;10:383–93.
55. Dahl LK. Salt intake and salt need. N Engl J Med. 1958; 258:1152–6.
56. Roy S, Arant B. Alkalosis from chloride-deficient Neo-Mull-Soy. N Engl J Med. 1979;301:615.
57. Oliver WJ, Cohen EL, Neel JV. Blood pressure, sodium intake, and sodium related hormones in the Yanomamo Indians, a "no-salt" culture. Circulation. 1975;52:146–51.
58. Elliott P, Stamler J, Nichols R, et al. Intersalt revisited: further analysis of 24 hour sodium excretion and blood pressure within and across populations. Br Med J. 1996;312:1249–53.
59. Sacks FM, Svetkey LP, Vollmer WM, et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. N Engl J Med. 2001;344:3–10.
60. Kumanyika SK, Herbert PR, Cutler JA, et al. Feasibility and efficacy of sodium reduction in the Trials of Hypertension Prevention, Phase I. Hypertension. 1993;22:502–12.
61. Trials of Hypertension Prevention Collaborative Research Group. The effects of nonpharmacologic interventions on blood pressure of persons with high normal levels. Results of the Trials of Hypertension Prevention, Phase I. JAMA. 1992;267:1213–20.
62. Trials of Hypertension Prevention Collaborative Research Group. Effects of weight loss and sodium reduction intervention on blood pressure and hypertension incidence in overweight people with high-normal blood pressure. The trials of Hypertension Prevention, Phase II. Arch Intern Med. 1997;157:657–67.
63. Stolarz-Skrzypek K, Kuznetsova T, Thijs L, et al. Fatal and nonfatal outcomes, incidence of hypertension, and blood pressure changes in relation to urinary sodium excretion. JAMA. 2011;305:1777–85.
64. Lancet Editorial. Salt and cardiovascular disease mortality. Lancet. 2011;377:1626.
65. Kolata G. Low-salt diet ineffective, study finds. Disagreement abounds. New York Times 3 May 2011. Retrieved from www.nytimes.com on 1 June 2011 at http://www.nytimes.com/2011/05/04/health/research/04salt.html?_r=3&ref=health.
66. The Nutrition Source, Harvard School of Public Health. Flawed science on sodium from JAMA. Why you should take the latest sodium study with a huge grain of salt. Retrieved from www.hsph.harvard.edu on 1 June 2011 at http://www.nytimes.com/2011/05/04/health/research/04salt.html?_r=3&ref=health.
67. Appel LJ, Frohlich ED, Hall JE, et al. The importance of population-wide sodium reduction as a means to prevent cardiovascular disease and stroke: a call to action from the American Heart Association. Circulation. 2011;123:1138–43.
68. US Department of Agriculture and US Department of Health and Human Services. Dietary guidelines for Americans. Dietary guidelines for Americans, 2010. 7th ed. Washington, DC: US Government Printing Office; 2010.
69. Johnson AG, Nguyen TV, Davis D. Blood pressure is linked to salt intake and modulated by the angiotensinogen gene in normotensive and hypertensive elderly subjects. J Hypertens. 2001;19: 1053–60.
70. MacGregor GA, Markandu ND, Sagnella GA, et al. Double-blind study of three sodium intakes and long-term effects of sodium restriction in essential hypertension. Lancet. 1989;2:1244–7.
71. Lewington S, Clarke R, Qizilbash N, et al. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002;360:1903–13.
72. Luft FC, Weinberger MH, Fineberg MS, et al. Effect of age on renal sodium homeostasis and its relevance to sodium sensitivity. Am J Med. 1987;82:9S–15.
73. Khaw KT, Barrett-Connor E. The association between blood pressure, age, and dietary sodium and potassium: a population study. Circulation. 1988;77:53–61.
74. Stamler R. Implications of the Intersalt study. Hypertension. 1991;17(1 Suppl):I16–20.
75. Cook NR, Cutler JA, Hennekens CH. An unexpected result from sodium—causal or causal? Hypertension. 1995;25:1153–4.
76. Bibbins-Domingo K, Chertow GH, Coxson PG, et al. Projected effect of dietary salt reductions on future cardiovascular disease. N Engl J Med. 2010;362:590–9.

Intravenous Fluid Administration

17

Eugene C. Corbett, Jr.

Introduction

This chapter highlights several considerations in the use of intravenous (IV) fluids in the geriatric patient, specifically sodium and water. It emphasizes the fact that these are not only the key elements of routine intravenous fluid orders, but also body nutrients, required in limits to avoid the adverse consequences of either excess or deficit.

The goals of intravenous fluid administration are to carefully achieve and maintain a euvolemic and isotonic environment within the body as well as to provide for a variety of nutritional and pharmacologic interventions. The selection of an appropriate IV solution is dependent upon the fluid volume and electrolyte status of the geriatric patient as well as any additional specific therapeutic goal. A relevant factor is the ability of the individual to sustain fluid volume changes resulting from intravenous salt and water therapy. Avoiding extracellular volume excesses in the elderly is a specific example, given the decreases in cardiac and renal function, as well as the greater limitations in interstitial storage volume related to aging. Basic water and sodium needs must relate to choice of IV fluids as a function of the volume status of the "typical" hospitalized patient as also their serum sodium concentration. For discussion of clinical conditions related to sodium aberrations, the reader is referred to additional pertinent literature [1–3] (Table 17.1). It is a point of emphasis that sodium and water are nutrients; there are upper and lower limits to the amounts required in order to maintain ideal physiologic homeostasis [4, 5].

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Water

For the purpose of considering the fluid and electrolyte status of a patient at any one time, it is useful to imagine the body as a cylinder containing four compartments (Fig. 17.1). Water-free mass ("flesh") represents, on average, one-third of the body volume. The remaining two-thirds in a normal weight individual represent water volume. In turn, approximately two-thirds of the total body water (TBW) is contained in the intracellular space, with the remaining third in the extracellular compartment. This latter space is further subdivided into the interstitial and the vascular spaces. In a normal individual, the interstitial space contains about two-thirds of the extracellular volume. The vascular space, the smallest of the body's fluid compartments, represents approximately one-third of the extracellular volume and about one-ninth of the body's water space overall.

Maintenance of the euvolemic state requires replacement of normal daily volume losses. These include primarily insensible and renal losses, the former including solute-free pulmonary ("free water") and solute-containing dermal water loss. Typically, dermal losses are very low in solute content barring exceptions such as in patients with mucoviscidosis. Because the kidney's water concentrating ability spans a large range and continually adapts to variations in water intake availability (e.g., urine-specific gravity can vary between 1.001 and 1.040, or between 30 and 1,200 mOsm/L), estimation of *approximate* water requirements using the "2/3 rule" is normally sufficient in the clinical setting (Fig. 17.1). Because there is an upper limit to renal solute concentrating ability, as well as a mandatory loss of insensible free water in expired air, most individuals require a minimum of 1.5–2 L of water replacement per day as follows:

1. Renal excretion: minimum 1 L daily.
   In a 24-h period, the human body under normal conditions produces about 1,000–1,500 mOsm of ionic and molecular waste for renal excretion. The upper limits of renal concentration ability are reached at about 1,200–1,500 mOsm/L. Under conditions of illness and therapeutic

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Table 17.1 Examples of sodium and water abnormalities

Hyponatremia with hypovolemia (decreased total body water (TBW) and Na; relatively greater decrease in Na)
Extrarenal losses
GI: vomiting, diarrhea, fistulas, ostomies
Third-space losses: pancreatitis, peritonitis, small-bowel obstruction, rhabdomyolysis, burns, postoperative period
Renal losses
Diuretics
Osmotic diuresis (glucose, urea, mannitol)
Mineralocorticoid deficiency
Salt-losing nephropathies
Hyponatremia with euvolemia (normal TBW; near-normal total body Na)
Hypothyroidism
Glucocorticoid deficiency
States that increase release of ADH (postoperative, narcotics, pain, emotional stress)
Syndrome of inappropriate ADH secretion
Medications: though ADH release, altered renal response or other pathophysiologic mechanisms (an important cause in the geriatric age group)
Primary polydipsia
Hyponatremia with hypervolemia (increased total body Na; relatively greater increase in TBW)
Extrarenal disorders
Congestive heart failure
Hepatic cirrhosis
Renal disorders
Nephrotic syndrome
Acute renal failure
Chronic renal failure
Syndrome of inappropriate ADH secretion
Hypernatremia with hypovolemia (decreased TBW and Na; relatively greater decrease in TBW)
Extrarenal losses
GI: vomiting, diarrhea
Skin: burns, excessive sweating
Renal losses
Diuretics medications
Osmotic diuresis (glucose, urea, mannitol)
Diabetes insipidus
Hypernatremia with euvolemia (relatively decreased TBW; increased total body Na)
Inability to access free water including restricted mobility
Patients on tube feeding
NPO on isotonic IV fluids only
Hypernatremia with hypervolemia (increased TBW, greater increase in Na)
Hypertonic IV fluid administration without free water
Total parenteral nutrition with inadequate free water
Mineralocorticoid excess

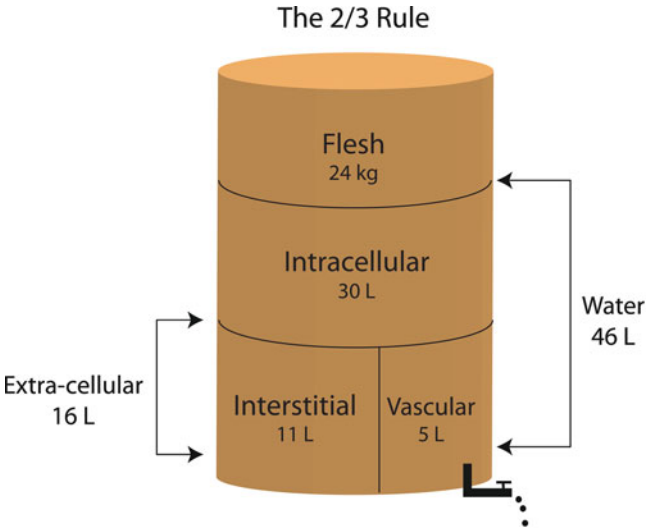

Fig. 17.1 The distribution of body water within a euvolemic 70-kg (154 lb) person (remember that 1 kg of water weight equals 1 L volume) (used with permission from the University of Virginia Health System Nutrition Support Traineeship Syllabus [9])

Table 17.2 Potential sources of fluid excess or loss in hospitalized patients

Intake	Output
Intravenous fluids	Stool/urine
Medications given via IV drip	Chest tubes
Water flushes given with crushed medications	Percutaneous drains
Water flushes to keep tubes patent	Biliary/pancreatic
Water contained in tube feedings or TPN	Wound drainage
	Ostomies
	Naso/oro gastric tube suction
	Excessive drooling/sialorrhea
	Fistulas
	Enterocutaneous
	Spit fistulas
	Insensible losses
	Accelerated insensible losses including
	Burns
	Tracheostomies
	Fever
	Kinair beds

Used with permission from the University of Virginia Health System Nutrition Support Traineeship Syllabus [9]

intervention, fluid requirements increase for solute excretion, e.g., increased waste excretion due to enhanced catabolism, pharmacologic degradation products, and increased acidotic excretion.

2. Minimal insensible loss is approximately 0.5–1 L daily.

Whereas renal fluid losses are a mix of water and solute waste, pulmonary water loss is solute-free water vapor. This is termed "insensible" loss because of the fact that it is not normally observed (except when breathing in a cold atmosphere) nor directly measured. Factors that increase insensible water loss include fever, increased ventilatory rate, tracheostomy, mechanical ventilation, as well as enhanced sweating (Table 17.2). Insensible loss normally

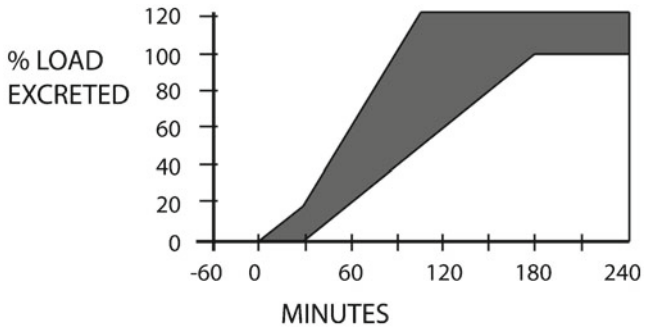

Fig. 17.2 Water elimination. The effect of a standard water load on renal function. *Shaded areas* indicate the range of values obtained in 24 healthy adults. A water load of 20 mL/kg was given between 0 and 30 min. The *bottom panel* indicates cumulative excretion expressed as a percentage of the total (from Felig [10], figure 9–22, p. 423, with permission of McGraw Hill Companies)

averages about 10 mL/kg body weight; in reality it is higher, around 15 mL/kg body weight minus that produced from endogenous metabolism.

3. Miscellaneous fluid losses: minor amounts of water are lost through stools, usually less than 150 mL/24 h. Gastrointestinal losses increase considerably in illness such as diarrhea or vomiting.

Thus, with an intake of approximately 2 L of water per day (equivalent to an IV infusion rate of about 85 mL/h), normal body water homeostasis can be maintained in the absence of exaggerated fluid gains or losses. For the average person on oral intake, about half of this comes from ingested fluids while the other half is contained within foods that are eaten.

Disease processes and care interventions add an additional challenge to the body's ability to maintain a euvolemic state. These include water losses that result from diarrhea, vomiting, increased sweating, and enhanced insensible loss, or the diuretic effects of drugs (Table 17.2). Gains in body fluid volume can result from cardiac failure, impairment in renal or hepatic function (low albumin), impaired capillary endothelial function in the setting of sepsis/trauma/ARDS, excessive water retention, effect of drugs, or excessive sodium intake.

Under normal physiological conditions, neurohumoral adjustments to changes in the body's water intake and losses begin to occur within minutes. For example, the intake of free water beyond the body's euvolemic need is generally eliminated within 3 h of ingestion (Fig. 17.2). On the other hand, vomiting results in an almost immediate increase in antidiuretic hormone (vasopressin) levels and the initiation of renal water conservation.

Sodium

The body's fluid volume is regulated to maintain an isotonic (iso-osmolar) state in the intracellular, interstitial, and intravascular compartments. Normally this is 290 ± 10 mOsm/L.

Table 17.3 Sodium distribution in the body

Compartment or tissue	Sodium distribution (%)
Plasma	11
Interstitial	29
Connective tissue	12
Bone	43
Exchangeable	14
Non-exchangeable	29
Intracellular	2.5
Transcellular	2.5
Total	100

The extracellular compartments of the body are dominated by sodium (~140 mEq/L) and chloride (~100 mEq/L). In contrast, the intracellular compartment is dominated by potassium (~150 mEq/L) and phosphate (~50 mEq/L). Thus, over 90% of dissolved body sodium is contained within the *vascular* and *interstitial* spaces, while over 90% of body potassium is located within the *intracellular* space. In addition, variable amounts of sodium are stored in bone, approximately half of which remains physiologically available (Table 17.3). Additionally, serum sodium concentration levels in most cases is a reflection of body water content. Hypernatremia generally denotes mean water depletion rather than increased body sodium. In general, dehydration is a term that suggests water loss, whereas the term volume also implies the inclusion of solutes such as sodium or blood. Hypernatremia more often than not, in the older population, denotes water loss as opposed to volume depletion.

Typically, the amount of *sodium excretion* in an individual on a daily basis is equivalent to his or her average sodium intake. Thus the amount of sodium excretion in 24 h varies from individual to individual over a large range. In the United States this is generally between 40 and 450 mEq (mmol). Under experimental conditions, human sodium conservation can be maintained with as little as 5–10 mEq intake in 24 h due to the ability of the kidney to tightly conserve sodium [6]. Potassium excretion also varies with intake. However, in contrast to the ability of the kidney to conserve sodium even at very low intake levels, renal potassium conservation is more limited. Thus, under conditions of no potassium intake and normal renal function in the adult, renal losses continue at a minimum level of approximately 40–60 mEq daily (also known as the "renal potassium leak").

Moreover, whereas water conservation and excretion regulatory mechanisms operate almost on a minute-to-minute basis, adjustments in renal excretion to daily variations in sodium intake typically take a *number of days* to respond (Figs. 17.2 and 17.3) [6, 7]. For example, when a hospitalized older patient receives an intravenous infusion which contains an amount of sodium *in excess* of his or her normal average intake, a number of days will pass before his or her urinary sodium excretion begins to match this higher intake level.

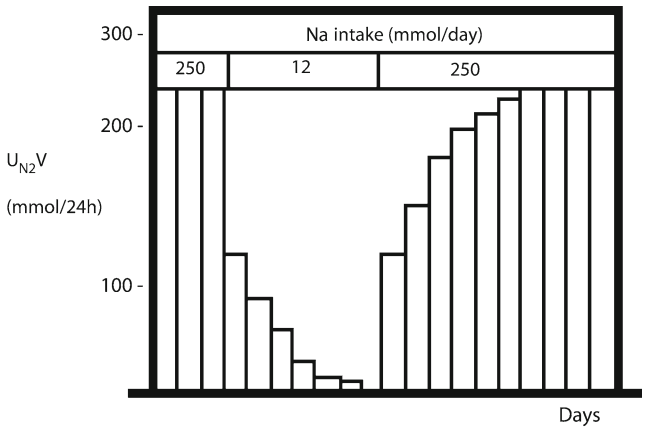

Fig. 17.3 Sodium elimination (from Simpson [11], p. 25, figure 1, with permission of Elsevier)

Table 17.4 Electrolyte content of IV solutions, per liter

Fluid	Na	K	Glucose	Tonicity	mOsm/L
0.9 NS[a]	154	0	0	Slightly hypertonic	304
0.45 NS	77	0	0	Hypotonic	154
0.25 NS	38	0	0	Hypotonic	77
Lactated ringers (LR)	130	4	0	Isotonic	280
D_5W	0	0	50 g	Hypotonic	0[b]
D_5W 0.45 NS	77	0	50 g	Hypotonic	154[b]
0.9 NS + 150 mEq $NaHCO_3$	308	0	0	Very hypertonic	616

Used with permission from the University of Virginia Health System Nutrition Support Traineeship Syllabus [9]

[a]One liter of 0.9 NS contains approximately two teaspoons of table salt

[b]*Note*: The 50 g of dextrose in a liter bottle equates to an osmolarity of 277 mOsm/L. However, the dextrose is rapidly metabolized and does not contribute to serum osmolarity unless the patient is hyperglycemic

The ramifications of the resulting sodium accumulation can be significant for patients who normally subsist on lower sodium intake levels such as the elderly population.

As an illustration, consider an elderly woman who is admitted to the hospital for dehydration secondary to pneumonia whose normal average sodium intake is 100 mEq daily (2,300 mg), a figure in the midrange of the recommended dietary allowance (RDA). On admission to the hospital, an IV infusion of normal saline (containing 154 mEq sodium/L) is begun at the rate of 150 mL/h, equivalent to 3.6 L/24 h. After 24 h, when she no longer appears dehydrated, her infusion rate is decreased to 125 mL/h for another 2 days after which it is discontinued because of adequate oral intake. Over the 72-h period of IV infusion, she has received a total of the following intravenous ingredients:

- 9.6 L of water
- 1,478 mEq of sodium (34,000 mg)

In contrast to her normal living circumstance in which she would have cumulatively taken in 300 mEq (6,900 mg) of sodium over the same time period of 72 h, this 3-day infusion of normal saline exceeded her usual intake by approximately 1,178 mEq (27,100 mg) of sodium. In adjusting this value to account for what was needed to correct for her level of dehydration on admission (a typical dehydration range would be 2–5% body weight), at most, about one-third of her total infusion was actually needed to bring her to euvolemic status. Thus, the remainder of the infused sodium (two-thirds of 1,178 = 785 mEq Na) represents an amount of sodium equivalent to seven or more additional days of intake beyond her usual amount. Because of the normal delay in adjustment of her renal sodium excretion to match the new in-hospital intake level (Fig. 17.3), her extracellular sodium content has therefore been increased by approximately 785 mEq. This results in an isotonic volume expansion of about 6 L (785 mEq/140 mEq/L = 6 L) and represents an excessive intake of 18,000 mg of sodium, or approximately 12 teaspoons of table salt. If her IV infusion had been continued for a longer period of time, or at a higher infusion rate, an additional amount of sodium would have been infused and accumulated in her extracellular compartment.

Particularly in patients with limited cardiac, renal, or hepatic function, such excesses in volume expansion through normal saline infusion will lead to interstitial edema and its cardiopulmonary consequences. Of additional concern, if her oral intake of water was also compromised because of limited water access, *her free water intake requirement would also not have been met*, potentially leading to hypernatremia [3] and the discomfort of excessive thirst. Adverse outcomes such as these are preventable with careful avoidance of excessive sodium infusion and provision of free water. The choice of the appropriate amount and concentration of hydration fluid, both sodium and water, requires the same care as the selection of a correct medication dose.

Tables 17.4 and 17.5 indicate sodium content levels in standard IV fluids and at commonly ordered infusion rates. For comparison, the RDA for sodium intake is between 47 and 147 mEq (1,100–3,300 mg) per day [5]. Because actual dietary sodium intake in the United States is generally higher than this and varies between 50 and 450 mEq/day (1,150–10,350 mg), sodium deficiency is rarely observed. The geriatric population generally consumes less sodium than the average, and remains at higher risk for suffering the consequences of excessive normal saline infusion.

One liter of normal saline contains 154 mEq (3,542 mg) of sodium, an amount just above the upper RDA range. This is equivalent to an amount just under two teaspoons of table salt per liter. In comparison, the average concentration of sodium in the extracellular body compartment is ~140 mEq/L. Thus, normal saline contains no free water and is slightly hypertonic to normal body osmolarity. For comparative interest, Table 17.6 contains the sodium content of common salt substitutes.

Table 17.5 Comparative sodium levels

	Sodium content		
Source	mEq	mg	NaCl (mg)
Lowest required intake [6]	5/day	115	287
Recommended dietary allowance	47–147	1,100–3,300	2,750–8,250
1 L 0.9 normal saline	154	3,542	8,855
US intake, range per day	50–450	1,150–10,350	2,875–25,875
0.45 NS infusions			
75 mL/h × 24 h	138	3,188	7,970
100 mL/h × 24 h	185	4,250	10,625
125 mL/h × 24 h	231	5,313	13,282
0.9 NS infusions			
75 mL/h × 24 h	277	6,371	15,927
100 mL/h × 24 h	369	8,487	21,217
125 mL/h × 24 h	462	1,0626	26,565
150 mL/h × 24 h	554	12,742	31,855
Addition of $NaHCO_3$ to 0.45 and 0.9 NS infusions/liter[a]			
75 mEq in 0.45 NS	152	3,496	8,740
150 mEq in 0.9 NS	304	6,992	17,480

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[a]Only occasionally ordered. The astute pharmacist will call attention to the hypertonic sodium load

Table 17.6 Salt and salt substitutes[a]

1 mEq (mmol) Na = 23 mg Na			
1 mg Na = 2.5 mg NaCl	Per teaspoon		
Product	mEq	mg	NaCl (mg)
Salt	100	2,300	5,750
Sea salt	95	2,176	5,440
Garlic salt	89	2,050	5,125
Garlic powder	0.04	1	2.5
Black pepper	0.04	1	2.5
Lemon pepper	28	487	1,217
Morton lite salt	48	1,100	2,750
Morton salt substitute	0	0	0
No salt	0.9	20	50
Nu-salt	0	0	0
Mrs. Dash seasonings	0	0	0
Chef Paul Prudhomme magic salt free all-purpose blend seasoning	0	0	0
Also salt	0	0	0
Blue crab bay herbs for seafood	0	0	0
Soy sauce	15	343	857
Low-sodium soy sauce	9	200	500
Vinegar	0	0	0
Mustard	3	65	162
Dill pickle (1 spear)	40	928	2,320
Beef bouillon (1 cube)	38	864	2,160
Salt	100	2,300	5,750
Sea salt	95	2,176	5,440

Used with permission from the University of Virginia Health System Nutrition Support Traineeship Syllabus [9]

[a]*Note*: Some products in the table may contain significant amounts of potassium indicating the need for provider and patient awareness regarding safety. For example: sea salt 150 mg, Morton liter salt 610 mg, no salt 800 mg, also salt 356 mg

Maintenance Fluid Requirements for IV Infusion

For the average person who is euvolemic, iso-osmolar (isotonic), and limited to IV replacement alone (NPO), a *minimum* of 2 L of IV water (85 mL/h) is recommended. Because the equivalent of 1 L of 0.9% normal saline contains sufficient sodium replacement for a 24-h period in the typical clinical circumstance, the remainder of the intravenous volume replacement can be provided in the form of free water as represented in a solution of 5% dextrose in water (D_5W). An equivalent example of a minimum standard IV "maintenance fluid" for 24 h would be achieved with an order of D_5 in half-normal (0.45) saline to run at 85 mL/h. This would provide approximately 2 L of volume containing 154 mEq of sodium plus a liter of free water replacement over a 24-h period. Writing for 75, 100, or 125 mL/h of 0.45 NS would provide, respectively, 1.8, 2.4, and 3 L of volume in 24 h. The obvious advantage of using 0.45 normal saline is that its volume contains half free water.

General Recommendations for IV Fluid Selection

The following guidelines are recommended for achieving and maintaining a euvolemic and isotonic internal environment under most clinical circumstances (Table 17.1):

1. Achieving euvolemia.
   (a) From a comparison of an individual's normal weight with his or her current body weight and clinical examination, determine the patient's volume status and estimate, if any, the degree of variation from euvolemia.
   (b) If euvo*lemic*, only maintenance fluids need to be prescribed, as in the patient who may be NPO.
   (c) The *dehydrated* patient is typically hypernatremic from water losses or poor intake and will ultimately require hypotonic fluid (Table 17.4) to fully correct volume status. Initial infusion with isotonic saline with slow correction of the hypernatremia is required in order to avoid the risk of adverse CNS outcomes [8]. Following normalization of sodium and correction of dehydration, maintenance fluid replacement should then be instituted.
   (d) Volume replacement because of additional clinical volume loss (diarrhea, blood loss, vomiting/NG suction, diuresis, and exaggerated insensible loss (fever)) needs to be estimated from clinical examination (typically for blood pressure, pulse, orthostasis, skin turgor, jugular venous pressure, edema), measured intake/output volume, body weight, and the sodium content of the specific fluid lost (Table 17.7).

Table 17.7 Sodium concentration in body fluids

Body fluid	Concentration (mEq/L)
Serum	135–145
Saliva	10–55
Gastric juice	10–100
Pancreatic juice	120–140
Bile	120–160
Intestinal	105–145
Stool/diarrhea	1–100
Skin	1–80

(e) The *volume-expanded* patient generally requires maintenance free water volume replacement and very limited sodium intake, as well as diuresis based on the clinical circumstance. If the patient is isotonic or hypertonic, fluid replacement should be limited to free water replacement only. This will also help facilitate natural sodium excretion (natriuresis).

2. Achieving isotonicity (iso-osmolar status).
   (a) Tonicity of body fluids can be measured directly (serum osmolarity), or estimated approximately from the serum sodium concentration ([Na]×2+10), or more exactly from the formula [Na]×2+glucose/18.
   (b) The *isotonic* patient requires only maintenance sodium replacement unless he or she is also dehydrated (see 1(c) and (d) above).
   (c) The *hypertonic* (*hypernatremic*) patient requires additional free water replacement according to the following formula:

$$\text{Average TBW} = 0.66\times \text{ body weight (kg)}$$

$$\text{Water deficit} = \text{TBW}\times\{\text{Serum[Na]}-140\}/140$$

Generally it is best to give no more than half of the calculated deficit over 12–24 h and recalculate the deficit based upon repeated clinical measurements. Examples include patients with renal (diabetes insipidus) or extrarenal volume losses (vomiting, diarrhea). Vital signs and clinical examination will dictate the type of fluid used for replacement.

   (d) The *hyponatremic* patient requires a determination of whether the hypotonic state needs correction, and if so, whether water restriction or sodium supplementation is required. Clinical findings, including the presence of an abnormal neurological status, generally clarify this circumstance.
      i. No correction is generally necessary if [Na] is >130 mEq/L and not trending downward (stable).
      ii. Water restriction (generally 1,200–1,500 mL/day) is required if a diagnosis of the syndrome of inappropriate antidiuretic hormone secretion (SIADH) applies, especially if the [Na] is <130 mEq/L and/or is trending downward.
      iii. Sodium supplementation is generally indicated only for the *rare* patient who is considered truly sodium depleted. Typically these patients are also volume depleted and generally respond to isotonic volume replacement with normal saline.

Note: As a general rule in evaluating disorders of sodium and water metabolism, in addition to the serum sodium concentration, the patient's vital signs and neurological status deserve primary attention in determining *the choice of fluid and rapidity of correction.* Vital signs (e.g., low blood pressure) must be given priority over the sodium value; in a hypotensive patient with hypernatremia, the choice of fluid would be normal saline to raise the blood pressure. The choice of fluid in a patient with hyponatremia and seizures or stupor might include judicious administration of hypertonic saline (e.g., 3% saline) with a view to partially correct the low serum sodium level. Gradual correction is generally prudent unless the disorder is rapid in onset.

Key Points

- Achievement and maintenance of a euvolemic and isotonic internal environment require careful adjustment of water and sodium intake that reflects the excesses and/or deficits of these physiologically linked nutrients.
- Optimal care of the fluid status also requires an appreciation of the limits of sodium and water handling, which can vary depending on such factors as age, renal and cardiac function, and the patient's routine intake of sodium.
- Under most clinical circumstances, careful attention to the amounts of infused sodium and water in conjunction with appropriate clinical assessment will provide for optimal establishment and maintenance of the patient's fluid status.
- Standard assessment methods include physical examination, an accurate body weight, fluid intake and output measurements, and serum electrolyte, renal function, and osmolarity determinations.
- Systematic application of these principles will insure that the internal fluid environment of the patient remains normal and adverse outcomes are minimized.

References

1. Androgue HJ, Madias NE. Hyponatremia. N Engl J Med. 2000; 342(21):1581–9.
2. Androgue HJ, Madias NE. Hypernatremia. N Engl J Med. 2000; 342(26):1493–9.

3. Palevsky PM, Bhagrath R, Greenberg A. Hypernatremia in hospitalized patients. Ann Intern Med. 1996;124:197–203.
4. Corbett EC. Nutrition: salt. In: Becker DM, Gardner LB, editors. Prevention in clinical practice. New York: Plenum; 1988. p. 351–4.
5. Dietary Guidelines for Americans 2005. USDHHS USDA: www.healthierus.gov/dietaryguidelines/dga2005/document.
6. Dahl LK. Salt intake and salt need. N Engl J Med. 1958;258(23):1152–7.
7. Strauss MB, Lamdin E, Smith WP, et al. Surfeit and deficit of sodium: a kinetic concept of sodium excretion. Arch Intern Med. 1958;102:527–30.
8. Rose BD, Post TW. Hyperosmolar States–hypernatremia. Clinical physiology of acid-base and electrolyte disorders, Chap. 24. 5th ed. New York: McGraw-Hill;2001. p. 775–8.
9. Parrish CR, Krenitsky J, McCray S. University of Virginia Health System Nutrition Support Traineeship Syllabus. Available through the University of Virginia Health System Nutrition Services in January 2003.
10. Felig P, Baxter JD, Frohman LA, editors. Endocrinology and metabolism. New York: McGraw Hill; 1995.
11. Simpson FO. Sodium intake, body sodium and sodium excretion. Lancet. 1988;332(8601):25–9.

B12 and Folic Acid

18

T.S. Dharmarajan and Srinivas Guptha Gunturu

B12 (Cobalamin)

Introduction

Vitamin B12 (B12, cobalamin) and folic acid are commonly consumed nutrients; deficiency of either may cause anemia and additional manifestations. The term B12 refers to several compounds known collectively as cobalamins; the most common are two therapeutic forms, hydroxocobalamin and cyanocobalamin, and two metabolically active coenzymes methylcobalamin and deoxyadenosylcobalamin. Hydroxocobalamin, produced by bacteria, is not a form normally present in humans and requires conversion to the active coenzyme form; it is the more common commercial preparation used outside the US. Cyanocobalamin is not found in nature; it is more air-stable and is formed by utilizing the affinity of hydroxocobalamin for cyanide. Like hydroxocobalamin, cyanocobalamin also has to undergo conversion in the body to the active coenzyme [1]. Chemically, B12 is 5, 6-dimethylbenzimidazolyl cyanocobamide. Cobalamin is the vitamin B12 molecule minus the cyanide group; cyanocobalamin is the most traditional commercial preparation used in the US [2, 3]. Several inactive forms of B12 termed as vitamin B12 analogues also exist; these forms may even have anti-B12 actions in humans, but serve as apoenzymes for bacteria [2].

The properties of this heat (but not light)-stable vitamin are provided in Table 18.1. Functions served by B12 include DNA and RNA synthesis; lipid, protein, and carbohydrate metabolism; maintenance of structural integrity of membranes and myelin sheaths; maintenance of bone marrow cellularity, cell-mediated immunity; and gastrointestinal epithelial and mucosal cell integrity [4, 5].

Epidemiology

B12 deficiency is a worldwide problem with prevalence ranging widely [6], affecting males more than females, with no race predilection [6, 7]. Based on National Health and Nutrition Examination Survey (NHANES III) [8] data, in New Mexico elders (>65 years), Hispanics had lower B12 levels compared to non-Hispanic Whites [9]; in 165,700 patients, B12 deficiency accounted for 17–20% of nutritional anemias and 6–7% of all anemias [10]. Surveys in the UK and the USA suggest that deficiency increases with age, with marginal status around 20%; in developing countries, deficiency is more common and noted at an earlier age due to low consumption of animal-source foods [11]. Although data on true prevalence is underestimated and varies with source, the range is 2–43% in the over 65 years group [11–15] based on criteria adopted [11–20]. In a US study, the prevalence of B12 deficiency was higher in African Americans and White centenarians than in octogenarians (35.3% vs. 22.8%) [21]. Deficiency appears equally prevalent in community and long-term care settings [14].

Vitamin B12 Absorption

B12 absorption involves a complex pathway involving multiple steps; a disruption of any single step can cause deficiency. Naturally available B12 is bound to dietary proteins. R protein, also termed Transcobalamin I (TC I), is produced by salivary glands and gastric granulocytes and epithelial cells [22, 23]. Upon ingestion, acid-peptic activity in the stomach facilitates release of cobalamin from food protein. At this stage, two proteins compete for B12: R protein and intrinsic factor from gastric parietal cells. Three steps follow. Step 1: in the

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Table 18.1 Properties of vitamin B12

Air-stable
Easy to crystallize and purify
Dark red crystals or crystalline red amorphous powder
Hygroscopic in its anhydrous form
Destroyed by metals and oxidizing or reducing agents
Sparingly water-soluble (1:80); aqueous solutions stable at pH 4.5–5
Unstable in light
Heat stable; not destroyed by autoclaving to 121°C

acid medium of the stomach, cobalamin conjugates with R protein which has greater affinity for B12 (than IF), and the complex passes into the duodenum. Step 2: in the duodenal alkaline pH (contributed by pancreatic bicarbonate) and aided by pancreatic proteases, the R binder is cleaved to release B12 from the B12-R binder complex; B12 is now ready to bind to intrinsic factor (IF) from the stomach for transport down the small intestine [24]. In physiologic states, IF in a milliliter of gastric juice can bind 50–60 ng of B12 [25]. Step 3: IF-B12 complex transported to the ileum attaches to cubulin and megalin or amnionless receptor complex in the ileal enterocyte; here it is actively absorbed through a process of endocytosis in the presence of ionic calcium and a pH over 6 [3, 26–28]. In summary, step 1 requires acid-peptic activity to severe B12 from food protein to complex with R factor in the stomach; step 2 beyond the stomach involves release of B12 from R factor in an alkaline medium and binding to gastric IF [18]. Aging by itself plays little role in absorption; it is the impact of disease and medications that causes deficiency at any age.

In the lysosomes of enterocyte, cobalamin is liberated and IF is recirculated [18]. Free B12 is complexed with transcobalamin II (TC II), also known as holotranscobalamin II (holo-TCII) in secretory vesicles of the ileal enterocyte, to be transported into circulation to liver and other organs of the body [3, 18]. The B12-binding proteins are TCs I, II and III, with half lives of days, hours, and minutes, respectively; once absorbed, B12 is bound to TC I (80–94%) and TC II (6–20%), with TC II the metabolically active component [29]. B12 participates in the enterohepatic circulation [24]. Liver secretes B12 bound to haptocorrins via bile into the intestine, to be lysed by pancreatic proteases and rebind with IF to resume the usual pathway [24]. About 1–3% of B12 is passively absorbed without IF, a fact substantiated by absorption of B12 even in pernicious anemia [5, 30–33]. B12 absorption through enterohepatic circulation is about 1.4 μg a day and is perhaps even more efficient in vegetarians; typical absorption after oral ingestion takes 4–6 h [34]. Liver stores 50–90% of B12 in the body, ranging from 1 to 10 mg. The absorption pathway is schematically presented in Fig. 18.1.

Inherited or acquired malabsorption disorders can affect any step in the pathway and impair absorption. Much of the excess B12 absorbed or injected in large doses is excreted in the urine; here the percentage of dose retained decreases, the total amount absorbed increases, and a larger dose is excreted [5]. B12 transport across the blood brain barrier is augmented by zinc and impaired by copper, with little clinical relevance [35].

Causes of B12 Deficiency

Although low intake of animal-source foods causes B12 deficiency as noted in vegetarians, the most common cause is food-cobalamin malabsorption [36] and not dietary deficiency [37]. Yet, the geriatric age group is vulnerable to nutrient deficiencies due to restricted diets, age-related physiological alterations in the GI tract including a less efficient enterohepatic circulation, chronic disease, and polypharmacy [18, 38]. The most common cause of B12 deficiency in older adults is *food-cobalamin malabsorption syndrome, also termed food-cobalamin syndrome (FCS),* defined as the inability to release cobalamin from food or its binding proteins; it usually results from atrophic gastritis related or unrelated to *Helicobacter pylori* infection, or long-term ingestion of acid-neutralizing agents [39, 40]. It is an exclusion diagnosis currently and may be better characterized in future [40].

Predispositions to B12 deficiency include male gender, age >75 years, strict vegan diet, avoidance of dairy products [16], decreased salivary gland secretions [29], decreased gastric acidity, atrophic gastritis, use of acid lowering drugs, total gastrectomy (within a year) [41], alcoholism [42], malabsorption syndromes such as celiac disease, pancreatic insufficiency, small intestinal bacterial overgrowth (SIBO), Crohn's disease, defective cellular metabolism (chronic N_2O toxicity) [5], Zollinger–Ellison syndrome, AIDS enteropathy [24], hypothyroidism [24], ileal disease, cholestyramine, metformin [18], genetic deficiencies of intrinsic factor, haptocorrin (TC I) deficiency or polymorphisms of TC II [29], and genetic polymorphisms in transcobalamins [36]. Relative deficiency can occur with increased requirements in diabetes mellitus, renal failure, smoking, alcohol consumption, and methylenetetrahydrofolate reductase (MTHFR) polymorphism 677 homozygosity [18]. *Diphyllbothrium latum*, the fish tapeworm, absorbs B12 and those infested develop deficiency. A select discussion of predisposing causes follows.

Drug–nutrient interactions as a cause of B12 deficiency are listed in Table 18.2. Although data is inconsistent, PPIs used over years may decrease the absorption of dietary vitamin B12, but not crystalline B12; the basis is perhaps a sustained reduction of gastric acidity, disrupting the essential first step in splitting B12 from food protein [43]. While long-term studies are few, chronic PPI use may warrant evaluation for B12 deficiency [20, 44, 45]. More recently, metformin has been incriminated as a cause of B12 deficiency; the drug impairs B12 absorption at the ileum, apparently through calcium depletion at the site [27, 28]. Addition of oral calcium

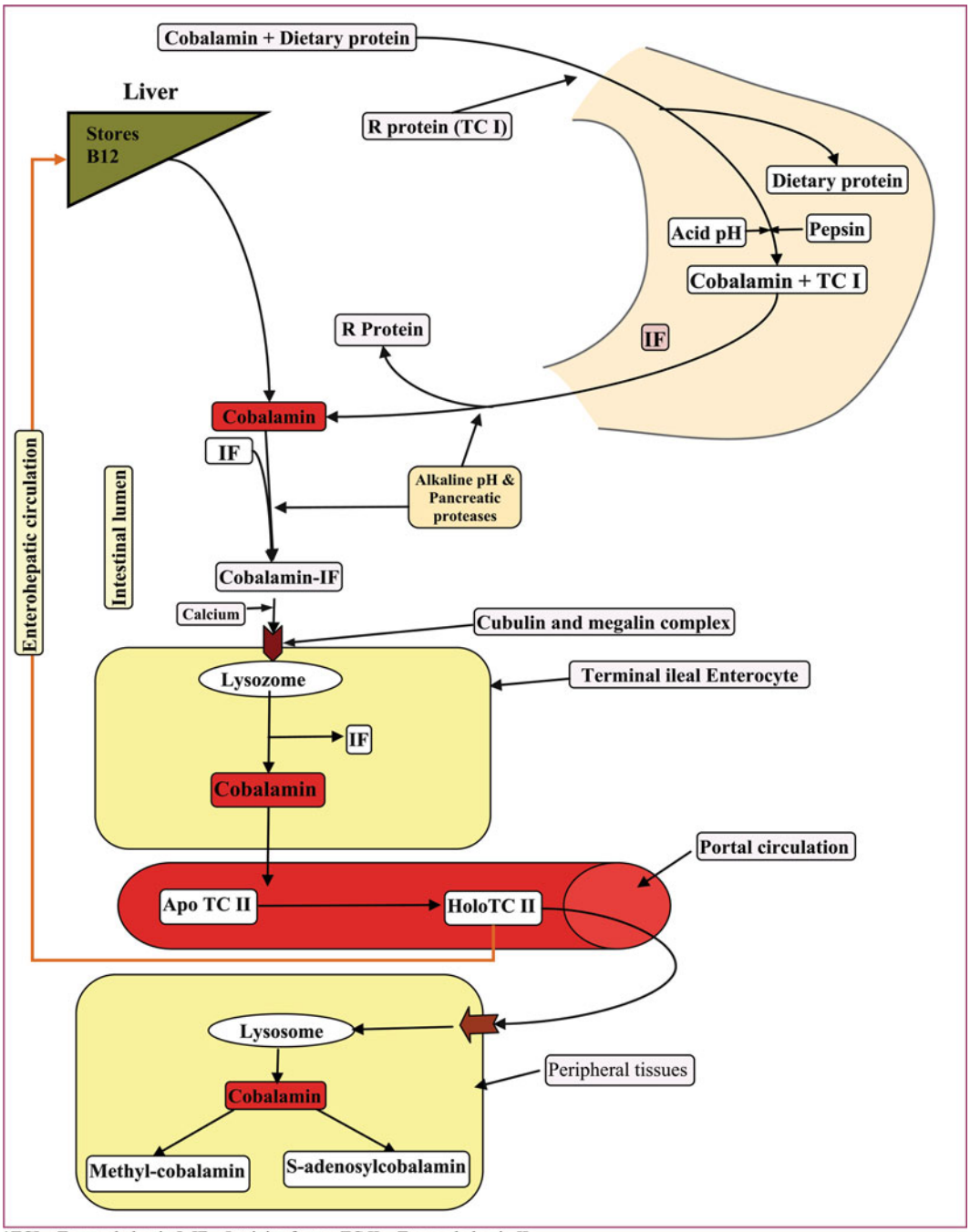

Fig. 18.1 Gastrointestinal absorption of Cobalamin

may minimize the problem. As metformin is a common first-line therapy in type 2 diabetes, a disorder common in the old, the finding has implications. It appears prudent to measure B12 levels when individuals are on medications that predispose to deficiency.

Chronic atrophic gastritis is a once popular classification as Type A or Type B (Strickland and McKay); Type A involves the fundus and body of the stomach and spares the antrum, while Type B predominantly involves the antrum. The fundus and body contain gastric parietal cells which secrete acid and IF; autoimmune Type A gastritis is pernicious anemia, associated with antibodies to IF and parietal cells. Type B gastritis is associated with *H. pylori a*nd NSAID use. In the past *pernicious anemia* (PA) was considered the most common cause of B12 deficiency [46], a view now challenged, with FCS considered today the most common basis, accounting for 40–50% of cases [47]. While PA increases in prevalence with age, it accounts for <10% of cases of B12 deficiency in the over 60 age group in the US [46], but may be more common in those of Scandinavian or North European descent. Pernicious

Table 18.2 Drug interactions with B12 [134, 135]

Medication	Comments
Neomycin	B12 deficiency due to malabsorption
Methotrexate	B12 deficiency but there is no significant effect on methotrexate efficacy
Phenytoin	B12 deficiency
Phenobarbital	B12 deficiency
Colchicine	Decreases IF-B12 receptors in ileal enterocytes
Levodopa	Increases homocysteine levels via methylation of levodopa
Isoniazid	B12 deficiency
Oral contraceptives	False low levels
Vitamin B6	Enhances absorption of B12
Vitamin C	Has no effect on B12 absorption
Metformin	B12 deficiency occurs through calcium depletion at the ileum
Proton pump inhibitors	Gastric acid suppression and failure to cleave B12 from food protein

anemia causes less than 2% of B12 deficiency in the UK older adults [37]. Antibodies in PA are directed at IF and occur in up to 70% of cases; while they are specific, their absence does not rule out PA [46]. On the other hand, parietal cell antibodies are nonspecific, occurring in up to 90% of cases and even noted with aging [46].

The association between *H. pylori infection* and B12 deficiency is novel and interesting. *H. pylori* infection is amongst the most common GI infections worldwide. Over half the cobalamin-deficient subjects were positive for *H. pylori* infection in a study; following treatment of the infection, 40% of the subjects improved their B12 levels [26]. Thus eradication of *H. pylori* through antibiotics may correct B12 deficiency. The mechanisms involved are speculative. Interestingly, while *H. pylori* infection and atrophic gastritis are more common in Japan than in the West, PA is uncommon in the Japanese [48].

SIBO that frequently occurs in blind, stagnant loop disorders is detailed in chapter 46. Bacteria in the small bowel, especially anaerobes, use up dietary cobalamin and produce analogues that serve no useful purpose to the host, and in fact compete with the dietary cobalamin for receptor sites [49]. In these patients serum folate levels may be normal or even elevated as bacteria synthesize folate [50–52]. Treatment involves administering a course of antibiotics.

Gastric surgery was performed for peptic ulcer decades ago; today, gastric bypass is commonly performed to address morbid obesity. Following surgery, cobalamin deficiency develops in a third at two years, with anemia occurring in nearly half the patients [53]. In addition to B12 deficiency, iron deficiency develops following gastric bypass, while folate deficiency is rare [53]. In a study of 72 postgastrectomy patients, iron deficiency was the most evident, followed by B12 and folate deficiency; iron plus B12 deficiency was the most common combination noticed [54].

B12 deficiency is common in Crohn's disease compared to ulcerative colitis [55]; in Crohn's disease, prior small intestinal surgery is an independent risk factor [55]. Deficiency increases proportionately to the extent of ileal involvement; levels should be routinely obtained in patients with inflammatory bowel disease. Levels are low in up to half the patients with HIV disease and increase with the presence of diarrhea; the mechanism involves disordered transport causing malabsorption [56].

On the contrary, B12 levels may be high in decompensated chronic liver disease, whereas plasma folate levels are low. The ratio between B12 and folic acid may be useful in the differential diagnosis of chronic liver disease [57]. In liver disease, myeloproliferative disorders and solid organ cancers, there is false elevation of B12 levels and increased binding to transcobalamin I and II, resulting in functional (B12) deficiency at the metabolic level [58, 59]. Uncommon disorders causing B12 deficiency include: Zollinger–Ellison syndrome, where pancreatic proteases are deactivated by acid gastric contents; chronic pancreatitis where the mechanism involves exocrine deficiency; intestinal lymphoma, amylodosis, and short bowel syndrome.

Requirements and Lifestyles

The recommended dietary allowance (RDA) from the Institute of Medicine is 2.4 μg of crystalline B12 per day in adults, expecting at least 50% is bioavailable [31, 60]. The usual daily intake in western diets is 3–30 μg/day [61]. B12 content of diets is provided in Table 18.3 and bioavailability after cooking for select foods in Table 18.4. Dietary content of B12 and folate differs markedly in commonly consumed foods, as depicted in Fig. 18.2. B12 is not present in several food sources such as spices, mustard, garlic, vegetables, fruits, and cooking oils. Estimated daily loss of B12 is 1 μg/day in normal physiological states and more with malabsorption [5]. In patients undergoing gastric bypass, prophylactic supplementation must be initiated [3].

In a cross-sectional European study, vegans had lower B12 concentrations (but higher folate concentrations) than vegetarians and omnivores; half the vegans were B12 deficient and at risk of developing clinical symptoms [62]. Low serum B12 levels are associated with few lifestyle factors, mainly vegetarianism and high coffee intake, unlike serum folate deficiency which was associated with smoking, alcohol intake, and unhealthy diets [63].

Clinical Manifestations

The progress of cobalamin depletion goes through successive stages of malabsorption, subtle preclinical deficiency, and finally overt clinical deficiency; the entire process taking years

Table 18.3 B12 content of various foods [136]

Food	B12 (μg/100 g)
Mollusks, clam, mixed species, canned, drained solids	98.89
Beef, variety meats and by-products, liver, cooked, pan-fried	83.13
Turkey, all classes, giblets, cooked, simmered, some giblet fat	33.25
Braunschweiger (a liver sausage), pork	20.09
Chicken, liver, all classes, cooked, simmered	16.84
Crustaceans, crab, Alaska king, cooked, moist heat	11.51
Margarine, vegetable oil spread, 60% fat, tub/bottle	10.83
Chicken, broilers or fryers, giblets, cooked, simmered	9.44
Fish, sardine, Atlantic, canned in oil, drained solids with bone	8.94
Crustaceans, crab, blue, cooked, moist heat	7.31
Fish, salmon, sockeye, cooked, dry heat	5.80
Milk, dry, nonfat, instant, with added vitamin A	4.00
Milk, buttermilk, dried	3.85
Cheese, Swiss	3.35
Beef, ground, 75% lean meat/25% fat, patty, cooked, broiled	2.81
Lamb, domestic, leg, whole (shank and sirloin)	2.64
Cheese, mozzarella, part skim milk, low moisture	2.29
Egg, yolk, raw, fresh	1.93
Salami, dry or hard, pork, beef	1.90
Crustaceans, shrimp, mixed species, cooked, breaded, and fried	1.87
Fast foods, hamburger, large, double patty, with vegetables	1.80
Cheese, feta	1.69
Cheese, muenster	1.48
Egg, whole, cooked, fried	1.39
Fast foods, cheeseburger, regular, single patty	1.31
Egg, whole, raw, fresh	1.29
Pork, fresh, loin, bone-in, separable lean only, cooked, pan-fried	0.76
Fast foods, burrito, with beans and meat	0.75

Table 18.4 Vitamin B12 content in μg/common measure of select foods and bioavailability [136, 137]

Meat and chicken
Cooked beef liver, lean meat, chicken, turkey: 13–83.3 μg/measure
Cooking meat for 35 min at 350 °F = 33% loss of bioavailability
Milk-based
Whole milk: 1.3–1.4 μg/measure; butter milk
Bioavailability: Boiling milk: 2–5 min = 30% loss, microwave: 5 min = 50% loss; pasteurization = 5–10% loss; refrigeration for 9 days = no loss noted
Fluorescent light exposure at 4 °C decreases B12 content
Cottage cheese; hard cheese; blue cheese: contains 20–60% of milk B12
Pizza cheese topping; 0.49 μg/measure
Eggs
Whole egg: 0.65 μg/measure; egg yolk: 0.32 μg/measure; egg white: 0.03 μg/measure
Bioavailability: Scrambled, boiled, and fried similar
Sea food
Salted and fermented salmon kidney has the highest B12 content
Fish: Salmon, sardine, trout, tuna, shell fish: 3–8.9 μg/measure
Loss of B12 from fish meat by boiling, steaming, sautéing, frying, and microwaving: 2.3–14.8%
Vegetables, fruits, nuts, nondairy beverages: contain little to no B12
Chick peas, beans, peanuts
Coffee, tea, lemonade, cranberry juice, grape drinks
Rice flour, wheat flour, couscous, oat bran, corn meal
Cabbage, spinach, brocolli, garland *Chrysanthemum*, taro, soybean
Strawberries, pears, oranges, raspberries, bananas, dates
Almonds, pecans, cashew nuts, Brazil nuts
Edible algae contain 38–72 μg pseudovitamin B12: May inhibit biologically active B12 [18]

[47, 64]. B12 deficiency is often asymptomatic. Presentation may range from day-to-day manifestations, or features that are hematological, neurological, psychiatric, or a combination (Table 18.5) [65]. The rate of cognitive function decline appears related to B12 levels and MMA levels, rather than homocysteine levels [66]. Neurological features may be irreversible if treated too late. B12 deficiency causes megaloblastosis of proliferating intestinal epithelium besides other cells, which in turn can cause malabsorption of several additional nutrients with consequent features. Patients with FCS have inability to absorb protein bound cobalamin, but can absorb crystalline B12 and exhibit a normal Schilling test [11].

Diagnosis

B12 deficiency should be suspected especially in high-risk individuals presenting with unexplained anemia, cognitive and psychiatric impairment, nonspecific gastrointestinal manifestations such as diarrhea, glossitis, or anorexia, with or without other nutrient deficiencies [19]. The "at risk group" is provided in Table 18.6. Hematological testing for macro-ovalocytosis, hypersegmentation of neutrophils, and cytopenias is a start, although not fully utilized in the present era. The differential diagnosis of macrocytosis also includes folate deficiency, alcoholism, reticulocytosis, hemolysis, hypothyroidism, and liver disease [67]. In fact, B12 deficiency is not the most common cause of macrocytosis. Bone marrow demonstrates increased erythroid/myeloid ratio, megaloblasts, and "asynchronism of maturation," referring to an immature nucleus despite maturation of hemoglobin [67]. Thus macrocytosis does not equate megaloblastosis; the latter is more specific for B12 (and folate) deficiency. Radioactive immunoassay testing for B12 is more sensitive compared to electro-chemiluminiscence immunoassay [68]. Ultimately testing involves a judicious choice of tests factoring patient preferences, costs, and yield [67, 69, 70]. A stepwise approach to screening and evaluation of B12 deficiency is provided in Table 18.7.

Testing involves assay of the vitamin or the metabolites. A low serum cobalamin <200 or 300 pg/mL is not by itself diagnostic for B12 deficiency, with at least two unrelated

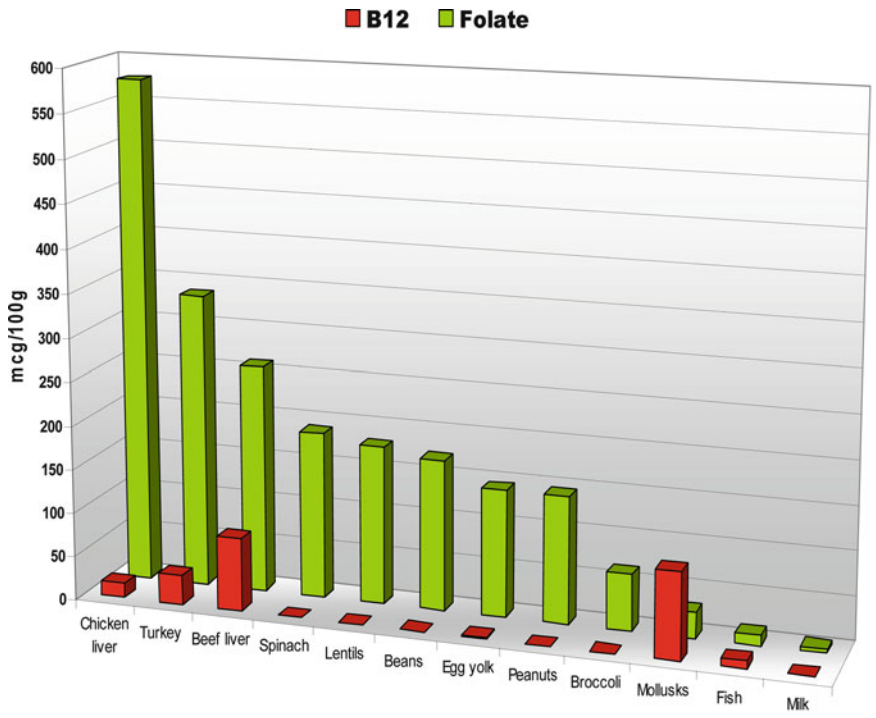

Fig. 18.2 B12 and Folate content of select foods

Table 18.5 Features of B12 deficiency

Asymptomatic or nonspecific
Day-to-day vague symptoms
Lethargy, fatigue, apathy
Weight loss
Hematological
Macro-ovalocytosis
Anemia
Hypersegmented neutrophils
Thrombocytopenia
Pancytopenia
Hemolytic jaundice
Neurological
Peripheral neuropathy
Spinal cord: subacute combined degeneration
Optic neuropathy
Gait abnormalities
Balance abnormality
Ataxia
Psychiatric
Depression, anxiety, psychosis
Cognitive impairment, progressing to dementia
Other
Gastrointestinal: glossitis
Malabsorption from GI mucosal epithelial involement
Pigmentation and vitiligo
Visual hallucinations with impaired vision (Charles Bonnet syndrome) [138]
Unexplained cough [139]
Urinary incontinence

biochemical abnormalities (MMA, homocysteine) required for diagnoses [5, 13, 69]. Some consider values below 80 pg/mL as diagnostic of deficiency, as also an MCV over 130 fL [69]. While the generally accepted cut-off was <200 pg/mL, there has been a suggestion to raise that level to between 300 and 350 pg/mL [18]. Hence, borderline levels between 200 and 350 pg/mL are indeterminate for B12 status and require further evaluation to ascertain status [13, 15]. HoloTC is the most sensitive measure of functional B12 status [37]. For screening purposes combined B12 and holoTC levels may better identify patients with deficiency [71]. In this context, serum B12 level <163 pg/mL coupled with HoloTC <40 pmol/L may be consistent with true vitamin B12 deficiency [72]. In summary, there are uncertainties about appropriate cut-offs warranting studies to determine definable endpoints [73]. Further, false elevations of B12 levels seen in liver injury, SIBO, alcoholism, and other disorders confound the diagnosis.

IF antibody specificity is 95% but sensitivity is only 50–70% for PA [5]. Parietal cell antibodies are nonspecific and occur with aging. Serum gastrin and pepsinogen I have high sensitivities (90–92%), but are nonspecific for PA [5].

The Schilling test was utilized in the past to differentiate the causes of B12 deficiency; the test is cumbersome, time-consuming, and does not help diagnose FCS, a common basis for deficiency. Recently CobaSorb and C-CobaSorb tests have been used to identify patients with malabsorption and adequacy of supplementation. In the CobaSorb test, holoTC

Table 18.6 Suggested approach to screening, diagnosis, and treatment of vitamin B12 deficiency [2, 15, 19, 38, 42, 67, 69, 70, 79, 140]

Screen at first opportunity the following
Those with clinical manifestations suggestive of deficiency
Hematological, neurological, psychiatric, or a combination
Consider adults at risk
Patients with malnutrition
Anemia, unexplained
Gastrointestinal: atrophic gastritis, *H. pylori* infection, small intestinal bacterial overgrowth, gastric bypass surgery, intestinal resection, Crohn's disease, chronic pancreatitis, malabsorption syndromes
Medications: metformin, PPIs, phenytoin, colchicine, etc.
Vegetarians and those on restricted diets
HIV infection
Autoimmune: pernicious anemia. hypothyroidism
Age: consider initial screen at age 65; earlier if warranted; and periodically thereafter
Check the B12 level:
Normal range: 211–910 pg/mL. Below this range, sensitivity is 97% and specificity is 60%; specificity increases to 90% if <100 pg/mL [42]
If >350 pg/mL: deficiency unlikely
If <100 pg/mL: likely to be deficiency
If 100–350 pg/mL, indeterminate range; further evaluation suggested
When levels are in the indeterminate range
Determine MMA levels: Normal range: 0.08–0.28 μmol/L
If <0.29 μmol/L: Unlikely to be B12-deficient
If >0.75 μmol/L: Likely to be B12-deficient
Homocysteine (not specific)
Holotranscobalamin levels may be useful to judge response
Following diagnosis of B12 deficiency
Determine the cause of vitamin B12 deficiency through further tests if appropriate
Extent of testing based on health status, life expectancy, costs, and patient preferences

Table 18.7 Treatment of B12 deficiency [70, 80–83, 87]

Routes of treatment
Intramuscular: 100–1,000 μg monthly or 1,000 μg every 3 months
Oral doses:500–2,000 μg daily
Intranasal: 500 μg weekly
Sublingual: 500–2,000 μg daily
Choice of route
Based on discussions: consider ease of administration, access to provider, quality of life, costs, and patient preferences
Advantages
Oral, intranasal, and sublingual: ease of administration, not provider-dependent
Intramuscular: safe and reliable; less frequent dosing
Disadvantages
Intramuscular; involves trips to the provider and may be provider-dependent
Oral: adherence may be an issue; dysphagia may be a contraindication
Intranasal and sublingual: nonadherence may be an issue; expensive
Monitoring B12 blood levels while on treatment
Annually if on oral, sublingual, or intranasal administration
If on injections under supervision, levels not required to be measured
Duration: usually for life
Adverse effects
Toxicity rare even with large doses, local site hematomas can occur
Hypokalemia may occur following initial replacement and predispose to arrhythmias

is measured before and after 3 days of ingesting cobalamin. If nonfasting holoTC is less than 75 pmol/L at baseline and increases by 10 pmol/L after ingesting cobalamin for 3 days, malabsorption is an unlikely cause of deficiency [74, 75]. In C-CobaSorb test, instead of cobalamin, cyanocoabalamin is used as it is not metabolized in the gut [70, 71, 76].

Biomarkers have application to detect B12 deficiency, based on the actions of cobalamin as a cofactor for methionine synthetase and methylmalonly-CoA mutase [77]. The reactions are depicted in Fig. 18.3. Homocysteine level >10 μmol/L is considered high, a risk for cardiovascular mortality [18]. Elevated homocysteine levels also occur in hypovolemia, chronic kidney failure, hypothyroidism, and folate and pyridoxine deficiencies [18]. MMA is elevated in B12 deficiency, but also in renal failure. HoloTC comprises 6-20% of total circulating B12; a level <40 pg/mL is consistent with B12 deficiency [71]. B12 <200 pg/mL may be subclinical, with normalization of electrophysiologic neurologic changes after B12 replacement [5]. Urinary excretion of formiminoglutamic acid excretion after histidine ingestion, propionate level, 2-methylcitrate levels, and deoxyuridine suppression test (dUST) have been used to diagnose subclinical deficiency [18, 29]. MMA and homocysteine fluctuate with time and do not predict or preclude response to B12 [42].

The four stages of cobalamin depletion are: (1) serum depletion: low holoTC; (2) Cell depletion: low holoTC, holohaptocorrin, and erythrocyte cobalamin; (3) biochemical deficiency: elevated homocysteine and MMA; (4) clinical deficiency: anemia and neuropsychiatric manifestations [2, 3, 18]. B12 deficiency may also be classified into three categories based on B12 and holoTC levels; probable: both B12 and holoTC are low; possible: either B12 or holoTC is low; unlikely: neither B12 nor holoTC is low [71].

Treatment

The clinical challenge is to diagnose B12 deficiency at the earliest and before clinical manifestations, offering opportunity to avert complications. Deficiency is treated by replacement of cobalamin provided through one of several routes: intramuscular, oral, sublingual [5, 78], and nasal [5]; most commonly used routes are intramuscular and oral due to their low cost [5]. In the scenario of clear deficiency with manifestations, the intramuscular route is the recommended initial approach to ensure adequate levels. With neurological complications, the window of opportunity to replace the vitamin and expect

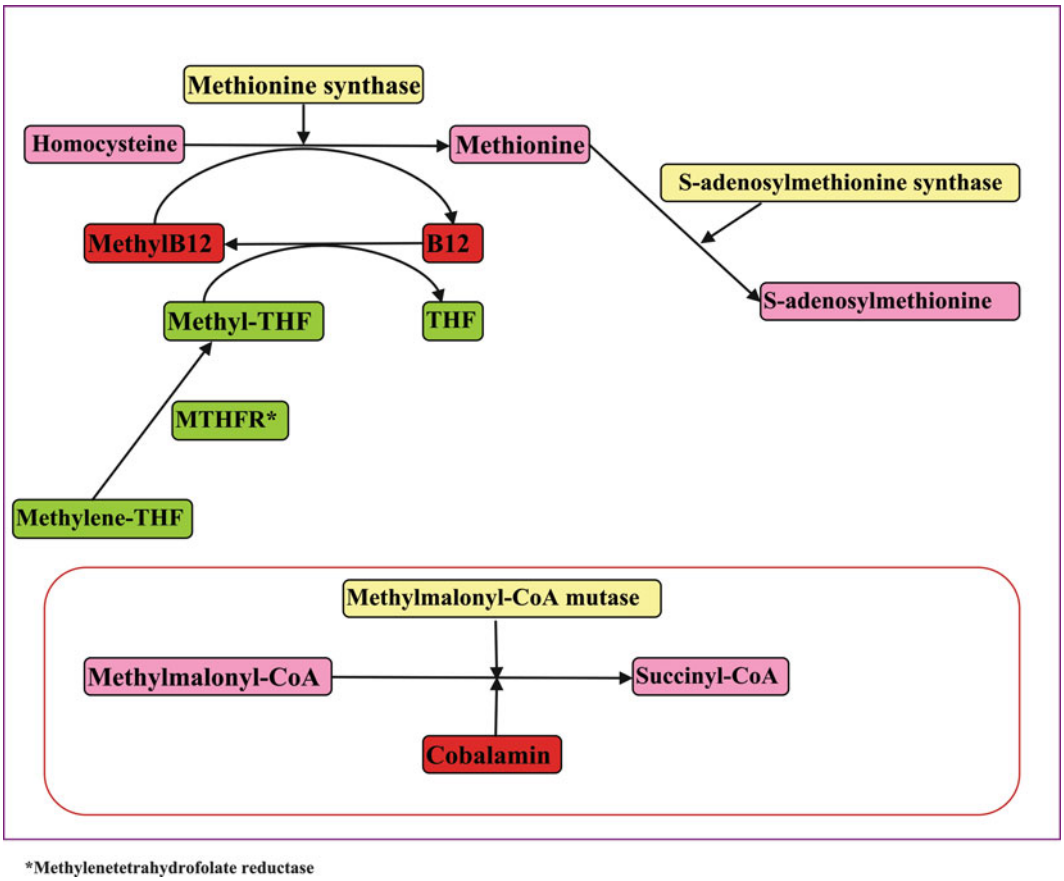

Fig. 18.3 Reactions utilizing B12 and Folate

improvement is limited; here the best option is to give large doses to replace body stores. Once initiated, maintenance of stores can be achieved through any route. In the absence of manifestations, the choice of route may follow a provider-patient discussion, based on convenience to the patient and preferences. Injections of B12 are inexpensive and toxicity is extremely unlikely, with excesses spilling into the urine.

Common dietary sources of B12 include meat, liver, fish, eggs, and milk [34]. However it is impractical to correct deficiencies through diet alone; it is difficult to get patients to change a lifetime dietary practice, as this may involve cultural or other beliefs and taste preferences. The oral route has become more popular and is suitable for subclinical or mild deficiency without neurological defects, and ideally after repleting stores with injections in the event of existing complications from deficiency [17]. Intramuscular routes utilize an initial dosage of 100–1,000 μg per day for up to a week in the presence of manifestations, with maintenance in doses ranging from 100 to 1,000 μg per month to 1,000 μg every 3 months [2, 65, 79].

Oral replacement has become an accepted route with good patient acceptance and is comparable to injections, as long as the regimen is adhered to [80–83]. Oral B12 in doses of 125–1,000 μg daily is effective and safe both in PA and food-cobalamin malabsorption [84]. Lifelong oral maintenance therapy ranges from 500–2,000 μg per day [17, 80].

Biweekly intramuscular treatment can normalize hematological parameters, but the response of neurological manifestations is highly variable and dependent on the duration of neurological damage; reversibility is slow, taking months to years. Treatment of severe anemia from B12 deficiency can be followed by transient hypokalemia [5]. Depression associated with B12 deficiency has a variable response, although biochemical markers improve. Cobalamin malabsorption from *H. pylori* gastritis can improve with treatment of *H. pylori* infection alone [5, 26]. Hydroxocobalamin may be used where cyanocobalamin is contraindicated, as in tobacco or tropical amblyopia and optic neuropathy in PA [85, 86]. Nasal hydroxocobalamin has a 2–5% bioavailability [85]. Ultimately the options in treatment provide a choice for the patient, with advantages and disadvantages (Table 18.7) [70, 87]. The bioavailability of B12 is highest with the injection, followed by nasal and oral routes [85]. Future targets for delivery of B12 may include recombinant human IF [88] in those unable to absorb free B12 and milk fortified with B12 [89].

Of interest, hydroxocobalamin has two additional roles. The first is the utility of hydroxocobalamin in the management of cyanide poisoning because of its affinity to bind cyanide; secondly, as B12-deficient smokers may be unable to break down cyanocobalamin, hydroxocobaalamin may be the better option in these individuals.

Monitoring B12 Status

Supplementation may be associated with variable increases in blood levels of B12 [90] MMA, and homocysteine measures may suggest effectiveness of B12 therapy. Most patients relapse in a year or two after stopping B12 therapy [5]. B12 levels are ideally monitored if on oral, intranasal, or sublingual therapy to verify adherence to treatment; injections under supervision do not require monitoring as levels of B12 can be high prompting some providers to discontinue therapy [2]. Potassium levels may drop following initiation of B12 therapy and may require monitoring based on clinical judgement. Likewise, iron and folate levels may decline if they are in the lower normal limits due to increase in hematopoesis.

Folic Acid

Introduction

Folic acid (FA) is a term derived from "foliage," referring to "leafy green vegetables" [91]. FA is water-soluble and the essential vitamin B9, chemically known as pteroylmonoglutamic acid. The physiological properties of folic acid were first noticed in 1931 by Lucy Willis after treating megaloblastic anemia with yeast and liver extracts [91, 92]. Folic acid is the synthetic form; folate is the natural form of vitamin in foods and that present in blood and tissues, the metabolically active form in humans. Folic acid is stable in solution, while folate oxidizes easily. Folate is involved in methyl transfer reactions in amino acid metabolism and synthesis of nucleic acids: conversion of serine to glycine, histidine catabolism, synthesis of thymidylate, methionine, and purine synthesis [92].

Epidemiology

NHANES III data suggest that folate deficiency in the US is more prevalent among non-Hispanic black and Mexican American people while non-Hispanic whites usually have higher levels [8]. Two percent of NHANES III population over age 60 years were folate-deficient, the cut-off being 3 ng/mL serum folate [8]. Anemia due to folate deficiency was seen in 180,000 of 2.8 million individuals, accounting to 6.4% of all anemias in those over 65 years [10, 12].

Absorption, Transport, and Storage

Folate absorption is both active and passive. The maximal sites of absorption are the duodenum and jejunum [92, 93]. Active absorption in this site is pH (5–6.5)-dependent and occurs via sodium-dependent folate carrier protein present on enterocytes [91]; it is a saturable process involving anion exchange and transmembrane pH gradient mechanisms [92, 94]. The intracellular transport of folate, a receptor-mediated endocytosis, depends on three proteins: reduced folate carrier (RFC1), the folate receptor, and a low pH folate proton-coupled folate carrier [91]. While proton-coupled folate transporter protein predominates in the proximal half of the small intestine where the pH is acidic, reduced folate carrier protein expressed in the apical membrane of enterocytes functions at neutral pH to absorb folate in the distal half of the small intestine [95]. Polyglutamates are hydrolysed to monoglutamate prior to absorption by pancreatic pteroylpolyglutamate hydrolase (PPH) [91]. Monoglutamate folate is absorbed passively, but not sufficiently to meet the daily requirements [91].

Hepatic first pass metabolism of folates is 95%. Serum folate levels are maintained by liver and enterohepatic circulation [91]. Up to 60–90 μg of folate are secreted into bile every day [93]. Folate concentrations peak within 30–60 min after a meal, with a plasma half life of 3–3.5 h [96]. In tissues, monoglutamates are converted to the polyglutamate form. Folate and its metabolites are excreted via the urine and feces. Red cell folate is stable and a better index of status than serum folate.

The normal daily adult western diet contains 600–700 μg of folate [93], with two thirds of food folate in polyglutamate form, requiring conversion to monoglutamate form for intestinal absorption [97, 98]. The ratio of monoglutamates to polyglutamates in natural folates is not a limiting factor for absorption [99]. Folate absorption is decreased by dietary fiber, tomatoes, orange juice, citrates, alcohol, antacids, zinc deficiency, malabsorption disorders such as chronic pancreatitis and colitis, and by medications such as cimetidine and sulfasalazine [91, 94, 100–102]. Folic is metabolized in the gut to 5-methyltetrahydrofolate, 5,10-methylenetetrahydrofolate, tetrahydrofolate, and 10-formyltetrahydrofolate [103]. Methylenetetrahydrofolate reductase (MTHFR) polymorphism (seen in 50% of individuals) is associated with decreased ability to convert dietary folate to its active metabolites [104]. While folate absorption and metabolism are normal in end stage renal disease, it is removed by hemodialysis, predisposing to deficiency [105].

Folate is bound to low-affinity binding proteins such as albumin (40%), alpha2-macroglobulin, and transferrin and high-affinity binding proteins such as folic acid-binding protein (FABP) [92, 106].

Table 18.8 Causes of folate deficiency [8, 36, 91, 94, 100–102, 104, 141–144]

Low intake of green leafy vegetables and legumes
Malabsorption
Inflammatory bowel disease—ulcerative colitis, Crohn's disease
Celiac disease
Tropical sprue
Scleroderma
Intestinal lymphoma
Amyloidosis
Surgical intestinal resection
HIV disease
Blind loop syndrome
Increased requirements: leukemias, psoriasis, cancers, etc.
Medications
Sulfasalazine
Metformin
Cimetidine
Phenytoin
Green tea
Phenobarbital
Functional deficiency secondary to antagonistic action of
Methotrexate
Trimethoprim
Pyrimethamine
Triamterene
Alcoholism
Smoking
Hemodialysis

Table 18.9 Features of folate deficiency [94, 127, 145]

Macro-ovalocytosis
Anemia
Megaloblastosis: gastrointestinal and bone marrow
Leucopenia
Thrombocytopenia
Glossitis, skin pigmentation
Proneness to atherosclerotic disease
Procarcinogenicity (although controversial) [127]
Decreased cognitive function
Depression
Worsening psoriasis [94]
Vitiligo [94]
Atrophy of the oro-pharyngeal mucosa [94]
Age-related macular degeneration [145]

Causes of Folic Acid Deficiency

Folic acid deficiency can be caused by a decrease in intake or absorption, increased requirements, drug interactions, increase in folate-binding by proteins, and increased loss from the body. Any intestinal disorder can cause deficiency (Table 18.8 provides a list).

Clinical Manifestations

Early stages of folic acid deficiency are asymptomatic. Deficiency usually occurs in conjunction with other nutrient deficiencies. Folic acid deficiency impairs marrow production of all three lineages; the result may be megaloblastic anemia, thrombocytopenia, leucopenia, and pancytopenia in any combination, with severe deficiency. In the preclinical stages, an increase in homocysteine levels is noted (Table 18.9). Macrocytosis occurs with other causes as stated earlier and less commonly from B12 and folate deficiency. The consequences of folate deficiency are megaloblastic changes in all proliferating cells including the blood, bone marrow, and in the rapidly proliferating cells of the GI tract; the epithelial changes in the gastrointestinal mucosa can be widespread and cause a secondary deficiency of folate, B12, and other nutrients.

Diagnosis of Folate Deficiency

Serum folate levels increase within an hour after ingestion and represent short-term folate status. Red cell folate reflects long-term folate status. Based on NHANES information, for red cell folate levels microbiological assessment (MA) is preferred to isotope dilution liquid chromatograph-tandem masospectrometry (LC-MS/MS), as red cell folate levels detected by LC-MS/MS are higher by 25% compared to MA [107]. Serum folate less than 3 ng/mL and red cell folate below 140 ng/mL are consistent with deficiency [108].

Folate Requirements

RDA of folates for adults in dietary folate equivalents (DFE) is 200–400 μg per day [97]. The tolerable intake level of synthetic folic acid is 1,000 μg per day [109]. Recommendations are similar in the old and the young. Folate is easily destroyed by heat, UV light, oxidation, and cooking [110]. Much is lost by cooking for 5 min and more than half after frying or boiling in water for 30 min. Folate is well dispersed in foods (Table 18.10), but absent in spices, mustard, garlic, and cooking oils. The bioavailability of food folate is lower than that for fortified folic acid and folic acid supplement [111]. Bioavailability varies with source; while it is close to 100% for free folic acid, it is less than 50% for food folate [112, 113]. However, folic acid is not the biological form of folate and requires reduction to tetrahydrofolate; the physiological form is 5-methyl tetrahydrofolate.

Folate Deficiency-Related Morbidity and Mortality

Folate adequacy has been suggested to lower risk for colorectal and other cancers, but the relationship is by no means certain [94, 104, 114]. The controversy also raises the question

Table 18.10 Folate content of various nutrients [146]

Food	FA, DFE* (μg)/100 g
Leavening agents, yeast, baker's, active dry	2350.00
Chicken, liver, all classes, cooked, simmered	576.53
Rice, white, long-grain, parboiled, enriched, dry	430.81
Cornmeal, self-rising, degermed, enriched, yellow	375.36
Turkey, all classes, giblets, cooked, simmered, some giblet fat	335.17
Wheat flour, white, all-purpose, self-rising, enriched	307.20
Bread, Italian	305.00
Wheat flour, white, all-purpose, enriched, bleached	291.20
Wheat flour, white, bread, enriched	288.32
Snacks, pretzels, hard, plain, salted	286.67
Spices, oregano, dried	266.67
Beef, variety meats and by-products, liver, cooked, pan-fried	260.00
Seeds, sunflower seed kernels, dry-roasted, with salt added	237.50
Bagels, plain, fortified	225.35
Cowpeas, common (blackeyes, crowder, southern), mature seeds, cooked, boiled	208.14
Dill weed, fresh	200.00
Bread, Indian, fry	195.56
Spinach, raw	190.00
Lentils, mature seeds, cooked, boiled, without salt	180.81
Seaweed, kelp, raw	180.00
Chickpeas (garbanzo beans, Bengal gram), mature seeds, cooked, boiled	171.95
Beans, pinto, mature seeds, cooked, boiled, without salt	171.93
Bread, white, commercially prepared (includes soft bread crumbs)	171.11
Mushrooms, shiitake, dried	166.67
Bread, mixed-grain (includes whole-grain, 7-grain)	165.38
Orange juice, frozen concentrate, unsweetened, undiluted	154.93
Parsley, raw	150.00
Bread, rye	150.00
Beans, black, mature seeds, cooked, boiled, without salt	148.84
Asparagus, cooked, boiled, drained	148.33
Okra, frozen, cooked, boiled, drained, without salt	146.20
Peanuts, all types, dry-roasted	144.62
Egg, yolk, raw, fresh	144.58
Crackers, cheese, sandwich-type with peanut butter filling	142.86
Beans, navy, mature seeds, cooked, boiled, without salt	140.11
Lettuce, cos or romaine, raw	140.00

*DFE: Dietary Folate Equivalent

of the protective ingredient, between folate, an anti-oxidant, and fiber in the dietary source. In inflammatory bowel disease patients with folate deficiency and hyperhomocysteinemia, there is an increased risk of colorectal cancer [115]. It was believed that folic acid intake would help decrease homocysteine levels and favorably impact cardiovascular morbidity and mortality, with suggestions for folic acid supplementation for primary stroke prevention [116]. Decreasing homocysteine by over 20% for more than 2 years appeared to decrease the incidence of first stroke with statistical significance [116]. However, a large recent meta-analysis failed to confirm a benefit for folic acid, B6 and B12 supplements on cardiovascular risk, vascular disease, cancer or total mortality [117, 118]. In older adults, lower folic acid levels are associated with depression and dementia.

Table 18.11 Alcohol effects on folate and its metabolic reactions [119, 120, 147]

Inhibition of methylation of tetraydrofolate (THF) from serine
Inhibits folate absorption in the intestine
Inhibits methylene tetrahydrofolate reductase
Inhibits methionine adenosyl transferase
Inhibits methylation of methionine and DNA
Inhibits homocysteine metabolism to glutathionine
Impairs the enterohepatic cycle
Increases urinary excretion of folate

Alcohol and Folate

The majority of chronic alcoholics (up to 80%) can be folate-deficient [119]. Alcohol intake, whether acutely, subacutely, or chronically, decreases intestinal absorption of folate, impairs the enterohepatic circulation, and increases urinary excretion of folate [120, 121]. Serum alcohol greater than 150 mg/dL inhibits reabsorption of filtered folate at the proximal renal tubule causing increase in urinary excretion of folate [120]. To counteract the chronic alcohol intake, folate receptors and reduced folate carriers in the proximal renal tubule decrease urinary folate excretion [120]. Acute alcohol ingestion with serum levels greater than 150 mg/dL increases urinary excretion of folate by fivefold, whereas chronic intake increases it by only onefold [120]. Effects of alcohol on intestinal absorption of folate and metabolism are complex and outlined in Table 18.11 [122, 123].

Treatment

Folic acid can be supplemented by oral, intramuscular, intravenous, and subcutaneous routes. The RDA for older adults is 400 μg per day, similar to that for younger adults. Folic acid is provided in a dose of 1–5 mg daily depending on severity of deficiency. Fortification has been implemented as a public health initiative in the USA to prevent folic acid deficiency-related complications (such as neural tube defects). Following folate fortification, the highest decrease in homocysteine concentrations was found in alcoholics and those with low intake of vegetables and fruits in older adults [124]. There is a nonlinear dose-relationship between folate levels and homocysteine levels [104, 125]. Homocysteine levels stabilize after increasing folate to certain levels [125]. There are suggestions that L-5-methyltetrahydofolate, the predominant dietary folate and transport form in circulation, may reduce the potential for masking the hematological

Table 18.12 A comparison of B12 and Folic acid deficiency

	Cobalamin deficiency	Folate deficiency
Presentation	Can be asymptomatic Megaloblastosis, GI and bone marrow Anemia, macrocytosis, pancytopenia Hypersegmented neutrophils Neurological manifestations Neuropsychiatric manifestations	Can be asymptomatic Megaloblastosis: GI and bone marrow Anemia, macrocytosis, pancytopenia Hypersegmented neutrophils Cognitive impairment Depression
Causes	Vegan or vegetarianism Medications Stomach or small intestinal surgery Several GI causes of malabsoprtion	Restricted dietary intake Alcoholism Increased utilization by cancers Losses (psoriasis, hemodialysis)
Diagnosis	Biomarker: B12 level, holoTC level Functional marker when B12 levels are indeterminate: MMA and tHcy (nonspecific) Bone marrow: megalobastosis Additional tests to evaluate the cause	Biomarker: Serum folate and RBC folate Functional marker: tHcy (nonspecific) Bone marrow: megalobastosis
Treatment	Intramuscular Oral and sublingual Intranasal	Oral Intramuscular Intravenous
Diet	Diet; predominantly animal sources	Diet: vegetables, fruits, animal source
Fortification	Fortification not implemented, under consideration	Folate fortification is a public health initiative and successful

symptoms of B12 deficiency and has a reduced likelihood for drug interactions [126].

As there is a concern about masking B12 deficiency with folate supplementation, folic acid intake from fortification is limited to 1 mg per day [127]. Folic acid intake can exceed 1 mg tolerable upper limit if fortified diets such as highly fortified cereals, noodles, pasta, rice, and over-the-counter supplements are consumed regularly [127]. Hence one should read food labels and factor the amount of folates taken as supplements or as fortified foods to keep daily intake below 1 mg. Folic acid in excessive amounts may decrease efficacy of anti-epileptic medications, worsen neurological manifestations of undiagnosed pernicious anemia, and decrease zinc absorption in the gut [100].

B12 and Folate Interactions

Patients with low B12 and high serum folates have the highest homocysteine and MMA levels [128–130]. This phenomenon is explained by irreversible oxidation of intracellular B12, decreasing cobalamin activity, decrease in holotranscobalamin, and the methyl-trap hypothesis. In B12 deficiency, methionine synthase is suboptimal in function leading to decline in methionine synthesis, causing elevated levels of homocysteine along with methyltetrahydrofolate [130]. High folate levels in association with low B12 may also suggest small intestinal bacterial overgrowth, where the bacteria assimilate B12 and produce folate [33]. Folate increases intracellular oxidation of B12 and inactivates cobalamin, decreasing its availability even further [32, 128]. This could be the basis for unmasking or worsening of neurological and psychiatric manifestations, following folic acid supplementation [31, 129]. There is no evidence of an effect of B12, folic acid, or B6 supplementation on cognition in those with normal or impaired cognition [131].

As foods are fortified with folic acid, there is potential for exacerbation of biochemical and clinical B12 deficiency, calling for food fortification with vitamin B12 [132]. B12 deficiency is common in the geriatric population, and new evidence suggests that the elderly respond poorly to doses less than 500 μg daily. But fortification with B12 is a complex issue and may even be ineffective, unlike in the case of folate; studies must instead target supplementation in special populations such as vegetarians and elderly [133].

A comparison of B12 and folic acid deficiency is provided in Table 18.12.

Key Points

- Early recognition of cobalamin deficiency poses opportunities to avert complications.
- Vitamin B12 deficiency, marginal or overt, occurs in 15–40% of older adults.
- Vitamin B12 absorption is an active, energy-mediated and complex process, but can also occur through passive diffusion from the intestinal lumen when available as large doses.
- Vitamin B12 is only present in foods of animal origin and not in fruits, vegetables, and grains.

- Asymptomatic states are common in B12 deficiency; manifestations indicate long-standing deficiency and can be hematological, neuropsychiatric, or a combination.
- The most common cause of B12 deficiency is food-cobalamin malabsorption.
- Blood assays help assess B12 status, supported by methylmalonic acid (MMA) and holoTC assays. In future, holoTC, which has a better diagnostic accuracy, may replace existing B12 assays as a primary screening test for suspected deficiency [148]. Assessing the cause of deficiency entails further testing.
- B12 can be supplemented through oral, sublingual, intranasal, or intramuscular routes.
- Folate is present in fruits and vegetables, unlike B12.
- Folate is easily lost during heating or frying.
- Folate deficiency presents with similar hematological parameters as that of B12, but without neurological manifestations; depression and dementia may occur.
- Folic acid deficiency is corrected by oral supplements, which are more bioavailable than folate in foods.
- Fortification of food is an effective public health initiative to avert deficiency.

References

1. Stover PJ. Vitamin B12 and older adults. Curr Opin Clin Nutr Metab Care. 2010;13:24–7.
2. Herbert V. Vitamin B12: an overview. In: Herbert V, editor. Vitamin B12 deficiency. London: Royal Society of Medicine; 1999. p. 1–8.
3. Herbert V, Das KC. Folic acid and vitamin B12. In: Shills ME, Olson JA, Shike M, editors. Modern nutrition in health and disease. 8th ed. Philadelphia: Lea & Febieger; 1994. p. 402–25.
4. Tamura J, Kubota K, Murakami H, et al. Immunomodulation by vitamin B12: augmentation of CD8+ T lymphocytes and NK cell activity in vitamin B12 deficient patients by methyl B12 treatment. Clin Exp Immunol. 1999;116:28–32.
5. Carmel R. How I treat cobalamin (vtiamin B_{12}) deficiency? Blood. 2008;112:2214–21.
6. Stabler SP, Allen RH. Vitamin B12 deficiency as a worldwide problem. Annu Rev Nutr. 2004;24(1):299–326.
7. Wickramasinghe SN. The wide spectrum and unresolved issues of megaloblastic anemia. Semin Hematol. 1999;36(1):3–18.
8. Wright JD, Bialostosky K, Gunter EW, et al. Blood folate and vitamin B12: United States, 1988–94. National Center for Health Statistics. Vital Health Stat. 1998;11(243):1–78.
9. Lindeman RD, Romero LJ, Kathleen MK, et al. Serum vitamin B12, C and folate concentrations in the New Mexico elder health survey: correlations with cognitive and affective functions. J Am Coll Nutr. 2000;19(1):68–76.
10. Patel KV. Epidemiology of anemia in older adults. Semin Hematol. 2008;45:210–7.
11. Allen LH. How common is vitamin B_{12} deficiency? Am J Clin Nutr. 2009;89(2):693S–6.
12. Guralnik JM, Eisenstaedt RS, Ferrucci L, Klein HG, Woodman RC. Prevalence of anemia in persons 65 years and older in the United States: evidence for a high rate of unexplained anemia. Blood. 2004;104(8):2263–8.
13. Dharmarajan TS, Norkus EP. Vitamin B12 deficiency in the elderly—population based research. In: Herbert V, editor. Vitamin B12 deficiency. London: Royal Society of Medicine; 1999. p. 27–34.
14. Dharmarajan TS, Ugalino JT, Kanagala M, Pitchumoni S, Norkus EP. Vitamin B12 status in hospitalized elderly from nursing homes and the community. J Am Med Dir Assoc. 2000;1(1):21–4.
15. Stabler SP. Screening the older population for cobalamin (vitamin B12) deficiency. J Am Geriatr Soc. 1995;43(11):1290–7.
16. Loikas S, Koskinen P, Irjala K, et al. Vitamin B12 deficiency in the aged: a population-based study. Age Ageing. 2007;36(2):177–83.
17. Lane LA, Rojas-Fernandez C. Treatment of vitamin B(12)-deficiency anemia oral versus parenteral therapy. Ann Pharmacother. 2002;36:1268–72.
18. Wolters M. Cobalamin: a critical vitamin in the elderly. Prev Med. 2004;39(6):1256–66.
19. Hvas AM, Nexo E. Diagnosis and treatment of vitamin B12 deficiency. An update. Haematologica. 2006;91:1506–12.
20. Dharmarajan TS, Kanagala MR, Murakonda P, Lebelt AS, Norkus EP. Do acid-lowering agents affect vitamin B12 status in older adults? J Am Med Dir Assoc. 2008;9(3):162–7.
21. Johnson MA, Hausman DB, Davey A, Poon LW, Allen RH, Stabler SP. Vitamin B_{12} deficiency in African American and White octogenarians and centenarians in Georgia. J Nutr Health Aging. 2010;14(5):339–45.
22. Neale G. B_{12} binding proteins. Gut. 1990;31:59–63.
23. Fernandes-Costa F, Metz J. Vitamin B12 binders (transcobalamins) in serum. Crit Rev Clin Lab Sci. 1982;18(1):1–30.
24. Seetharam B, Yammani RR. Cobalamin transport proteins and their cell-surface receptors. Expert Rev Mol Med. 2004;5(18):1–18.
25. Quadros EV. Advances in the understanding of cobalamin assimilation and metabolism. Br J Haematol. 2009;148(2):195–204.
26. Kaptan K, Beyan C, Ural AU, et al. Helicobacter pylori—is it a novel causative agent in vitamin B_{12} deficiency? Arch Intern Med. 2000;160(9):1349–53.
27. de Jager J, Kooy A, Lehert P, et al. Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomised placebo controlled trial. BMJ. 2010;340(4):c2181.
28. Liu KW. Metformin-related vitamin B12 deficiency. Age Ageing. 2006;35(2):200–1.
29. Werder SF. Cobalamin deficiency, hyperhomocysteninemia, and dementia. Neuropsychiatr Dis Treat. 2010;6:159–95.
30. Carmel R. Cobalamin (vitamin B_{12}). In: Shils ME, Shike M, Ross AC, Caballero B, Cousins RJ, editors. Modern nutrition in health and disease. Philadelphia: Lippincott Williams & Wilkins; 2006. p. 482–97.
31. Johnson MA. If high folic acid aggravates vitamin B12 deficiency what should be done about it? Nutr Rev. 2007;65(10):451–8.
32. http://www.douglaslabs.com/pdf/pds/B12.pdf. Accessed 18 Dec 2011.
33. Baik HW, Russell RM. Vitamin B12 deficiency in the elderly. Annu Rev Nutr. 1999;19:357–77.
34. Petrus AK, Fairchild TJ, Doyle RP. Traveling the vitamin B12 pathway: oral delivery of protein and peptide drugs. Angew Chem Int Ed. 2009;48(6):1022–8.
35. Loonen AJM, Schmeets MGJ, ter Braak GIJM, van Bavel LP. The influence of zinc on the uptake of vitamin B12 by the cerebrospinal fluid. Int J Geriatr Psychiatry. 2003;18(6):540–1.
36. Allen LH. Causes of vitamin B12 and folate deficiency. Food Nutr Bull. 2008;29(2 Suppl):S20–34; discussion S35–27.
37. McNulty H, Scott JM. Intake and status of folate and related B vitamins considerations and challenges in achieving optimal status. Br J Nutr. 2008;99 Suppl 3:S48–54.

38. Dharmarajan TS, Adiga GU, Norkus EP. Vitamin B12 deficiency: recognizing subtle symptoms in older adults. Geriatrics. 2003;58(3):30–8.
39. Dali-Youcef N, Andres E. An update on cobalamin deficiency in adults. QJM. 2009;102(1):17–28.
40. Serraj K, Vogel T, Federici L, et al. Food-cobalamin syndrome. Presse Med. 2009;38:55–62.
41. Adachi S, Kawamoto T, Otsuka M, et al. Enteral vitamin B12 supplements reverse postgastrectomy B12 deficiency. Ann Surg. 2000;232(2):199–201.
42. Fragasso A, Mannarella C, Ciancio A, Sacco A. Functional vitamin B_{12} deficiency in alcoholics: an intriguing finding in a retrospective study of megaloblastic anemic patients. Eur J Intern Med. 2010;21(2):97–100.
43. Ito T, Jensen RT. Association of long-term proton pump inhibitor therapy with bone fractures and effects on absorption of calcium, vitamin B12, iron, and magnesium. Curr Gastroenterol Rep. 2010;12:448–57.
44. Den Elzen WPJ, Groeneveld Y, De Ruijter W, et al. Long-term use of proton pump inhibitors and vitamin B12 status in elderly individuals. Aliment Pharmacol Ther. 2008;27(6):491–7.
45. Dharmarajan TS, Norkus EP. Does long-term PPI use result in vitamin B12 deficiency in elderly individuals? Nat Clin Pract Gastroenterol Hepatol. 2008;5(11):604–5.
46. Toh BH, van Driel IR, Gleeson PA. Pernicious anemia. N Engl J Med. 1997;337(20):1441–8.
47. Carmel R. Cobalamin, the stomach, and aging. Am J Clin Nutr. 1997;66(4):750–9.
48. Haruma K, Komoto K, Kawaguchi H, et al. Pernicious anemia and *Helicobacter pylori* infection in Japan: evaluation in a country with a high prevalence of infection. Am J Gastroenterol. 1995; 90(7):1107–10.
49. Allen RH, Stabler SP. Identification and quantitation of cobalamin and cobalamin analogues in human feces. Am J Clin Nutr. 2008;87:1324–5.
50. Elphick HL, Elphick DA, Sanders DS. Small bowel bacterial overgrowth. An underrecognized cause of malnutrition in older adults. Geriatrics. 2006;61(9):21–6.
51. Bures J. Small intestinal bacterial overgrowth syndrome. World J Gastroenterol. 2010;16(24):2978.
52. Quigley EMM, Abu-Shanab A. Small intestinal bacterial overgrowth. Infect Dis Clin North Am. 2010;24(4):943–59.
53. Vargas-Ruiz AG, Hernandez-Rivera G, Herrera MF. Prevalence of iron, folate, and vitamin B12 deficiency anemia after laparoscopic Roux-en-Y gastric bypass. Obes Surg. 2008;18(3):288–93.
54. Beyan C, Beyan E, Kaptan K, Ifran A, Uzar AI. Post-gastrectomy anemia: evaluation of 72 cases with post-gastrectomy anemia. Hematology. 2007;12(1):81–4.
55. Yakut M, Üstün Y, Kabaçam G, Soykan I. Serum vitamin B12 and folate status in patients with inflammatory bowel diseases. Eur J Intern Med. 2010;21(4):320–3.
56. Ehrenpreis ED. Who is at risk of vitamin B12 deficiency? In: Herbert V, editor. Vitamin B12 deficiency. London: Royal Society of Medicine; 1999. p. 35–9.
57. Muro N, Bujanda L, Sarasqueta C, et al. Plasma levels of folate and vitamin B_{12} in patients with chronic liver disease. Gastroenterol Hepatol. 2010;33(4):280–7.
58. Baker H, Leevy BC, DeAngelis B, et al. Cobalamin (vitamin B12) and holotranscobalamin changes in plasma and liver tissue in alcoholics with liver disease. J Am Coll Nutr. 1998;17(3):235–8.
59. Ermens AAM, Vlasveld LT, Lindemans J. Significance of elevated cobalamin (vitamin B12) levels in blood. Clin Biochem. 2003; 36:585–90.
60. Yates AA. National nutrition and public health policies: issues related to bioavailability of nutrients when developing dietary reference intakes. J Nutr. 2001;131:1331S–4.
61. Andres E, Dali-Youcef N, Vogel T, Serraj K, Zimmer J. Oral cobalamin (vitamin B12) treatment. An update. Int J Lab Hematol. 2009;31(1):1–8.
62. Gilsing AM, Crowe FL, Lloyd-Wright Z, et al. Serum concentrations of vitamin B_{12} and folate in British male omnivores, vegetarians and vegans: results from a cross-sectional analysis of the EPIC-Oxford cohort study. Eur J Clin Nutr. 2010;64(9):933–9.
63. Thuesen BH, Husemoen LL, Ovesen L, Jorgensen T, Fenger M, Linneberg A. Lifestyle and genetic determinants of folate and vitamin B_{12} levels in a general adult population. Br J Nutr. 2010;103(8):1195–204.
64. Carmel R. Introduction: beyond megaloblastic anemia. Semin Hematol. 1999;38(1):1–2.
65. Oh RC, Brown DL, et al. Vitamin B12 deficiency. Am Fam Physician. 2003;67(5):979–86.
66. Tangney CC, Tang Y, Evans DA, et al. Biochemical indicators of vitamin B12 and folate insufficiency and cognitive decline. Neurology. 2009;72:361–7.
67. Zittoun J, Zittoun R. Modern clinical testing strategies in cobalamin and folate deficiency. Semin Hematol. 1999;36(1):35–46.
68. Xavier JM, Costa FF, Annichino-Bizzacchi JM, Saad STO. High frequency of vitamin B12 deficiency in a Brazilian population. Public Health Nutr. 2010;13(8):1191–7.
69. Snow CF. Laboratory diagnosis of vitamin B12 and folate deficiency: a guide for the primary care physician. Arch Intern Med. 1999;159(12):1289–98.
70. Dharmarajan TS, Norkus EP. An algorithmic approach to the screening of vitamin B12 status and the treatment of identified deficiency. In: Herbert V, editor. Vitamin B12 deficiency. London: Royal Society of Medicine; 1999. p. 49–51.
71. Miller JW. Measurement of total vitamin B12 and holotranscobalamin, singly and in combination, in screening for metabolic vitamin B12 deficiency. Clin Chem. 2005;52(2):278–85.
72. Bamonti F, Moscato GA, Novembrino C, et al. Determination of serum holotranscobalamin concentrations with the AxSYM active B(12) assay: cut-off point evaluation in the clinical laboratory. Clin Chem Lab Med. 2010;48(2):249–53.
73. Bailey RL, Carmel R, Green R, et al. Monitoring of vitamin B-12 nutritional status in the United States by using plasma methylmalonic acid and serum vitamin B-12. Am J Clin Nutr. 2011;94(2):552–61.
74. Hvas AM, Morkbak AL, Nexo E. Plasma holotranscobalamin compared with plasma cobalamins for assessment of vitamin B12 absorption; optimisation of a non-radioactive vitamin B12 absorption test (CobaSorb). Clin Chim Acta. 2007;376:150–4.
75. Hvas A-M, Morkbak AL, Hardlei TF, Nexo E. The vitamin B12 absorption test, CobaSorb, identifies patients not requiring vitamin B12 injection therapy. Scand J Clin Lab Invest. 2011;71(5): 432–8.
76. Hardlei TF, Morkbak AL, Bor MV, Bailey LB, Hvas AM, Nexo E. Assessment of vitamin B12 absorption based on the accumulation of orally administered cyanocobalamin on transcobalamin. Clin Chem. 2009;56(3):432–6.
77. Chatthanawaree W. Biomarkers of cobalamin (vitamin B_{12}) deficiency and its application. J Nutr Health Aging. 2011;15(3):227–31.
78. Delpre D, Stark P, Niv Y. Sublingual therapy for cobalamin deficiency as an alternative to oral and parenteral cobalamin supplementation. Lancet. 1999;354(9180):740–1.
79. Dharmarajan TS, Norkus EP. Approaches to vitamin B_{12} deficiency. Early treatment may prevent devastating complications. Postgrad Med. 2001;110(1):99–105.
80. Elia M. Oral or parenteral therapy for B_{12} deficiency. Lancet. 1998;352(9142):1721–2.
81. Andres E, Vogel T, Federici L, Zimmer J, Kaltenbach G. Update on oral cyanocobalamin (vitamin B_{12}) treatment in elderly patients. Drugs Aging. 2008;25(11):927–32.

82. Butler CC, Vidal-Alaball J, Cannings-John R, et al. Oral vitamin B_{12} versus intramuscular vitamin B12 for vitamin B12 deficiency: a systematic review of randomized controlled trials. Fam Pract. 2006;23(3):279–85.
83. Seal EC, Metz J, Flicker L, Melny J. A randomized, double-blind, placebo-controlled study of oral vitamin B12 supplementation in older patients with subnormal or borderline serum vitamin B12 concentrations. J Am Geriatr Soc. 2002;50(1):146–51.
84. Troilo A, Mecili M, Ciobanu E, Boddi V, D'Elios MM, Andres E. Oral vitamin B12: efficacy and safety data in 31 patients with pernicious anemia and food-cobalamin malabsorption. Presse Med. 2010;39(12):e273–9.
85. van Asselt DZB, Merkus FWHM, Russell FGM, Hoefnagels WHL. Nasal absorption of hydroxocobalamin in healthy elderly adults. Br J Clin Pharmacol. 1998;45:83–6.
86. Freeman AG. Hydroxocobalamin versus cyanocobalamin. J R Soc Med. 1996;89:659.
87. Pitchumoni CS, Dharmarajan TS. Vitamin B_{12}: the gastrointestinal system and aging. Pract Gastroenterol. 2001;25(12):27–40.
88. Hvas AM, Buhl T, Laursen NB, et al. The effect of recombinant human intrinsic factor on the uptake of vitamin B12 in patients with evident vitamin B12 deficiency. Haematologica. 2006;91:805–8.
89. Dhonukshe-Rutten RAM, Zutphen M, Groot LCPGM, et al. Effect of supplementation with cobalamin carried either by a milk product or a capsule in mildly cobalamin-deficient elderly Dutch persons. Am J Clin Nutr. 2005;82:568–74.
90. Garcia A. Cobalamin and homocysteine in older adults: do we need to test for serum levels in the work-up of dementia? Alzheimers Dement. 2007;3:318–24.
91. Donnelly JG. Folic acid. Crit Rev Clin Lab Sci. 2001;38(3): 183–223.
92. Lucock M. Folic acid: nutritional biochemistry, molecular biology, and role in disease processes. Mol Genet Metab. 2000; 71(1–2):121–38.
93. Hoffbrand AV. Folate absorption. J Clin Pathol Suppl (R Coll Pathol). 1971;5(S24):66–76.
94. Gisondi P, Fantuzzi F, Malerba M, Girolomoni G. Folic acid in general medicine and dermatology. J Dermatolog Treat. 2007;18(3):138–46.
95. Said Hamid M. Intestinal absorption of water-soluble vitamins in health and disease. Biochem J. 2011;437(3):357–72.
96. Czeczot H. Folic acid in physiology and pathology. Postepy Hig Med Dosw. 2008;68:405–19.
97. Melesa-Boonstra A, Verhoef P, West C. Quantifying folate bioavailability: a critical appraisal of methods. Curr Opin Clin Metab Care. 2004;7:539–45.
98. Melse-Boonstra A, West CE, Katan MB, Kok FJ, Verhoef P. Bioavailability of heptaglutamyl relative to monoglutamyl folic acid in healthy adults. Am J Clin Nutr. 2004;79:424–9.
99. Mckillop DJ, McNulty H, Scott JM, et al. The rate of intestinal absorption of natural food folates is not related to the extent of folate conjugation. Am J Clin Nutr. 2006;84:167–73.
100. Butterworth CE, Tamura T. Folic acid safety and toxicity: a brief review. Am J Clin Nutr. 1989;50:353–8.
101. Rajesh G, Girish BN, Vaidyanathan K, et al. Folate deficiency in chronic pancreatitis. J Pancreas. 2010;11(4):409–10.
102. Jiang Y, Zhao J, Jiang T, et al. Genetic polymorphism of methylenetetrahydrofolate reductase G1793A, hyperhomocysteinemia, and folate deficiency correlate with ulcerative colitis in central China. J Gastroenterol Hepatol. 2010;25(6):1157–61.
103. Schmitz JC, Stuart RK, Priest DG. Disposition of folic acid and its metabolites: a comparison with leucovorin. Clin Pharmacol Ther. 1994;55(5):501–8.
104. Rampersaud GC, Kauwell GPA, Bailey LB. Folate a key to optimizing health and reducing disease risk in the elderly. J Am Coll Nutr. 2003;22(1):1–8.
105. Ghandour H, Bagley PJ, Shemin D, et al. Distribution of plasma folate forms in hemodialysis patients receiving high daily doses of L-folinic or folic acid. Kidney Int. 2002;62:2246–9.
106. Waxman S, Schreiber C. Characteristics of folic acid binding protein in folate deficient serum. Blood. 1973;42:291–301.
107. Yetley EA, Pfeiffer CM, Phinney KW, et al. Biomarkers of folate status in NHANES: a roundtable summary. Am J Clin Nutr. 2011;94(1):303S–12.
108. Neuhouser ML, Beresford SAA. Folic acid: are current fortification levels adequate? Nutrition. 2001;17:868–72.
109. Eichholzer M, Tönz O, Zimmermann R. Folic acid: a public-health challenge. Lancet. 2006;367(9519):1352–61.
110. Bassett MN, Samman NC. Folate content and retention in selected raw and processed foods. Arch Latinoam Nutr. 2010;60(3):298–305.
111. Bailey RL, Dodd KW, Gahche JJ, et al. Total folate and folic acid intake from foods and dietary supplements in the United States: 2003-2006. Am J Clin Nutr. 2010;91(1):231–7.
112. Hannon-Fletcher MP, Armstrong NC, Scott JM, et al. Determining bioavailability of food folates in a controlled intervention study. Am J Clin Nutr. 2004;80:911–8.
113. Menke A, Weimann HJ, Achtert G, Schuster O, Menke G. Absolute bioavailability of folic acid after oral administration of a folic acid tablet formulation in healthy volunteers. Arzneimittelforschung. 1994;44(9):1063–7.
114. Koren G, Goh YI, Klieger C. Folic acid: the right dose. Can Fam Phys. 2008;54:1545–7.
115. Phelip JM, Ducros V, Faucheron JL, Flourie B, Roblin X. Association of hyperhomocysteinemia and folate deficiency with colon tumors in patients with inflammatory bowel disease. Inflamm Bowel Dis. 2008;14(2):242–8.
116. Wang X, Qin X, Demirtas H, et al. Efficacy of folic acid supplementation in stroke prevention: a meta-analysis. Lancet. 2007;369(9576):1876–82.
117. Albert CM, Cook NR, Gaziano JM, et al. Effect of folic acid and B vitamins on risk of cardiovascular events and total mortality among women at high risk for cardiovascular disease: a randomized trial. JAMA. 2008;299(17):2027–36.
118. Clarke R, Halsey J, Lewington S, et al. Effects of lowering homocysteine levels with B vitamins on cardiovascular disease, cancer, and cause-specific mortality: Meta-analysis of 8 randomized trials involving 37 485 individuals. Arch Intern Med. 2010;170(18): 1622–31.
119. Markowitz JS, McRae AL, Sonne SC. Oral nutritional supplementation for the alcoholic patient: a brief overview. Ann Clin Psychiatry. 2000;12(3):153–8.
120. Romanoff RL, Ross DM, McMartin KE. Acute ethanol exposure inhibits renal folate transport, but repeated exposure upregulates folate transport proteins in rats and human cells. J Nutr. 2007;137(5):1260–5.
121. Fernandez O, Carreras O, Murillo ML. Intestinal absorption and enterohepatic circulation of folic acid: effect of ethanol. Digestion. 1998;59(2):130–3.
122. Hamid A, Kaur J. Long-term alcohol ingestion alters the folate-binding kinetics in intestinal brush border membrane in experimental alcoholism. Alcohol. 2007;41(6):441–6.
123. Lemos C, Azevedo I, Martel F. Effect of red wine on the intestinal absorption of thiamine and folate in the rat: comparison with the effect of ethanol alone. Alcohol Clin Exp Res. 2005;29(4):664–71.
124. Knoops KTB, Spiro A, Groot LCPGM, et al. Do dietary patterns in older men influence change in homocysteine through folate fortification? The normative aging study. Public Health Nutr. 2007;12(10):1760–6.
125. Anderson CAM, Jee SH, Charleston J, et al. Effects of folic acid supplementation on serum folate and plasma homocysteine concentrations in older adults: a dose-response trial. Am J Epidemiol. 2010;172(8):932–41.

126. Pietrzik K, Bailey L, Shane B. Folic acid and L-5-methyltetrahydrofolate: comparison of clinical pharmacokinetics and pharmacodynamics. Clin Pharmacokinet. 2010;49(8):535–48.
127. Dietary reference intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic acid, Biotin, and Choline. 1998; http://www.nap.edu/catalog.php?record_id=6015. Accessed 31 Aug 2011.
128. Johnson MA, Dwyer JT, Jensen GL, et al. Challenges and new opportunities for clinical nutrition interventions in the aged. J Nutr. 2011;141:535–41.
129. Selhub J, Morris MS, Jacques PF. In vitamin B12 deficiency, higher serum folate is associated with increased total homocysteine and methylmalonic acid concentrations. Proc Natl Acad Sci U S A. 2007;104(50):19995–20000.
130. Miller JW, Garrod MG, Allen LH, Haan MN, Green R. Metabolic evidence of vitamin B-12 deficiency, including high homocysteine and methylmalonic acid and low holotranscobalamin, is more pronounced in older adults with elevated plasma folate. Am J Clin Nutr. 2009;90(6):1586–92.
131. Balk EM, Raman G, Tatsioni A, Chung M, Lau J, Rosenberg IH. Vitamin B6, B12, and folic acid supplementation and cognitive function: a systematic review of randomized trials. Arch Intern Med. 2007;167(1):21–30.
132. Selhub J, Paul L. Folic acid fortification: why not vitamin B_{12} also? Biofactors. 2011;37(4):269–71.
133. Carmel R. Efficacy and safety of fortification and supplementation with vitamin B12: biochemical and physiological effects. Food Nutr Bull. 2008;29(2 Suppl):S177–87.
134. http://www.whfoods.com/genpage.php?tname=nutrient&dbid=107. Accessed 29 May 2011.
135. home.caregroup.org/clinical/altmed/interactions/Drugs.htm. Accessed 23 June 2011.
136. USDA National nutrient database for standard reference, release 22: vitamin B12 (mcg) content of selected foods per common measure, vitamin B-12 sorted by nutrient content. Accessed 31 Aug 2011.
137. Watanabe F. Vitamin B12 sources and bioavailability. Exp Biol Med. 2007;232(10):1266–74.
138. Bourgeois V, Desbordes M, Follet M, Haouzir S, Guillin O. Charles Bonnet syndrome and vitamin B12 deficiency: a case report. General Hospital Psychiatry. 2010;32(4):446.e447-446.e448.
139. Bucca CB, Culla B, Guida G, et al. Unexplained chronic cough and vitamin B-12 deficiency. Am J Clin Nutr. 2011;93(3):542–8.
140. Stabler SP, Lindenbaum J, Allen RH. Vitamin B-12 deficiency in the elderly: current dilemmas. Am J Clin Nutr. 1997;66(4):741–9.
141. Steger GG, Mader RM, Vogelsang H, Schofl R, Lochs H, Ferenci P. Folate absorption in Crohn's disease. Digestion. 1994;55(4):234–8.
142. Billings RE. Interactions between folate metabolism, phenytoin metabolism, and liver microsomal cytochrome P450. Drug Nutr Interact. 1984;3(1):21–32.
143. http://emedicine.medscape.com/article/204066-overview#aw2aab6b2b3aa. Accessed 30 Aug 2011.
144. Dietary supplemental fact sheet: Folate. http://ods.od.nih.gov/pdf/factsheets/Folate-HealthProfessional.pdf. Accessed 22 Aug 2011.
145. Christen WG, Glynn RJ, Chew EY, et al. Folic acid, pyridoxine, and cyanocobalamin combination treatment and age-related macular degeneration in women: the women's antioxidant and folic acid cardiovascular study. Arch Intern Med. 2009;169(4):335–41.
146. USDA National nutrient database for standard reference, release 18: Folate, DFE (mcg) content of selected foods per common measure, sorted by nutrient content. 31 Aug 2011.
147. http://www.nature.com/nrc/journal/v7/n8/fig_tab/nrc2191_F4.html. Accessed 26 Aug 2011.
148. Heil SG, deJonge R, de Rotte MC et al. Screening for metabolic vitamin B12 deficiency by holotranscobalamin in patients suspected of vitamin B12 deficiency: a multicenter study. Ann Clin Biochem. 2012;499(Pt 2):184–9.

Iron, Copper, and Zinc

19

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Iron

Introduction

Iron is an essential micronutrient necessary for oxygen carrying capacity, enzyme function, immune function, etc. In the humans, total body iron stores average 3–5 g [1]. While iron regulation is clear, mechanisms for excretion are less well defined. In the USA, the National Health and Nutrition Examination Survey (NHANES) III (1999–2000) shows a prevalence of iron deficiency at 6% in the over 70 years age group and 9% in the 50–69 years group [2]. The prevalence of anemia varies based on the setting; the NHANES III data reveals a third of anemia in the over 65 age group to be nutritional, with iron deficiency alone or in combination with other nutrients accounting for 22% of the causes for anemia [3].

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Physiology of Iron Absorption, Transport, and Storage

Iron in the diet is present in two forms: heme (10–15%) and non-heme (85–90%) [4]. Non-heme form comprises the major component, up to 15 mg of elemental iron in the average daily American diet. Heme iron constitutes up to 5 mg of elemental iron in the average daily intake; its absorption from the intestinal lumen to the systemic circulation is far from clear [5].

There are two hypotheses proposed for nonheme iron absorption. One is hepcidin based and the second is enterocyte based. Iron absorption mainly takes place in the duodenum and proximal jejunum; the absorption is variable and ranges from 1 to 50% due to interactions with food, nutrients, mucosal or systemic inflammation, and iron stores. Factors that can decrease the bioavailability of iron are listed in Table 19.1. Ferrous sulfate absorption without food is 24.1% and with food the absorption declines to 8.2%. The absorption of iron is not parallel to the iron content in the preparation.

Iron in food that is in ferric form is poorly absorbed, but is absorbed following conversion to ferrous form by a reductase on the luminal surface of the enterocyte. Ferrous form is competitively transported into the enterocyte by a divalent metal ion transporter (DMT1) which also transports copper, zinc, molybdenum, cobalt, cadmium, nickel, and lead. DMT1 expression is regulated by body iron stores. Gastric acidity promotes retention of iron in ferrous form, enhancing its absorption. Enterocyte iron is either transported into the systemic circulation or attaches to a storage protein, apoferritin, forming ferritin. The enterocyte iron pool regulates iron responsive elements/iron responsive protein (IRE/IRP) to influence iron absorption. Iron transport into the systemic circulation is tightly regulated by hepcidin at the ferroportin–hephaestin complex of the enterocyte. Iron released into the systemic circulation is attached to transferrin and transported to liver, bone marrow, and other tissues (Fig. 19.1).

Hepcidin is a 25-amino acid peptide produced by hepatocytes [6]; production is dependent on iron status, inflammation, hypoxia, and erythropoietin activity. This regulation of iron

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absorption is termed the "gut–liver axis" [7]. Hepcidin inhibits iron absorption through degradation of DMT1 [8] and additional molecular mechanisms; its level is upregulated in the presence of inflammation and iron overload and is downregulated in the presence of hypoxia, anemia, and activity of erythropoietin [9].

Body iron is excreted via the shedded dermal epithelial cells; unabsorbed iron and enterocyte ferritin are lost through feces (1–2 mg/day) [4]. The iron released from red blood cells into the reticuloendothelial system is transported by transferrin (most important functional pool) for new red blood cell formation (20–30 mg/day) [4]. Hepcidin inhibits this step in erythropoiesis resulting in anemia of chronic disease [7], where even adequate iron stores cannot be utilized for RBC formation (Fig. 19.2). After 50 years of age, the daily iron requirement is 8 mg [10]. Liver and macrophages are the main storage sites for iron [4].

Table 19.1 Factors that decrease iron bioavailability [20, 50–52]

Organic
Phytates
Polyphenols/tannins (tea)
Eggs
Gluten
Soy protein
Bananas
Fiber—ispagula and psyllium
Trace elements: calcium, zinc
Gastric acid reducing agents
Proton pump inhibitors
Antacids
H2 blockers
Sodium bicarbonate
Helicobacter pylori infection

Iron Content in Food

Seaweed, dry cocoa powder, and chicken liver are high in content, with chicken liver carrying the highest heme iron content per weight coupled with high bioavailability. Most fruits and vegetables have low iron content, barring artichoke; spinach iron is low in bioavailability. Oils and dairy have no iron [11]. Fortified cereal has up to 18 mg of nonheme iron, whereas white bread has 0.9 mg per serving [10] (Table 19.2).

Iron Deficiency

Older adults prone to iron deficiency include vegetarians or lacto-vegetarians, those with dietary restrictions including low intake of meat or chicken, prior history of multigravida pregnancy, intestinal malabsorption, celiac disease, inflammatory bowel disease, blood loss, chronic kidney disease, and others. Obesity increases hepcidin levels with a decline in iron absorption [12]. On average, each hemodialysis patient loses 6–8 g of iron per year solely due to dialysis-related blood loss [13]. Serum erythropoietin and soluble

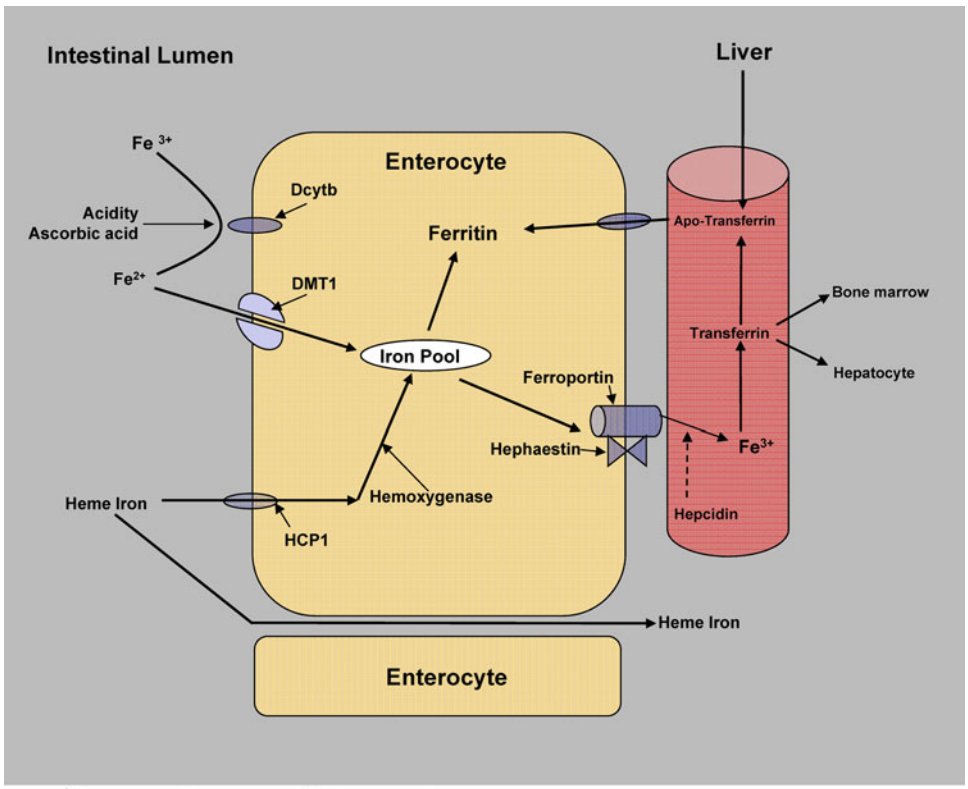

Fig. 19.1 Iron absorption and transport

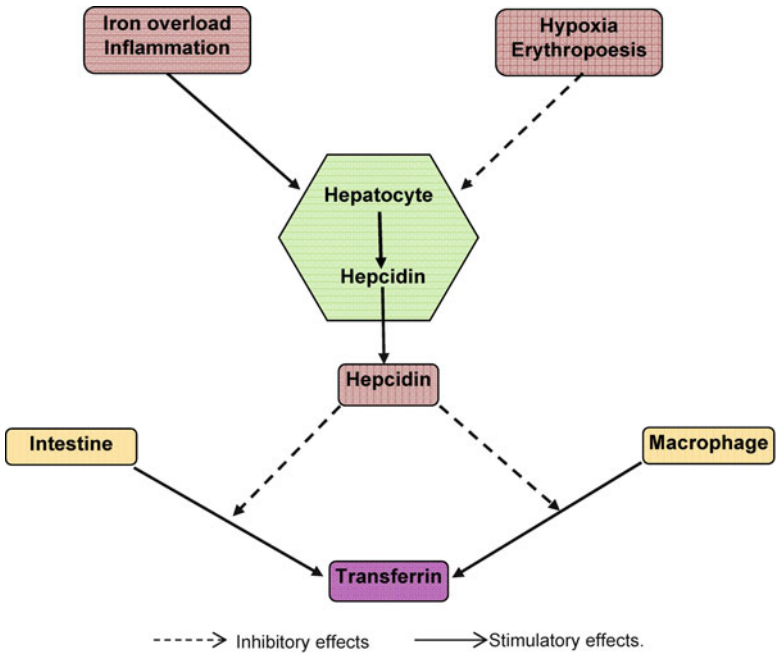

Fig. 19.2 Hepcidin and iron transport

Table 19.2 Iron content in mg per 100 g of various food sources [11]

High (≥5 mg/100 g food)
Cocoa
Chicken
Cashew nuts
Oat bran
Organ meats
Spirulina
Moderate (1–5 mg/100 g food)
Dried fruits and nuts: Almonds, pecans, raisins, figs, dates
Whole grain wheat flour
Fruits: Artichokes
Egg yolk
Shrimp, fish
Domestic lamb
Pork
Vegetables: Spinach, beans
Low (≤1 mg/100 g food)
Vegetables: Lettuce, cabbage, broccoli, potatoes, asparagus
Fruits: Bananas, peaches
Orange juice, lemon juice
Coffee

transferrin receptors (sTfR) significantly increase and induce functional iron deficiency with the use of infliximab [14]. Erythropoietic stimulating agents used to target higher hemoglobin levels create a functional iron deficient state by using up iron stores for erythropoiesis; at this stage, the agents are ineffective unless iron stores are repleted [15].

Clinical Features of Iron Deficiency

Symptoms and signs of iron deficiency are nonspecific. Fatigue, malaise, generalized weakness, decreased exercise tolerance, impaired cognitive abilities, irritability, aguesia, bald tongue, pale conjunctiva, koilonychia, restless leg syndrome, depressed immune function, and altered appetite and food habits are known to occur. Alternatively, the presentation may be worsening of organ function, typically cardiac or cerebrovascular [16]. The most common cause of iron deficiency is blood loss of gastrointestinal or genitourinary origin. Iron deficiency may result from malabsorption, such as in celiac disease. In developing nations, iron deficiency commonly results from blood loss due to parasitic gut infections. Iron deficiency should prompt evaluation for a cause; it is typically from blood loss. In older adults, the gastrointestinal tract is a likely source.

Diagnosis

Clinical and laboratory markers aid diagnosis. Microcytic hypochromic anemia characterized by serum ferritin levels <15 ng/mL or transferrin saturation (TSAT, referring to serum iron/total iron binding capacity × 100) <20% are both diagnostic of iron deficiency. The pitfall with serum ferritin assay is that it is a positive acute phase reactant and therefore elevated values in the hospitalized patients may mask iron deficiency. It is suggested that ferritin <70 ng/mL is an optimal cutoff for a diagnosis of iron deficiency in patients with acute or chronic inflammation [17]. Hence, ferritin assay and TSAT are ideal tests only in the stable ambulatory or long-term care settings. Serum ferritin, an intracellular protein, is a good index of storage iron. Bone marrow biopsy is a helpful diagnostic test, but seldom attempted these days [1]. Also useful are measures of soluble transferrin receptors, sTfR-ferritin index, zinc protoporphyrin/heme ratio (ZPP/H), and

Table 19.3 Differentiation of iron deficiency from other causes

	Iron deficiency anemia	Anemia of chronic disease	Thalassemia	Sideroblastic anemia
Serum iron	Low (<15 ng/mL)	Low	Normal to high	Variable
Total iron binding capacity (TIBC)	High (>400 μg/dL)	Normal or low	Normal	Normal
Serum ferritin	Low (<15 ng/mL)	Normal or high	50–300 ng/mL	50–300 ng/mL
RBC morphology	Microcytic and hypochromic	Normocytic or microcytic	Microcytic, hypochromic (target cells)	Microcytic or ringed sideroblasts
Transferrin saturation	Low (<20%)	Low	30–80%	30–80%
Hb electrophoresis	Normal	Normal	Abnormal	Normal

Table 19.4 Parenteral iron formulations [18, 53, 54]

Formulation	Elemental iron content (mg/mL)	Comments
Iron dextran	50	Anaphylactic reactions; life threatening 1/100 patients exposed. Drug intolerance in 2.5% [53]. Less utilized today
Iron gluconate	12.5	Nausea, flushing, headache, diarrhea can occur. 3.3 allergy episodes/million doses/year. Adverse drug events 29.5% by 4 weeks. Drug intolerance is 0.4% [53]. Life threatening adverse drug event (ADE) incidence: 0.9 per 10^6 doses [55]
Iron sucrose	20	Releases free iron rapidly into the systemic circulation, with increased susceptibility for infections. Administration of 200–300 mg over 2 h IV infusion is safe [54]. Life-threatening ADE incidence is 0.6 per 10^6 doses [55]
Ferumoxytol	30	Large doses (510 mg) can be administered in less than half a minute without a test dose [53]. Fewer drug-related adverse events
Ferric carboxymaltose	50	Large doses can be provided in <15 min; equals efficacy to iron sucrose. Up to 1 g (15 mg/kg) can be provided in a single dose without a test dose [56]. Adverse events: headache, dizziness, nausea, abdominal pain, constipation, diarrhea, and injection-site reactions [23]
Iron isomaltoside 1000	100	Up to 1.7 g (20 mg/kg) of iron can be administered in a single dose without requiring a test dose [56]. Contraindicated decompensated liver cirrhosis, hepatitis, and active rheumatoid arthritis [57]

reticulocyte hemoglobin concentration [18]. Transferrin receptor concentrations are high in iron deficiency.

Hypochromic, microcytic anemias (HMAs) are not solely from iron deficiency [16]; they also occur in anemia of chronic disease, rarely vitamin B2 deficiency, thalassemia major, beta thalassemia trait, sideroblastic anemia, hemoglobin H disease, hereditary transferrin deficiency, aferritinemia, and lead poisoning. Table 19.3 provides a differential diagnosis.

Treatment of Iron Deficiency [18, 19]

Iron Replacement

Total iron deficit can be calculated using Ganzoni formula: body weight [kg] × (target hemoglobin-actual hemoglobin) [g/dL] × 2.4 + depot iron [mg]. Iron may be replaced either via oral or parenteral route based on the deficit of iron, tolerance for formulation, and patient's condition. Iron can be safely supplemented in oral forms. Formulations vary in elemental iron content but are approximately of similar bioavailability; individual tolerance is variable (Table 19.4). Side effects are gastrointestinal and the main basis for poor adherence to oral therapy; they include nausea, vomiting, anorexia, altered taste, constipation, black discoloration of stools, and diarrhea. Oral iron formulations may interact and alter bioavailability of nutrients and medications. Ascorbic acid and orange juice increase iron bioavailability, as also meat, poultry, and fish [20]. Iron preparations may decrease the absorption and efficacy of levothyroxine, bisphosphonates, quinolones, tetracyclines, and captopril among others (Table 19.1).

It may be best to initiate oral iron with one pill daily (e.g., ferrous sulfate 325 mg) and if tolerated increase the dose to two or three times daily [21]. Oral iron is available as ferrous sulfate, fumarate, gluconate, succinate, and as polysaccharide iron complex or in combination with ascorbic acid. The amount of oral iron consumed can make a difference; in a study of 90 adults aged >80 years, three different formulations of oral iron (15, 50, and 150 mg doses) produced a similar response in improving ferritin levels and hemoglobin, but the highest intolerance to oral iron, manifested as gastrointestinal complaints was in the group receiving the largest dose [22]. Chronic use of proton pump inhibitors and H2 blockers impair iron absorption through reduction of gastric acidity. Replacement of iron matters, in that it is effective in iron deficiency anemia. It is not uncommon to come across older adults who remain anemic from iron deficiency because of blood loss years earlier.

Three generations of intravenous iron formulations exist. The oldest agent, iron dextran, is infrequently used for fear

Table 19.5 Iron–Zinc interactions with dietary ligands [45]

Dietary ligand	Mineral	Effects
Ascorbic acid	Iron	Increase in iron uptake
	Zinc	No effect
	Iron–zinc	Increase in iron uptake, none on zinc
Phytic acid	Iron	Decrease in iron uptake
	Zinc	Decrease in zinc uptake
	Iron–zinc	Decrease in iron and zinc uptake
Tartaric acid	Iron	Increase in iron uptake
	Zinc	Increase in zinc uptake
	Iron–zinc	Decrease in iron uptake, increase in zinc uptake
Tannic acid	Iron	Decrease in iron uptake
	Zinc	Increase in zinc uptake
	Iron–zinc	Decrease in iron uptake; increase in zinc uptake
Cysteine	Iron	Increase in iron uptake
	Zinc	Decrease in zinc uptake
	Iron–zinc	Decrease in iron and zinc uptake
Histidine	Iron	Increase in iron uptake
	Zinc	Decrease in zinc uptake
	Iron–zinc	Decrease in iron and zinc uptake
Methionine	Iron	Increase in iron uptake
	Zinc	Decrease in zinc uptake
	Iron–zinc	Decrease in iron uptake; increase in zinc uptake

of anaphylactic reactions. Subsequently iron administered as sucrose and gluconate preparations were better tolerated. The newest agents include ferric carboxymaltose and ferrumoxytol, which are effective, well tolerated and can be provided in large doses. Parenteral iron is indicated when oral iron is poorly tolerated and along with the use of erythropoietic stimulating agents which produce a functional iron deficiency. Ferric carboxymaltose can be given less frequently in larger doses [23]. Although ferric carboxymaltose is expensive, it may be an option compared to iron sucrose (which requires multiple doses and more resource utilization) [24] (Table 19.5). Long-term use of iron formulations may increase the risk of atherosclerosis, infection, diabetes, and cardiovascular mortality [25–27]. While treating iron deficiency, it must be borne in mind that higher iron stores may increase cancer risk; lower iron stores correlated with lower cancer risk in the Iron (Fe) in Atherosclerosis Study (FeAST) trial [28].

Copper

Copper is an essential micronutrient involved in multiple body functions including mitochondrial respiration, synthesis of hemoglobin, iron metabolism, redox reactions, cofactor role in metalloenzymes, neuronal transmitter synthesis and transport mechanisms across synapses, lipid metabolism, inflammatory activity, etc. [29–31]. Reference ranges in >50-year age group are 10.7–16.5 μmol/L for men and 12.7–19.5 μmol/L for women [32]. RDA for copper is 0.9 mg/day; the median intake of copper in the USA is 1–1.6 mg/day [33]. The major source of dietary copper include shellfish, nuts, legumes, liver, meats, and the germ of grains; cocoa, dried fruits, and vegetables are lower in content. Milk is low in content.

Copper Absorption, Transport, and Storage

Copper absorbed across the gastrointestinal tract binds to proteins (albumin, transcuperin) and amino acids; absorption is enhanced by dietary methionine, lectins, chlorides, carbonates, acetates, and sulfates and decreased by cysteine and molybdenum [29]. Dietary copper is absorbed from the stomach, duodenum, and proximal jejunum [29]. Copper stores are maintained by the portohepatic circulation [34]. Dietary copper content is up to 7 mg/day; most of the absorbed copper is transported to liver via portal vein and the rest excreted in feces [34]. Intracellular copper is regulated by importers (CTR proteins) and exporters (ATP7A and B) [30]. CTR proteins are present in enterocytes, liver, and kidney [31]. Copper exporters ATP7A and B regulate copper excretion. Mutations in ATP7B lead to decrease in copper export from hepatocytes and neuronal cells leading to intracellular copper toxicity and Wilson's disease [34]. The largest stores of copper are in liver (9%) and brain (7.3%) [35]. Between 65 and 95% of copper is bound to ceruloplasmin [34].

Copper and iron interact in the absorption process. Iron deficiency is associated with increase in hepatic copper levels. Increased intake of inorganic iron salts lead to copper deficiency; although there is iron accumulation, the interactions lead to anemia, which is often normocytic and hypochromic [36]. Copper deficiency alters iron metabolism. Copper deficiency is associated with hip fractures [37], anemia [38], neutropenia, age-related macular degeneration [39], and progression of atherosclerosis [40]. Deficiency is implicated in the development of amyloid plaques and neurofibrillary tangles in Alzheimer's disease [35]. Ceruloplasmin and serum copper levels are used to detect deficiency, but are not sensitive tests. Although serum copper and zinc levels are not linked to mortality in older adults, the copper-to-zinc ratio is directly related to all cause mortality regardless of age, gender, and other confounding factors [41].

Zinc

Dietary Content and Absorption

Zinc is an essential micronutrient with several functions. It is a component of over 250 enzymes including alkaline phosphatase, reverse transcriptase, DNA polymerase, and has roles in immune responses, apoptosis, bone metabolism, neurobehavioral, and gonadal functions [42, 43]. Zinc containing enzymes serve as scavenging free radicals and are implicated in the aging process. Zinc is present in most organs; 85% of total body zinc (2–3 g) [44] is in muscle and bone, the rest in liver, skin, and other tissues. Zinc bioavailability is high from foods such as shellfish, oysters, crab, pork, beef, and chicken, but low from vegetarian diets such as legumes, nuts, whole grains, and seeds [20]. Zinc absorption varies with the food source, intake of other nutrients, and perhaps body stores. Twenty to 40% of oral zinc is absorbed, mostly in the small intestine, less in the stomach and large intestine; absorption is increased by the presence of amino acids.

When dietary zinc is excessive or large amounts of zinc are administered over long periods of time, copper deficiency can result. While zinc induces intestinal metallothionein (MT), copper has greater affinity for MT than zinc and displaces zinc, getting trapped. Although zinc decreases copper absorption, conversely, copper does not affect zinc absorption. Supplemental iron provided as ferrous form has an inhibitory effect on zinc absorption, which is greater than for ferric iron; the basis is competition for uptake at the receptor level. The mechanism initially was attributed to competitive inhibition at the receptor level, but it is now believed to be a result of noncompetitive inhibition at the enterocyte [45] (Table 19.5).

Requirements and Consequences of Deficiency

Daily requirement for zinc is 8 mg/day for women and 11 mg/day for men [33]. Zinc deficiency is not uncommon in the elderly and is secondary to poor dietary intake, decreased absorption, and the use of medications such as loop diuretics which excrete zinc in urine [46].

Zinc is mostly intracellular, with measures of serum zinc not an accurate reflection of total body stores; erythrocyte zinc may be a better indication. Clinical manifestations of Zn deficiency include dermatitis, diarrhea, aguesia, alopecia, immune dysfunction, impaired wound healing, night blindness, age-related macular degeneration [47], hypertension [48], and osteoporosis [49]. Zinc is a component of therapy for the long-term management of macular degeneration. The cornea, a tissue with high zinc concentration, is affected by zinc deficiency. Zinc dermatitis involves the extremities and adjacent to body orifices.

References

1. Muñoz M. An update on iron physiology. World J Gastroenterol. 2009;15(37):4617.
2. Iron deficiency—United States, 1999–2000. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5140a1.html. Accessed 7 Sep 2010.
3. Guralnik JM. Prevalence of anemia in persons 65 years and older in the United States: evidence for a high rate of unexplained anemia. Blood. 2004;104(8):2263–8.
4. Munoz M, Garcia-Erce JA, Remacha AF. Disorders of iron metabolism. Part 1: molecular basis of iron homoeostasis. J Clin Pathol. 2011;64:281–6.
5. Zhu A, Kaneshiro M, Kaunitz JD. Evaluation and treatment of iron deficiency anemia: a gastroenterological perspective. Dig Dis Sci. 2010;55(3):548–59.
6. Young B, Zaritsky J. Hepcidin for clinicians. Clin J Am Soc Nephrol. 2009;4(8):1384–7.
7. Babitt JL, Lin HY. Molecular mechanisms of hepcidin regulation: implications for the anemia of CKD. Am J Kidney Dis. 2010;55(4):726–41.
8. Brasse-Lagnel C, Karim Z, Letteron P, et al. Intestinal DMT1 cotransporter is down-regulated by hepcidin via proteasome internalization and degradation. Gastroenterology. 2011;140(4):1261–71.
9. Ganz T. Hepcidin and iron regulation, 10 years later. Blood. 2011;117(17):4425–33.
10. Dietary supplement fact sheet: iron. http://ods.od.nih.gov/factsheets/Iron_pf.asp. Accessed 20 Sep 2010.
11. USDA National Nutrient Database for Standard Reference, Release 17. http://www.nal.usda.gov/fnic/foodcomp/Data/SR17/wtrank/sr17a303.pdf. Accessed 4 Oct 2010.
12. Amato A, Santoro N, Calabrò P, et al. Effect of body mass index reduction on serum hepcidin levels and iron status in obese children. Int J Obes. 2010;34(12):1772–4.
13. Faich G, Strobos J. Sodium ferric gluconate complex in sucrose: safer intravenous iron therapy than iron dextrans. Am J Kidney Dis. 1999;33(3):464–70.
14. Katsanos K, Cavalier E, Ferrante M, et al. Intravenous iron therapy restores functional iron deficiency induced by infliximab. J Crohns Colitis. 2007;1(2):97–105.
15. Dharmarajan TS, Widjaja D. Erythropoiesis-stimulating agents in anemia: use and misuse. J Am Med Dir Assoc. 2009;10(9):607–16.
16. Dharmarajan TS, Pais W, Norkus EP. Does anemia matter? Anemia, morbidity, and mortality in older adults: need for greater recognition. Geriatrics. 2005;60(12):22–7, 29.
17. Quinn C, Uzbeck M, Saleem I, et al. Iron status and chronic kidney disease predict restless legs syndrome in an older hospital population. Sleep Med. 2011;12(3):295–301.
18. Clark SF. Iron deficiency anemia: diagnosis and management. Curr Opin Gastroenterol. 2009;25(2):122–8.
19. Macdougall IC. Strategies for iron supplementation: oral versus intravenous. Kidney Int Suppl. 1999;55 Suppl 69:S61–6.
20. Hunt JR. Bioavailability of iron, zinc and other trace minerals from vegetarian diets. Am J Clin Nutr. 2003;78(Suppl):633S–9.
21. Fick DM, Cooper JW, Wade WE, Waller JL, Maclean JR, Beers MH. Updating the Beers criteria for potentially inappropriate medication use in older adults results of a US consensus panel of experts. Arch Intern Med. 2003;163(22):2716–24.
22. Rimon E, Kagansky N, Kagansky M, et al. Are we giving too much iron? Low-dose iron therapy is effective in octogenarians. Am J Med. 2005;118(10):1142–7.
23. Lyseng-Williamson KA, Keating GM. Ferric carboxymaltose: a review of its use in iron-deficiency anaemia. Drugs. 2009;69(6):739–56.

24. Bager P, Dahlerup JF. The health care cost of intravenous iron treatment in IBD patients depends on the economic evaluation perspective. J Crohns Colitis. 2010;4(4):427–30.
25. Luan DC, Zhao Z, Li H, Li X, Li SJ, Liu ZM. Body iron stores and dietary iron intake in relation to diabetes in adults in North China. Diabetes Care. 2008;31:285–6.
26. Tzonou A, Lagiou P, Trichopoulou A, Tsoutsos V, Trichopoulos D. Dietary iron and coronary heart disease risk: a study from Greece. Am J Epidemiol. 1998;147(2):161–6.
27. Neven E, De Schutter TM, Behets GJ, Gupta A, D'Haese PC. Iron and vascular calcification. Is there a link? Nephrol Dial Transplant. 2011;26(4):1137–45.
28. Mascitelli L, Goldstein MR. Inhibition of iron absorption by polyphenols as an anti-cancer mechanism. Q J Med. 2011;104(5): 459–61.
29. Krupanidhi S, Sreekumar A, Sanjeevi CB. Copper and biological health. Indian J Med Res. 2008;128:448–61.
30. Banci L, Bertini I, Cantini F, Ciofi-Baffoni S. Cellular copper distribution: a mechanistic systems biology approach. Cell Mol Life Sci. 2010;67(15):2563–89.
31. Lutsenko S. Human copper homeostasis: a network of interconnected pathways. Curr Opin Chem Biol. 2010;14(2):211–7.
32. Milne DB, Johnson PE. Assessment of copper status effect of age and gender on reference ranges in healthy adults. Clin Chem. 1993;39(5):883–7.
33. Dietary reference intakes for vitamin a, vitamin k, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. 2001. http://search.nap.edu/nap-cgi/skimchap.cgi?recid=10026&chap=224-257. Accessed 1 Nov 2010.
34. van den Berghe PVE, Klomp LWJ. New developments in the regulation of intestinal copper absorption. Nutr Rev. 2009;67(11): 658–72.
35. Hung YH, Bush AI, Cherny RA. Copper in the brain and Alzheimer's disease. J Biol Inorg Chem. 2009;15(1):61–76.
36. Gambling L, Andersen Henriette S, McArdle Harry J. Iron and copper, and their interactions during development. Biochem Soc Trans. 2008;36(6):1258.
37. Hirota K, Hirota T. [Nutrition-related bone disease]. Nippon Rinsho. 2006;64(9):1707–11.
38. Knovich MA, Il'yasova D, Ivanova A, Molnar I. The association between serum copper and anaemia in the adult Second National Health and Nutrition Examination Survey (NHANES II) population. Br J Nutr. 2008;99(6):1226–9.
39. Hammond Jr BR, Johnson MA. The age-related eye disease study (AREDS). Nutr Rev. 2002;60(9):283–8.
40. Giacconi R, Muti E, Malavolta M, et al. The +838 C/G MT2A polymorphism, metals, and the inflammatory/immune response in carotid artery stenosis in elderly people. Mol Med. 2007;13(7–8): 388–95.
41. Mocchegiani E, Malavolta M, Lattanzio F, et al. Cu to Zn ratio, physical function, disability, and mortality risk in older elderly (ilSIRENTE study). Age. 2012;34(3):539–52.
42. Stefanidou M, Maravelias C, Dona A, Spiliopoulou C. Zinc: a multipurpose trace element. Arch Toxicol. 2005;80(1):1–9.
43. Meunier N, O'Connor JM, Maiani G, et al. Importance of zinc in the elderly: the ZENITH study. Eur J Clin Nutr. 2005;59:S1–4.
44. Maret W, Sandstead H. Zinc requirements and the risks and benefits of zinc supplementation. J Trace Elem Med Biol. 2006;20(1): 3–18.
45. Iyengar V, Pullakhandam R, Nair KM. Dietary ligands as determinants of iron-zinc interactions at the absorptive enterocyte. J Food Sci. 2010;75(8):H260–4.
46. Miyata S. Zinc deficiency in the elderly. Nippon Ronen Igakkai Zasshi. 2007;44(6):677–89.
47. Berson EL. Nutrition and retinal degenerations. Int Ophthalmol Clin. 2000;40, Fall(4):93–111.
48. Tubek S. Role of zinc in regulation of arterial blood pressure and in the etiopathogenesis of arterial hypertension. Biol Trace Elem Res. 2007;117:39–51.
49. Yamaguchi M. Role of nutritional zinc in the prevention of osteoporosis. Mol Cell Biochem. 2009;338(1–2):241–54.
50. Lynch SR. Interaction of iron with other nutrients. Nutr Rev. 1997;55(4):102–10.
51. McColl KEL. Effect of proton pump inhibitors on vitamins and iron. Am J Gastroenterol. 2009;104:S5–9.
52. Muhsen K, Cohen D. Helicobacter pylori infection and iron stores a systematic review and meta-analysis. Helicobacter. 2008;13: 323–40.
53. Singh A, Patel T, Hertel J, Bernardo M, Kausz A, Brenner L. Safety of ferumoxytol in patients with anemia and CKD. Am J Kidney Dis. 2008;52(5):907–15.
54. Chandler G, Harchowal J, Macdougall I. Intravenous iron sucrose: establishing a safe dose. Am J Kidney Dis. 2001;38(5):988–91.
55. Munoz M, Garcia-Erce JA, Remacha AF. Disorders of iron metabolism. Part II: iron deficiency and iron overload. J Clin Pathol. 2011;64:287–96.
56. Gozzard D. When is high-dose intravenous iron repletion needed? Assessing new treatment options. Drug Des Devel Ther. 2011;5: 51–60.
57. www.monofer.com/download.ashx?file…dosing+card.pdf. Accessed 9 May 2011.

Vitamin D and Calcium

20

T.S. Dharmarajan and Amit Sohagia

Introduction

Vitamin D deficiency has received much attention in the last several years and become a subject of discussion in the lay press and medical literature [1–9]. Known as a sunshine vitamin, its major role is in calcium homeostasis and skeletal health. Vitamin D truly is a prohormone rather than a vitamin, requiring conversion to the active hormone form. Although structurally similar to a steroid hormone [7], it is generally referred to as a vitamin, which includes vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol).

Prevalence and Epidemiology

Vitamin D deficiency prevalence has been referred to as a pandemic. In the United States, based on the National Health and Nutrition Examination Survey (NHANES) data (2005 and 2006) half to two-thirds have circulating levels of 25-OH vitamin D (25OHD) below the 30–76 ng/mL range, with the mean levels 24 ng/mL for several age groups [10]. The prevalence of levels ≤20 ng/mL was 41.6% [11]. Data suggests that 40–100% of US and European older community adults are deficient in vitamin D; deficiency is highest in the older institutionalized and hospitalized, with 60% of nursing home residents and 57% of hospitalized vitamin D deficient [10–13]. The issue is not solely an old age problem; the young are not immune either and are potentially at risk. Fifty-two percent of Hispanic and black adolescents in Boston and 48% of white preadolescent girls in Maine had 25OHD levels below 20 ng/mL [11, 14, 15], indicating a need for effective intervention [16]. Dress style is an influence, with a higher prevalence in females described from Jordan [12]. In a pain clinic, 93% of patients with nonspecific musculoskeletal pain were deficient [17]. Those with chronic liver disease have a high likelihood of severe vitamin D deficiency [18].

A role for vitamin D has been implicated in reducing the risk of many chronic disorders including type II diabetes, multiple sclerosis, rheumatoid arthritis, cancers, heart disease, and infections. The role of calcium is intricately linked to vitamin D, parathormone (PTH), and calcitonin [1–4].

Physiology: Vitamin D Metabolism and Functions

The sources for vitamin D are three: dermal synthesis, dietary sources such as salmon and fatty fish, and supplements including multivitamins. With sunlight exposure, 7-dehydrocholesterol (provitamin D_3) in the epidermis and dermis is converted non-enzymatically to previtamin D_3, which isomerizes to form D_3 [19–21]. Ozone efficiently absorbs UVB radiation; little vitamin D formation occurs in the early morning and late afternoon. Vitamin D_3 from the skin and dietary vitamin D undergo sequential hydroxylation, first in the liver to 25(OH)D and then in the kidney to the biologically active form, 1,25-dihydroxyvitamin D ($1,25[OH]_2D$). The highest circulating form of the vitamin is 25(OH)D, also the storage form, while the active metabolite is ($1,25[OH]_2D$) [5]. Excessive solar UV-B irradiation does not lead to vitamin intoxication because excess previtamin is photolyzed to inactive photoproducts [22, 23]. Melanin in the skin functions similar to a sunscreen, decreasing synthesis. Further,

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$1,25(OH)_2D$ may also regulate keratinocyte differentiation and negative feedback. Several factors, including serum phosphorus and parathyroid hormone (PTH), regulate renal production of $1,25(OH)_2D$. Calcium metabolism is regulated by $1,25(OH)_2D$ through interaction with its major target tissues, the bone, and the intestine.

The $1,25(OH)_2D$ ligand binds with affinity to the vitamin D receptor (VDR), to increase intestinal absorption of both calcium and phosphorus. Musculoskeletal roles for vitamin D include bone formation, resorption and mineralization, and maintenance of neuromuscular function. Circulating $1,25(OH)_2D$ reduces serum parathyroid hormone (PTH) levels directly by decreasing parathyroid gland activity and indirectly by increasing serum calcium. $1,25(OH)_2D$ regulates bone metabolism in part by interacting with the VDR in osteoblasts, releasing biochemical signals to form mature osteoclasts. The osteoclasts release calcium into the blood (Fig. 20.1).

With vitamin D deficiency, there is a significant decline in gut calcium and phosphorus absorption. The calcium absorption rises substantially with correction of vitamin D levels. Low calcium stores trigger an increased PTH release, in an attempt to restore calcium homeostasis by increasing renal tubular reabsorption of calcium, bone calcium mobilization, and enhancing the production of $1,25(OH)_2D$. In summary, PTH hypersecretion is the price paid to correct hypovitaminosis D and calcium deficiency; typically PTH levels begin to rise when 25(OH)D levels fall below 30 ng/mL [24]. This was perhaps one reason to set a lower acceptable range level for normal vitamin D status.

Calcium Metabolism

Calcium (Ca) homeostasis needs to be preserved for muscle contraction, nerve conduction, hormone regulation, and blood coagulation, besides other metabolic processes. Maintenance of body calcium stores is dependent on dietary intake, calcium absorption from the gastrointestinal (GI) tract, and renal calcium excretion. With a balanced diet, roughly 1,000 mg of Ca is ingested daily and about 200 mg secreted into the GI tract in bile and other secretions. Depending on the circulating vitamin D levels, roughly 200–400 mg of Ca is absorbed from the intestine each day. The remaining 800–1,000 mg is lost in the stool. Ca balance is maintained through renal calcium excretion averaging 200–300 mg/day [25, 26].

Both extracellular and intracellular Ca concentrations are tightly regulated by bidirectional Ca transport across the plasma membrane of cells and intracellular organelles. Ionized Ca acts as an intracellular second messenger and is involved in skeletal muscle contraction, excitation–contraction coupling in cardiac and smooth muscle, and activation of protein kinases and phosphorylation. Ca is also involved in the action of other intracellular messengers, such as cyclic adenosine monophosphate (cAMP) and mediates responses for gastrointestinal hormones such as glucagon, secretin, and cholecystokinin.

Despite the important intracellular roles, roughly 99% of body Ca is in bone, as hydroxyapatite crystals. Roughly 1% of bone Ca is freely exchangeable with extracellular Ca, and serves a buffer role. Total serum Ca concentration ranges from 8.8 to 10.4 mg/dL (2.20–2.60 mmol/L), with 40–45% bound to plasma proteins, primarily albumin. The balance includes ionized Ca and a fraction complexed with ions such as citrate. Total Ca, the value obtained by laboratory measurement, includes protein-bound, complexed, and ionized fraction. The physiologically active form (which is the free Ca) is about 50% of the total Ca; it would be the relevant measure, but is technically difficult and restricted to situations with altered protein binding.

Current Intake of Vitamin D and Calcium

NHANES (2005–2006) data estimated the average intake of vitamin D for males and females from foods alone ranged from 144 to 288 IU/day. Thirty-seven percent of the US population used a dietary supplement containing vitamin D to enhance intake. Table 20.1 provides age-based vitamin D and calcium requirements. Over the past 20 years, mean serum 25(OH)D concentrations in the USA have slightly declined among men, but not women; reasons were largely from simultaneous increases in body weight, reduced milk intake, and greater use of sun protection when outside [27–29].

The NHANES 2003–2006 data suggested that the mean calcium intake for males ranged from 871 to 1,266 mg/day depending on life stage group; for females, the range was 748–968 mg/day. Groups falling below desirable intakes included women aged 51–70 years, and both men and women over 70 years. Overall, females are less likely than males to obtain recommended intake of calcium from food. About 43% of the US population and most older women use dietary supplements containing calcium, which helped increase calcium intake, with some older women even exceeding the upper limit [27, 29, 30].

Only 30% of calcium ingested is actually absorbed in the gut and depends on the amount consumed (the efficiency of absorption decreases as calcium intake increases), age, and life stage (absorption decreases with age). Hence higher calcium intake is recommended for females aged over 50 years and for both males and females older than 70 years, Vitamin D status plays an important role; components in food (phytic acid and oxalic acid) bind to calcium, inhibiting absorption. Foods with high levels of oxalic acid include spinach, collard greens, sweet potatoes, rhubarb, and beans. Foods high in phytic acid include fiber-containing whole-grains, wheat bran, beans, seeds, nuts, and soy isolates. High intakes of sodium, protein, and caffeine increase calcium excretion [31, 32].

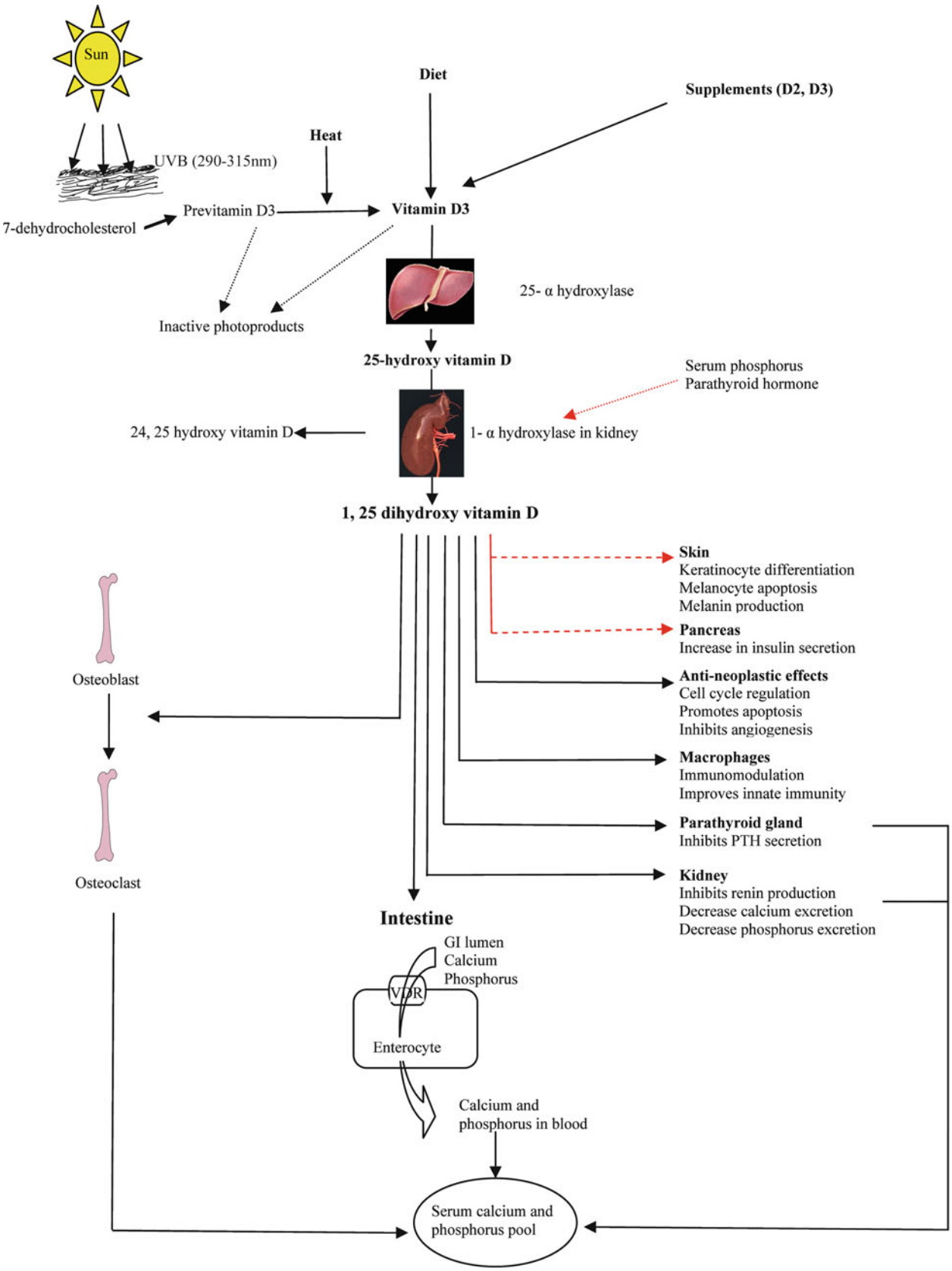

Fig. 20.1 Vitamin D metabolism and it effects. *Dotted red line* denotes inhibitory effect

Table 20.1 Age-based Recommended Dietary Allowance (RDA) for vitamin D and calcium [29]

Age group	Vitamin D (IU)	Calcium (mg)
Children (4–8 years)	600	800
Teenagers (9–18 years)	600	1,300
Adults (19–50 years)	600	1,000
Adults (51–70 years)	600	1,000 (males), 1,200 (females)
Older Adults (>70 years)	800	1,200

Table 20.2 Risk factors for vitamin D deficiency [1–6, 8, 11, 19]

Older age, predisposed to associated with by several factors
Down regulation of vitamin D receptors with age
Darker skin pigmentation: less efficient synthesis
Insufficient exposure to sunlight: lack of UV-B rays
Medications that inactivate or impair vitamin D metabolism (e.g., anticonvulsants, rifampin, corticosteroids)
Obesity (body mass index > 30 kg/m^2): less outdoor activity, sequestration of vitamin
Sedentary lifestyle: less outdoor activity and exposure to sunlight
Excessive clothing: diminished exposure of skin to sunlight
Season: cold climates, time of day, lack of sunlight, latitude
Confinement to indoors
Use of sunscreens, can block most of the UV B ray effects
Living in high altitude
Malabsorption (celiac disease, short gut syndrome, gastric by-pass surgery, and others)
Chronic liver disease (decreased 25 hydoxylase activity)
Chronic kidney disease (decreased hydroxylase activity, renal losses with proteinuria)

Risk Factors for Vitamin D Deficiency

The hitherto recommended intake of 400 IU/day has been questioned as being very low. Poor intake of vitamin D with insufficiency is reported across all age groups, geographic regions, and seasons. As sunlight exposure is erratic, and propaganda about the relationship of sunlight to skin cancer is high, supplements are often the preferred option to achieve minimum recommended daily intakes. The tendency to remain indoors either as a preference or from disability, and excessive coverage of skin by clothing all impair dermal synthesis. Obesity is associated with low levels of the vitamin, partly from inadequate exercise, decreased exposure to sunlight and from sequestration of vitamin D in body fat [5]. Table 20.2 lists risk factors for vitamin D deficiency.

Recent guidelines from Canada and the USA issued within months differ significantly [29, 33]. The Canadian guidelines recommend a higher intake, while the US guidelines are more conservative and recommend lower amounts. The US guidelines have expressed skepticism in that several vitamin D related consequences are debatable and require further research.

Calcium Deficiency and at Risk People

Diseases

Inadequate calcium intake is not associated with consequences in the short term; circulating blood levels of calcium are maintained by tight regulation. Hypocalcemia results primarily from disease (e.g., osteomalacia, gastrectomy, hypomagnesemia, malabsorption) or rarely as an adverse effect of from medications (e.g., loop diuretics). Manifestations with severe hypocalcemia include numbness and tingling in the fingers, muscle cramps, convulsions, lethargy, and abnormal cardiac rhythm. If left untreated, calcium deficiency leads to tetany and death. Over time, inadequate calcium intake causes osteopenia and osteoporosis, with a higher risk for bone fractures. Although frank calcium deficiency is uncommon, suboptimal dietary calcium intake leads to health consequences over time, most evident in the following situations.

Postmenopausal Women

Menopause leads to bone loss because decline in estrogen levels increases bone resorption and decreases calcium absorption. Annual decline in bone mass is 3–5% in the years immediately after menopause, with the decline below 1% per year after age 65. Merely increasing calcium intake does not fully offset this bone loss [34]. Amenorrhea secondary to reduced circulating estrogen levels or induced by exercise results in decreased bone mass and stress fractures [35].

Lactose Intolerance

Lactose-intolerant individuals are at risk of calcium inadequacy as they tend to avoid dairy products. Lactase declines with age, with a higher incidence of lactose intolerance in the elderly. Data suggests that most people with lactose intolerance can consume up to 12 g of lactose (present in 8 oz of milk), with minimal to no symptoms, especially if consumed with other foods; larger amounts of dairy products can be consumed if spread over the day and eaten with other dietary items [36]. Options to reduce symptoms include eating low-lactose dairy products such as aged cheeses (cheddar and Swiss), yogurt, or lactose-reduced and lactose-free milk. To ensure adequate calcium intake, individuals with lactose-intolerance must choose nondairy food sources or a calcium supplement [37].

Vegetarians

Vegetarians might absorb less calcium than omnivores because they consume more plant products containing oxalic

and phytic acids. On the other hand, vegetarian diets which contain less protein than typical omnivore diets, are associated with lower calcium losses in urine [38].

Sources of Vitamin D

Sunlight and Diet

Solar ultraviolet-B (wavelengths of 290–315 nm) irradiation is the primary source of vitamin D (other than diet) for most people. Dietary sources of vitamin D are limited: they include oily fish such as salmon, mackerel, and sardines; fish oils such as cod liver oil; and shiitake mushrooms. Several foods are fortified in the USA, including milk, some yogurts, artificial milk, some cereals, and margarine. Table 20.3 provides food sources of vitamin D [39–43].

Sun exposure and UV-B radiation (with a wavelength of 290–320 nm) of uncovered skin converts cutaneous 7-dehydrocholesterol to previtamin D_3 and in turn to vitamin D_3. Season, time and length of day, cloudiness, smog, skin melanin content, clothing, pigmentation, and sunscreen are all factors that influence the extent of radiation exposure, effects, and vitamin D dermal synthesis. Ample opportunities help synthesize vitamin D through sunlight exposure and increase hepatic and fat stores in spring, summer, and fall in most latitudes. Cloud cover and shade reduce UV light exposure; likewise radiation does not penetrate glass adequately. Sunscreens with a sun protection factor (SPF) of 8 or more blocks most synthesis. Approximately 15–30 min of sun exposure between 10 AM and 3 PM at least 2–3 times a week to face, arms, legs or back without sunscreen may suffice; another option is the use of commercial tanning beds that emit 2–6% UV-B radiation. If neither is possible, dietary sources or supplements are the only options left [1, 39, 40, 44, 45].

Despite the importance of sunlight in vitamin D synthesis, it is prudent to limit skin exposure to UV rays. UV radiation is a carcinogen responsible for most skin cancers including metastatic melanoma. Lifetime cumulative UV damage to skin is also largely responsible for much of the extrinsic age-associated cosmetic changes. The American Academy of Dermatology recommends photoprotective measures such as sunscreen as precaution. Data is inadequate to determine whether UV-B-induced synthesis of vitamin D can occur without a risk of skin cancer [46–48].

Table 20.3 Dietary sources of vitamin D [39–42, 84]

Fortified sources	
Cereal	100 IU per serving
Milk, including soy or almond milk	100 IU per 8 oz
Orange juice (some brands)	100 IU per 8 oz
Yogurt (some brands)	100 IU per 8 oz
Butter	56 IU per 3.5 oz
Cheese, some, esp. cheddar	100 IU per 3 oz
Margarine	429 IU per 3.5 oz
Yolk of egg	20 IU per egg
Nonfortified food sources	
Dry mushrooms (shiitake)	1,600 IU per 3.5 oz
Cod liver oil	400 IU per teaspoon
Egg yolk	20 IU per yolk
Mackerel (canned)	250 IU per 3.5 oz
Salmon (canned)	300–1,000 IU per 3.5 oz
Salmon (fresh, farmed)	100–250 IU per 3.5 oz
Sardines (canned)	300 IU per 3.5 oz
Tuna fish (canned)	230 IU per 3.6 oz
Cod liver oil	1,360 IU per tsp

Dietary Supplements

While sunlight and dermal synthesis of vitamin D are good options, ultimately the practical option may be appropriate use of supplements in older people [49]. Vitamin D in supplements and fortified foods is available in two forms, D_2 (ergocalciferol) and D_3 (cholecalciferol) that differ chemically only in side-chain structure. Vitamin D_2 is manufactured by the UV irradiation of ergosterol in yeast, while vitamin D_3 is manufactured by irradiation of 7-dehydrocholesterol from lanolin and chemical conversion of cholesterol. The half life of D_3 is longer than D_2 and its bioavailability may be marginally better. In practice there is little difference between the two. In chronic kidney disease especially stages 4 and 5, vitamin D analogues may be required (Table 20.4) [50].

Table 20.4 Vitamin D: forms and doses [1, 3, 5, 42, 50]

Form of vitamin D	Dose	Comments
Ergocalciferol (D_2)	Capsule, tablets, drops, syrup: 100–50,000 IU Injection: 300,000–600,000 IU	Used for fortification and in supplements. Half life: 8–10 days
Cholecalciferol (D_3)	Tablets, caps: 400–50,000 IU	Used in fortified food. Half life: 25–30 days
Calcifediol (25-hydroxy vitamin D_3)	Capsules: 20, 50 μg	Used in presence of liver disease
Calcitriol (1,25-dihydroxyvitamin D_3)	Capsules: 0.25–0.5 μg Oral solution: 1 μg/mL Injection: 1–2 μg/mL	Used in presence of chronic kidney disease
Dihydrotachysterol (synthetic analogue of D_2)	Tablets: 0.125, 0.2, 0.4 mg Solution: 0.2 mg/mL Capsules: 0.125 mg	Vit D analogue for CKD. Rapid onset of action

Table 20.5 Common foods source for calcium [27, 32, 51, 52]

Food source	mg/serving
Dairy products	
Yogurt, plain, low fat, 8 oz	415
Milk, buttermilk, 8 oz	285
Cheddar cheese, 1.5 oz	306
Milk, reduced-fat (2% milk fat), 8 oz	297
Milk, whole (3.25% milk fat), 8 oz	291
Mozzarella, part skim, 1.5 oz	275
Ice cream, vanilla, ½ cup	85
Cottage cheese, 1% milk fat, 1 cup unpacked	138
Swiss cheese 2 oz	438
Chocolate milk, 1 cup	280
Romano cheese, 1.5 oz	452
Non-dairy products	
Bread, white, 1 oz	31
Bread, whole-wheat, 1 slice	20
Broccoli, raw, ½ cup	89
Salmon, pink, canned, solids with bone, 3 oz	181
Orange juice, calcium-fortified, 6 oz	200–260
Spinach, cooked, ½ cup	120
Okra, cooked ½ cup	88
Ready-to-eat cereal, calcium-fortified, 1 cup	100–1,000
Soy beverage, calcium fortified, 1 cup	368
Tofu ½ cup	253
Sardines 3 oz	325
Oatmeal, plain and flavored, fortified, 1 packet	99–110
White beans, canned ½ cup	96

Sources of Calcium

Food

Milk, yogurt, and cheese are rich natural sources of calcium and major food derivatives of the nutrient. Nondairy sources include vegetables, such as Chinese cabbage, kale, and broccoli, but the bioavailability does not match dairy sources. Most grains do not have high amounts of calcium unless fortified; however, they do contribute dietary calcium because grains are consumed often and are a major dietary component. Fortified foods include several fruit juices, tofu, and cereals (Table 20.5) [49, 51].

Dietary Supplements

The two main calcium supplements are carbonate and citrate. Calcium carbonate is both inexpensive and easily available. While carbonate has more elemental calcium than citrate (40% vs. 21%), the latter may be better absorbed in the presence of reduced gastric acidity. Citrate may be marginally more expensive. In the final analysis, there is little to substantiate one over the other. Other calcium forms include gluconate, lactate, and phosphate. Calcium citrate malate is a well-absorbed form in some fortified juices. Calcium carbonate is absorbed most efficiently when it is consumed with food, and in the presence of acid, whereas calcium citrate is absorbed irrespective of the gastric food and acid content [52]. Calcium citrate may be a better choice in presence of reduced gastric acid states from use of proton pump inhibitors.

The percentage of calcium absorbed depends on the total amount of elemental calcium consumed at a given time; as the amount increases, the percentage absorption decreases. Absorption is highest in doses ≤500 mg. Hence, larger doses of calcium such as 1,000 mg/day are best split several times daily. Gastrointestinal side effects include a variable combination of gas, bloating, and constipation; more recently calcium supplements have been linked to nephrolithiasis with long-term use [52, 53].

Gastrointestinal Factors Contributing to Vitamin D Insufficiency

Aside from inefficient cutaneous synthesis of vitamin D (four times less in the old than young adults), vitamin D insufficiency results from drug nutrient interactions and increase in body fat. Aging is associated with down regulation of VDRs. Medication effects are complex and occur by inducing the CYP enzymes and inactivation of the vitamin in the liver. Statins, calcium channel blockers, and digoxin interfere with vitamin D synthesis when consumed together. Estrogen, isoniazid, and thiazide diuretics raised blood vitamin D level while antacids, anti-seizure medications (phenytoin, phenobarbital), cholestryamine, and rifampin decrease vitamin D levels [54, 55]. Corticosteroids reduce calcium absorption and impair vitamin D metabolism, contributing to osteoporosis.

Older adults suffer from several gastrointestinal disorders that predispose to deficiency, including any cause of malabsorption (celiac disease, chronic pancreatitis, short gut syndrome, Crohn's disease, among others) [55–58]. Patients presenting for bariatric surgery may be expected to develop insufficiency and need lifetime monitoring for metabolic bone disease from vitamin D and calcium deficiency [59–61]. Hepatic causes such as end stage liver disease particularly biliary cirrhosis, cholestatic liver disease, and alcoholic cirrhosis are all associated with defective 25 hydroxylation; the AASLD (American Association for the study of Liver Diseases) recommends vitamin D and calcium supplements in these situations (Table 20.6) [18].

Manifestations

Patients with osteomalacia may be asymptomatic or present with skeletal consequences include bone pain (best elicited by exerting pressure on the bone), bilateral proximal muscle weakness (myopathy), gait and balance abnormalities, and a

Table 20.6 Vitamin D deficiency in common gastrointestinal disorders [55–61]

Gastro intestinal disorders	Possible mechanism
Gastrectomy	Decrease intake, malabsorption, bacterial overgrowth
Gastric bypass	Malabsorption secondary to decrease absorptive surface area and dumping syndrome
Celiac disease	Malabsorption secondary to villous atrophy of proximal small bowel
Inflammatory bowel disease	Malabsorption secondary to epithelial damage, small intestinal stricture or surgery (in Crohn's disease), medication effect (steroid)
Primary biliary cirrhosis	Severe jaundice can decrease ability to absorb dietary vitamin D from the gut. Decrease in bile acid secretion contributory factor
Chronic liver disease including cirrhosis	Impaired synthesis, impaired absorption secondary to impaired bile acid production or gut edema associated with portal hypertension
Small intestinal bacterial overgrowth	Malabsorption of fat soluble vitamins
Exocrine pancreatic insufficiency	Malabsorption with or without steatorrhea

Table 20.7 Manifestations and consequences from vitamin D deficiency [22, 33, 42, 76]

Complaints and findings
Asymptomatic or silent, until marked deficiency occurs
Bone discomfort, pain and tenderness over long bones, ribs, and back
Pain is bilateral and symmetrical
Gait disturbance and impaired balance
Increased risk of falls
Generalized muscle weakness with poor endurance
Proximal muscle weakness and aches, bilateral and symmetrical
Low back pain
Hypocalcemia and features of tetany
Laboratory test abnormalities (calcium, phosphorus, alkaline phosphatase)
Osteomalacia, evidenced by radiographs or laboratory tests
Suggested, but not confirmed relationships
Immunomodulatory effects in: multiple sclerosis, type 1 diabetes, psoriasis, rheumatoid arthritis, inflammatory bowel disease, and periodontal disease
Susceptibility to infections
Association with depression and schizophrenia
Cardiovascular effects: hypertension, chronic heart failure
Uncontrolled cell growth and proliferation, with potential for cancer of the breast, colon, prostate, and others

consequent higher risk for falls (Table 20.7). When symptomatic, the levels are likely to be quite low. Data suggests that physical performance improves in adults aged 70–89 years with increase in 25(OH)D levels to over 20 ng/mL [62]. Osteomalacia in older adults commonly coexists with

Table 20.8 Comparison of osteoporosis and osteomalacia

Variable	Osteoporosis	Osteomalacia
Age of occurrence	Mostly older adults	Young and old
Causative factors	Age related; postmenopausal Secondary: endocrine, drugs, smoking, myeloma, inactivity	Vitamin D or phosphorus deficiency, renal tubular acidosis, hereditary forms
Pathology	Mineral to matrix ratio remain normal Bone mass reduced	Mineral to matrix ratio decreased Bone mass variable
Bone volume	Decreased	Normal to decreased
Serum calcium, phosphorus	Normal	Normal to low
Serum alkaline phosphates	Normal	Normal to increased
25 OH vitamin D level	Normal	Low
Definite diagnosis	DEXA	Bone biopsy
DEXA	Value below mean	variable
Radiologic features	Axial skeleton predominantly involved with thinning of bone and proneness to fracture	Symmetric pseudofractures or fragility fracture in appendicular skeleton

osteoporosis; however, the clinical manifestations and evaluation differ. While osteomalacia is a qualitative disorder from failure of mineralization of bone (and can result from causes other than vitamin D deficiency), osteoporosis is a quantitative disorder (Table 20.8) [63, 64].

Vitamin D and Extraskeletal Health

Mounting evidence suggests that vitamin D deficiency may be linked to several chronic disorders, including cancer and cardiovascular disease [65]. VDRs in brain, prostate, breast, colon, pancreas, heart, skin, and cells of immune system bind to the active $1,25(OH)_2D$ to regulate numerous genes that regulate cell proliferation, differentiation, apoptosis, and angiogenesis. Vitamin D controls genomic signaling pathways, with a potential role in diverse conditions such as psoriasis, diabetes mellitus type 1 and type 2 [1, 66, 67], rheumatoid arthritis, multiple sclerosis, hypertension [20, 68], heart disease including heart failure [69] and cancer (e.g., colon, breast, prostate). A link to neurocognitive functioning is claimed [70], as also an association with odds of frailty in older women [71]. Vitamin D replete states may reduce costs of care and confer survival benefits in critical illness [72]. Finally, a prospective study of the over 65 age group in NHANES III showed the risk of death to be 45% lower in those with 25(OH)D values over 40 ng/mL [12, 73], a finding supported by another meta-analysis [74] (Table 20.7).

Assessment of Vitamin D Status

The serum 25(OH)D level is the standard measure of vitamin D status. While $1,25(OH)_2D$ is the active form, the short circulating half life (4–6 h) provides labile and misleading levels. Laboratory measurements are not uniform or consistent. The radioimmunoassay and competitive protein binding assays for 25(OH)D are fraught with technical difficulties; the recent switch has been to LC-MS (liquid chromatography tandem mass spectroscopy) which measures both $25(OH)D_2$ and $25(OH)D_3$ quantitatively [3, 5, 6].

There exists lack of uniform agreement with the terms "normal, insufficient, and deficient" status. Vitamin D preferred (or desirable) blood level is 30–60 ng/mL (75–150 nmol/L), insufficiency is 21–29 ng/mL, and deficiency is <20 ng/mL; the normal range used by several laboratories is 20–100 ng/mL (50–250 nmol/L).

In osteomalacia, calcium and phosphorus may be normal to low and alkaline phosphatase values normal to high; all three assays are normal in osteoporosis (Table 20.8). A low score in the Mini Nutritional Assessment scale is associated with a greater likelihood of lower vitamin D values [60].

A bone biopsy in osteomalacia demonstrating lack of mineralization (or widening or osteoid) is diagnostic. DEXA scans, which are useful in osteoporosis, have no role in the evaluation of osteomalacia.

Vitamin D and Calcium Toxicity

Vitamin D intoxication (levels over 150 ng/mL) is rare but may be a result of intentional or inadvertent intake of large amounts for weeks. Recent data from a study in older women demonstrated that the annual administration of 500,000 U vitamin D was associated with an increase in hypercalcemia, falls and fractures [75] suggesting that large intermittent doses may be handled differently from smaller, regular long-term administration. Thus falls may occur with both deficiency [76] and intoxication. Vitamin D intoxication is associated with hypercalcemia, hyperphosphatemia, headache, nausea, vomiting, nephrolithiasis, vascular calcification, and pancreatitis [77]. Patients with chronic granulomatous disorders may be sensitive to the macrophage production of $1,25(OH)_2D$ and resultant hypercalcemia. Excessive sun exposure does not result in vitamin D toxicity, because of the protective mechanisms; a cut off in synthesis occurs through photodegradation of previtamin D_3 and vitamin D_3. It is claimed that toxicity is unlikely at vitamin D intake below 10,000 IU/day, with the Institute of Medicine (IOM) setting the upper limit at 4,000 IU/day [29].

Chronic use of calcium supplements has come under scrutiny. Hypercalcemia can lead to vascular and tissue calcification, with damage to heart, vessels, and kidneys [78]. The use of calcium (1,000 mg/day) and vitamin D (400 IU) by postmenopausal women was associated with a 17% increase in nephrolithiasis over 7 years in the Women's Health Initiative study. Overall, hypercalcemia rarely results from dietary calcium intake; it is most commonly associated with excessive use of supplements, primary hyperparathyroidism or malignancy. The high intake of calcium from supplements, but not foods, has received attention for adverse outcomes. NHANES data (2003–2006) indicate that 5% of women over 50 years consume calcium (from foods and supplements) that exceeds the upper limits by 300–365 mg daily [79, 80]. A systematic review suggested that vitamin D supplements in moderate to high doses may reduce cardiovascular risk, whereas calcium supplements seem to have minimal cardiovascular effects [80]. In summary, the biological plausibility for the benefit of vitamin D in prevention of cardiovascular disease and diabetes is not supported by consistent evidence; data from future research may provide clearer implications [81].

Prevention and Treatment Strategies

Prevention and treatment guidelines have been recently released in USA [29] and Canada [33]. The IOM US report based on evidence from observational studies suggests a level of 20 ng/mL as acceptable to protect the majority against adverse outcomes. The IOM recommendations for daily requirements differ with age groups; for adults aged 51–70 years, the RDA is 600 IU/day for males and females; for those over 70 years it is 800 IU/day [29]. Calcium intake for the age group 51–70 years is 1,000 mg/day for males and 1,200 mg/day for females; for those over 70 years, it is 1,200 mg/day [29].

The Osteoporosis Canada guideline statement suggests that 25(OH)D levels be at least 30 ng/mL (75 nmol/L); the recommended intake of vitamin D for high-risk and older adults is 800–2,000 IU daily, with consideration for higher doses. In individuals being treated with medications for osteoporosis, a measure of vitamin D status is recommended after 3–4 months of adequate supplementation; doses up to 2,000 IU are regarded as safe and do not require monitoring [33].

A common approach correct vitamin D deficiency is to administer 50,000 IU capsules of vitamin D_2 weekly for 4–8 weeks and monthly thereafter [1–5] and levels repeated in 3 months. An alternate option is 1,000–2,000 IU/day of vitamin D_2 or D_3. Intermittent doses may be metabolized differently from daily doses [5, 75]. Cutaneous exposure to sunlight or artificial UV-B such as a tanning bed is an option. Exposure to direct sunlight is helpful, with darker skinned people requiring longer exposure. Patients with intestinal malabsorption, mild to moderate hepatic dysfunction, and those on anticonvulsants or corticosteroids may benefit from higher doses of 1,000 IU/day vitamin D_3 or 50,000 IU every 2 weeks;

those with chronic kidney disease may require analogues of vitamin D, such as calcitriol or paricalcitriol [6, 7, 22, 82]. Hypovitaminosis D was corrected by daily administration of 2,000 IU D_3 for 6 months in most but not all older veterans in a recent study; the regimen appeared safe [83].

More recently, the interaction between calcium and vitamin D has received more emphasis. High calcium intake appears to increase the half life of 25(OH)D [84]. Trials suggest better outcomes in lowering fracture risk with vitamin D and calcium combined than vitamin D or calcium alone [84].

Key Points

- Vitamin D deficiency is extremely common in all ages, in all geographic zones, and frequently affects the geriatric population. Providers must identify the ones prone to deficiency [85].
- The vulnerability of older patients results from impaired dermal synthesis of the vitamin, lack of exposure to sunlight, and inadequate consumption of the vitamin in diet.
- Geriatric individuals at risk and the ones who present with symptoms require testing for vitamin D status
- Manifestations vary from being asymptomatic to presentation with muscle and bone pains.
- Gait and balance disorders are common, predisposing to falls.
- Diagnosis of vitamin D deficiency is easily confirmed through a blood test for 25(OH)D.
- The relationship of vitamin D status to several chronic disorders has been raised, but awaits confirmation through further research.
- Prevention and management are easy and inexpensive; calcium is a required supplement with vitamin D.
- The preferred form of calcium is through diet (dairy products) rather than supplements.
- Vitamin D is best administered in smaller doses regularly rather than large intermittent doses.

References

1. Holick MF. Vitamin D deficiency. N Eng J Med. 2007;357:266–81.
2. Holick MF. The vitamin D deficiency pandemic and consequences for nonskeletal health: mechanisms of action. Mol Aspects Med. 2008;29(6):361–8.
3. Holick MF. Vitamin D status: measurement, interpretation and clinical application. Ann Epidemiol. 2009;19(2):73–8.
4. Holick MF, Chen TC. Vitamin D deficiency: a worldwide problem with health consequences. Am J Clin Nutr. 2008;87(Suppl):1080s–6.
5. Rosen CJ. Vitamin D insufficiency. N Eng J Med. 2011;364:248–54.
6. Kennel KA, Drake MT, Hurley DL. Vitamin D deficiency in adults: when to test and how to treat? Mayo Clin Proc. 2010;85(8):752–8.
7. Thacher TD, Clarke BL. Vitamin D insufficiency. Mayo Clin Proc. 2011;86(1):50–60.
8. Holick MF, Siris ES, Binkeley N, et al. Prevalence of vitamin D inadequacy among North American postmenopausal women receiving osteoporosis therapy. J Clin Endocrinol Metab. 2005;90:3215–24.
9. Lyman D. Undiagnosed vitamin D deficiency in the hospitalized patient. Am Fam Physician. 2005;71(2):299–304.
10. Ginde AA, Liu MC, Camargo Jr CA. Demographic differences and trends of vitamin D insufficiency in the US population, 1988–2004. Arch Intern Med. 2009;169:626–32.
11. Forrest KY, Stuhldreher WL. Prevalence and correlates of vitamin D deficiency in US adults. Nutr Res. 2011;31(1):48–54.
12. Batieha A, Khade Y, Jaddou H, et al. Vitamin D status in Jordan: dress style and gender discrepancies. Ann Nutr Metab. 2011;58(1):10–8.
13. Bischoff-Ferrari HA, Giovannucci E, Willett WC, et al. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. Am J Clin Nutr. 2006;84:18–28.
14. Gordon CM, Depeter KC, Feldman HA, et al. Prevalence of vitamin D deficiency among healthy adolescents. Arch Pediatr Adolesc Med. 2004;158:531–7.
15. Sullivan SS, Rosen CJ, Halteman WA, et al. Adolescent girls in Maine at risk for vitamin D insufficiency. J Am Diet Assoc. 2005;105:971–4.
16. Vieth R, Bischoff-Ferrari H, Boucher BJ, et al. The urgent need to recommend an intake of vitamin D that is effective. Am J Clin Nutr. 2007;85(3):649–50.
17. Plotnikoff GA, Quigley JM. Prevalence of severe hypovitaminosis D in patients with persistent, nonspecific musculoskeletal pain. Mayo Clin Proc. 2003;78(12):1463–70.
18. Arteh J, Narra S, Nair S. Prevalence of vitamin D deficiency in chronic liver disease. Dig Dis Sci. 2010;55(9):2624–8.
19. Holick MF. Vitamin D and sunlight: strategies for cancer prevention and other health benefits. Clin J Am Soc Nephrol. 2008;3(5):1548–54.
20. Holick MF. Vitamin D: important for prevention of osteoporosis, cardiovascular heart disease, Type -1 diabetes, autoimmune diseases and some cancers. South Med J. 2005;98(10):1024–7.
21. Tsiaras WG, Weinstock MA. Factors influencing vitamin D status. Acta Derm Venereol. 2011;91(2):115–24.
22. Holick MF. High prevalence of vitamin D inadequacy and implications for health. Mayo Clin Proc. 2006;81(3):353–73.
23. Oudshoorn C. Ageing and vitamin D deficiency: effects on calcium homeostasis and considerations for vitamin D supplementation. Br J Nutr. 2009;101(11):1597–606.
24. Steingrimsdottir L, Gunnarasson O, Indridarson OS, et al. Relationship between serum parathyroid hormone levels, vitamin D insufficiency and calcium intake. JAMA. 2005;294:2336–41.
25. Moe SM. Disorders of calcium, phosphorus, and magnesium. Am J Kidney Dis. 2005;45(1):213–8.
26. Fleet JC, Schoch RD. Molecular mechanisms for regulation of intestinal calcium absorption by vitamin D and other factors. Crit Rev Clin Lab Sci. 2010;47(4):181–9.
27. Bailey RL, Dodd KW, Goldman JA, et al. Estimation of total usual calcium and vitamin D intakes in the United States. J Nutr. 2010;140:817–22.
28. Looker AC, Pfeiffer CM, Lacher DA, et al. Serum 25-hydroxyvitamin D status of the US population: 1988–1994 compared with 2000–2004. Am J Clin Nutr. 2008;88:1519–27.
29. IOM report on calcium and vitamin D. Washington, DC: Institute of Medicine; 2010. http://www.iom..edu/Reports/2010/Dietary-Reference-Intakes-for-calcium-and-vitamin-D/. Accessed 5 Nov 2011.
30. Ervin RB, Wang C-Y, Wright JD, Kennedy-Stephenson J. Dietary intake of selected minerals for the United States population: 1999–2000. Advance data from vital and health statistics, number 341. Hyattsville, MD: National Center for Health Statistics; 2004.
31. Heaney RP, Recker RR, Stegman MR, Moy AJ. Calcium absorption in women: relationships to calcium intake, estrogen status, and age. J Bone Miner Res. 1989;4:469–75.

32. Committee to Review Dietary Reference Intakes for Vitamin D and Calcium, Food and Nutrition Board, Institute of Medicine, Dietary reference intakes for calcium and vitamin D. Washington, DC: National Academy Press; 2010.
33. Hanley DA, Cranney A, James G, et al. Vitamin D in adult health an disease: a review and guideline statement from osteoporosis Canada. CMAJ. 2010;182(12):1315–9.
34. Devine A, Wilson SG, Dick IM, et al. Effects of vitamin D metabolites of intestinal calcium absorption and bone turnover in elderly women. Am J Clin Nutr. 2002;75:283–8.
35. Nattiv A. Stress fractures and bone health in track and field athletes. J Sci Med Sport. 2000;3:268–79.
36. Wilt TJ, Shaukat A, Shamliyan T, et al. Lactose intolerance and health. Evid Rep Technol Assess. 2010;192:1–410.
37. Weaver CM. Should dairy be recommended as part of a healthy vegetarian diet? Point. Am J Clin Nutr. 2009;89(5):1634S–7.
38. Kerstetter JE, O'Brien KO, Caseria DM, et al. The impact of dietary protein on calcium absorption and kinetic measures of bone turnover in women. J Clin Endocrinol Metab. 2005;90:26–31.
39. Ashwell M, Stone EM, Stolte H, et al. UK Food Standards Agency Workshop Report: an investigation of the relative contributions of diet and sunlight to vitamin D status. Br J Nutr. 2010;104(4): 603–11.
40. Holden JM, Lemar LE. Assessing vitamin D contents in foods and supplements: challenges and needs. Am J Clin Nutr. 2008; 88(Suppl):551s–3.
41. Holick MF. Vitamin D. In: Shils ME, Shike M, Ross AC, et al., editors. modern nutrition in health and disease. 10th ed. Philadelphia: Lippincott Williams & Wilkins; 2006.
42. Grant WB, Holick MF. Benefits and requirements of vitamin D for optimal health: a review. Altern Med Rev. 2005;10(2):94–111.
43. Millen AE, Wactawski-Wende J, Pettinger M, et al. Predictors of serum 25-hydroxyvitamin D concentrations among postmenopausal women: the Women's Health Initiative Calcium plus Vitamin D clinical trial. Am J Clin Nutr. 2010;91(5):1324–35.
44. Calvo MS, Whiting SJ, Barton CN. Vitamin D fortification in the United States and Canada: current status and data needs. Am J Clin Nutr. 2004;80:1710S–6.
45. Byrdwell WC, DeVries J, Exler J, et al. Analyzing vitamin D in foods and supplements: methodologic challenges. Am J Clin Nutr. 2008;88:554S–7.
46. International Agency for Research on Cancer Working Group on Ultraviolet (UV) Light and Skin Cancer. The association of use of sunbeds with cutaneous malignant melanoma and other skin cancers: a systematic review. Int J Cancer. 2006;120:1116–22.
47. American Academy of Dermatology. Position statement on vitamin D. November 1; 2008.
48. Wolpowitz D, Gilchrest BA. The vitamin D questions: how much do you need and how should you get it? J Am Acad Dermatol. 2006;54:301–17.
49. Bischoff-Ferrari HA, Staehelin HB. Importance of vitamin D and calcium at older age. Int J Vitam Nutr Res. 2008;78(6):286–92.
50. Brown AJ. Therapeutic uses of vitamin D analogues. Am J Kidney Dis. 2001;38 Suppl 5:S3–19.
51. U.S. Department of Agriculture. USDA nutrient database for standard reference, Release 24;2011. http://www.nal.usda.gov/fnic/foodcomp. Accessed 26 May 2012.
52. Straub DA. Calcium supplementation in clinical practice: a review of forms, doses, and indications. Nutr Clin Pract. 2007;22: 286–96.
53. Quesada Gómez JM, Blanch Rubió J, Díaz Curiel M, Díez Pérez A. Calcium citrate and vitamin D in the treatment of osteoporosis. Clin Drug Investig. 2011;31(5):285–98.
54. Stechschulte SA, Kirsner RS, Federman DG. Vitamin D: bone and beyond, rationale and recommendations for supplementation. Am J Med. 2009;122:793–802.
55. Javorsky BR, Maybee N, Padia SH, Dalkin AC. Vitamin D deficiency in gastrointestinal disease. Pract Gastroenterol. 2006;3:52–72.
56. Katz S, Weinerman S. Osteoporosis and gastrointestinal disease. Gastroenterol Hepatol. 2010;6(8):506–17.
57. Slater GH, Ren CJ, Siegel N, et al. Serum fat-soluble vitamin deficiency and abnormal calcium metabolism after malabsorptive bariatric surgery. J Gastrointest Surg. 2004;8(1):48–55; discussion 54–5.
58. Abreu MT, Kantorovich V, Vasiliauskas EA, et al. Measurement of vitamin D levels in inflammatory bowel disease patients reveals a subset of Crohn's disease patients with elevated 1,25-dihydroxyvitamin D and low bone mineral density. Gut. 2004;53(8):1129–36.
59. Williams SE. Metabolic bone disease in the bariatric surgery patient. J Obesity. 2011;2011:634614.
60. Formiga F, Ferrer A, Almeda J, et al. Utility of geriatric assessment tools to identify 85 years old subjects with vitamin D deficiency. J Nutr Health Aging. 2011;15(2):110–4.
61. Aarts E, van Groningen L, Horst R, et al. Vitamin absorption: consequences of gastric bypass surgery. Eur J Endocrinol. 2011;164(5):827–32.
62. Houston DK, Tooze JA, Hausman DB, et al. Change in 25-hydroxyvitamin D and physical performance in older adults. J Gerontol A Biol Sci Med Sci. 2011;66(4):430–6.
63. Van den bergh JP, Bours SP, van Geel TA, Geusens PP. Optimal use of vitamin D when treating osteoporosis. Curr Osteoporos Rep. 2011;9(1):36–42.
64. Papaioannou A, Morin S, Cheung AM, et al. 2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: summary. CMAJ. 2010;182(17):1864–73.
65. Chapman IM. Nutritional disorders in the elderly. Med Clin North Am. 2006;90:887–907.
66. Harris SS. Does vitamin D deficiency contribute to increased rates of cardiovascular disease and type 2 diabetes in African Americans? Am J Clin Nutr. 2011;93(5):1175S–8.
67. Cavalier E, Delanaye P, Souberbuelle JC, et al. Vitamin D and type 2 diabetes mellitus: where do we stand? Diabetes Metab. 2011; 37(4):265–72.
68. Bhandan SK, Pashayan S, Liu IL, et al. 25-Hydroxyvitamin D levels and hypertension rates. J Clin Hypertens. 2011;13(3):170–7.
69. Agarwal M, Phan A, Willix Jr R, et al. Is vitamin D deficiency associated with heart failure:? A review of current evidence. J Cardiovasc Pharmacol Ther. 2011;16(3–4):354–63.
70. Nimitphong H, Holick MF. Vitamin D, neurocognitive functioning and immunocompetence. Curr Opin Clin Nutr Metab Care. 2011;14(1):7–14.
71. Ensrud KE, Ewing SK, Fredman L, et al. Circulating 25hydroxy vitamin D levels and frailty status in older women. J Clin Endocrinol Metab. 2010;95(12):5210–2.
72. McKinney JD, Bailey BA, Garett LK, et al. Relationship between vitamin D status and ICU outcomes in veterans. J Am Med Dir Assoc. 2011;12(3):208–11.
73. Kendrick J, Targher G, Smits G, Chonchol M. 25-Hydroxyvitamin D deficiency is independently associated with cardiovascular disease in the Third National Health and Nutrition Examination Survey. Atherosclerosis. 2009;205(1):255–60.
74. Aurier P, Gandini S. Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials. Arch Intern Med. 2007;167:1730–7.
75. Sanders KM, Stuart AL, Williamson EJ, et al. Annual high dose oral vitamin D and falls and fractures in older women. A randomized controlled trial. JAMA. 2010;202:1815–22.
76. Dharmarajan TS, Akula M, Kuppachi S, Norkus EP. Vitamin D deficiency in community older adults with falls of gait imbalance: an under-recognized problem in the inner city. J Nutr Elder. 2005;25(1):7–19.
77. Heaney RP, Vieth R, Hollis BW. Vitamin D efficacy and safety. Arch Intern Med. 2011;171(3):266.

78. Reid IR, Bolland MJ, Grey A. Does calcium supplementation increase cardiovascular risk? Clin Endocrinol (Oxf). 2010;73(6):689–95.
79. Curhan GC, Willett WC, Speizer FE, et al. Comparison of dietary calcium with supplemental calcium and other nutrients as factors affecting the risk for kidney stones in women. Ann Intern Med. 1997;126(7):497–504.
80. Wang L, Manson JE, Song Y, Sesso HD. Systematic review: vitamin D and calcium supplementation in prevention of cardiovascular events. Ann Intern Med. 2010;152(5):315–23.
81. Shapses SA, Manson JE. Vitamin D and prevention of cardiovascular disease and diabetes. Why the evidence falls short. JAMA. 2011;305:2565–6.
82. Chu MP, Alagiakrishnan K, Sadowski C. The cure of ageing: vitamin D-magic or myth? Postgrad Med J. 2010;86(1020):608–16.
83. Cherniack LP, Florez HJ, Hollis BW, et al. The response of elderly veterans to daily vitamin D3 supplementation of 2000 IU: a pilot efficacy study. J Am Geriatr Soc. 2011;59:286–90.
84. Lips P. Interaction between vitamin D and calcium. Scand J Clin Lab Inv Suppl. 2012;243:60–4.
85. Cutillas-Marco E, Fuertes-Prosper A, Grant WB, et al. Vitamin D deficiency in South Europe: effect of smoking and aging. Photodermatol Photoimmunol Photomed. 2012;28(3):159–61.

Dietary Fiber in Health and Disease

21

C.S. Pitchumoni and Fisseha Y. Ghidey

Introduction

Based on epidemiologic data gathered from Afro-Asian countries, Burkitt and colleagues postulated that the high incidence of colon cancer, diverticulosis, irritable bowel syndrome, hemorrhoids, atherosclerosis, coronary heart disease, diabetes, obesity, hyperlipidemia, gallstones, hiatal hernia, and varicose veins in the western world are secondary to prolonged dietary fiber (DF) deprivation [1]. Currently, the general belief is that fiber is not the sole basis for the pathogenesis of these diverse disorders. However, there is general acceptance that DF is an essential dietary nutrient that cannot be designated as roughage. The United States Senate report of 1977, in a landmark publication on dietary goals, first recommended a change in the diet [2]. An awareness since created in the literature has not increased fiber intake to an acceptable level.

Definition: Plant Fiber and Dietary Fiber

Dietary fiber was originally defined as the edible component of plants resistant to digestion and absorption by humans in the small intestine, with complete or partial fermentation in the large intestines. The current definition by the US department of Agriculture includes functional fiber sources: polysaccharides, oligosaccharides, lignins, and associated substances [3]. DF is fermented by the colonic bacteria or excreted in the stool unchanged. Traditionally, the categorization of DF as water soluble or insoluble has stood the test of time [4].

Types of DF

1. Insoluble fiber (IF)
   (a) *Cellulose* is a polymer of glucose linked by beta 1,4 bonds and is the basic and most abundant structural material of the plant cell wall. Cellulose differs from starch, also a polysaccharide, in that it is not digested in the human small intestine
   (b) *Hemicelluloses* are non-cellulose polysaccharides, which form the cell wall matrix, and are mostly the branched polymers of pentose and hexose sugars (xylose, arabinose, mannose, galactose, and uronic acid derivatives). These are insoluble in water, but soluble in alkaline medium.
   (c) *Lignins* are non-carbohydrate polymers of aromatic alcohols and present in the encrusting substance of the mature plant cell wall, along with cellulose. As the plant matures, the lignin content increases with increasing rigidity.
   The main sources for cellulose and hemicelluloses are bran products and whole wheat, while for lignins, they are cereal grains and potatoes.
2. *Soluble fiber* (*SF*) holds water and forms gels in the digestive tract.
   (a) *Pectins* are complex mixtures of colloidal polysaccharides which form the cell wall matrix and bind adjacent cell walls.
   (b) *Gums* are exudates at the sites of injury to plants (gum arabic, gum karaya, sterculia urens, gum tragacanth) and are water-soluble polysaccharides.
   (c) *Mucilages* are polysaccharides synthesized by plant cells which prevent the desiccation of the seed endosperm.
   (d) *β-Glucans* are polymers composed of β linked glucose units, found mostly in barley grain. Other sources of β-glucans include oats, mushrooms, and yeast [5–8].

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Several studies demonstrate a beneficial effect for β-glucan rich foods on serum cholesterol levels, glycemic control, infection, and cancer prevention [9]. Higher doses of β-glucans also modulate appetite by modifying peptide YY, GLP-1, CCK, and ghrelin levels in overweight adults [10]. Peptide YY is a member of the pancreatic polypeptide family synthesized and released from the endocrine L-cells of ileum, colon, and rectum in response to food intake. Consumption of β-glucan enriched bread reduces hunger and promotes early satiety [11, 12]. β-Glucans have also been associated with lower and improved plasma cholesterol level and decreased glycemic index [13–16].

Whole grain foods, cooked dry beans, vegetables, fruits, nuts, and peas are plant-based sources of high DF content [17]. Oat bran, barley, legumes, fruits (apples, oranges, apricots), and vegetables (carrots, brussel sprouts) are rich sources of SF. The commercial sources of pectin are citrus peels and apple residues after juice extraction. Certain sea weeds and seeds (agar, red algae, algin derivatives, brown algae, and carrageenan) are sources for gums. Gums are frequently used as food additives because they form viscous solutions preventing aggregation of the small particles of the dispersed phase. They aid in keeping solids dispersed in chocolate milk and reduce crystal growth in ice cream. Examples include flax seeds and psyllium seeds (Ispaghula).

The vegetable sources of fiber contain a mixture of soluble and insoluble fibers in various concentrations. Bran is the husk of cereal grains. Commercially available fiber supplements are derived from plant sources such as psyllium (Metamucil, Effersyllium) or semi-synthetic such as methyl cellulose or synthetic, such as calcium polycarbophil.

Whole grains include the entire grain seed termed the kernel. Refined grains are milled to remove the bran and germ from the grain. This is done to give grains a finer texture and improve their shelf life, but in the process there is removal of dietary fiber, iron, and several B vitamins. Enriched grains are grain products fortified with B vitamins (thiamin, riboflavin, niacin, folic acid) and iron. Most refined grain products are enriched [17]. Clinical uses of high fiber diet are tabulated in Table 21.1.

Physiological Properties of Dietary Fiber

Factors which determine physiological properties include ability to (a) retain water (b) form gel, increase viscosity, thereby increasing the bulk, (c) exchange cations (d) form products of bacterial degradation in the large intestine and (e) modulate immunity.

The *water holding capacity* is greater for soluble fibers such as pectins, gums, and mucilages than for insoluble fibers such as cellulose, hemicellulose, and lignins.

The *gel forming capacity* determines the viscosity of the luminal contents in the intestine. Water-soluble fibers are better gel formers than water-insoluble fibers. Gels act more like solids than liquids in the lumen.

Promotion of cytokine production (TNF-α and IL-1-β) is a property of β-glucans. The cytokines bind to glucan receptors in macrophage and neutrophils that form part of the non-specific immune system. β-Glucans suppress secretion of superoxide anion and hydrogen peroxide, increases activity of natural killer cells and lymphokine activated killer cells [18, 19].

Providing an energy source for colonic epithelial cells is another important physiological property. Short chain fatty acids (SCFAs) are partially absorbed into the circulation mediating favorable changes in glucose and lipid metabolism [20–22].

The Physiologic Responses

These include (a) alterations in intestinal motility, (b) reduction of glycemic response and glycemic index, and (c) possible interference with nutrient absorption. Glycemic index describes the manner in which foods affect blood glucose

Table 21.1 Components and properties of dietary fiber chemical component predominant source effects

Water-insoluble		
Cellulose	All plant cell walls	No effect on gastric emptying
	Wheat bran, peels of apples, and pears	No effect on glucose absorption
Hemicelluloses	Whole grains	Decreases colonic transit time
	All woody plant tissues	Moderate binding of bile acids
Lignins	Cereal grains, potatoes	No effect on cholesterol
		Increase stool bulk and frequency of bowel movements
Water-soluble		
Pectins	Bananas, oranges, and apples	Delay gastric emptying
		Improve in glucose tolerance
Gums	Oatmeal, legumes (guar, locust bean)	Normalize colonic transit time
		Bind bile acids
		Lower cholesterol
Mucillages	Psyllium, seeds, sea weed	Increase stool bulk and frequency of bowel movements
β-Glucan	Barley, oats	Lowers cholesterol, reduces body weight, favorable alteration of serum glucose/insulin kinetics

Table 21.2 Proposed clinical benefits for a high fiber diet

Disorders	Mechanism	Effects
Metabolic syndrome [33–35]		
Hypercholesterolemia	Increased excretion of fecal fat, neutral steroids, and fecal bile acids with compensatory bile acid synthesis from cholesterol	Selective lowering of LDL
Glucose intolerance	Slow gastric emptying Increased viscous gel formation in the intestinal lumen Stimulation of glycolysis and attenuation of gluconeogenesis by SCFA	Decreases glucose absorption
Obesity	Early satiety Decreased gastric emptying Decreased absorption of food Increased insulin sensitivity	Weight reduction
Colonic [36–39]		
Constipation	Increased bulk and fluidity of feces Shortened intestinal transit time	Promotes regular bowel movement
Diverticulosis	Lowers segmental contraction in sigmoid colon	Prevents hypertrophy of muscularis muscle and protrusion of pouches of mucosa through muscularis
Colon cancer and polyps	Reduces exposure time of colonic mucosa to carcinogens Dilutes carcinogens because of increased water content	

Table 21.3 Physiologic properties and clinical responses of fiber

1	2	3	4
Water holding	Gel formation	Bile acid sequestration	Colonic fermentation
Softens stool	Increases viscosity	Loss of bile acid in the stool	Increases bulk and produces intestinal gas and SCFA
↓	↓	↓	↓
Reduces intracolonic pressures Reduces the need to strain	Reduces glycemic index Delays gastric emptying	Promotes production of bile acid from cholesterol	SCFA is absorbed Inhibits cholesterol synthesis
↓	↓	↓	↓
Prevents			
Constipation	Improves glycemic control	Reduces serum cholesterol	Prevents constipation
Hemorrhoids	Early satiety		
Diverticulosis Colon cancer			

level in the postprandial period, controlled for the carbohydrate. The glycemic load, the arithmetic product of the glycemic index, and the amount of carbohydrate affect the postprandial sugar levels with different dietary items [23]. Highly processed grains have a high glycemic index (e.g., white rice) in comparison with minimally or unprocessed grains, fruits, legumes, and non-starchy vegetables which have a low glycemic index [24].

The physiological properties of DF stated above and the physiological responses mentioned here are determined by a series of alterations of fiber containing food taking place during the transit down the intestine (Table 21.2). The clinical benefits and potential side effects of DF result from interactions involving fiber at different locations of the gastrointestinal tract, as discussed below (Table 21.3).

Alterations in Gastrointestinal Function

A high fiber diet requires chewing, a process that stimulates saliva to neutralize regurgitated acid in the esophagus, and provides a potential therapeutic effect in GERD, besides promoting dental hygiene. The amount of dietary fiber influences meal size and caloric intake. Fiber-rich foods are not calorie dense and cause early satiety, a property beneficial in weight reduction.

1. Stomach: The action of DF on gastric emptying is variable. Soluble fiber increases the viscosity of gastric contents and delays emptying, while water-insoluble fiber either has no effect or enhances gastric emptying. The form of food is also important. Cooked whole rice grains leave the stomach slower when ground [25]. The rate of gastric emptying affects nutrient absorption. The blunting

of glucose absorption (glycemic index) from a fiber-rich carbohydrate meal, rich in gums, is partly due to its effect on gastric emptying.

2. Small intestine: DF may reduce the speed of absorption of nutrients by affecting the meal solubility in the aqueous phase. Digestion of foods containing soluble fiber with high viscosity is slower than foods containing insoluble fibers [26].
   (a) Lignins and gums bind bile acids in the intestinal lumen. The soluble fiber in oat bran binds phospholipids, reducing their availability in the aqueous phase. The absorption of lipids is thus reduced and loss of bile acids is increased.
   (b) As a result of fiber containing viscous polysaccharides, the viscosity of intestinal contents increases decreasing the rate but not the total amount of nutrient absorption.
   (c) The water-insoluble fiber increases peristaltic activity and decreases intestinal transit time. Soluble dietary fiber has a variable effect on the transit time.
3. Large intestine
   (a) Undigested fiber increases fecal bulk and fluidity. Bacteria in the large intestine ferment soluble fiber. Cereal fiber is most effective in increasing fecal bulk because this fiber is incompletely degraded. Fiber from fruits and vegetables adds to fecal bulk, but is degraded and fermented to a greater degree by colonic microflora, with the formation of SCFAs.
   (b) Prebiotics are defined as non-digestible food ingredients that beneficially affect the host by selectively stimulating the activity of bacteria in the colon improving host health [27]. Examples of probiotics include oligosaccharides such as fructo-oligosaccharides and galacto-oligosaccharides. The role of prebiotics is discussed in another chapter.
   (c) Recent evidence indicates that soluble fiber may be protective against Crohn's disease by preventing *Escherichia coli* translocation. Soluble plant fiber in plantains and broccoli significantly blocked *E. coli* translocation across specialized microfold (M) cells of the gut epithelium and Peyer's patches. Further evidence strengthens the immunoregulatory properties of DF [28].

Recommendations and Actual Consumption of DF

The current recommendation for diabetic patients is 25–50 g of fiber per day [29]. The average intake of DF for most Americans is 15 g/day [30] which is far lower than the recommended intake of 14 g per 1,000 kcal according to Institute of Medicine based on data on the relationship of fiber consumption and CHD risk [31]. According to Nutrition Facts Panel, the recommended amount is 25 g in a 2,000 kcal diet. Any food is considered a "good source of fiber" if it has 10% of the recommended amount and an "excellent source of fiber" if it contains 20% of the recommended amount, which translates to 2.5 and 5 g per serving, respectively [4]. Dietary sources of fiber are listed in Table 21.4, with foods of low fiber content in Table 21.5.

Side Effects of DF

The most frequent problem encountered with a high fiber diet is poor acceptability and tolerance. The older adult not used to a high fiber diet may develop gaseousness, bloating, diffuse abdominal pain, and diarrhea. Tolerance improves if the quantity of fiber introduced to the diet initially is small and progressively increased. Due to difficulties encountered with chewing fiber-rich diets, older adults prefer fruit juices to fresh fruits. Overall, co-morbidities such as cognitive impairment, along with functional limitations such as oropharyngeal dysphagia, limit the intake of fiber-rich food in older adults.

Interference with mineral absorption—A concern raised based on in vitro experiments and short-term in vivo studies using large doses of a single source of DF is that a high-fiber diet could reduce absorption of trace elements in the elderly particularly in those on marginal intake of minerals. Most natural fiber sources such as whole grains, fruits, and vegetables are excellent sources of micronutrients. A well-chosen vegetarian diet consumed over time does not cause mineral deficiency. The position of the American Dietetic Association is that appropriately planned total vegetarian diets are healthy, nutritionally adequate, and may provide health benefits in certain diseases [32].

Pancreatic enzyme inhibition and exaggeration of steatorrhea by a high-fiber diet in patients with pancreatic exocrine insufficiency is theoretical. Case reports suggest that colonic volvulus is more frequent in populations on a high-fiber diet.

Key Points

- Dietary fiber (DF) is plant material in the diet resistant to digestion in the small intestine but can be digested to short chain fatty acids (SCFAs) in the large intestine.
- Based on solubility DF is categorized as soluble and insoluble.
- Soluble fiber includes pectins, gums, and mucilages. Dietary sources are oat bran, barley, legumes, fruits (apple pulp, oranges), and vegetables such as carrots.

Table 21.4 Sources of dietary fiber

Food	Standard portion size	Calories in standard portion	Dietary fiber in standard portion (g)
Beans (navy, pinto, black, kidney, white, great northern, lima), cooked	½ Cup	104–149	6.2–9.6
Bran ready-to-eat cereal (100%)	1/3 Cup (about 1 oz)	81	9.1
Split peas, lentils, chickpeas, or cowpeas, cooked	½ Cup	108–134	5.6–8.1
Artichoke, cooked	½ Cup hearts	45	7.2
Pear	1 Medium	103	5.5
Soybeans, mature, cooked	½ Cup	149	5.2
Plain rye wafer crackers	2 Wafers	73	5.0
Bran ready-to-eat cereals (various)	1/3 to ¾ cup (about 1 oz)	88–91	2.6–5.0
Asian pear	1 Small	51	4.4
Green peas, cooked	½ Cup	59–67	3.5–4.4
Whole-wheat English muffin	1 Muffin	134	4.4
Bulgur, cooked	½ Cup	76	4.1
Mixed vegetables, cooked	½ Cup	59	4.0
Raspberries	½ Cup	32	4.0
Sweet potato, baked in skin	1 Medium	103	3.8
Blackberries	½ Cup	31	3.8
Soybeans, green, cooked	½ Cup	127	3.8
Prunes, stewed	½ Cup	133	3.8
Shredded wheat ready-to-eat cereal	½ Cup (about 1 oz)	95–100	2.7–3.8
Figs, dried	¼ Cup	93	3.7
Apple, with skin	1 Small	77	3.6
Pumpkin, canned	½ Cup	42	3.6
Greens (spinach, collards, turnip greens), cooked	½ Cup	14–32	2.5–3.5
Almonds	1 oz	163	3.5
Sauerkraut, canned	½ Cup	22	3.4
Whole wheat spaghetti, cooked	½ Cup	87	3.1
Banana	1 Medium	105	3.1
Orange	1 Medium	62	3.1
Guava	1 Fruit	37	3.0
Potato, baked, with skin	1 Small	128	3.0
Oat bran muffin	1 Small	178	3.0
Pearled barley, cooked	½ Cup	97	3.0
Dates	¼ Cup	104	2.9
Winter squash, cooked	½ Cup	38	2.9
Parsnips, cooked	½ Cup	55	2.8
Tomato paste	¼ Cup	54	2.7
Broccoli, cooked	½ Cup	26–27	2.6–2.8
Okra, cooked from frozen	½ Cup	26	2.6

Source: Ref. [40]

- Insoluble fiber includes cellulose, hemicellulose, and lignins. Bran products, whole wheat cereal grains, and potatoes mainly with skin are rich sources of insoluble fiber.
- β-Glucans are polymers of β linked glucose units, found in oats, barley, mushrooms, and yeast.
- Physiological properties of DF are determined by their ability to retain water, form gel, increase viscosity, exchange cations, form products of bacterial degradation in the large intestine, and immune modulation.
- The physiologic responses are mainly altered gastrointestinal motility, effects on nutrient absorption, and metabolic responses such as glycemic control.
- Therapeutic effects of DF are mostly documented in hypercholesterolemia, glucose intolerance, obesity, and a variety of colonic disorders such as constipation, diverticular disease, colon cancer, polyps, and hemorrhoids.
- Potential side effects of DF include interference with mineral (nutrient) and drug absorption, poor tolerance

Table 21.5 Foods of low fiber content

Canned or cooked fruits without skins, seeds or membranes
Canned or well-cooked vegetables without seeds, hulls or skin; e.g., carrots, string beans, peppers
Crackers, cookies
Cereals with no more than 1 g of dietary fiber per serving
Eggs
Fats, oils, and dressings
French toast
Milk/yogurt/cheese
Muffins, waffles
Noodles or macaroni
Plain pasta
Raw fruit without skin or membranes
Smooth (creamy) peanut butter-upto 2 tablespoons a day
Strained fruit and vegetable juice
Tender cuts of meat, poultry, and fish
Tofu
White bread
White rice

Abstracted and modified from ref. [41]

especially in the elderly because of gaseousness, bloating, diffuse abdominal discomfort, and diarrhea.

- Daily requirement of DF is 38 and 25 g for adult men and women respectively.

References

1. Burkitt DP, Walker ARP, Painter NS. Effect of dietary fiber on stools and transit times and its role in the causation of disease. Lancet. 1972;2:1408–11.
2. US senate report: dietary goals for the United States. Report of the select committee on nutrition and human needs. Washington, DC: US Government Printing Office; 1977.
3. AACC. The definition of dietary fiber. AACC report. CFW. 2001;46:112–26.
4. Raninen K, Lappi J, Mykkänen H, et al. Dietary fibers as immunoregulatory compounds in health and disease. Ann N Y Acad Sci. 2010;1190:70–85.
5. Arndt EA. Whole grain barley for today's health and wellness needs. CFW Res. 2006;51:20–2.
6. Pins JJ, Kaur H. A review of the effects of barley β-glucan on cardiovascular and diabetic risk. CFW Res. 2006;51:8–11.
7. Wood PJ. Cereal β-glucan in diet and health. J Cereal Sci. 2007;46:230–8.
8. Lazaridou A, Biliaderis CG. Molecular aspects of cereal β-glucan functionality: physical properties, technological applications and physiological effects. J Cereal Sci. 2007;46:101–8.
9. Kim SY, Song HJ, Lee YY, et al. Biomedical issues of dietary fiber β-glucan. J Korean Med Sci. 2006;21:781–9.
10. Beck EJ, Tapsell LC, Batterham MJ, Tosh SM, Huang XF. Increases in peptide Y-Y levels following oat β-glucan ingestion are dose-dependent in overweight adults. Nutr Res. 2009;29:705–9.
11. Karhunen LJ, Juvonen KR, Huotari A, et al. Effect of protein, fat, carbohydrate and fibre on gastrointestinal peptide release in humans. Regul Pept. 2008;149:70–8.
12. Vitaglione P, Lumaga RB, Stanzione A, et al. Beta-glucan-enriched bread reduces energy intake and modifies plasma ghrelin and peptide YY concentrations in the short term. Appetite. 2009;53:338–44.
13. Behall KM, Scholfield DJ, Hallfrisch J. Lipids significantly reduced by diets containing barley in moderately hypercholestrolemic men. J Am Coll Nutr. 2004;23:55–62.
14. Behall KM, Scholfield DJ, Hallfrisch J. Comparison of hormone and glucose responses of overweight women to barley and oats. J Am Coll Nutr. 2005;24:182–8.
15. Keenan JM, Goulson M, Shamliyam T, et al. The effects of concentrated barley β-glucan on blood lipids in a population of hypercholestrolemic men and women. Br J Nutr. 2007;97:1162–8.
16. Li J, Kaneko T, Qin LQ, et al. Effects of barley intake on glucose tolerance, lipid metabolism, and bowel function in women. Nutrition. 2003;19:926–9.
17. U.S. Department of Agriculture U.S. Department of Health and Human Services Dietary Guidelines for Americans; 2010. Accessed 30 March 2011. www.health.gov/dietaryguidelines/dga2010/dietaryguidelines2010.pdf. Accessed 12 May 2012.
18. Kupfahl C, Geginat G, Hof H. Lentinan has a stimulatory effect on innate and adaptive immunity against murine Listeria monocytogenes infection. Int Immunopharmacol. 2006;6:686–96.
19. Wakshull E, Brunke-Reese D, Lindermuth J, et al. PGG-glucan, a soluble beta-(1,3)-glucan, enhances the oxidative burst response, microbicidal activity, and activates an NF-kappa B-like factor in human PMN: evidence for a glycosphingolipid beta-(1,3)-glucan receptor. Immunopharmacology. 1999;41:89–107.
20. Slavin J. Why whole grains are protective: biological mechanisms. Proc Nutr Soc. 2003;62:129–34.
21. Topping DL, Clifton PM. Short chain fatty acids and human colonic function: roles of resistant starch and non-starch polysaccharides. Physiol Rev. 2001;81:1031–64.
22. Roy CC, Kien CL, Bouthillier L, et al. Short- chain fatty acids: ready for prime time? Nutr Clin Pract. 2006;21:639–40.
23. Monro JA, Shaw M. Glycemic impact, glycemic glucose equivalents, glycemic index, and glycemic load: definitions, distinctions, and implications. Am J Clin Nutr. 2008;87(1):237S–43.
24. Venn BJ, Green TJ. Glycemic index and glycemic load: measurement issues and their effect on diet-disease relationships. Eur J Clin Nutr. 2007;61 Suppl 1:S122–31.
25. Blackwood AD, Salter J, Dettmar PW, et al. Dietary fibre, physicochemical properties and their relationship to health. J R Soc Promot Health. 2000;120:242–7.
26. Dikeman CL, Fahey GC. Viscosity as related to dietary fiber: a review. Crit Rev Food Sci Nutr. 2006;46(8):649–63.
27. de Vrese M, Schrezenmeir J. Probiotics, prebiotics, and synbiotics. Adv Biochem Eng Biotechnol. 2008;111:1–66.
28. Roberts CL, Keita AV, Duncan SH, et al. Translocation of Crohn's disease *Escherichia coli* across M-cells. Contrasting effects of soluble plant fibers and emulsifiers. Gut. 2010;59:1331–9.
29. Anderson JW, Randles KM, Kendall CW, Jenkins DJ. Carbohydrate and fiber recommendations for individuals with diabetes: a quantitative assessment and meta-analysis of the evidence. J Am Coll Nutr. 2004;23:5–17.
30. Wright JD, Wang CY. Trends in intake of energy and macronutrients in adults from 1999–2000 through 2007–2008. NCHS Data Brief. 2010;1–8.
31. Institute of Medicine of The National Academies Press, Food and Nutrition Board, 2009. Consensus study. Dietary reference intakes for energy, carbohydrate, fiber, fatty acids, cholesterol, protein and amino acids.
32. Craig WJ, et al. Position paper of the American Dietetic Association: vegetarian diets. J Am Diet Assoc. 2009;109:1266–82.

33. Reyna NY, Cano C, Bermudez VJ, Medina MT, Souki AJ, Ambard M, et al. Sweeteners and beta-glucans improve metabolic and anthropometrics variables in well controlled type 2 diabetic patients. Am J Ther. 2003;10:438–43.
34. Jenkins AL, Jenkins DJ, Zdravkovic U, Wursch P, Vuksan V. Depression of the glycemic index by high levels of beta-glucan fiber in two functional foods tested in type 2 diabetes. Eur J Clin Nutr. 2002;56:622–8.
35. Khossousi PS, Binns C, Dhaliwal S, et al. The effect of a fibre supplement compared to a healthy diet on body composition, lipids, glucose, insulin and other metabolic syndrome risk factors in overweight and obese individuals. Br J Nutr. 2011;105:90–100.
36. Sturtzel B, Mikulits C, Gisinger C, Elmadfa I. Use of fiber instead of laxative treatment in a geriatric hospital to improve the wellbeing of seniors. J Nutr Health Aging. 2009;13(2):136–9.
37. Ravikoff JE, Korzenile JR. The role of fiber in diverticular disease. J Clin Gastroenterol. 2011;45:S7–11.
38. Strutzel B, Dietrich A, Wagner K-H, et al. The status of vitamins B6, B12, folate, and of homocysteine in geriatric home residents receiving laxatives or dietary fiber. J Nutr Health Aging. 2010;3:219–23.
39. Christina CD, Ruth HK, Elizabeth AS, et al. Dietary fiber and colorectal cancer risk: a nested case control study using food diaries. J Natl Cancer Inst. 2010;102:614–26.
40. U.S. Department of Agriculture, Agricultural Research Service, Nutrient Data Laboratory. 2009. USDA National Nutrient Database for Standard Reference, Release 22. Accessed 5 April 2011.
41. http://www.mayoclinic.com/health/low-fiber-diet/MY00744. Accessed 1 March 2011.

Healthy Diet for the Older Adult

22

Sirakarn Tejavanija and Sunil S. Jhangiani

Introduction

Globally, older adults make up a large percentage of the population, with the fastest growing segment in America being individuals age 85 and over [1]. While this can be attributed to improved access to health care, better socioeconomic conditions and advances in medical technologies, the fact remains that healthy longevity as defined by absence of a medical condition is not on the increase. Most of the older adults suffer at least one chronic condition by age 50 and many have multiple conditions [2], such as hypertension, osteoarthritis, diabetes, and heart disease [3]. Alterations due to chronic illnesses (influencing appetite and nutrient absorption), coupled with the physiological (Table 22.1) changes of aging [4–6] place the older adult at an increased risk for nutritional disorders, especially undernutrition.

Compounding this problem is the increased prevalence of overweight and obesity in the older adult with almost a third of over 60-year-old Americans having a body mass index (BMI) in the obese category [7]. This weight gain occurs mainly due to diminished energy expenditure relative to energy intake (Table 22.1). Studies also confirm that just a third of adults over age 60 engage in any type of regular exercise [8].

The nutritional status of the older adult can thus be compromised in two ways: undernutrition or overnutrition. Although, there are reports of the obesity survival paradox [9] in older adults, a recent analysis of 19 well-controlled studies that included individuals age 19–84 revealed that those with BMI measurements 30–34.9 had a 1.44 greater risk of dying than those who had a BMI 22.5–24.9 [10]. Obesity clearly places the older adult at increased risk for medical conditions that further compromise their health, mobility, and productivity. These changes that have been most dramatic over the last 2 decades have resulted in a profound shift in the practice of clinical nutrition. From a time when nutrition experts and policy makers were concerned more about undernutrition and its impact on health, we now face an epidemic of obesity that is devastating to the health and wellness of the older adult. Just four of ten noninstitutionalized older men or women in America assess their heath as excellent or very good [11]. In addition, studies in the United States and elsewhere have revealed that certain subgroups of the elderly, namely the poor, those with little education, minorities and at times women have diets that are more likely to be deficient in essential vitamins and minerals. Data from a recent "Older Americans 2010" [12] report reveal that in general, individuals aged 65 and over tend to meet diet quality standards for fruits, total grains, and meat and beans, however, the consumption of vegetables, whole grains, and milk remain below standards. In addition, SoFAAS, i.e. Solid Fats (pizza, cheeses, butter, sausage, etc.), Alcoholic beverages, and Added Sugars (soda, donuts, energy drinks, etc.) contribute a large percentage of the saturated fat, sodium, and calorie intake in the older adult. Early interventions with appropriate diet and lifestyle recommendations can delay and even prevent potential adverse outcomes in those segments of the older population who consume unhealthy diets.

Healthy Diet Recommendations

The body's needs for calories, essential vitamins, minerals, and even fluids fluctuate to keep pace with the physiological changes that accompany aging. Dietary requirements not only vary with age and from individual to individual, but change over the years. Counseling the older adult on a healthy diet can be viewed as "primary prevention" to promote health and prevent the development of nutritional disorders, or "secondary prevention" as part of a strategy against early

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Table 22.1 Physiologic changes in aging that affect nutritional status

Body systems	Physiologic changes	Nutrition-related consequences
Energy metabolism	Decreased basal metabolic rate Decreased energy expenditure from physical activity	Altered energy balance that leads to undernutrition or overnutrition
Body composition	Increased fat mass Progressive generalized loss of skeletal muscle mass, strength, and function, ("sarcopenia") [4] Progressive bone loss	Sequestration of vitamin D in the excess adipose tissue Osteoporosis
Oral cavity and Pharynx	Problems with swallowing Dry mouth (xerostomia) Poor dentition Loss of taste	Inappropriate or unhealthy food choices Lower nutrient intake
Endocrine system	Decreased estrogen, testosterone, and growth hormone levels Insulin resistance Decreased synthesis of Previtamin D_3 in the skin	Bone loss Glucose intolerance Risk of vitamin D deficiency
Gastrointestinal system	Reduced secretion of saliva and digestive enzymes Hypo or achlorhydria Slower peristalsis	Decreased bioavailability of nutrients Decreased vitamin B12 and iron absorption Constipation
Musculoskeletal system	Sarcopenia and osteoarthritis that may diminish mobility	Decreased energy expenditure relative to intake with weight gain
Renal system	Alterations in glomerular filtration rate (GFR), diluting and concentrating ability of the kidneys	Dehydration or fluid overload
Nervous system	Anorexia of aging [5] Blunted thirst regulation Sensory impairment i.e. taste alteration (dysgeusia) [6] Mood alterations, depression	Decreases food intake Dehydration Higher tendency to add salt or sugar to foods Tendency to overeat with resultant overweight state

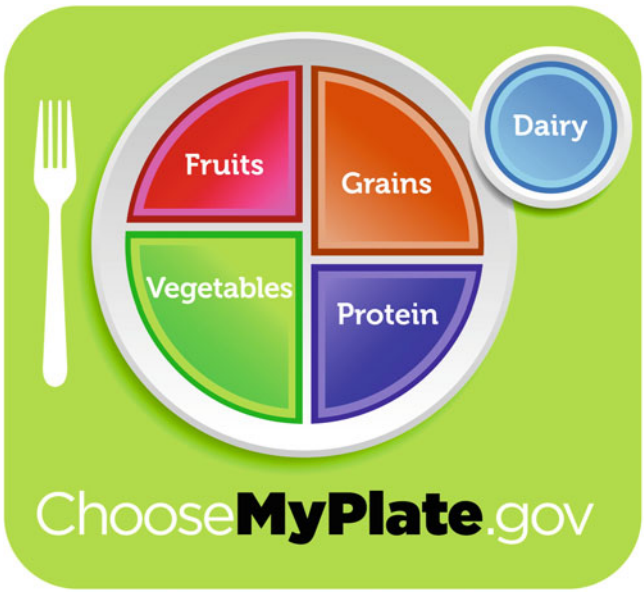

Fig. 22.1 My Plate Guide to Healthy Eating (Image courtesy of U.S. Department of Agriculture, www.choosemyplate.gov)

disease, or "tertiary prevention" to address nutritional-related complications from disease. In this section, we focus on general dietary recommendations for the older adult based on the 2010 dietary guidelines for Americans released in January 2011(www.dietaryguidelines.gov) [13], which encompass two overarching concepts for older adults (and all Americans); namely maintaining calorie balance to achieve and sustain healthy weight and a focus on consuming nutrient-dense foods and beverages. This is the first time that the U.S. government is directly calling on older adults who are overweight to not gain additional weight and to work toward healthy weight to reduce the risk of chronic disease and associated disabilities [13].

Current Dietary Guidelines

In terms of a graphic nutrition tool, the latest plate-shaped icon (Choose MyPlate.gov) released by the U.S. Department of Agriculture (USDA) in mid 2011 [14] is simple and easy to understand. The different sections on this icon (Fig. 22.1), designed to complement the 2010 dietary guidelines, demonstrate clearly the recommended food groups—with fruits and vegetables making up half the diet, with vegetables taking up a greater portion of the half. Grains and proteins (e.g., meat and fish) occupy the other half, with grains taking up a larger portion. A smaller adjacent circle highlights the importance of dairy products. The protein section includes foods from meat, poultry, seafood, beans and peas, eggs, processed soy products, nuts, and seeds. With an emphasis

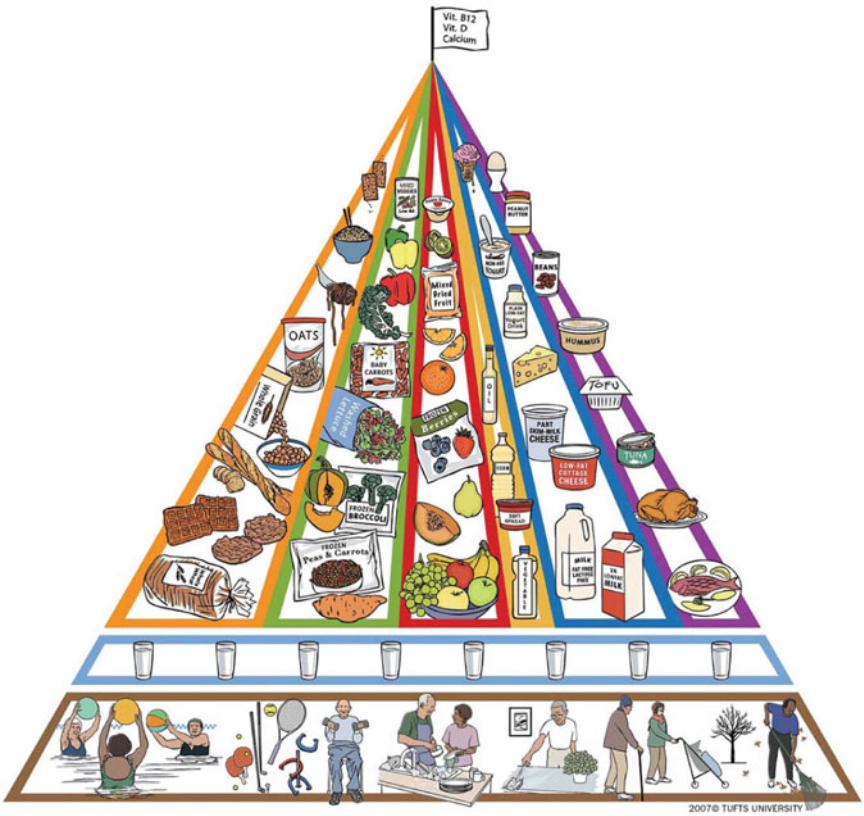

Fig. 22.2 *The Modified MyPyramid for Older Adults*. The food icons distributed throughout the Pyramid represent the good choices within each food category. The two-layered foundation solidifies the importance of hydration and physical activity. The flag at the top denotes that some older adults may need additional vitamin D, vitamin B12, and calcium (Copyright 2007 Tufts University. For full article see ref. [15])

on lean or low fat meats and poultry choices, the new guidelines call for a step up in fish/seafood (8 oz of cooked seafood per week) consumption. Beans and peas, nuts and seeds, and soy products can easily meet the protein requirements of vegetarians. Since oils provide essential nutrients they are represented in the USDA food patterns but are not listed as a separate food group. To understand the food group, the older adult is directed to the web site www.ChooseMyPlate.gov, designed around the icon. While the plate is easier to understand the components of a healthy diet for consumers of all ages and diverse backgrounds; also referenced is the *Modified MyPyramid for Older Adults* with the different food icons distributed through vertical bands on the pyramid representing variety, portions, and good choices within each category [15]. The two-layered foundation at the base represents the importance of fluids and physical activity and the flag atop the pyramid, emphasizes the importance of calcium, vitamin D, and vitamin B12 in older adults (Fig. 22.2).

Table 22.2 summarizes the 2010 healthful dietary recommendations for a representative older adult with prompts for good choices within each of the major food groups. Table 22.3 summarizes areas of special concern for the older adult [16, 17] such as fiber, fluids, and other nutrients covered in the latest 2010 dietary guidelines. Table 22.4 highlights potential strategies for food safety practices that the older adult would find easy to follow.

Special Considerations

Whole Grains

Whole grains and their products contain all naturally-occurring essential nutrients of the entire grain seed and include brown rice, wild rice, buckwheat, bulgur (cracked wheat), oatmeal, popcorn, millet, whole rye, etc. "Refined grains," on the other hand are whole grains that are milled to remove the bran and germ and in the process they become devoid of dietary fiber, iron, many B vitamins, and other essential micronutrients. Whole grains, therefore are better sources of fiber and other nutrients including selenium, potassium, and magnesium [16].

Recommended daily amount of total grain intake for men and women aged greater than 50 years old are 6 and 5 oz equivalents (servings), respectively [13]. At least 3 oz equivalents [14] should be from whole grains, with one ounce equivalent of grains being equal to 16 g of grains; 1 slice of bread; 1 cup of ready-to-eat cereal; ½ cup of cooked rice,

Table 22.2 Healthy diet for an older adult[a]

Food group	Daily recommended amounts	Good choices[b]
Grains	6 oz 3 oz from whole grains (50%)	Oatmeal, whole wheat pasta, brown bread, brown rice, bulgur, buckwheat, etc.
Vegetables	2.5 cups Raw or cooked; fresh, frozen or canned. Preferably dark green and orange Option: 100% vegetable juice	Broccoli, collard greens, carrots, butternut squash, sweet potatoes, pumpkin, lentils, tofu, eggplant, etc.
Fruits	Two cups Fresh, canned, frozen or dried Can be 100% juice	Apples, bananas, apricots, grapes, blueberries, kiwi, papaya, oranges, etc.
Dairy	3 cups of milk	Low or nonfat milk Foods made from milk: yogurt, cheeses (American or Cheddar) For lactose intolerance: milk alternatives from almonds, soy, rice, hazelnuts etc.
Meat and Beans	5 oz Most of it from fish, beans, peas, nuts, and seeds Bake, broil or grill	Fish rich in Omega-3's; salmon, trout, herring Lima beans, split peas, red kidney beans, pinto beans Chicken, turkey, eggs Lean cuts of beef, pork etc.
Oils and Fats[c]	Five teaspoons Prefer oils over solid fats Limit saturated fats <10% of calories and cholesterol <300 mg Trans fats: Negligible intake	Olive oil for salad dressing Canola and soybean oil for cooking, walnut and sesame oil as flavoring agents Prefer seafood over meat/poultry Almonds, walnuts, avocados, seeds Limit fried foods, margarine

[a]Based on a 1,800 cal food pattern for a 67-year-old female, 5 ft, 5 in. tall, weighing 155 lb, physically active 30–60 min a day with a BMI of 28. The amount recommended is with the intent of attaining a healthier weight

[b]While the older adult should be encouraged to increase the consumption of food items in the Good Choices column, they should be advised to decrease the consumption of refined grains, starchy vegetables, whole milk, meats with visible fat, processed meats, and deep fried foods

[c]Total fat intake should be limited to 25–35% of calories, protein at 0.8 g/kg, and carbohydrates 45–55% of calories [14]. Saturated fats need to be reduced to <7% of calories and cholesterol <200 mg in older adults at high risk for cardiovascular disease

Table 22.3 Healthy diet for older adults: specific considerations

Nutrients/other items	Daily recommended amounts	Good choices
Fiber [16]	Men: 30–38 g Women: 21–25 g	Black beans, navy beans, pinto beans, whole grains, nuts, fruits, and vegetables, prefer foods over supplements
Fluids [17]	6–8 glasses of water (8 oz)	Soups and fruits which are high in fluid content, sip water frequently and with each meal and snacks
Calcium	1,000 mg: Men 51–70 years old 1,200 mg: Women >51 and Men >70 years old Upper Limit: 2,000 mg	Low and nonfat milk, cheese, yogurt, broccoli
Vitamin D	600 IU: Men and Women, 51–70 800 IU: Men and Women, >70 Upper Limit: 4,000 IU	Fish, beef liver, fortified milk, yogurt or cereal, sunlight exposure
Vitamin B12	2.4 μg	Beef, salmon, clams, tuna, dairy products, fortified cereals. Vegans and vegetarians need supplements
Alcohol[a]	Females: One drink or less Men: Two drinks or less	One drink is 12 oz of regular beer (5% alcohol), 5 oz of wine (12% alcohol) or 1.5 oz of 80% proof (40% alcohol) distilled spirits. One drink is 0.6 oz alcohol
Sodium [19]	1.5 g/day for adults >51 equals ¾ teaspoon salt	Minimize use of processed food, no adding extra salt
Potassium	Adequate Intake (AI) 4,700 mg	Potatoes, oranges, raisins, prune juice, dairy products

[a]Higher intake of alcohol is associated with impairment of activities of daily living, hence not included in the Modified MyPyramid [15]

Table 22.4 Practicing food safety: simple strategies for the older adult

Clean: Wash hands, utensils, and cutting boards before and after contact with raw meat, poultry, seafood, and eggs
Separate: Keep raw meat and poultry apart from foods that will not be cooked such as fresh vegetables to be used in salads
Cook: Use a food thermometer. You can't tell if food is cooked safely by how it looks
Chill: Chill leftovers and takeout foods within 2 h and keep the refrigerator at 40°F or below

cooked pasta, or cooked cereal; 1 6-in. diameter tortilla (6 in. diameter); 1 5-in. diameter pancake; or one and half tablespoons of whole wheat flour. A recent National Institutes of Health/American Association of Retired Persons (NIH-AARP) study involving 388,000 people aged 51–70 found that those consuming a high fiber diet including whole grains had a lower risk of dying over a 9 year period than those who consumed lower amounts of fiber [18].

Adding rolled oats to a cup of yogurt; trying whole wheat pasta instead of regular pasta; and using brown rice instead of white rice are some suggestions to increase consumption of whole grains.

Vitamins and Minerals

Except for a few specific nutrients such as Vitamin D, Vitamin B12, and calcium, the once-promising approach of vitamin and mineral supplementation to promote health and prevent disease appears to have lost steam over the years [19]. There is also a growing concern amongst nutrition experts that high folic acid intakes may in fact increase the risk of cancer and other health problems [20]. Recent changes in the recommendations for vitamin D and calcium [21] from the Institute of Medicine (IOM) continue to suggest the importance of Vitamin D and calcium intake, but place limits on the amounts; as excessive consumption has not necessarily been proven to be beneficial and may predispose to risk of kidney stones.

The physiologic decline in gastric acid secretion in the older adult or alteration in pH through use of H2 blockers or proton pump inhibitors may reduce the absorption of iron and vitamin B12. Inclusion of iron rich foods such as lean red meats, poultry, seafood, plant foods such as white beans, lentils, and foods enriched with iron such as breads and cereals can help maintain and improve iron status. Vitamin B12 deficiency is associated with depression, neurological disorders, memory, and hearing loss in older adults. While intake of B12 containing foods (Table 22.3) may help, the absorption of B12 is complex and interfered with by several steps in the pathway (see Chap. 18); adults aged 50 and over, vegetarians and vegans would benefit from supplements of Vitamin B12 for maximum health benefits.

While numerous trace minerals, vitamins and other nutrients such as zinc, vitamins C and E, lutein, and beta-carotene have been promoted to help prevent or slow the onset of age-related macular degeneration, eating at least five or more servings of fruits and vegetables is the preferred means to obtain these vital nutrients. The just released 2010 U.S. Dietary Guidelines call for a reduction in the recommended daily sodium intake to 1,500 mg from the previous threshold of 2,300 mg/day for all adults aged 51 and over and those with diabetes, hypertension, and chronic kidney disease [13].

Physical Activity

A healthy diet should be used in conjunction with adequate physical activity. Most older adults do not engage in adequate physical activity. The 2008 physical activity guidelines for active older Americans [22], aged 50 and over, call for moderate or vigorous aerobic and muscle-strengthening activities for at least up to 30 min a day. The American Heart Association (AHA) emphasizes both diet and physical activity among the seven components that help maintain good cardiovascular health; the components being weight, diet, physical activity, blood sugar, cholesterol, blood pressure, and smoking status. Yoga is a light exercise which improves quality of life and is increasingly popular among older adults, involving stretch, massage, and strengthening of muscles. Yoga may be coupled to a healthy diet and exercise.

The different types of exercises are summarized in Tables 22.5 and 22.6.

The Need to Deal with Global Issues

A United Nation's Population Division has estimated that the world's population will reach 9.2 billion in 2050, with the number of people over age 60 tripling from the current 700 million to 2.0 billion [23]. Proper nutritional guidance thus takes on considerable importance from both a domestic and global perspective to maintain the health and emotional independence of the older adult. In all likelihood counseling the older adult on diet and physical activity will be a greater proportion of what health care professionals do in the near future. From a health services perspective, the United States Patient Protection & Affordable Care Act enacted in March 2010 makes it possible for older Americans covered under Medicare to receive free preventive care services that incentivize health care providers to

Table 22.5 Physical activity guidelines for older adults

Types of exercise	Intensity	Total amount of time and frequency	Considerations
Aerobic	Moderate High (vigorous) *or* combination of moderate and high	At least 150 min per week At least 75 min per week	A general rule of thumb is that 2 min of moderate-intensity activity are equivalent to 1 min of high-intensity activity
Muscle strengthening	Either moderate or high	At least 2 days per week No specifics on amount of time recommended	Performed to the point at which it would be difficult to do another repetition without help

Table 22.6 Types of exercise with a variety of physical activity options

Types of exercise	Examples of physical activities
Endurance activity	Walking, swimming, jogging, dancing, playing tennis etc.
Strength exercises	Wrist curls, arm curls, side arm raises, elbow extension, chair dips, leg raises, knees curls, and toe stands.
Balance exercises	Standing on toes, walking heel to toe, back leg raises, side leg raises, hip extension, and balance walk
Flexibility exercises	Neck stretch, back stretch, shoulder and upper arm stretch, leg stretch, thigh stretch, calf and lower back stretch, and yoga

counsel the elderly on a healthy diet and exercise regimen. Furthermore, from a health policy perspective, the U.S. Department of Health and Human Services (HHS) recently released the Healthy People 2020 goals that reflect the nutrition and health concerns of older Americans with new measures that focus on people with dementias, including Alzheimer's disease [24].

Advances in nutritional science have clearly demonstrated limitations to the nutrient and supplement-based approach of prior years [25]. Food-based dietary guidelines as covered in this chapter; although generalized, hold promise for mitigating the risk of chronic disease as well as promoting health. To this effect, it becomes imperative that all essential nutrients be derived from food sources; this will ensure that the older adult obtains not only the necessary macro and micronutrients, but also the naturally occurring carotenoids, flavonoids, and isoflavones [26]. Some researchers believe [27] that a poor or near-poor older adult may not be able to afford healthful foods such as fruits and vegetables. However, economic data provided by the USDA and other sources suggest that a diet could be made increasingly more healthful by shifting purchases toward more plant-based foods [28] as alluded to in this chapter. It may be difficult to change long-standing habits in the old; for example, the overall consumption of whole grains in the United States is low, as noted in the 1999–2004 National Health and Nutrition Examination Survey (NHANES) data; in the 51+ year age group, those who consumed the most servings of whole grains had better quality and nutrient intakes [29]. However, an analysis of 13,562 abstracts and 481 articles for the United States Preventive Service Task Force concluded that counseling to improve diet and physical activity changed behavior and was associated with improvements in adiposity, blood pressure, and lipids [30]. Further, the role of low micronutrients as a cross-sectional and longitudinal correlates of mobility disability is consistent with studies confirming the benefits of a diet rich in fruits and vegetables [31]. Finally, when following the lifestyle factors of the oldest old, the centenarians, we learn that it is diet and nutrition (and activity) that play a significant role in their exceptional longevity and maintenance of optimal cognitive, mental and physical health into advanced age [32].

Although the older adult population in America and globally is quite diverse, these healthful diet and lifestyle guidelines are associated with favorable outcomes with respect to the health, wellness, and quality of life regardless of race, ethnicity, and socio-economic status [33]. Efforts to prevent disability in the old should also include targeting the overweight and obese [34].

Key Points

- Favor vegetables, fruits, whole grain foods, and low fat dairy products.
- The diet must be appropriately balanced for portion sizes.
- A healthy diet and physical activity go hand in hand.
- Limit solid fats, salt, alcohol, and added sugars.
- The needs for calcium, vitamin D, and vitamin B12 are best individualized.

References

1. Hobbs F. Population profile of the United States. The elderly population. U.S. Census Bureau. 2011. http://www.census.gov/population/www/pop-profile/elderpop.html. Accessed 19 Jan 2011.
2. Cowie CC, Rust KF, Ford ES, et al. Full accounting of diabetes and prediabetes in the US population in 1988–1994 and 2005–2006. Diabetes Care. 2009;32:287–94.
3. Older Persons health. Fast Stats. Centers for Disease Control and Prevention. 2011. http://www.cdc.gov/nchs/fastats/older_americans.htm. Accessed 12 Jan 2011.
4. Burton LA, Sumukadas D. Optimal management of sarcopenia. Clin Interv Aging. 2010;5:217–28.
5. Moley JE. Decreased food intake with aging. J Gerontol A Biol Sci Med Sci. 2001;56A:81–3.

6. Position paper of the American Dietetic Association. Nutrition across the spectrum of aging. J Am Diet Assoc. 2005;105:616–33.
7. Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and trends in obesity among US Adults, 1999–2008. JAMA. 2010;303:235–41.
8. Physical activity and older Americans. Benefits and strategies. Agency for Health Care Quality and Research. 2011. http://www.ahrq.gov/ppip/fig4txt.htm. Accessed 19 Jan 2011.
9. Schmidt DS, Salahudeen AK. Obesity-survival paradox-still a controversy? Semin Dial. 2007;20:486–92.
10. Berrington de Gonzalez A, Hartge P, Cerhan J, et al. Body-mass index and mortality among 1.46 million white adults. N Engl J Med. 2010;363:2211–9.
11. A profile of older Americans: 2009. Health and Health care. Administration on Aging (AOA). 2011. http://www.aoa.gov/AoAroot/Aging_Statistics/Profile/2009/14.aspx. Accessed 19 Jan 2011.
12. Older Americans 2010: Key indicators of Well-Being. 2011. http://www.agingstats.gov/agingstatsdotnet/Main_Site/Data/2010_Documents/Docs/OA_2010.pdf. Accessed 15 Jan 2011.
13. Dietary Guidelines for Americans: Report of the Dietary Guidelines Advisory Committee on the Dietary Guidelines for Americans. 2010. http://www.cnpp.usda.gov/dgas2010-dgacreport.htm. Accessed 1 Feb 2011.
14. Nutrition Plate Unveiled, Replacing Food Pyramid: Simpler design shows a Healthful Diet. 2011. http://www.nytimes.com/2011/06/03/business/03plate.html/?_r=1&scp=1&sq=nutrition%20plate%20unveiled,%20replacing%20food%20pyramid&st=cse. Accessed 4 June 2011.
15. Lichtenstein AH, Rasmussen H, Yu WW, Epstein SR, Russell RM. Modified MyPyramid for older adults. J Nutr. 2008;138:5–11.
16. DRI table for carbohydrate, fiber, fat, fatty acids and protein National Academy of Sciences. Institute of Medicine. Food and Nutrition Board. (2002/2005). http://www.iom.edu/Global/News%20Announcements/~/media/C5CD2DD7840544979A549EC47E56A02B.ashx. Accessed 15 Jan 2011.
17. Dietary reference intakes for electrolytes and water. 2011. http://www.iom.edu/Global/News%20Announcements/~/media/442A08B899F44DF9AAD083D86164C75B.ashx. Accessed 15 Jan 2011.
18. Park Y, Subar A, Hollenbeck A, Schatzkin A. Dietary fiber intake and mortality in the NIH-AARP diet and health study. Arch Intern Med. 2011;171(12):1061–8.
19. Clarke R, Halsey J, Lewington S, et al. Effects of lowering homocysteine levels with B vitamins on cardiovascular disease, cancer and cause-specific mortality: meta-analysis of 8 randomized trials involving 37385 individuals. Arch Intern Med. 2010;170:1622–31.
20. Lomangino K. B-Vitamin meta-analysis shows no benefit, no harm from supplementation. Clin Nutr Insight. 2011;37:9–11.
21. Ross C, Manson J, Abrams S, et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. J Clin Endocrinol Metab. 2011;96:53–8.
22. U.S. Department of Health and Human Service. 2008 Physical Activity Guidelines for Americans. http://www.health.gov/paguidelines/guidelines/chapter5.aspx. Accessed 18 Jan 2011.
23. Ideas Galore. World's Population to Reach 9.2 Billion in 2050. 2011. http://affleap.com/world-population-to-reach-9-2-billion-in-2050/. Accessed 12 Jan 2011.
24. Sullivan M. Healthy People 2020 goals reflect graying of America. Intern Med News. 2010;43:2.
25. Mozaffarian D, Ludwig D. Dietary guidelines in the 21st century—a time for food. JAMA. 2010;304:681–2.
26. Marian M, Sacks G. Micronutrients and older adults. Nutr Clin Pract. 2009;24:179–95.
27. Drewnowski A. The cost of US foods as related to their nutritive value. Am J Clin Nutr. 2010;92:1181–8.
28. Bernstein A, Bloom D, Rosner B, et al. Relation of food cost to healthfulness of diet among US women. Am J Clin Nutr. 2010;92:1197–203.
29. O'Neil CE, Nicklas TA, Zanovec M, et al. Whole-grain consumption is associated with diet quality and nutrient intake in adults: the National Health and Nutrition Examination Survey, 1999–2004. J Am Diet Assoc. 2010;110(10):1461–8.
30. Lin JS, O'Connor E, Whitlock EP, et al. Behavior counseling to promote physical activity and a healthful diet to prevent cardiovascular disease in adults: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med. 2010;153:736–50.
31. Milaneschi Y, Tanaka T, Ferrucci L. Nutritional determinants of mobility. Curr Opin Clin Nutr Metab Care. 2010;13(6):625–9.
32. Hausman DB, Fischer JG, Johnson MA. Nutrition in centenarians. Maturitas. 2011;68:203–9.
33. Position of the American Dietetic Association. Individualized nutrition approaches for older adults in health care communities. J Am Diet Assoc. 2010;110:1549–53.
34. Wee CC, Huskey KW, Ngo LH, et al. Obesity, race and risk for death of functional decline among Medicare beneficiaries. A cohort study. Ann Intern Med. 2011;154:645–55.

Part V

Imaging

Endoscopy in Older Adults: Risks, Benefits, Considerations

23

Noelle O'Shea and Frank J. Lukens

Endoscopy is a safe procedure irrespective of age [1]. The chapter examines the risks, benefits, and considerations with regards to esophagogastroduodenoscopy (EGD) and colonoscopy in older adults.

Esophagogastroduodenoscopy

Upper endoscopy provides direct visualization of the esophagus, stomach, and duodenum. It aids in the diagnosis and management of inflammatory, benign, and malignant processes in these areas. It also provides a means to manage conditions such as esophageal variceal disease, removal of ingested objects, acute gastrointestinal bleeding, and peptic ulcer. Tables 23.1 and 23.2 outline the indications for and the possible findings on EGD.

Endoscopy in the elderly may be efficacious in addressing the long-term consequences of reflux disease, including peptic strictures. Older adults experiencing dysphagia or dyspepsia have higher probability of organic disease [2]. With regards to reflux disease and cost-effectiveness of EGD in patients aged over 60 years, endoscopy led to symptom and quality of life improvement as well as a 48% reduction in proton pump inhibitor use [3]. In a 65–89-year group who underwent EGD for dyspepsia, gastrointestinal blood loss, and suspected upper tract carcinoma, endoscopy uncovered radiologically undetected disease in 45% of these patients [4]. In nearly 25,000 patients with dyspepsia, when EGDs were performed by the same endoscopist in 77% of the cases, repeat EGD occurred at a low but substantial rate, with lower yield than the initial EGD, suggesting that optimizing the need for and timing of follow-up endoscopy is a priority [5]. Overall, EGD is a procedure with good diagnostic yield in older adults presenting with dyspepsia and dysphagia.

Colonoscopy

Colonoscopy provides a direct visualization of the large intestine. Colonoscopy allows a means to screen for colorectal cancer, obtain biopsies, place stents, remove polyps, treat, or investigate acute and chronic bleeding, and dilate strictures. Tables 23.3 and 23.4 outline the indications for colonoscopy and possible findings.

The incidence of colorectal cancer doubles each decade after age 40 [2]. A study comparing the prevalence of neoplasia and mean gain in life expectancy in patients aged 50–54, 75–59, and over 80 undergoing screening colonoscopy with findings of higher prevalence of neoplasia and lower extension of life expectancy concluded that screening colonoscopy led to only a 15% expected gain in life expectancy in the old [2]. The US Preventive Services Task Force recommends against screening colonoscopy in patients aged 75 or greater due to the lack of evidence demonstrating benefits outweighing risks [6]. Thus, in the elderly, colorectal cancer screening or surveillance with colonoscopy should be individualized to the patient, based on comorbidity and life expectancy [1]. However, there appears a benefit to colonoscopy when the octogenarian experiences rectal bleeding, iron deficiency anemia, and a positive fecal occult blood test. Additionally, increasing age, weight loss, rectal bleeding and iron deficiency anemia are clinical characteristics that carry a higher predictive value for finding carcinoma on colonoscopy [2].

Colonoscopy in the old may be a challenging procedure. Success rates, defined as being able to reach the cecum or ileocolic junction, vary from 48 to 94%, with rates directly related to the quality of the colonic preparation [2]. Extensive diverticular disease, common in older adults, can be a factor limiting a successful study.

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Table 23.1 Indications for esophagogastroduodenoscopy (EGD) [18]

High yield	Low yield
Dysphagia and odynophagia	Symptoms, that are functional in origin
Persistent abdominal symptoms despite therapy, including dyspepsia	Metastatic adenocarcinoma, if results do not alter management
Persistent vomiting, etiology unclear	
Familial adenomatous polyposis syndromes	
Bleeding, occult, acute, and chronic	
Abnormal imaging	
Achalasia	
Treatment/surveillance of esophageal varices	
Foreign body removal	
Iron deficiency anemia	

Table 23.2 Possible findings on EGD

Esophagus	Stomach	Duodenum
Esophagitis	Gastric folds (Menetrier's)	Ulcers
Barrett's esophagus	Erosions, gastritis and ulcers	Erosions
Esophageal carcinoma	Ulcer disease	Celiac disease
Diverticula (Zenker's)	Malignant lesions	Polyps
Varices	Polyps	Duodenitis
Mallory-Weiss tears	Gastroparesis (retained food)	Diverticula
Achalasia	Pyloric obstruction	
Motility disturbances	Portal hypertensive gastropathy Gastric varices Dieulafoy lesions Bezoars	

Table 23.3 Indications for colonoscopy [19, 20]

High yield	Low yield
Anemia—unexplained iron deficiency	Constipation
Bleeding—acute/chronic	Flatulence
Occult blood loss	Pain
Assessment for inflammatory disease	Change in bowel habits
Genetic cancer risk	
Abnormal imaging	
Screening/surveillance—colorectal cancer	
Significant diarrhea—unknown etiology	
Foreign body removal	

Table 23.4 Possible findings on colonoscopy

Submucosal lesions (secondary carcinoma, large vessel hemangiomas)
Polyps
Carcinomas
Inflammatory bowel disease (ulcerative colitis, Crohn's disease)
Hemorrhoids
Diverticular disease
Angiodysplasias

Poor colonic preparation is the single most important impediment to adequate colonoscopy in this group; the preparation is less adequate compared to the young regardless of the type of preparation used [2]. Adequate colonic preparation is a problem in the older age group and presents barriers to proper visualization and completion of the procedure. As part of the preparation, the provider should address directions for the patient's usual medications, revision of medications as indicated (e.g., insulin and antihypertensives) and take steps for the avoidance of falls from the preparation related volume loss. In a study, octogenarians were four times more likely to have poor colonic preparation compared to nonoctogenarians (16% vs. 4%), despite both groups adequately tolerating the preparation [7]. With regards to bowel perforation during colonoscopy, patients 80 or older have a much higher incidence of perforation compared to the overall population (0.119% vs. 0.082%) [2].

Overall, colonoscopy is an effective procedure in the elderly, but with slightly lower success rates; this may relate to inadequate fluid intake or reduced colonic motility influenced by comorbidity and effect of medications.

Preprocedure Preparation

Prior to EGD or colonoscopy, cessation of oral intake for at least 6 h for solids and 4 h for liquids is recommended, with typically nothing to eat or drink after midnight prior to the procedure [8]. Patients are allowed to take medications with a sip of water. In diabetics, one-half the usual morning dose of insulin can be administered with the other half administered with the post-procedure meal; oral hypoglycemic agents are withheld [8]. Patients are instructed to take certain medications, in particular anti-seizure, cardiac, and antihypertensives with a sip of water. Herbal medications should be discontinued a few days prior to the procedure. Anticoagulants are discussed below. Aspirin for cardiac prophylaxis need not be discontinued pre-procedure.

Prior to colonoscopy, patients require a bowel preparation; caution should be exercised in using formulations (osmotic preparations) that cause fluid or electrolyte shifts in patients with renal or cardiac disease [9]. Additionally, magnesium and phosphate preparations are best avoided in chronic kidney disease. In the elderly over 75 years, two studies found polyethylene glycol (PEG) and oral sodium

Table 23.5 Most common side effects to colonoscopy preparations [9]

Electrolyte and fluid imbalance, worsening renal function
Abdominal discomfort
Dizziness
Bloating
Nausea and vomiting

Table 23.6 Bowel preparations [10]

Name	Flavor	Comparison with gold standard
Colyte (PEG)	Yes (cherry, citrus-berry, lemon-lime, orange, pineapple)	Gold standard
GoLYTELY (PEG)	Yes (pineapple)	Gold standard
NuLYTELY (sulfate-free PEG)	Yes (cherry, lemon-lime, orange, pineapple)	Less salty, more palatable than PEG and comparable to PEG in terms of effective colonic cleansing and patient tolerance
TriLyte (sulfate-free PEG)	Yes (cherry, citrus-berry, lemon-lime, orange, pineapple)	Less salty, more palatable than PEG and comparable to PEG in terms of effective colonic cleansing and patient tolerance
Halflytely (low-volume PEG)	Yes (lemon-lime)	Comparable to PEG in terms of colonic cleansing with improved patient tolerance

Instructions: (1) no solid food for at least 2 h prior to taking the solution. 240 mL (8 oz) every 10 min until rectal output clear or 4 L consumed. (2) Only clear liquids on the day of preparation. Four bisacodyl delayed-release tablets (5 mg) at noon. Wait for bowel movement or up to 6 h then 240 mL (8 oz) every 10 min until 2 L are consumed

phosphate (NaP) equally effective in bowel preparation; however, phosphates must be avoided in the presence of impaired kidney function [9]. Adverse effects of phosphate preparations include phosphate nephropathy, hyperphosphatemia and water and electrolyte imbalance [10]. Table 23.5 lists the common side effects of colonoscopy preparations.

PEG is a nonabsorbable solution that passes through the bowel without net absorption or secretion, thus minimizing fluid and electrolyte shifts [10]. Isotonic PEG has been safely used in patients with serum electrolyte imbalance, advanced hepatic dysfunction, acute and chronic renal failure, and congestive heart failure [10]. PEG does not alter the histologic features of colonic mucosa [10]. Table 23.6 lists options for bowel preparations.

The elderly are more likely to have pacemakers or implantable cardioverter defibrillators (ICDs) in place; evaluation of these devices with the assistance of cardiology personnel should be considered prior to endoscopy as ICDs require to be inactivated prior to use of electrocautery [1]. With regards to required studies prior to endoscopy, screening for coagulopathy, chest radiography, preoperative ECG, blood typing, hemoglobin and hematocrit, routine urinalysis, and chemistry tests in otherwise healthy patients are not routinely recommended [11]. However, laboratory testing may be individualized based on the perceived level of risk as determined by the medical history or physical examination of the patient [11].

Sedation, Analgesia, and Safety

The purpose of sedation and analgesia is to relieve patient anxiety and discomfort while improving the outcome of the study [12]. Most endoscopic procedures (EGD/colonoscopy) are performed with conscious sedation. Due to several reasons, geriatric patients have increased sensitivity to sedation that may result in hypoxia and mild hypotension [12]. Hence, sedation should be provided with caution, and at an appropriate dose by one familiar with the agents used. Pulmonary stress in the elderly was compared in adults over 60 years with those below 30, with measures of human atrial natriuretic peptide (hANP) and human natriuretic peptide (hBNP) levels post-procedure; the findings suggested increased atrial load during endoscopy, emphasizing the possibility of volume overload in the elderly during endoscopy [2]. Endoscopy suites must be adequately equipped with personnel trained to handle resuscitation.

Topical pharyngeal anesthetic sprays with lidocaine, tetracaine, and benzocaine may be used for upper endoscopy; a meta-analysis of pharyngeal anesthesia with intravenous/intramuscular sedation indicated improved ease of endoscopy or improved patient tolerance as judged by the endoscopist [12]. Potential side effects to topical pharyngeal anesthetic sprays include aspiration, anaphylactoid reactions, and methemoglobinemia [12].

The most common benzodiazepines used are midazolam and diazepam; most endoscopists prefer midazolam due to fast onset of action, short duration of action, and high amnestic properties [12]. Today meperidine is a drug that is limited or best avoided in older adults; nor-meperidine, its metabolite, accumulates in kidney disease and causes neurologic adverse effects. Likewise diazepam is generally avoided in older adults due to its long half live and adverse effects. Propofol is an ultrashort acting agent that provides sedative, amnestic, and hypnotic effects with no analgesic properties that should be dose reduced in the elderly due to decreased clearance of the medication [12]. The combination of propofol and midazolam are synergistic; a study of over 200 patients found a 59% reduction in the propofol dosage when also using midazolam [13]. In an analysis, 347 patients aged 70 or older with high-level comorbidity (ASA score of class III or higher) who underwent endoscopy had a 28-day mortality rate of 2.9%, but had no procedure-associated mortality or major side effects [13]. In a prospective observational study on propofol sedation in 351 patients over 85 years, oxygen desaturation was more frequent [13]. In a retrospective comparative analysis of elderly with high comobidity, sensitivity to propofol was high, indicating that lower propofol doses should be used in this age group, although there was no significant increase in the complication

rate [13]. In a study where 241 patients aged over 90 underwent endoscopy with propofol sedation over a 2-year period, low-dose propofol sedation was safe for this age group [14].

Management of Anticoagulation

Considerations when preparing a patient on anticoagulants for endoscopy include the risk of complications of the underlying gastrointestinal disorder linked to anticoagulation, bleeding due to the endoscopic intervention carried out in this setting, and thromboembolic events related to the interruption of anticoagulation. Tables 23.7, 23.8, and 23.9 provide the peri-procedure anticoagulation recommendations and risk of complications.

Aspirin and nonsteroidal anti-inflammatory drugs in standard doses do not increase the risk of significant bleeding after EGD with biopsy, colonoscopy with biopsy, polypectomy, or biliary sphincterotomy. Elective procedures in patients with recently placed vascular stent or acute coronary syndrome should be deferred until the patient has received antithrombotic therapy for the minimum recommended time. In patients on dual antiplatelet therapy or monotherapy with a thienopyridine, consider continuing aspirin or starting aspirin in the periendoscopic period.

Table 23.7 Bleeding risk of procedures [15–17]

Low bleeding risk procedures	High bleeding risk procedures
Diagnostic EGD	Colonoscopy with polypectomy
Flexible sigmoidoscopy	Gastric polypectomy
Colonoscopy with/without biopsy	Laser ablation and coagulation
Diagnostic ERCP	Endoscopic sphincterotomy
EUS	Pneumatic/bougie dilation of strictures
Push enteroscopy	PEG tube placement
	EUS guided fine needle aspiration

Table 23.8 Thromboembolic risk [15–17]

Low thromboembolic risk conditions	High thromboembolic risk conditions
Deep venous thrombosis	Atrial fibrillation in valvular disease
Chronic/paroxysmal atrial fibrillation not associated with valvular disease	Mechanical valves, mitral
Bioprosthetic valves	Mechanical valves with prior thromboembolic event
Mechanical valves, aortic	

Special Considerations in Geriatrics

Often, in the elderly, endoscopy may be indicated following acute illness, such as following an acute myocardial infarction. In such situations, the need for endoscopy must be weighed against safety considerations for each patient.

While preparing the patient for colonoscopy, pre-procedure preparations have to be carefully monitored, especially in diabetics (on insulin) and those with heart disease sensitive to volume changes and those prone to orthostasis. Precautions should be taken to avoid falls. Appropriate dosing of medications in the pre- and post-procedure states must be addressed..

Key Points

- Endoscopy is a safe procedure irrespective of age.
- In older adults, colorectal cancer screening or surveillance with colonoscopy should be individualized based upon patient's general health and comorbidity.
- Caution should be exercised in choosing a bowel preparation. Isotonic polyethylene glycol is generally acceptable and has a reasonable safety profile, including in those with hepatic, renal, or cardiac disease.
- Geriatric patients are sensitive to sedation; caution must be exercised with the choice of agent, rate of administration, and cumulative dose.
- If on anticoagulants, considerations include bleeding complications related to anticoagulation vs. thromboembolic events arising from interrupting anticoagulation.

Table 23.9 Bleeding/thromboembolic risk [15–17]

Low bleeding risk	High bleeding risk/low thromboembolic risk	High bleeding risk/high thromboembolic risk
No adjustment in anticoagulation, irrespective of the underlying condition	Consider continuing ASA/NSAIDs	Continue ASA/NSAID
Elective procedures best avoided when INR is above therapeutic range	Warfarin therapy should be discontinued 3–5 days before procedure LMWH discontinued at least 8 h pre procedure (earlier in CKD) Individualize reinstitution of clopidogrel therapy	Warfarin therapy is discontinued 3–5 days before procedure; begin LMWH concomitantly LMWH therapy should be discontinued at least 8 h before procedure; reinstitution individualized Heparin discontinued 4–6 h before procedure; resumed 4–6 h after procedure Individualize reinstitution of clopidogrel therapy

ASA aspirin; *NSAID* nonsteroidal anti-inflammatory drug; *LMWH* low molecular weight heparin

References

1. Qureshi WA, Zuckerman MJ, Adler DG et al. ASGE guideline: modifications in endoscopic practice for the elderly. Gastrointest Endosc. 2006;63(4):566–9.
2. Jafri S, Monkemuller K, Lukens F. Endoscopy in the elderly: a review of the efficacy and safety of colonoscopy, esophagogastroduodenoscopy, and endoscopic retrograde cholangiopancreatography. J Clin Gastroenterol. 2010;44(3):161–6.
3. Delaney BC, Wilson S, Roalfe A. Cost effectiveness of initial endoscopy for dyspepsia in patients over age 60 years: a randomized controlled trial in primary care. Lancet. 2000;356:1965–9.
4. Gibbins FJ, Collins HJ, Hall RG, et al. Endoscopy in the elderly. Age Ageing. 1974;3:240–4.
5. Ladabaum U, Dinh V. Rate and yield of repeat upper endoscopy in patients with dyspepsia. World J Gastroenterol. 2010;16(20):2520–5.
6. Calonge N, Petitti D, DeWitt et al. US Preventive Services Task Force. Screening for colorectal cancer: US Preventive Services Task Force recommendation statement. Ann Intern Med. 2008;149:680–2.
7. Lukens FJ, Loeb DS, Machicao VI, et al. Colonoscopy in octogenarians: A Prospective Outpatient Study. Am J Gastroenterol. 2002;97:1722–5.
8. Faigel DO, Eisen GM, Baron TH et al. ASGE preparation of patients for GI endoscopy. Gastrointest Endosc. 2003;57(4):446–50.
9. Mamula P, Adler DG, Conway JD et al. ASGE Technology Status Evaluation Report—colonoscopy preparation. Gastrointest Endosc. 2009;69(7):1201–9.
10. Wexner SD, Beck DE, Baron TH et al. ASGE consensus document—a consensus document on bowel preparation before colonoscopy: prepared by a task force from the American Society of Colon and Rectal Surgeons (ASCRS), the American Society for Gastrointestinal Endoscopy (ASGE), and the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES). Gastrointest Endosc. 2006;63(7):894–909.
11. Levy MJ, Anderson MA, Baron TH et al. ASGE guideline—position statement on routine laboratory testing before endoscopic procedures. Gastrointest Endosc. 2008;68(5):827–32.
12. Lichtenstein DR, Jagannath S, Anderson MA et al. ASGE guideline—sedation and anesthesia in GI endoscopy. Gastrointest Endosc. 2008;68(5):815–26.
13. Kerker A, Hardt C, Schlief H, et al. Combined sedation with midazolam/propofol for gastrointestinal endoscopy in elderly patients. BMC Gastroenterol. 2010;10:11.
14. Horiuchi A, Nakayama Y, Tanaka N, et al. Propofol sedation for endoscopic procedures in patients 90 years of age and older. Digestion. 2008;78:20–3.
15. Eisen GM, Baron TH, Dominitz JA et al. ASGE guideline on the management of anticoagulation and antiplatelet therapy for endoscopic procedures. Gastrointest Endosc. 2002;55(7):775–9.
16. Zuckerman MJ, Hirota WK, Adler DG et al. ASGE guideline: the management of low-molecular-weight heparin and nonaspirin antiplatelet agents for endoscopic procedures. Gastrointest Endosc. 2005;61(2):189–94.
17. Anderson MA, Ben-Menachem T, Gan SI et al. ASGE guideline—management of antithrombotic agents for endoscopic procedures. Gastrointest Endosc. 2009;70(6):1060–70.
18. Cohen J, Safdi MA, Deal SE et al. U.S. Department of Health and Human Services: National Guideline Clearinghouse—Quality indicators for esophagogastroduodenoscopy. 2006. http://www.guideline.gov.
19. Cotton PB, Williams CB, Hawes RH, Saunders BP. Practical gastrointestinal endoscopy: the fundamentals. 6th ed. Hoboken: Wiley-Blackwell Publishing; 2008. p. 22–175.
20. Rex DK, Petrini J, Baron T et al. U.S. Department of Health and Human Services: National Guideline Clearinghouse—Quality indicators for colonoscopy. 2006. http://www.guideline.gov.

Wireless Capsule Endoscopy

24

C.S. Pitchumoni and Neelam G. Gidwaney

Wireless video capsule endoscopy (VCE) was first introduced by Paul Swain, a gastroenterologist, in 2000 [1–3]. In 2001, the Food and Drug Administration approved the use of a wireless video capsule endoscope. Since then, gastroenterologists have gained the ability to directly visualize the entire small bowel mucosa [1, 3], hereinto considered the "black box" of the gastrointestinal tract. VCE is an effective diagnostic tool to detect and manage obscure gastrointestinal bleeding (OGIB), iron deficiency anemia, inflammatory bowel disease, and tumors of the small intestine without the discomfort of an endoscope, need for intravenous sedation, air insufflation, or radiation exposure [4, 5] (Table 24.1). Over 750,000 VCE examinations have been performed, many in the over 65 age group [6]. With aging trends, VCE will be a useful and popular imaging study in the geriatric population [6].

The Instrument

PillCam® SB (Given Imaging, Yokneam, Israel), an 11×26 mm capsule-shaped camera, is powered by two batteries to allow a total transit time of 7–8 h, sufficient for 80–90% of capsules to reach the cecum and image the entire small bowel [1, 2, 7]. Improved technology has further extended battery time to provide increased imaging time (11 h for the MiroCam™) (IntroMedic (Seoul, Korea)) [2]. Once removed from its magnetic holder, the disposable capsule is activated; it contains four light-emitting diodes (MiroCam™ and EndoCapsule™ each with six light-emitting diodes) to illuminate the bowel lumen, an antenna, and two metal oxide semiconductor cameras to transmit the images to an external device for analysis and storage. Using a radiofrequency band signal all the images captured by the capsule are transmitted to a recording unit worn by the patient around the waist. Following the examination, the recording unit is connected to a computer to retrieve the images [3].

Although VCE can be performed after an overnight fast and an empty stomach without intestinal cleansing, a bowel preparation, particularly in the elderly, enhances the visualization of the mucosa, increases the likelihood of a complete cecal examination, and prevents smudging of the camera lens [1, 8]. A half-day bowel preparation using polyethylene glycol (PEG) enhances quality and diagnostic yield [2]. Patients fast 8–12 h prior to the procedure may drink hours after the capsule is swallowed. The ingested capsule passively travels through the gastrointestinal tract while the cameras in the capsule capture images at 2–3 color frames per second [2]. The capsule is evacuated usually 24–48 h later with stool [1]. Currently, capsules are available for the esophagus and small intestine; in the near future capsules will be available for large bowel [1, 9, 10]; they are aptly named to diagnose specific disorders of a given segment of the gastrointestinal tract. A complete examination of the small bowel is possible in over 80% of patients [11, 12].

Indications for Wireless Capsule Endoscopy (Table 24.1)

Obscure Gastrointestinal Bleeding: Overt and Occult

Gastrointestinal bleeding has been traditionally divided into upper (above the ligament of Treitz) and lower GI bleeding. Following the invention of VCE and balloon enteroscopy, a change has been proposed to redefine the location of GI bleeding to include "mid-GI bleeding" (bleeding from the ampulla

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Table 24.1 Indications for video capsule endoscopy

Obscure gastrointestinal bleeding: overt and occult
Diagnosis and management of Crohn's disease
Diagnosis of small bowel neoplasms
Surveillance of inherited polyposis syndromes
Evaluation of abnormal small bowel imaging
Evaluation of anemia (including celiac disease)

of Vater to the terminal ileum) [13, 14]. The most common indication for VCE is OGIB, defined as bleeding of unknown origin that persists or recurs following a negative initial esophagogastric and colonoscopic evaluation [11, 15, 16]. OGIB (approximately 5% of GI bleeding) [16] may be categorized as overt or occult; overt is defined as clinically evident bleeding and occult bleeding refers to situations where clinically evident bleeding is not apparent [14, 16]. OGIB sources are subtle mucosal lesions that do not cause significant small bowel deformity [17]. OGIB is most commonly from vascular ectasia (22–29%), followed by ulcers due to NSAID use, inflammatory bowel disease or of uncertain origin (6–12%) [11, 18]. Tumors of the small bowel account for 3–5% of OGIB [7, 19]. Establishing a diagnosis for OGIB can be difficult, and incurs cost and time; extensive testing including small bowel radiology, EGD, push enteroscopy (to visualize small bowel mucosa 50–100 cm distal to the ligament of Treitz), balloon-assisted enteroscopy, and colonoscopy often fail to demonstrate the bleeding source [20–23]. VCE has improved the diagnostic yield in these patients, identifying a bleeding source in about half of those with OGIB. When comparing VCE with CT angiogram, small bowel barium radiography, push enteroscopy, and cross-sectional imaging, VCE has a higher diagnostic yield in determining a cause for OGIB [20, 23]. VCE detects pathology in 87% of patients, with a miss rate of 10%, whereas other comparative modalities detect pathology only in 13% of patients, with a 73% miss rate [24]. VCE can detect occult OGIB with iron-deficiency anemia (IDA) in 30–50% of patients and obscure OGIB with or without IDA in 50–80% of patients. Nonetheless, in roughly 30% of IDA cases, a definitive diagnosis cannot be made [16]. In obscure OGIB, the sooner the VCE is performed following the bleeding event, the greater is the diagnostic yield. When EGD and colonoscopy are negative, based on the clinical situation, VCE or angiographic study as a diagnostic procedure may be chosen [13].

Anemia

The Third National Health and Nutrition Examination Survey (NHANES III 1998–1996) indicated that over nine million US citizens have anemia, with iron deficiency accounting for a fifth of the causes in the over 65 age group. Anemia is a marker for increased disease-related morbidity including hospitalization and mortality [17, 25]. VCE can help visualize the small bowel following EGD and colonoscopy [14, 17, 25]. The most frequent lesions found in anemia are angiodysplasias, jejunal/ileal ulcers, tumors/polyps, erosive gastritis, Crohn's disease, jejunal and ileal mucosal atrophy (celiac disease) [25].

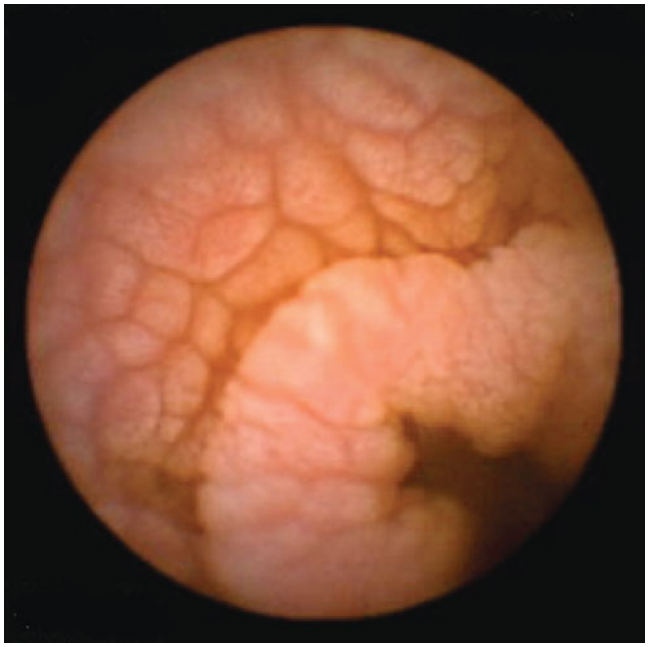

Fig. 24.1 Celiac disease: mosaic pattern suggestive of celiac disease [17]

Missed cases of celiac disease on routine EGD examination are accidentally diagnosed following VCE. The prevalence of celiac disease in the elderly and the clinical importance of diagnosing this disease are discussed in chapter 52. The mucosal changes include mucosal atrophy (lack of villi), layering, mosaic pattern, scalloping, ulcerations and intussusception [17] (Figs. 24.1, 24.2, and 24.3).

NSAID-Induced Ulcers and Capsule Endoscopy

NSAID use is common among older adults and accounts for 1–2% of serious gastrointestinal outcomes (ulceration, perforation, bleeding) [26]. NSAIDs increase gastrointestinal permeability 12 h following administration; inflammatory changes of the small bowel are visible through VCE within 10 days of ingesting NSAIDs [26] (Fig. 24.4). Small bowel inflammation is visible after just a week of NSAID use. NSAID use is linked to a variety of lesions in the small and large bowel including bleeding, protein loss, strictures, increased intestinal permeability, and NSAID enteropathy [19, 27]. Serious complications of NSAID use include diaphragm-like strictures (diaphragm disease, Fig. 24.5) and small bowel perforations [26].

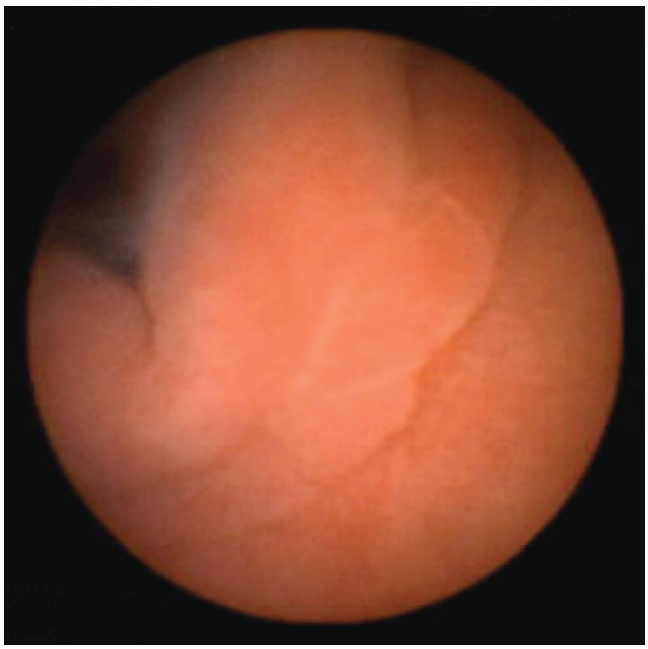

Fig. 24.2 Celiac disease: mucosal atrophy suggestive of celiac disease [17]

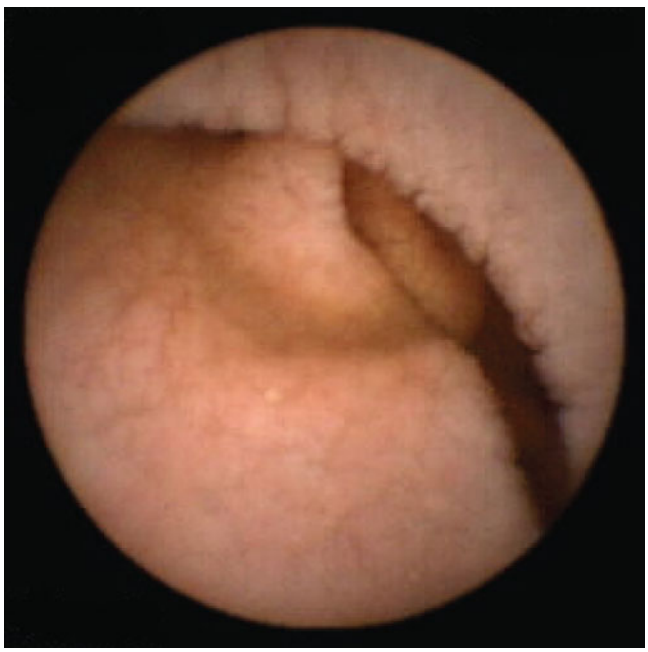

Fig. 24.3 Celiac disease: scalloping suggestive of celiac disease

Crohn's Disease and VCE

VCE is an effective tool for the diagnosis of suspected Crohn's disease in patients with normal upper endoscopy and colonoscopy, identification of a bleeding source, determining extent of disease, evaluation of patients with intermediate colitis, and response to anti-inflammatory therapy [1, 28, 29]. The diagnostic yield of VCE in suspected Crohn's disease ranges from 40 to 70% for both known and suspected Crohn's disease [1, 29], but it is unclear whether abnormalities detected are always clinically relevant. Patients with Crohn's disease are at increased risk of retention of capsule

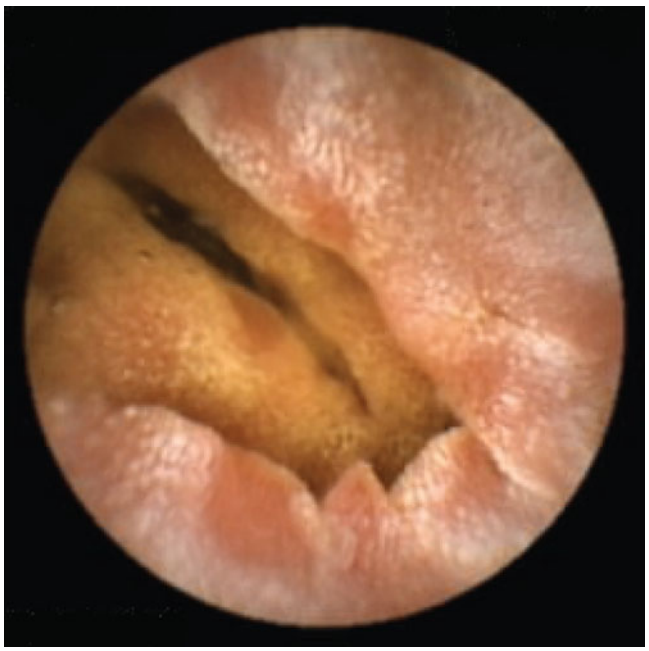

Fig. 24.4 Seventy-five-year-old woman with arthritis and chronic iron deficiency anemia. Medications include ferrous sulfate daily and Ibuprofen daily. Evaluation with EGD and colonoscopy was negative. Video capsule endoscopy (VCE) showed numerous NSAID-induced ulcers

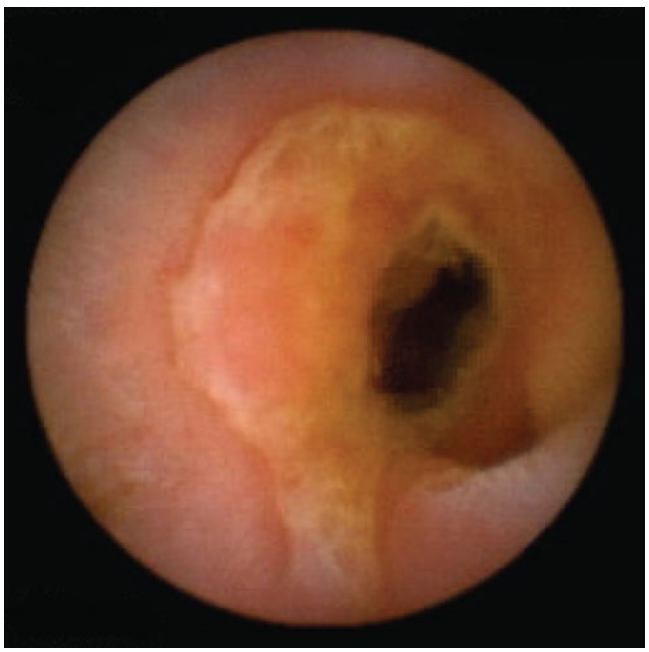

Fig. 24.5 Sixty-five-year-old woman with severe abdominal pain and iron deficiency anemia. Initial evaluation with EGD and CT scan of the abdomen and pelvis were negative. Multiple circumferential ulcers found on VCE as seen above (diaphragm lesions)

[27]. The benefit from a prior small bowel follow through or CT scan of the abdomen is not clear. Agile patency capsule (Given Imaging) reliably predicts safe capsule endoscopy [30]. The passage of the agile capsule in the stool by the patient, the absence of radiofrequency signal detected by a handheld scanner or absence of the capsule on abdominal radiography almost excludes an obstructing lesion and a safe subsequent real capsule endoscopy [7, 30].

Small Bowel Tumors

Small bowel tumors (see Figures 24.6 and 24.7) represent 2% of all gastrointestinal malignancies with lymphomas accounting for 12% of primary neoplasms of the small bowel [31]. A major prognostic factor is the stage of the disease, to determine treatment. Diagnostic modalities including endoscopic ultrasound, computed tomography, and magnetic resonance imaging usually fail to detect lymphomas of the small bowel [31]. VCE is a useful diagnostic tool for gastrointestinal tumors since approximately 6.5% of gastrointestinal lymphomas originate within the small and large bowel [31]. Patients presenting with gastric lymphoma can be screened with VCE for small bowel involvement as the treatment strategy can be altered based on gastrointestinal findings [31]. VCE also has a role in assessing the successful treatment of and follow-up of patients with known gastrointestinal lymphoma [31].

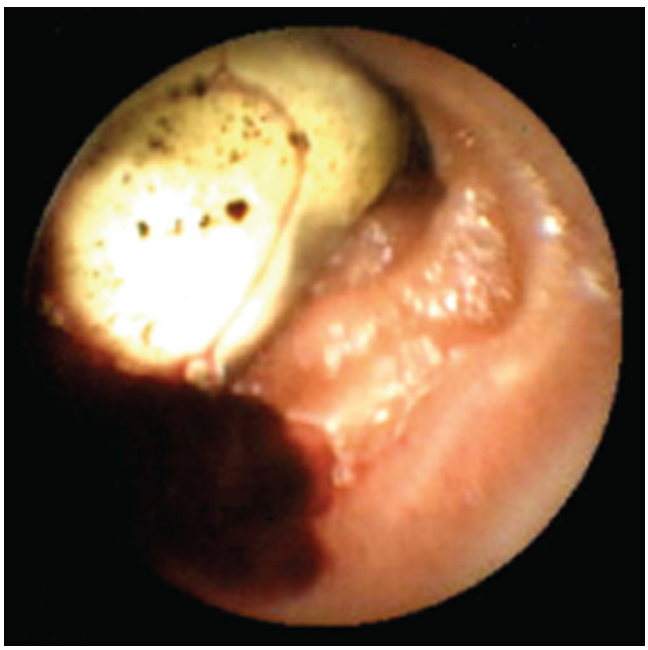

Fig. 24.6 Seventy-four-year-old man presented with LGIB. Multiple EGDs and colonoscopies were nondiagnostic. VCE showed food particles covering a small intestinal tumor with active bleeding

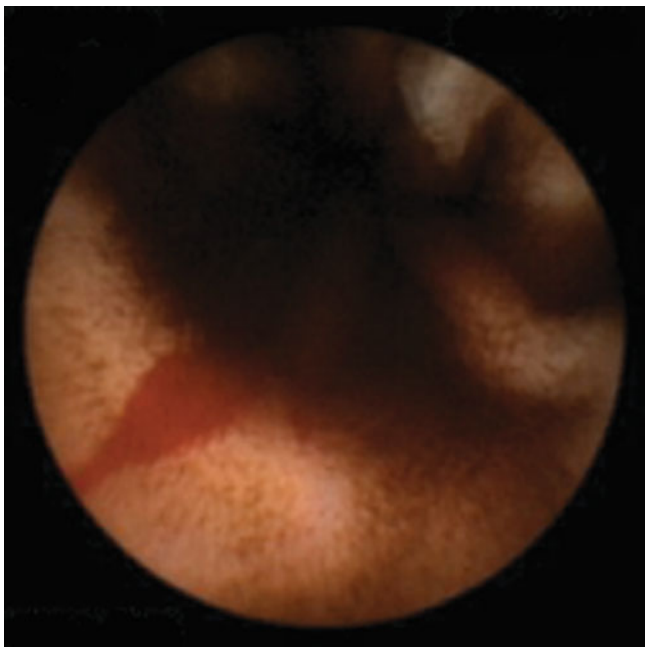

Fig. 24.7 Eighty-year-old man presented with severe anemia. An EGD and colonoscopy were negative. VCE demonstrated active bleeding in the distal ileum

Special Considerations of Video Capsule Endoscopy in the Older Adult (Table 24.2)

The most common indication for VCE in the older adult is obscure or occult gastrointestinal bleeding, whereas in the younger adult, it is used to evaluate suspected small bowel Crohn's disease and chronic diarrhea of unknown origin [6].

The failure rate of VCE in the general population is about 20%, similar to that observed in the older adult [6]. A major difference between the younger (age <65) and older age group (age >65) is the small bowel transit time, which influences completion of the procedure [6]. One way to overcome prolonged transit time or impaired swallowing in the older adult is to place the capsule beyond the pylorus with the assistance of an upper gastrointestinal endoscope [32]. Another consideration is the interference of signal transmission with the concomitant use of cardiac pacemakers or other implanted electromechanical devices (such as pacemaker) (Table 24.2),

Table 24.2 Concerns in performing video capsule endoscopy in the elderly

Inadequate visualization
Poor preparation in older adults with impairments
Motility disorders/incomplete visualization of the small bowel
Capsule retention
Concerns with pacemakers

a common scenario in the older adult [4, 33]. These problems appear to be more perception than reality [2, 4, 11, 33].

Contraindications for Capsule Endoscopy

An important concern with VCE is the potential retention of the capsule within the gastrointestinal tract [27, 28, 34]. Capsule retention is seen in patients with (a) prior abdominal surgery, (b) suspected obstruction, (c) small bowel strictures, and (d) Crohn's disease [11, 34, 35]. In the event the capsule is not spontaneously excreted and cannot be removed endoscopically, surgery may be required [27]. The risk of capsule retention and impaction increases with the aforementioned concerns when the capsule gets lodged in a narrowed segment of small bowel and causes further obstruction (Fig. 24.8). The retention rate is about 1%; most patients are asymptomatic and have partial obstruction or symptomatic complete intestinal obstruction [29]. Capsule retention in Crohn's disease can reach 8% [1]. Failure of the passage of the capsule is an acceptable outcome in patients if it demonstrates a site of obstruction when surgery to remove the capsule results in clinical improvement for which the VCE was originally performed [27].

Absolute contraindications include clinical or radiographic evidence of gastrointestinal obstruction, active and extensive Crohn's disease with or without presence of strictures, and extensive intestinal diverticulosis [11].

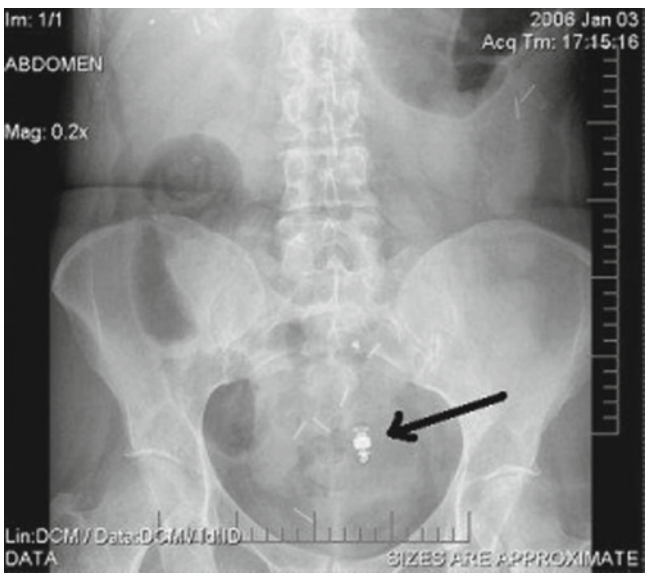

Fig. 24.8 Retained capsule

Limitations of Capsule Endoscopy

There are a few limitations for VCE. The expected life span of the battery is a maximum of 8 h and 45 min. About 10–20% of capsules do not reach the cecum; here battery failure can cause inadequate visualization of small bowel pathology [36]. Battery failure is more common in patients with delayed gastric emptying or when the capsule sits in the stomach for over 1.5 h [11]. Image quality may be influenced by the presence of bile, poor bowel preparation, or residual barium from previous radiographic studies. Up to 40% of all lesions can be missed due to inability to control the velocity or direction of the capsule passage [35]. Furthermore, the images are not in real-time; therefore on-the-spot treatment and histopathologic confirmation of the findings is not possible [35].

Key Points

- Wireless video capsule endoscopy (VCE) is a noninvasive method of visualizing the entire small bowel.
- VCE is an effective diagnostic tool to detect obscure gastrointestinal bleeding sites in the small bowel.
- VCE is an effective tool to evaluate anemia in the elderly, tumors of the small bowel, Crohn's disease, and nonsteroidal ulcers.
- With VCE, there is no discomfort of passage of an endoscope and the problems associated with intravenous sedation.
- The older adult may find it difficult to swallow the capsule; postgastric surgery and gastroparesis may pose delay in the capsule exiting the stomach. Endoscopic placement of the capsule may be needed.
- Other problems with VCE in the elderly include inadequate visualization, capsule retention, and an occasional need for surgical removal of the retained capsule.
- Theorized concerns in using VCE in patients with pacemakers are not proven.

References

1. Eliakim R. Video capsule endoscopy of the small bowel. Curr Opin Gastroenterol. 2010;26(2):129–33.
2. Moglia A, Menciassi A, Dario P, Cuschieri A. Capsule endoscopy: progress update and challenges ahead. Nat Rev Gastroenterol Hepatol. 2009;6(6):353–62.
3. Moglia A, Pietrabissa A, Cuschieri A. Capsule endoscopy. BMJ. 2009;339:796–9.

4. Payeras G, Piqueras J, Moreno VJ, Cabrera A, Menendez D, Jimenez R. Effects of capsule endoscopy on cardiac pacemakers. Endoscopy. 2005;37(12):1181–5.
5. Swain P. Wireless capsule endoscopy. Gut. 2003;52 Suppl 4:iv48–50.
6. Papadopoulos AA, Triantafyllou K, Kalantzis C, Adamopoulos A, Ladas D, Kalli T, et al. Effects of ageing on small bowel video-capsule endoscopy examination. Am J Gastroenterol. 2008;103(10): 2474–80.
7. McAlindon ME, Sanders DS, Sidhu R. Capsule endoscopy: 10 years on and in the frontline. Frontline Gastroenterol. 2010;1:82–7.
8. Gerson LB. Preparation before capsule endoscopy: the value of the purge. Gastroenterology. 2009;137(3):1166–8; discussion 8.
9. Eliakim R, Fireman Z, Gralnek IM, Yassin K, Waterman M, Kopelman Y, et al. Evaluation of the PillCam Colon capsule in the detection of colonic pathology: results of the first multicenter, prospective, comparative study. Endoscopy. 2006;38(10):963–70.
10. Lee NM, Eisen GM. 10 years of capsule endoscopy: an update. Expert Rev Gastroenterol Hepatol. 2010;4(4):503–12.
11. Liao Z, Gao R, Xu C, Li ZS. Indications and detection, completion, and retention rates of small-bowel capsule endoscopy: a systematic review. Gastrointest Endosc. 2010;71(2):280–6.
12. Van Gossum A, Munoz-Navas M, Fernandez-Urien I, Carretero C, Gay G, Delvaux M, et al. Capsule endoscopy versus colonoscopy for the detection of polyps and cancer. N Engl J Med. 2009; 361(3):264–70.
13. Laine L, Sahota A, Shah A. Does capsule endoscopy improve outcomes in obscure gastrointestinal bleeding? Randomized trial versus dedicated small bowel radiography. Gastroenterology. 2010;138(5):1673–80 e1; quiz e11–2.
14. Pasha SF, Hara AK, Leighton JA. Diagnostic evaluation and management of obscure gastrointestinal bleeding: a changing paradigm. Gastroenterol Hepatol (NY). 2009;5(12):839–50.
15. Zuckerman GR, Prakash C, Askin MP, Lewis BS. AGA technical review on the evaluation and management of occult and obscure gastrointestinal bleeding. Gastroenterology. 2000;118(1):201–21.
16. Rockey DC. Occult and obscure gastrointestinal bleeding: causes and clinical management. Nat Rev Gastroenterol Hepatol. 2010;7(5):265–79.
17. Muhammad A, Pitchumoni CS. Newly detected celiac disease by wireless capsule endoscopy in older adults with iron deficiency anemia. J Clin Gastroenterol. 2008;42(9):980–3.
18. Lin S, Rockey DC. Obscure gastrointestinal bleeding. Gastroenterol Clin North Am. 2005;34(4):679–98.
19. Allison MC, Howatson AG, Torrance CJ, Lee FD, Russell RI. Gastrointestinal damage associated with the use of nonsteroidal antiinflammatory drugs. N Engl J Med. 1992;327(11):749–54.
20. Saperas E, Dot J, Videla S, Alvarez-Castells A, Perez-Lafuente M, Armengol JR, et al. Capsule endoscopy versus computed tomographic or standard angiography for the diagnosis of obscure gastrointestinal bleeding. Am J Gastroenterol. 2007;102(4):731–7.
21. Leung WK, Graham DY. Obscure gastrointestinal bleeding: where do we go from here? Gastroenterology. 2010;138(5):1655–8.
22. Friedman S. Comparison of capsule endoscopy to other modalities in small bowel. Gastrointest Endosc Clin N Am. 2004;14(1): 51–60.
23. Triester SL, Leighton JA, Leontiadis GI, Fleischer DE, Hara AK, Heigh RI, et al. A meta-analysis of the yield of capsule endoscopy compared to other diagnostic modalities in patients with obscure gastrointestinal bleeding. Am J Gastroenterol. 2005;100(11): 2407–18.
24. Lewis BS, Eisen GM, Friedman S. A meta-analysis of capsule endoscopy versus alternative modalities in the diagnosis of small bowel pathologies. Gastrointest Endosc. 2004;59(5):P105.
25. Riccioni ME, Urgesi R, Spada C, Cianci R, Pelecca G, Bizzotto A, et al. Unexplained iron deficiency anaemia: is it worthwhile to perform capsule endoscopy? Dig Liver Dis. 2010;42(8):560–6.
26. Maiden L, Thjodleifsson B, Theodors A, Gonzalez J, Bjarnason I. A quantitative analysis of NSAID-induced small bowel pathology by capsule enteroscopy. Gastroenterology. 2005;128(5): 1172–8.
27. Cheifetz AS, Lewis BS. Capsule endoscopy retention: is it a complication? J Clin Gastroenterol. 2006;40(8):688–91.
28. Swain P. Wireless capsule endoscopy and Crohn's disease. Gut. 2005;54(3):323–6.
29. Fleischer D. Capsule imaging. Clin Gastroenterol Hepatol. 2005; 3(7 Suppl 1):S30–2.
30. Spada C, Spera G, Riccioni M, Biancone L, Petruzziello L, Tringali A, et al. A novel diagnostic tool for detecting functional patency of the small bowel: the Given patency capsule. Endoscopy. 2005;37(9):793–800.
31. Flieger D, Keller R, May A, Ell C, Fischbach W. Capsule endoscopy in gastrointestinal lymphomas. Endoscopy. 2005;37(12): 1174–80.
32. Yachimski PS, Friedman LS. Gastrointestinal bleeding in the elderly. Nat Clin Pract Gastroenterol Hepatol. 2008;5(2):80–93.
33. Dirks MH, Costea F, Seidman EG. Successful videocapsule endoscopy in patients with an abdominal cardiac pacemaker. Endoscopy. 2008;40(1):73–5.
34. Lewis B. How to prevent endoscopic capsule retention. Endoscopy. 2005;37(9):852–6.
35. Papadakis KA, Lo SK, Fireman Z, Hollerbach S. Wireless capsule endoscopy in the evaluation of patients with suspected or known Crohn's disease. Endoscopy. 2005;37(10):1018–22.
36. Tatar EL, Shen EH, Palance AL, Sun JH, Pitchumoni CS. Clinical utility of wireless capsule endoscopy: experience with 200 cases. J Clin Gastroenterol. 2006;40(2):140–4.

GastroIntestinal Radiology

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Judith K. Amorosa and C.S. Pitchumoni

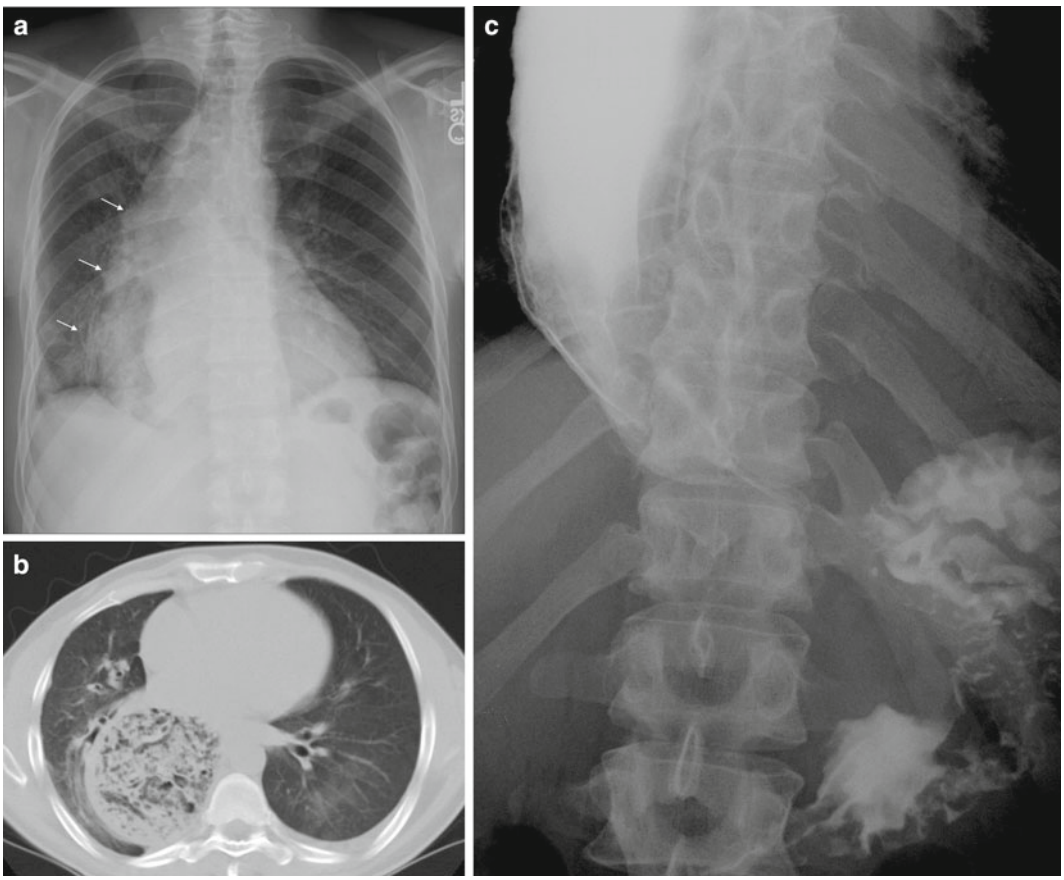

Fig. 25.1 A 73-year-old woman is evaluated for progressive dysphagia, for solid foods and liquids. She has frequent episodes of regurgitation of undigested food and weight loss. Now she presents with acute chest pain. (**a**) PA chest X-ray shows a mass density along the entire right mediastinum (*white arrows*). (**b**) Axial CT with pulmonary window setting through the lower chest shows particulate material in a distended esophagus. (**c**) Esophagram shows distended esophagus filled with contrast, demonstrating beak like narrowing in its distal portion in the area of achalasia. Diagnosis: Achalasia

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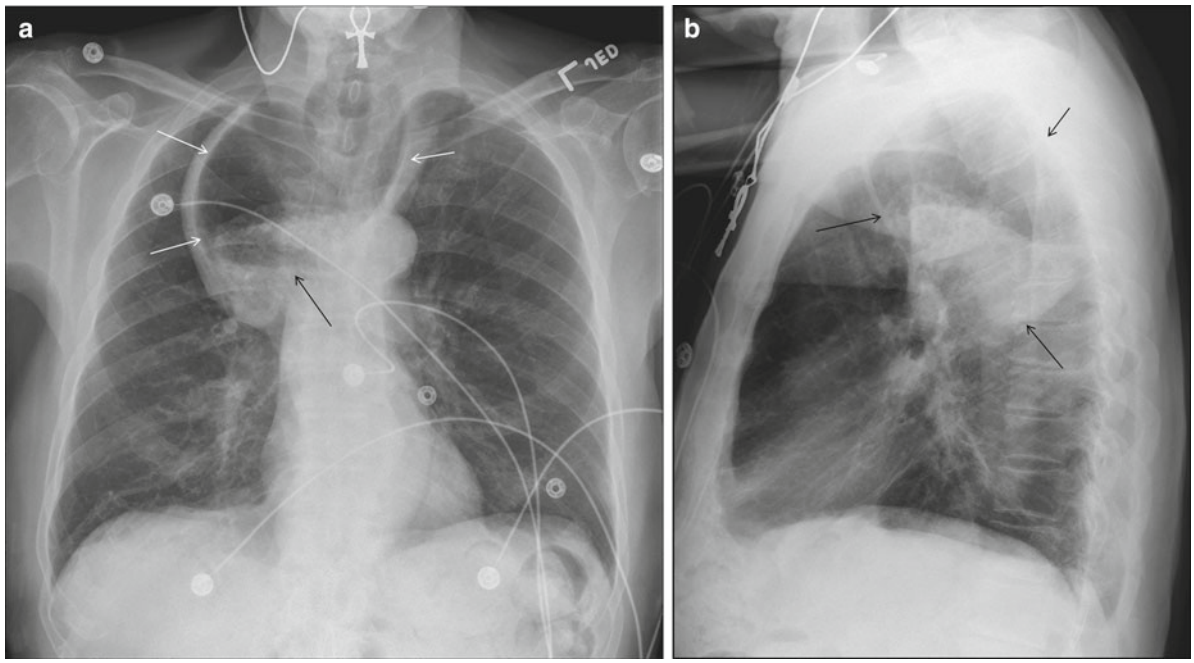

Fig. 25.2 A 90-year-old man presents with halitosis and otherwise asymptomatic. (**a**) PA chest X-ray shows a large air-fluid (*black arrow*) containing structure (*white arrows*) in the upper chest. (**b**) Lateral chest X-ray shows the air-fluid containing structure (*black arrows*) to be in the superior posterior portion of the chest. This is a large Zenker's diverticulum filled with food. Diagnosis: Zenker's diverticulum

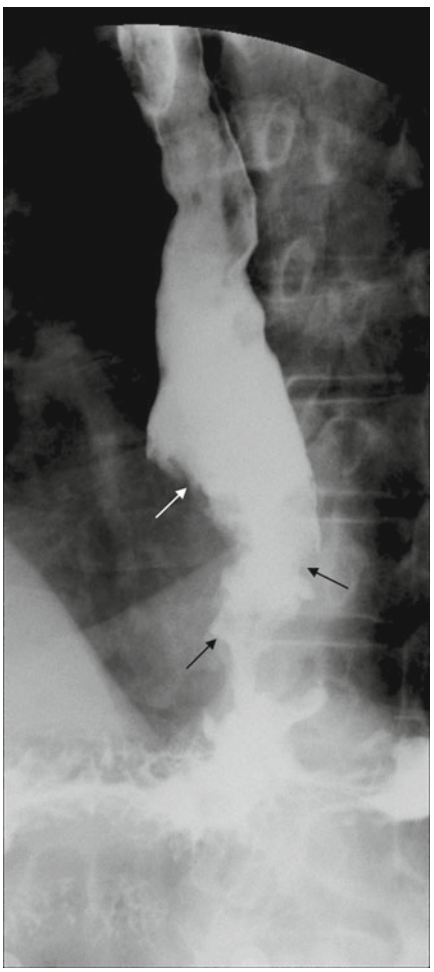

Fig. 25.3 A 65-year-old man with dysphagia and weight loss for a month, unable to keep down solid foods. Esophagram shows irregular narrowing of the distal esophagus with a shelf like appearance (*white arrow*) due to the mass protruding into the lemen. The more distal irregularities indicate tumor masses (*black arrows*). Diagnosis: Esophageal cancer

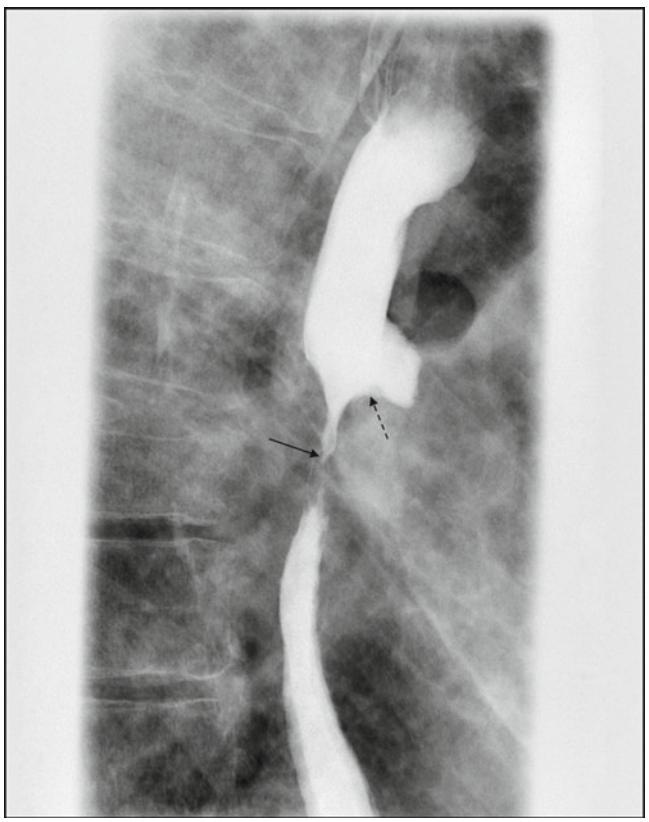

Fig. 25.4 A 68-year-old man with difficulty swallowing and weight loss. Esophagram shows a high grade stenosis (2 cm) and irregular narrowing more distally (*solid black arrow*). Shelf like deformity (*dash black arrow*) proximally is secondary to tumor mass. Diagnosis: Esophageal cancer

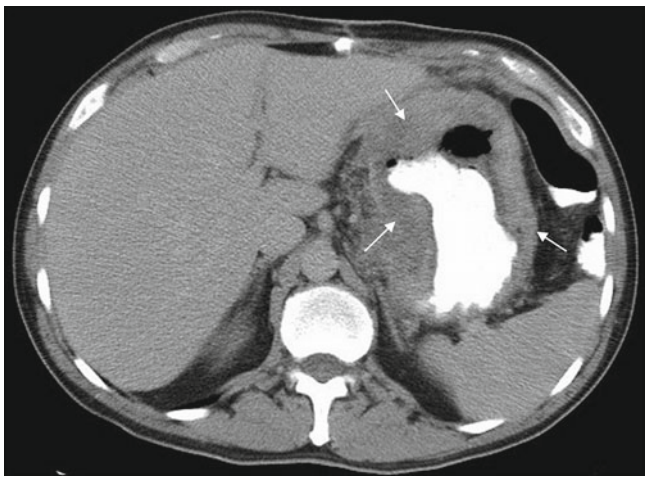

Fig. 25.5 An 80-year-old man is evaluated for a 3-month history of progressive, dull, constant, non-radiating epigastric pain. The patient has had weight loss with early satiety and nausea. Axial oral contrast enhanced CT image at the level of the gastric fundus shows a thick infiltrating mass (*white arrows*) which surrounds the irregular contrast filled lumen. Diagnosis: Gastric cancer

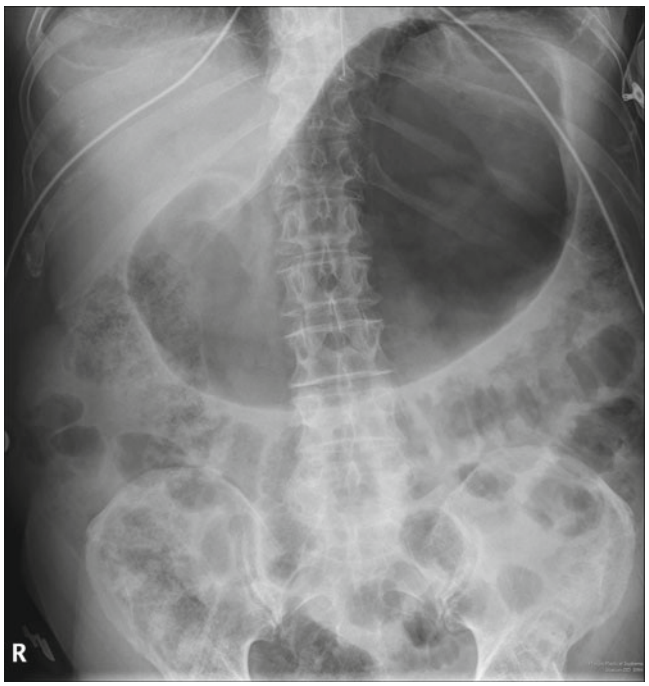

Fig. 25.6 A 70-year-old woman with long standing, hard to control type 2 diabetes mellitus is evaluated for a 6-month history of nausea, vomiting, early satiety, and postprandial bloating. Supine abdominal image shows distended, air filled stomach. Diagnosis: Gastroparesis

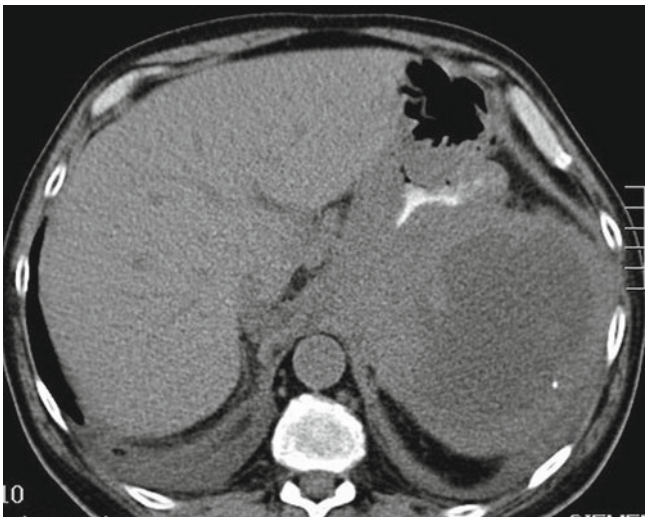

Fig. 25.7 A 67-year-old man with left upper quadrant abdominal pain, early satiety, and vomiting. Axial oral contrast enhanced CT image shows contrast in the fundus, a large mass displacing the fundus. The mass contains low density material (probably necrotic tumor). Diagnosis: Gastric tumor

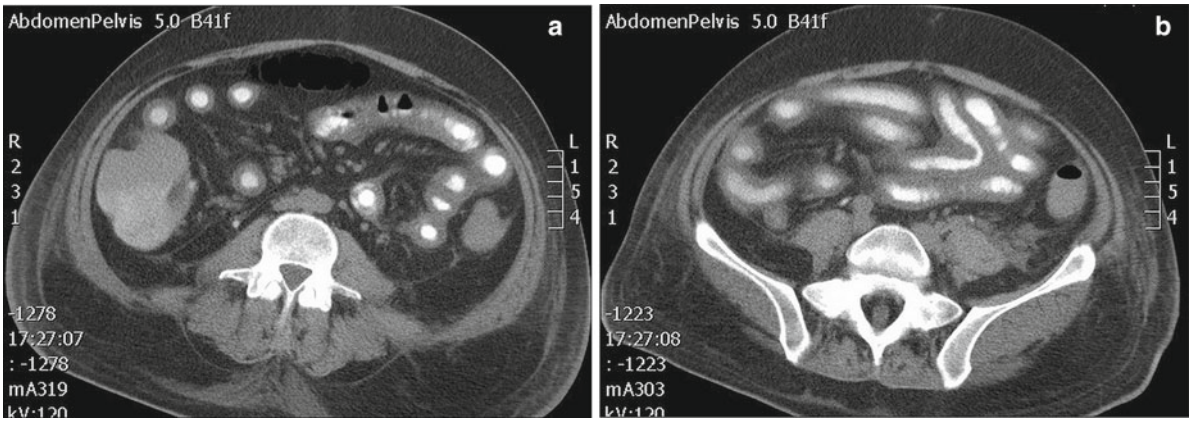

Fig. 25.8 A 74-year-old woman after returning from a trip developed severe diarrhea and crampy abdominal pain. (**a**, **b**) Axial oral contrast enhanced CT images in the lower abdomen/upper pelvis level shows diffuse small bowel, predominantly ileal wall thickening without definite obstruction. Diagnosis: Enteritis

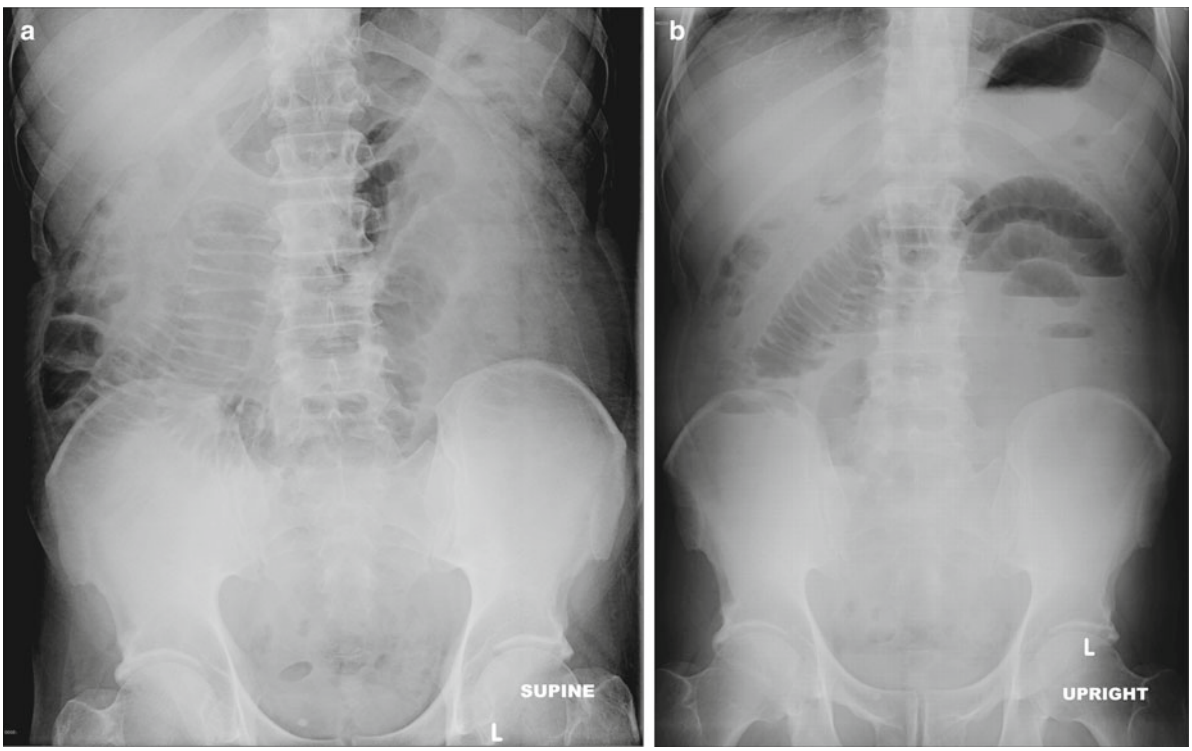

Fig. 25.9 A 69-year-old man with a history of prior abdominal surgery presents with abdominal distention. (**a**) Supine abdominal image shows distended loops of bowel in the mid abdomen with circumferential markings (valvulae conniventes) indicating the presence of distended small bowel loops. Some air is present in the colon, suggesting the diagnosis of partial small bowel obstruction (SBO). (**b**) Erect, upright abdominal image shows no free air, air fluid levels in the distended small bowel loops are present. Diagnosis: Partial small bowel obstruction

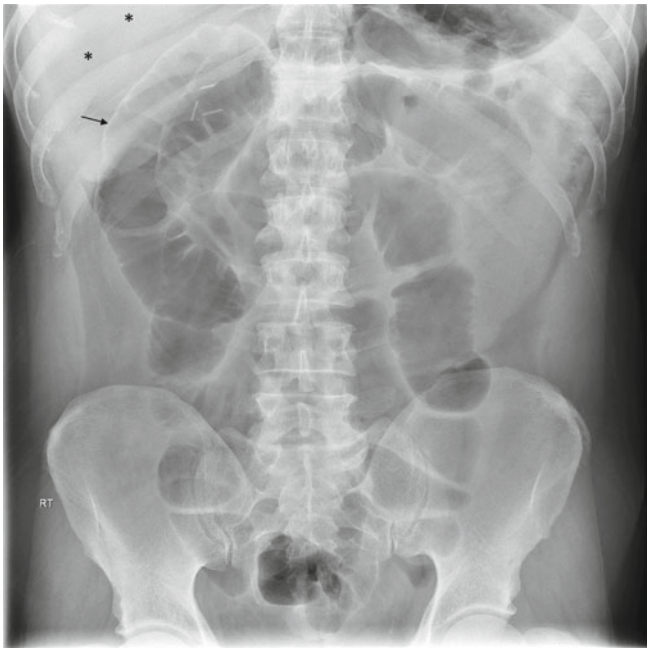

Fig. 25.10 A 68-year-old woman presents with acute abdominal pain. Supine abdominal image shows previous cholecystectomy and free air. Bowel loops are seen with air on both sides of the intestinal wall (termed the Rigler sign) (*black arrow*); the area of lucency depicts extra luminal air (*asterisks*). This is difficult to detect, warranting confirmation with a left lateral decubitus or erect image. Diagnosis: Free air in the peritoneal cavity

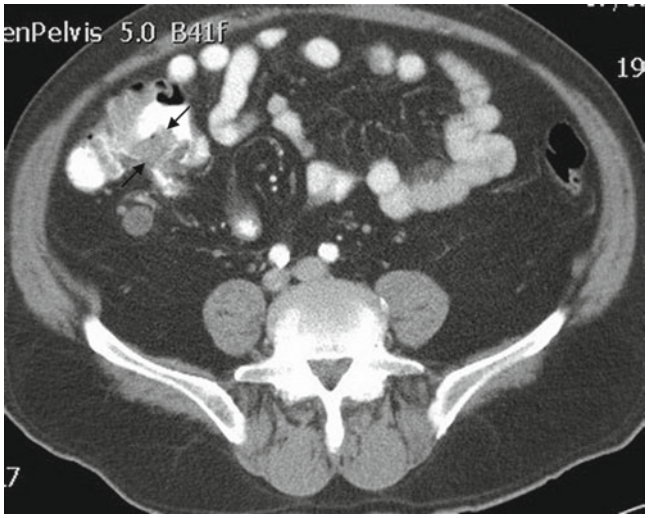

Fig. 25.11 A 77-year-old man with iron deficiency anemia. Axial oral and intravenous contrast enhanced CT image through the lower abdomen shows a mass in the cecum (*black arrows*). Diagnosis: Cecal carcinoma

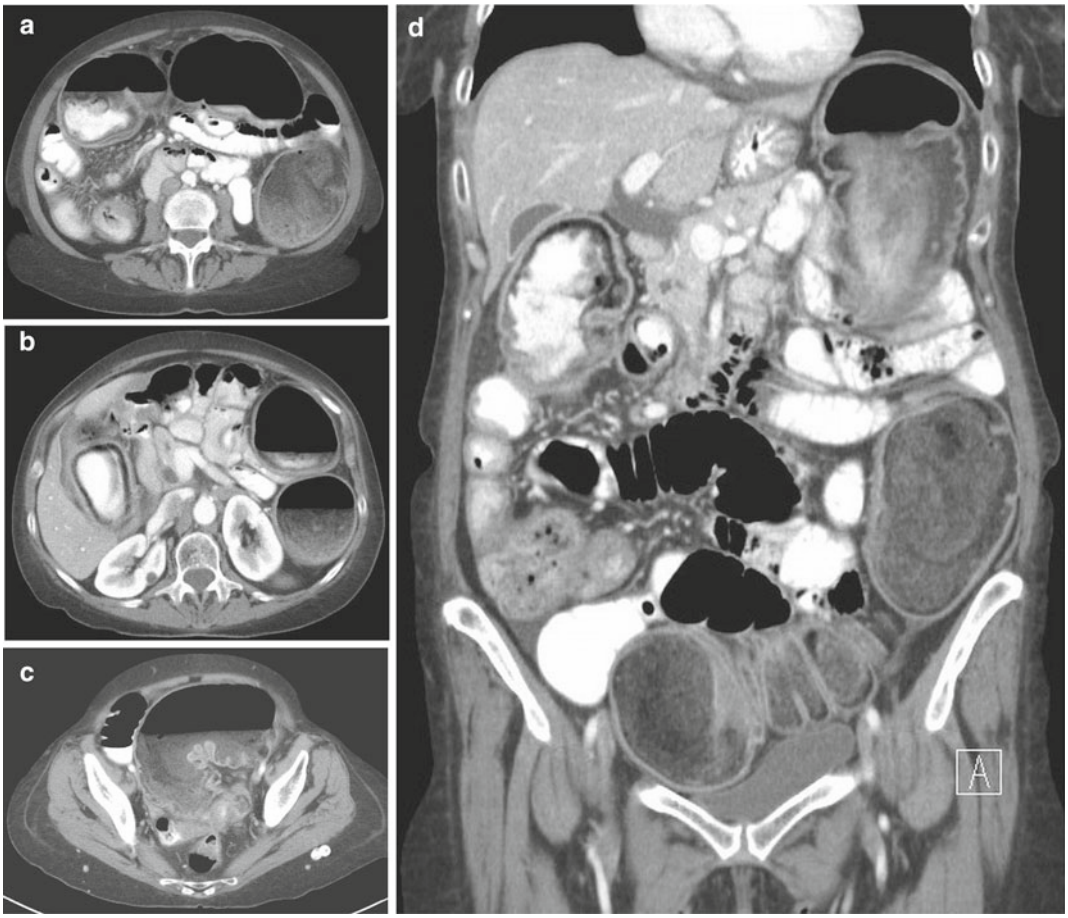

Fig. 25.12 A 68-year-old woman with distended abdomen and severe constipation. (**a**) Axial oral and intravenous contrast enhanced CT image through the upper abdomen shows the markedly distended colon: hepatic flexure is on the *right* and splenic flexure on the *left*. (**b**) Axial oral and intravenous contrast enhanced CT image through the mid abdomen shows distended, fecal material filled colon. Note the contrast filled normal caliber small bowel loops. (**c**) Axial oral and intravenous contrast enhanced CT image through the lower pelvic level shows the distended sigmoid colon and the collapsed rectum. (**d**) Coronal reconstructed CT image through the mid abdomen shows the colonic distention. Diagnosis: Cancer, sigmoid colon, with obstruction

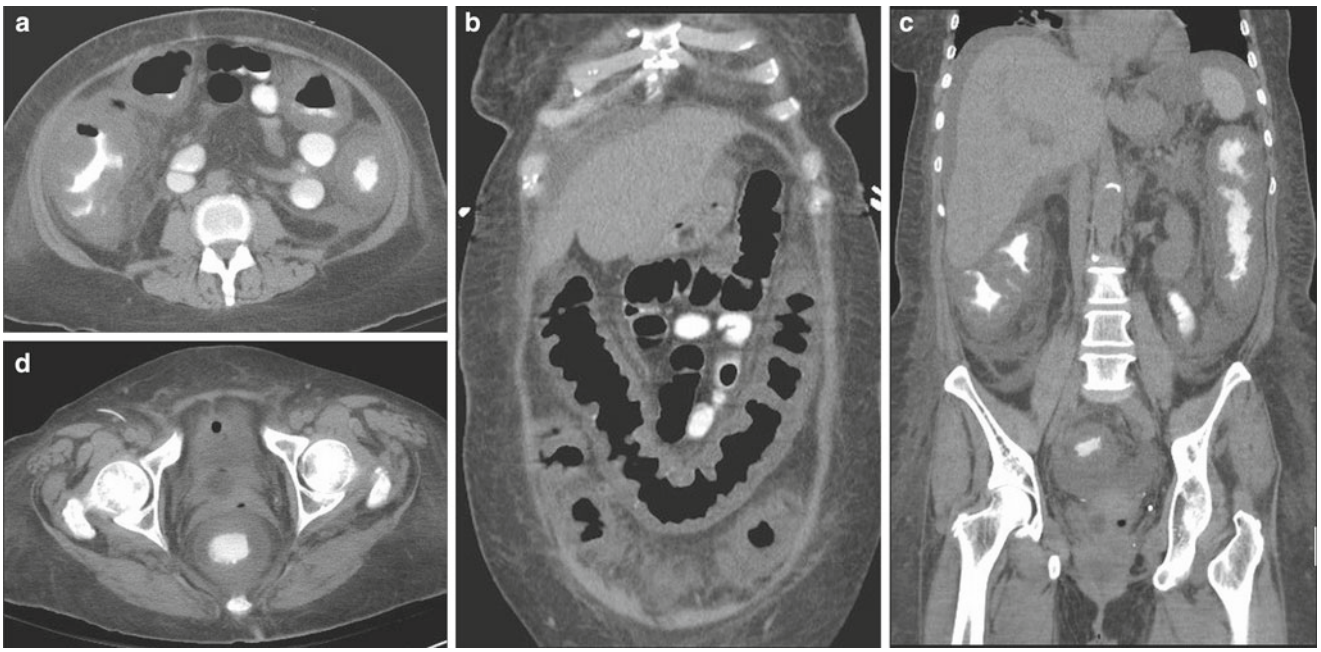

Fig. 25.13 A 72-year-old man on treatment for malignancy developed severe bloody diarrhea in the last 48 h. (**a**) Axial oral contrast enhanced CT image through the mid abdomen demonstrates marked thickening of the ascending and descending colon. (**b**) Coronal reconstructed CT image through the anterior abdomen shows markedly thickened colonic wall; note that air is present in the nondependent portion of the colon. (**c**) Coronal reconstructed CT image through the posterior abdomen (see vertebrae) shows colonic wall thickening, and of note, contrast in the dependent portion of the colon. (**d**) Axial oral contrast enhanced CT image through the lower pelvis shows markedly thickened rectal mucosa. Diagnosis: Severe colitis, pseudomembranous due to *C. difficile* infection

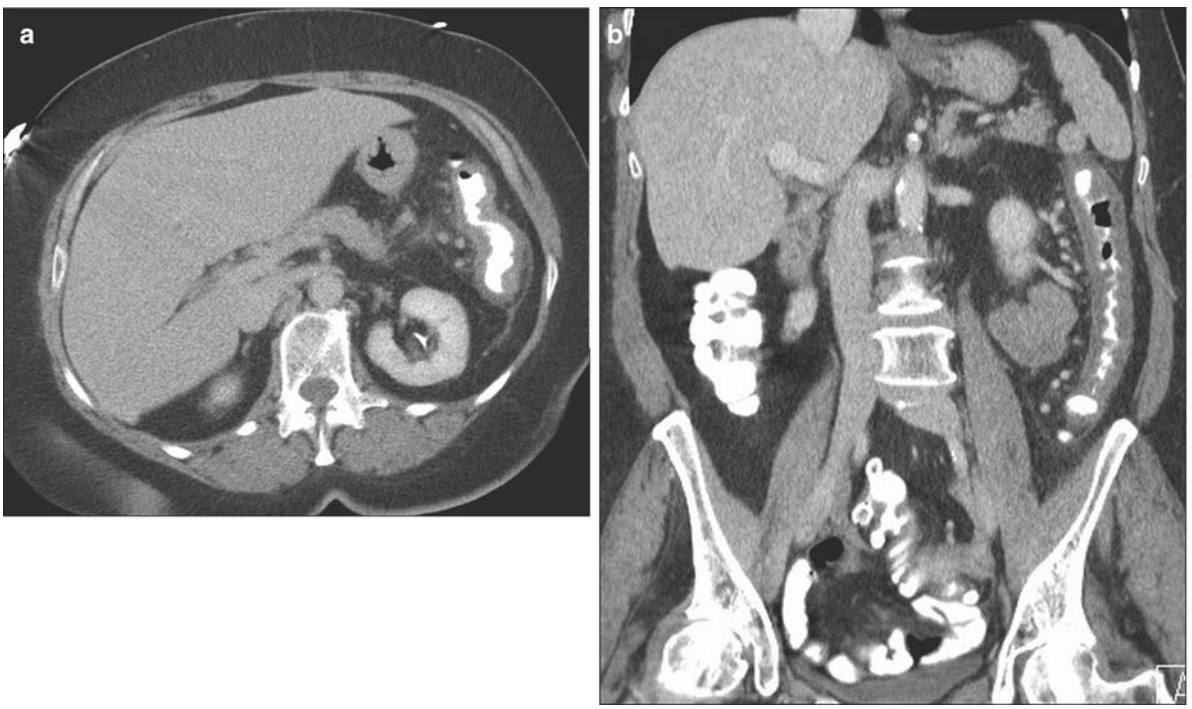

Fig. 25.14 An 82-year-old man presents with bloody diarrhea. He has a history of coronary artery disease and hyperlipidemia. (**a**) Axial oral and intravenous contrast enhanced image through the upper abdomen shows at the level of the splenic flexure thick colonic wall suggestive of ischemic colitis. (**b**) Coronal reconstructed image through the mid to posterior abdomen shows a thickened descending colonic wall, with a normal cecum. Diagnosis: Ischemic colitis

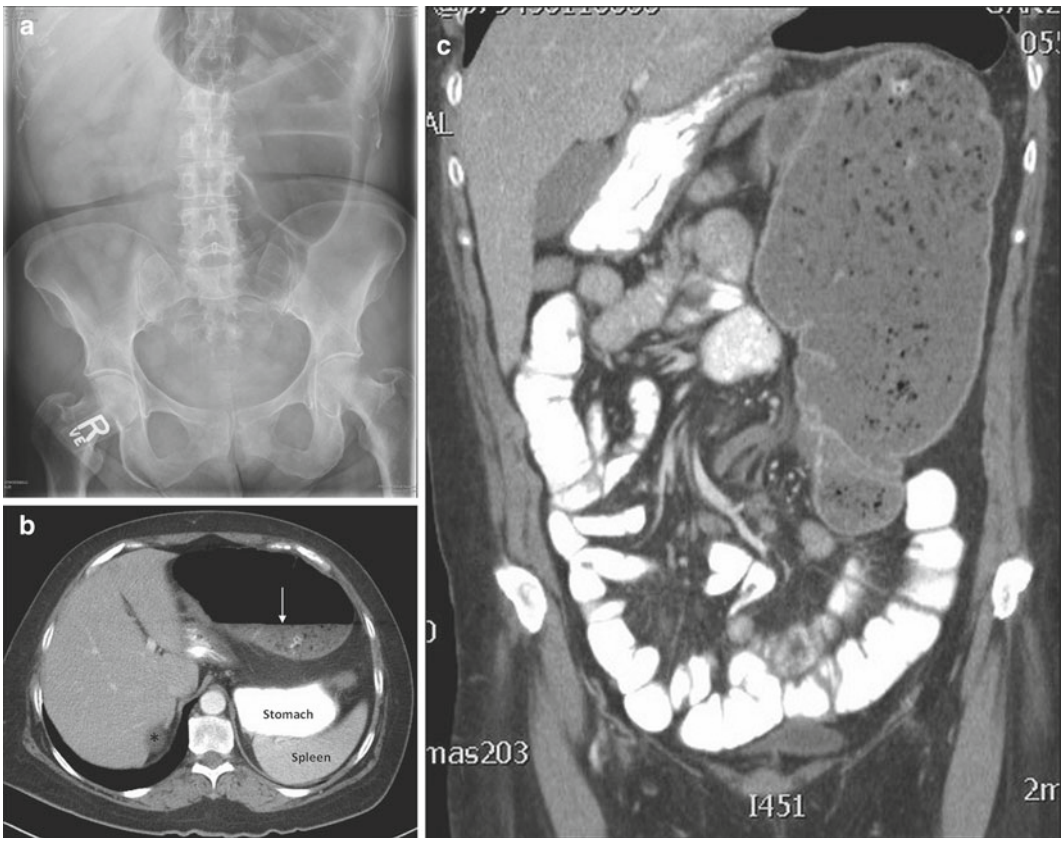

Fig. 25.15 A 65-year-old woman presents with acute diffuse abdominal pain. (**a**) Supine abdominal image shows a markedly distended air filled structure in the area of the stomach, with prominent haustral markings. (**b**) Axial oral and intravenous contrast enhanced image through the upper abdomen shows contrast filled gastric fundus and air and fecal material level in a more anterior structure (*fat containing right adrenal mass, reflecting an adenoma). (**c**) Coronal reconstructed image through the anterior abdomen shows markedly distended cecum filled with fecal material located in the mid to left upper abdomen. Diagnosis: Cecal volvulus

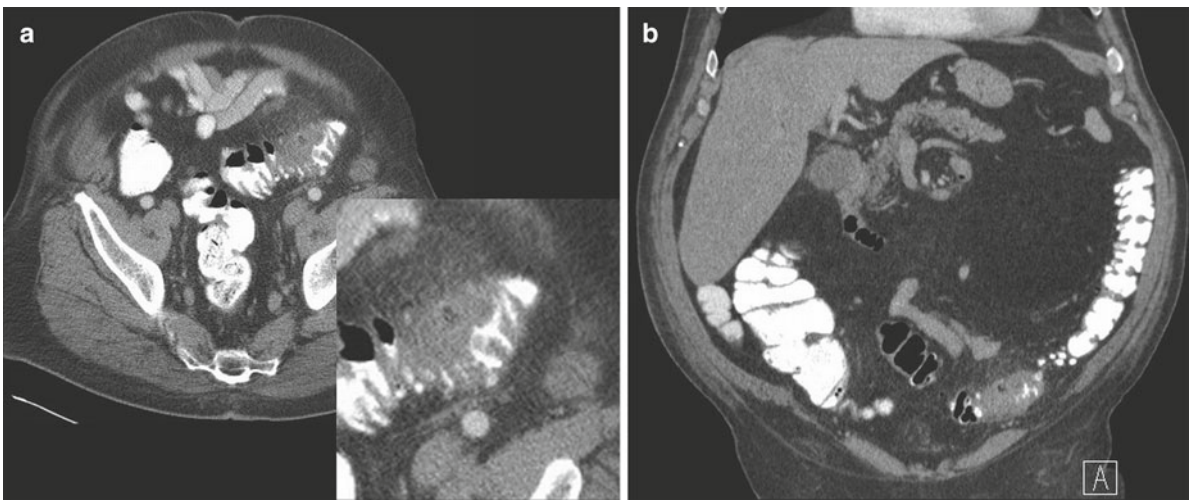

Fig. 25.16 An 83-year-old man with fever, leukocytosis, left lower quadrant (LLQ) abdominal pain, and tenderness. (**a**) Axial oral and intravenous contrast enhanced CT image through the mid pelvis with enlargement (inset) shows abnormal sigmoid colon with multiple diverticula. An intramural abscess is apparent, with soft tissue density and an air pocket. Adjacent to the abnormal sigmoid is infiltration of pericolic fat. (**b**) Coronal reconstructed CT image shows the abnormal sigmoid with an intramural abscess with air. Diagnosis: Diverticulitis with abscess

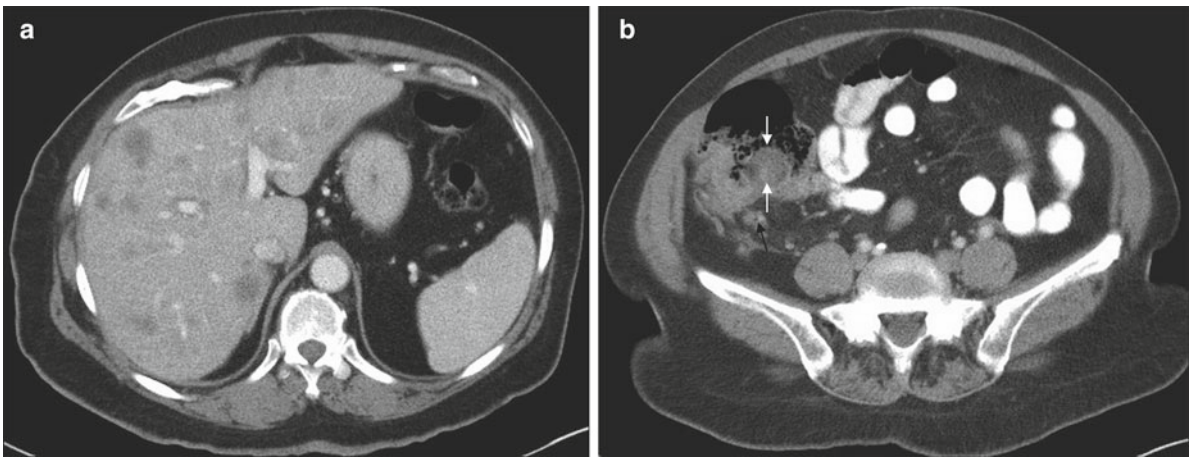

Fig. 25.17 A 77-year-old man with anemia and RUQ abdominal pain. (**a**) Axial oral and intravenous contrast enhanced CT image through the upper abdomen shows multiple focal liver lesions. (**b**) Axial oral and intravenous contrast enhanced CT image through the lower abdomen shows a mass (*white arrows*) in the cecum. An enlarged mesenteric lymph node is visible (*black arrow*). Diagnosis: Cecal carcinoma with hepatic metastases

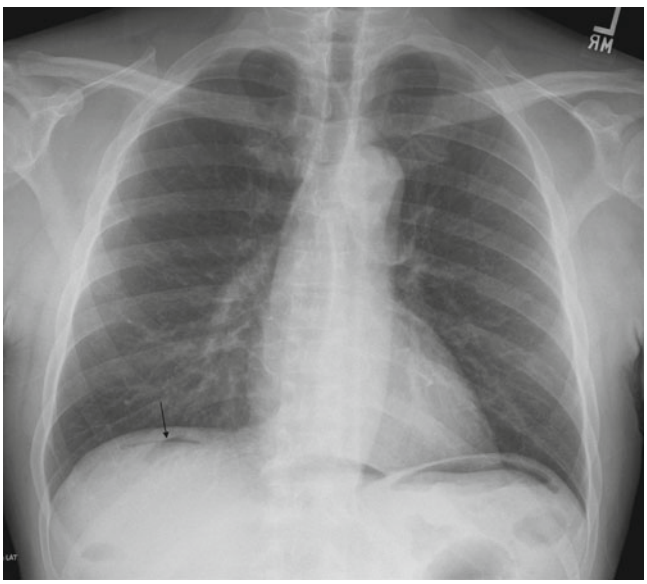

Fig. 25.18 A 73-year-old man presents with acute abdominal pain. Erect, upright PA (frontal) chest X-ray shows air (*black arrow*) under the diaphragms indicating free air in the peritoneal cavity, usually from a perforated viscus. Diagnosis: Perforated viscus

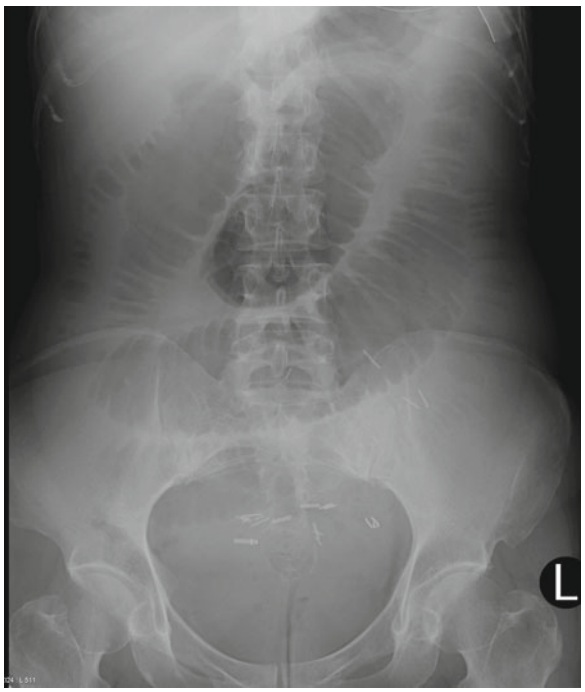

Fig. 25.19 A 65-year-old woman with prior colectomy now presents with abdominal pain and distension. Supine abdominal image shows surgical clips in the pelvis and distended small bowel loops. Diagnosis: Intestinal obstruction

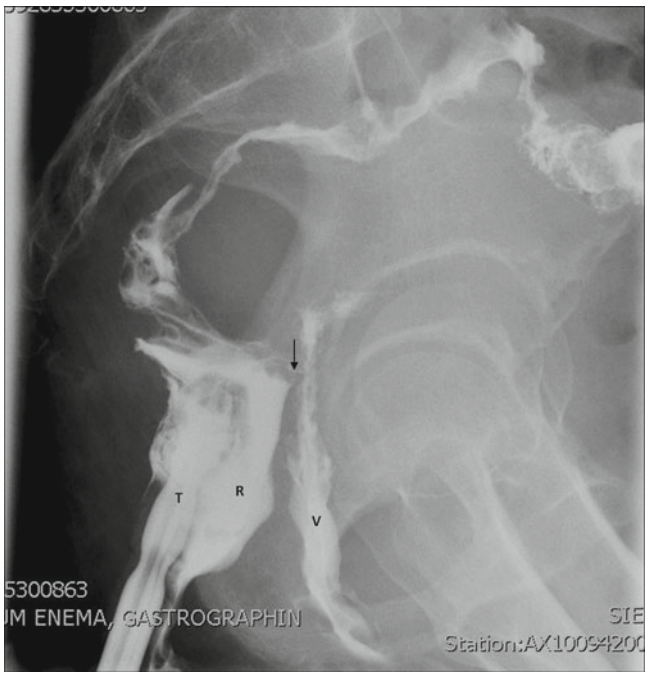

Fig. 25.20 A 78-year-old woman with prior radiation therapy now presents with foul smelling vaginal discharge. Lateral rectal image during gastrographin enema via rectal tube (T) shows a fistulous communication (*black arrow*) between the rectum (R) and vagina (V). Diagnosis: Rectovaginal fistula

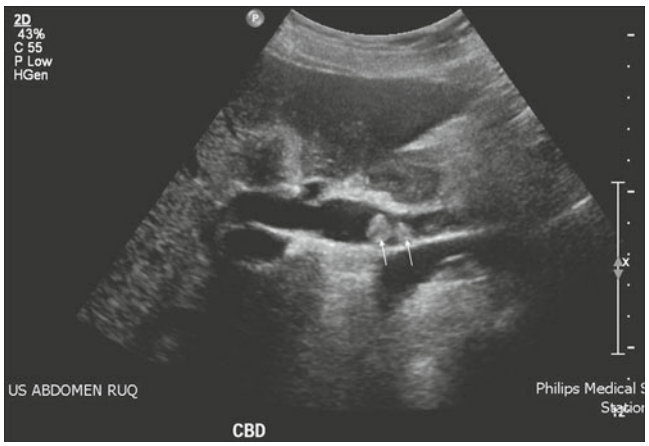

Fig. 25.21 A 67-year-old woman with a history of previous cholecystectomy has recurrent symptoms of biliary colic. Right upper quadrant ultrasound sagittal image shows a dilated CBD (common bile duct) with two round stones (*white arrows*), confirming stones in the CBD (choledocholithiasis). Diagnosis: Choledocholithiasis

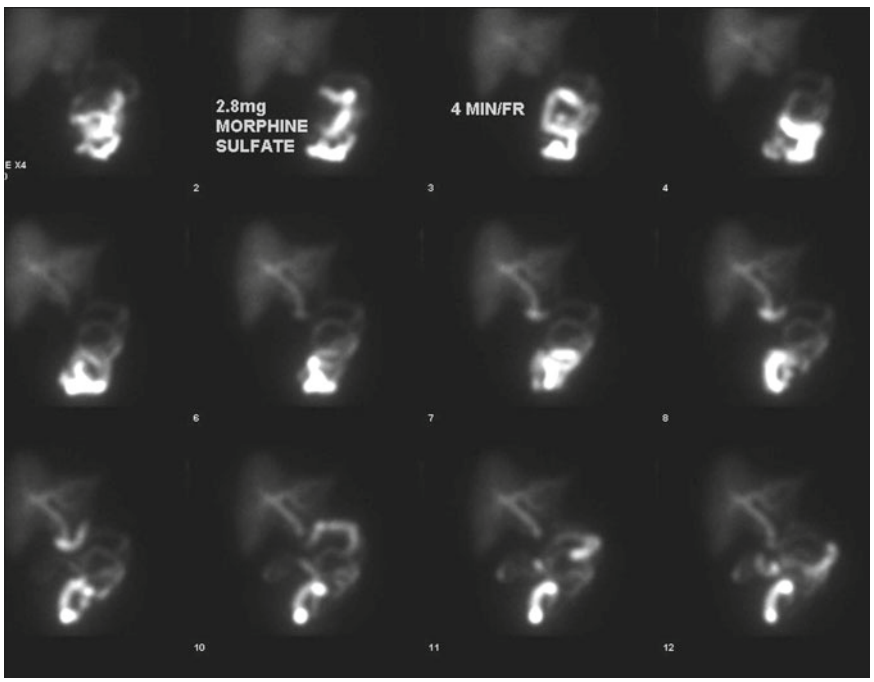

Fig. 25.22 A 72-year-old woman with RUQ abdominal pain. Hepatobiliary scan shows excretion of the radioactive tracer into the biliary tree and into the duodenum and more distal small bowel. The structure not filled with the radioactive tracer is the gallbladder indicating occluded cystic duct due to inflammation. Diagnosis: Acute cholecystitis

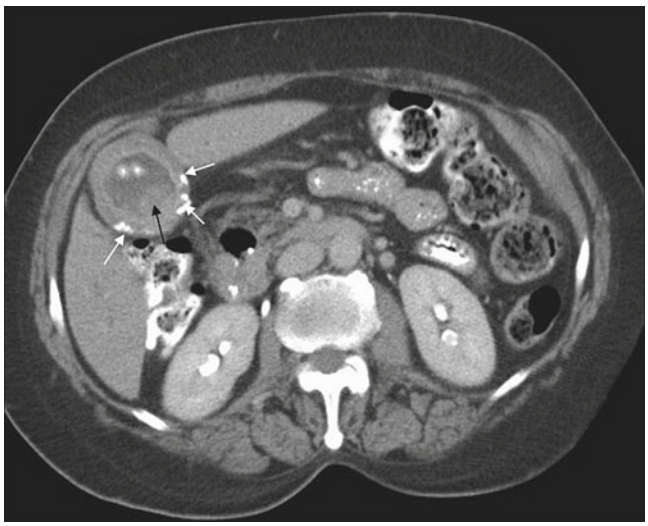

Fig. 25.23 A 77-year-old woman known to have gallstones presents with RUQ abdominal pain for about 6 weeks; she is afebrile. Axial oral and intravenous contrast enhanced CT image through the gallbladder shows thick gallbladder wall (about 6 mm), intermittent gallbladder wall calcification (*white arrows*), two gallstones, and a mass (*black arrows*) protruding into the gallbladder lumen. Diagnosis: Gallstones and gallbladder cancer

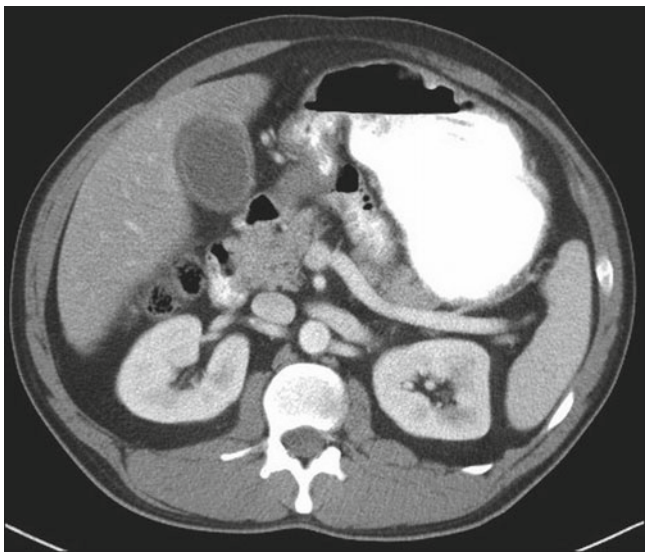

Fig. 25.24 A 67-year-old woman presents with postprandial RUQ abdominal pain that radiates to her right shoulder accompanied by fever, nausea, and vomiting. Axial oral and intravenous contrast administration through the upper abdomen shows gallbladder wall thickening. Diagnosis: Acute cholecystitis

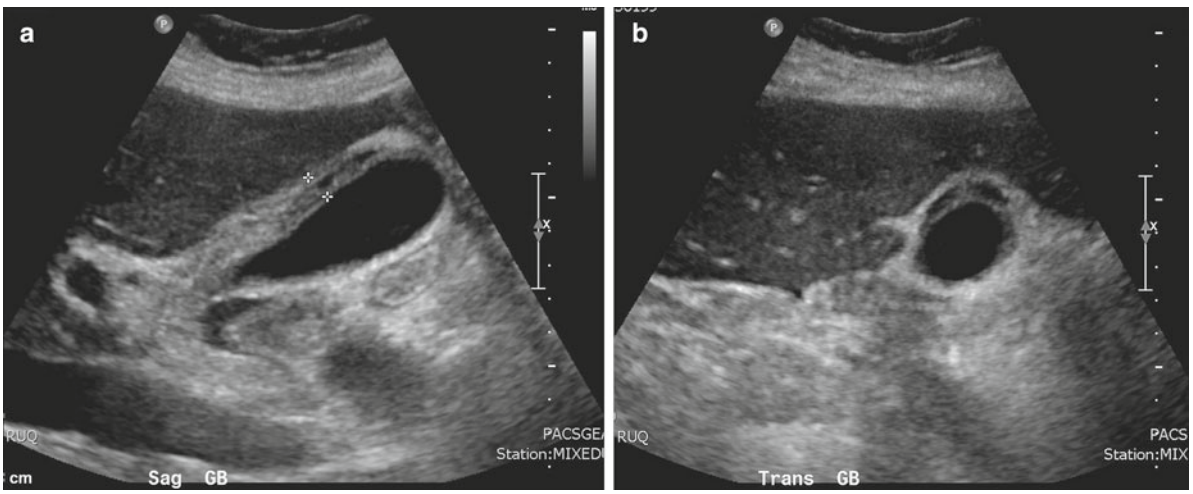

Fig. 25.25 A 79-year-old man with sepsis, severe RUQ abdominal pain and tenderness. (**a**) Sagittal real-time ultrasound shows thick gallbladder wall (6 mm) (*asterisks*). (**b**) Transverse real-time ultrasound shows thick gallbladder wall (6 mm). Diagnosis: Acute cholecystitis

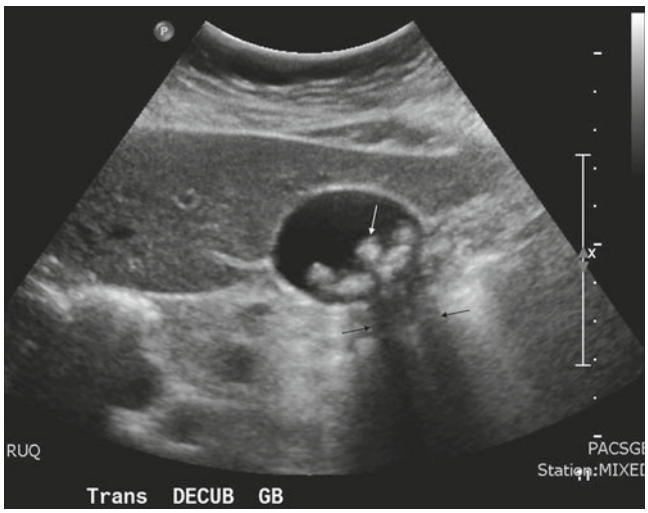

Fig. 25.26 A 65-year-old woman with RUQ abdominal pain and tenderness. Right upper quadrant decubitus ultrasound image shows multiple echogenic foci with acoustic shadowing (*black arrows*) within the gallbladder; these are gallstones (*white arrow*). Diagnosis: Gallstones

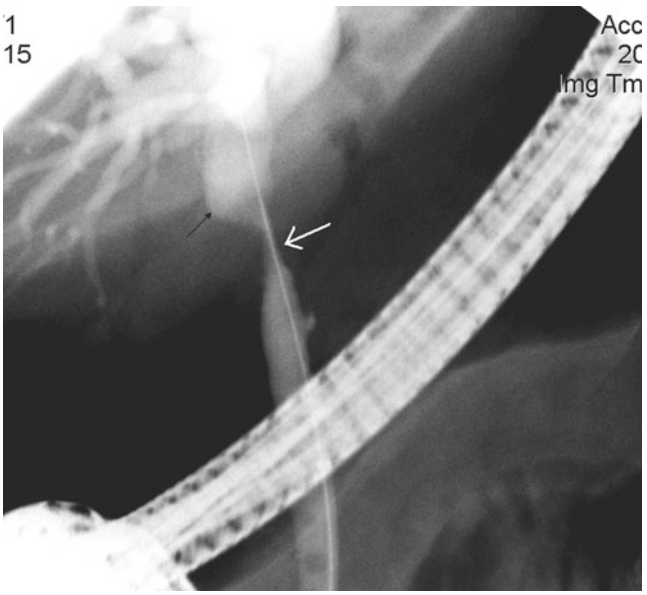

Fig. 25.28 A 65-year-old woman presents with jaundice. Spot image during ERCP shows catheter (*white arrow*) traversing biliary stricture; a dilated proximal CBD (*black arrow*) is present. Diagnosis: CBD stricture (courtesy of Satya Kastuar, MD. Saint Peters University Hospital)

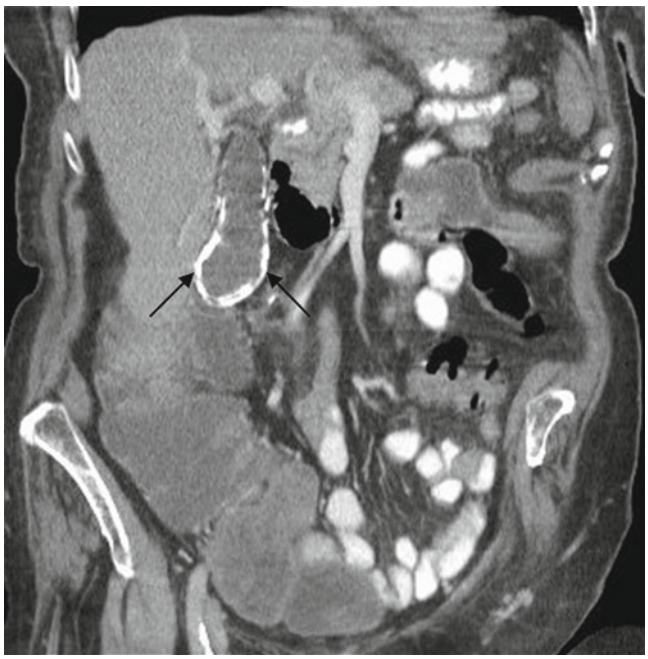

Fig. 25.27 A 75-year-old woman with upper abdominal pain. Coronal reconstructed oral and intravenous contrast enhanced CT image shows calcified gallbladder wall (*black arrows*). Diagnosis: Porcelain gallbladder

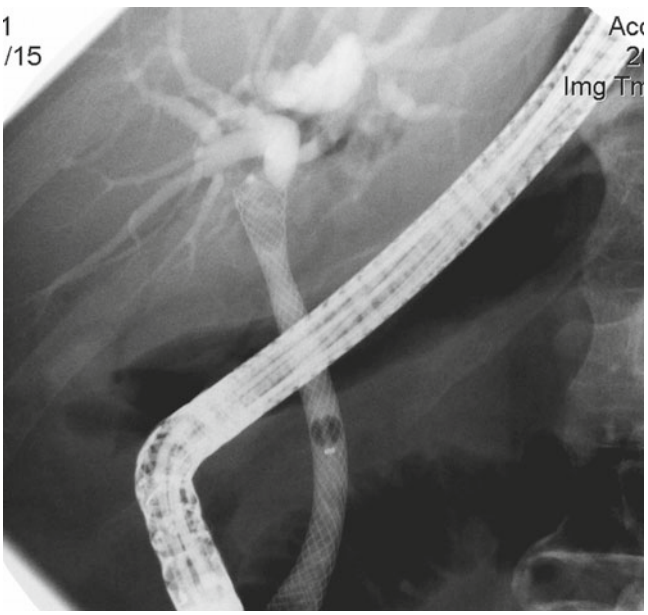

Fig. 25.29 A 70-year-old woman presents with jaundice and pruritus. Spot image during ERCP shows a metallic stent placed for the management of malignant stricture. Diagnosis: Biliary stent in place (courtesy of Satya Kastuar, MD. Saint Peters University Hospital)

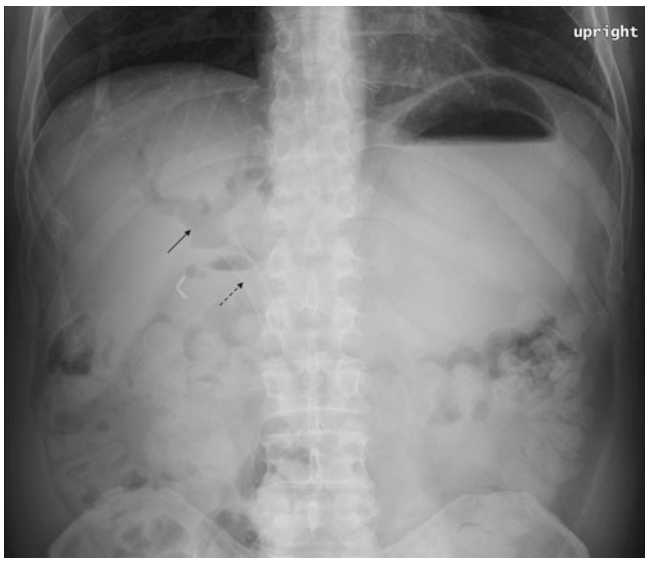

Fig. 25.30 A 68-year-old woman with a history of cholecystectomy, now status post-ERCP. Erect image of the upper abdomen demonstrates air in the biliary tree (*solid black arrow*), biliary stent in the CBD (*dash black arrow*), surgical clips for cholecystectomy, and moderately distended stomach. Diagnosis: Air in the biliary tree; stent in place

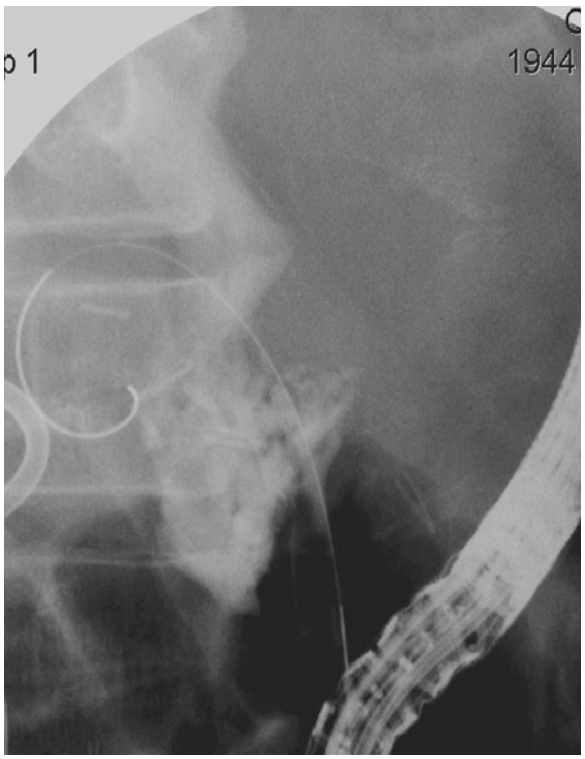

Fig. 25.32 A 65-year-old woman presents with severe RUQ abdominal pain the day after laparoscopic cholecystectomy. Spot image during ERCP shows *prominent* bile leak. Diagnosis: Postcholecystectomy complication: bile leak (courtesy of Satya Kastuar, MD. Saint Peters University Hospital)

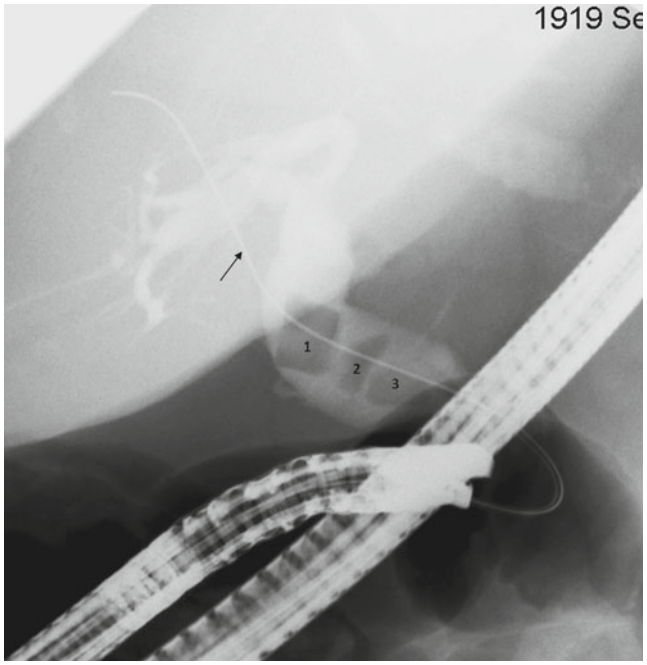

Fig. 25.31 A 70-year-old woman presents with RUQ abdominal pain and abnormal LFTs. Spot image during ERCP shows the endoscope through which a wire (*black arrow*) has been introduced into the biliary system. There are three stones (labeled 1, 2, 3) in the dilated CBD. Diagnosis: CBD stones (courtesy of Satya Kastuar, MD. Saint Peters University Hospital)

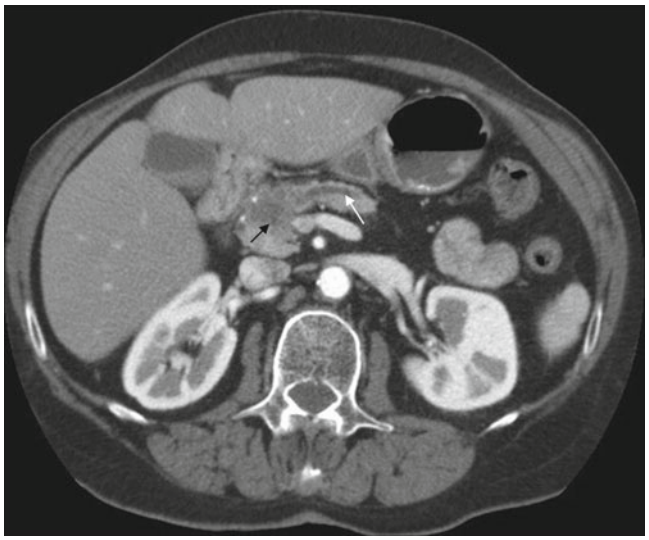

Fig. 25.33 A 79-year-old man presents with epigastric discomfort associated with weight loss, light colored stools, and dark urine. Axial intravenous contract enhanced CT image at the level of the head of the pancreas shows a 1.5 cm low attenuation area in the head of the pancreas (*black arrow*) with pancreatic duct dilatation (*white arrow*), suggesting an adenocarcinoma of the pancreas. Diagnosis: Pancreatic cancer

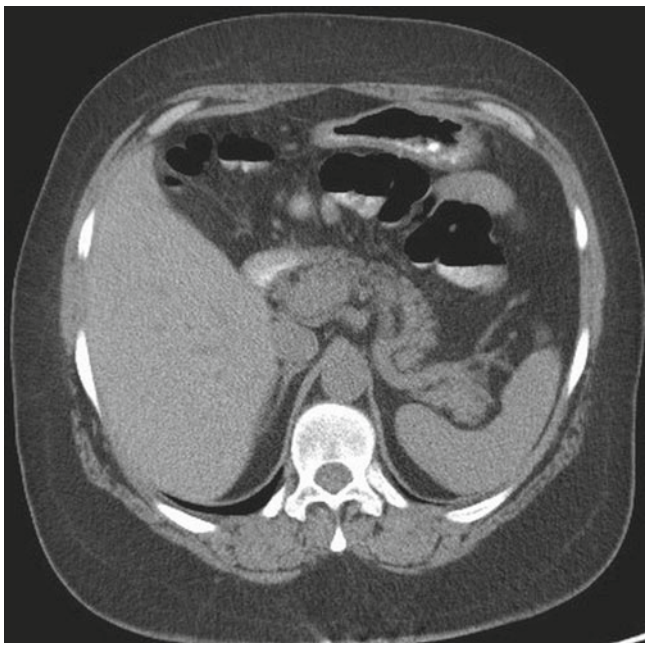

Fig. 25.34 A 72-year-old woman with previous left nephrectomy on follow-up CT. Axial oral contrast enhanced CT image at the level of the pancreas demonstrates a normal pancreas. Diagnosis: Normal pancreas

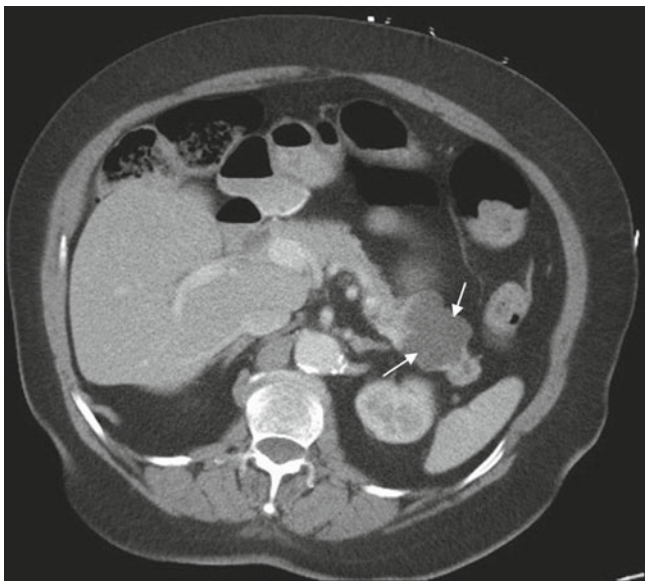

Fig. 25.35 A 76-year-old asymptomatic man had a chest CT as part evaluation to exclude lung cancer because of a long history of smoking. On a prior image of that CT a pancreatic mass was suspected, so a dedicated CT abdomen and pelvis was done. Axial intravenous contrast enhanced CT image at the level of the body and tail of the pancreas shows a 3.5 cm multilobulated mass (*white arrows*) with low attenuation material (40 HU—soft tissue density, not fluid) with enhancing borders, suggesting a cystic tumor. Diagnosis: Cystic tumor, tail of pancreas

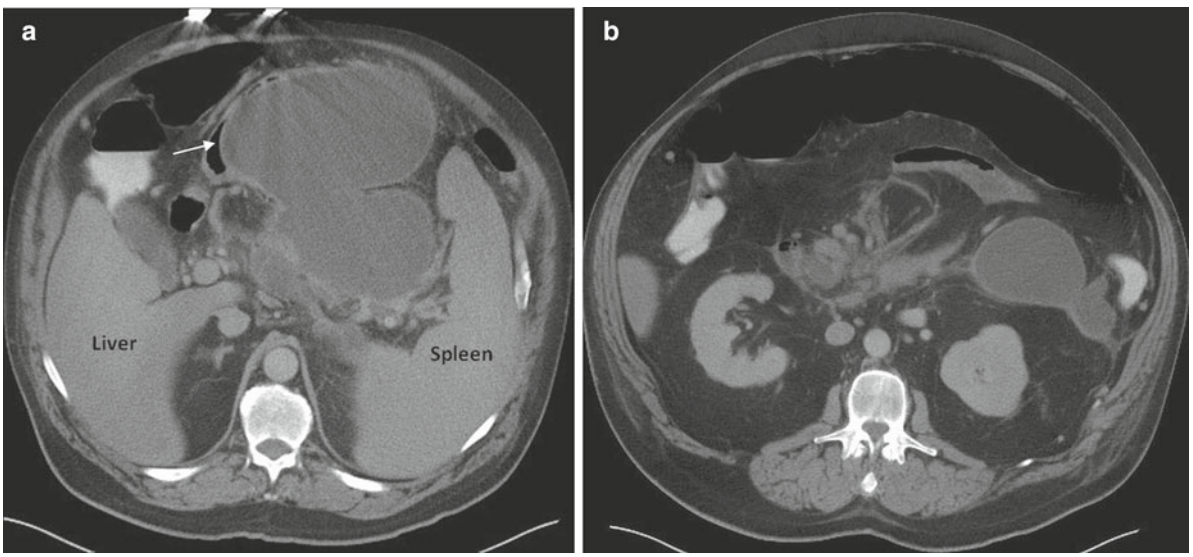

Fig. 25.36 A 65-year-old man with a history of chronic pancreatitis and severe abdominal pain with vomiting. (**a**) Axial oral and intravenous contrast enhanced CT image through the upper abdomen shows a large fluid collection anterior to the area of the pancreas; a definite normal pancreas is not identifiable. This collection is displacing the stomach (*white arrow*). (**b**) Axial oral and intravenous contrast enhanced CT image through the level of the kidneys demonstrates fluid beyond the tail of the pancreas in the retroperitoneal space; the collection is in the anterior pararenal space. Diagnosis: Pseudocyst of the pancreas

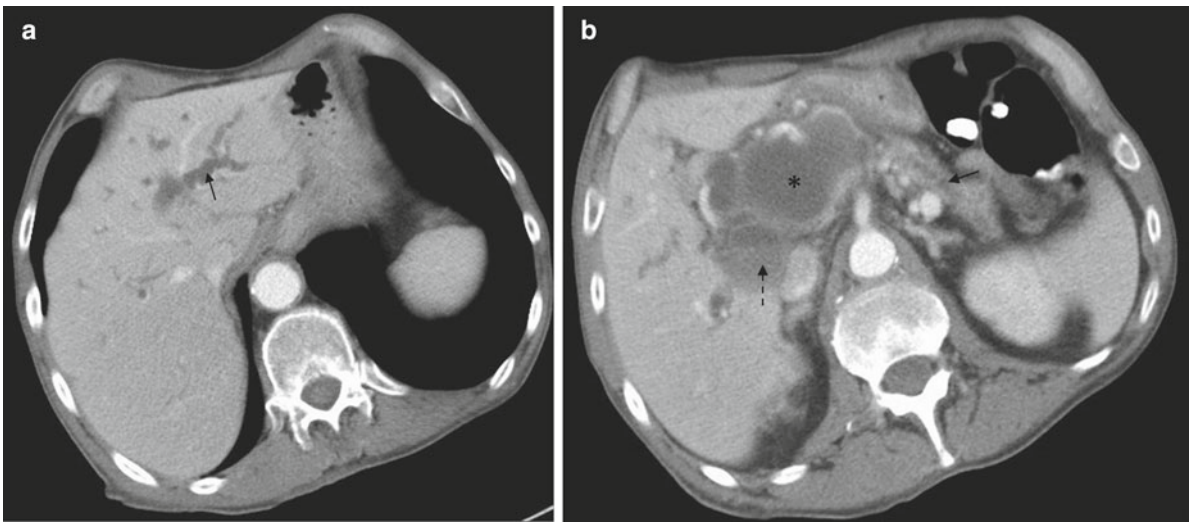

Fig. 25.37 A 72-year-old man presents with chronic upper abdominal pain. (**a**) Axial oral and intravenous contrast enhanced CT image through the upper abdomen shows intrahepatic biliary dilatation (*black arrow*). (**b**) Axial oral and intravenous contrast enhanced CT image through the level of the pancreas shows a fluid filled cyst (*asterisk*) near the area of the head of the pancreas and a dilated pancreatic duct (*solid black arrow*). There is sludge in the gallbladder (*interrupted black arrow*). Diagnosis: Cystic tumor of the pancreas

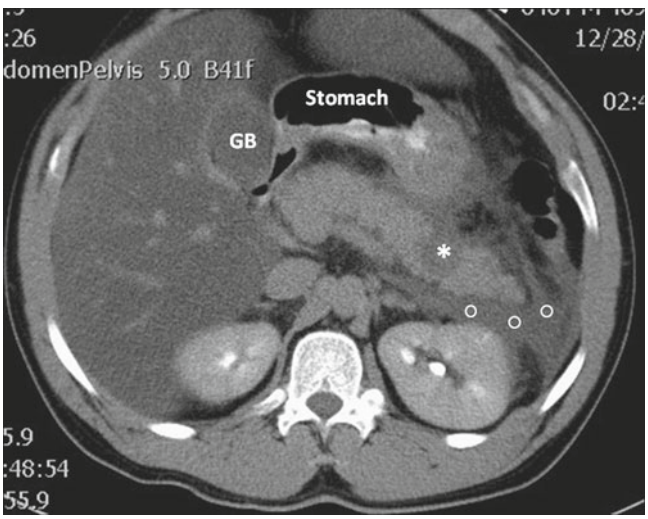

Fig. 25.38 A 65-year-old man with upper abdominal pain. Axial oral and intravenous contrast enhanced CT image through the upper abdomen shows diffuse low density liver which indicates fatty infiltration. Focal low attenuation area (*asterisk*) is in the tail of the pancreas. There is fluid (*white circles*) around the tail of the pancreas and focal pancreatitis. Diagnosis: Fatty liver and focal pancreatitis

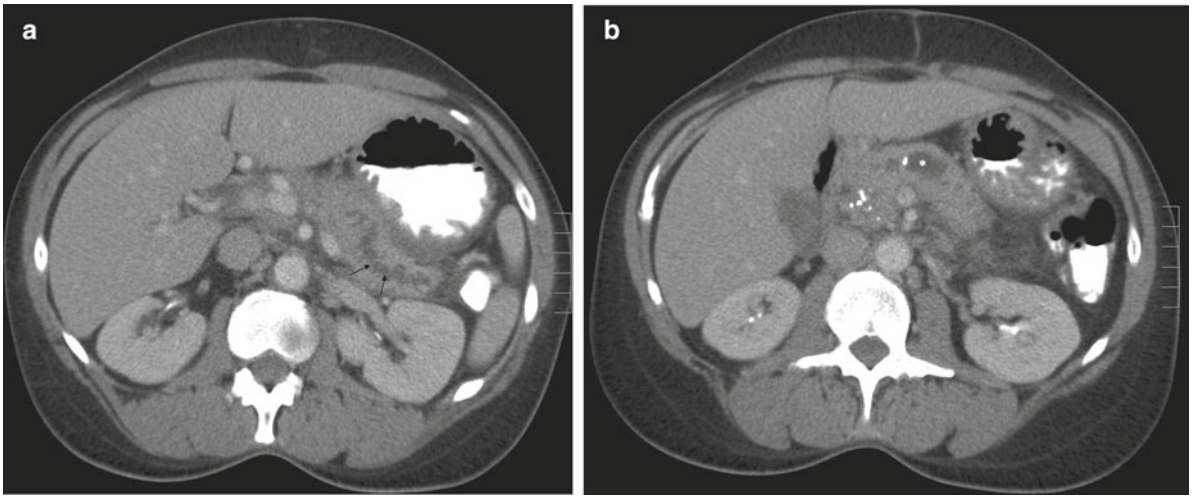

Fig. 25.39 A 66-year-old man with long standing alcohol history presents with weight loss, postprandial abdominal pain that radiates to the back that is worse with meals. He has six to eight bowel movements a day usually following a meal. (**a**) Axial oral and intravenous contrast enhanced CT image through the level of the pancreas shows irregularly dilated pancreatic duct (*black arrows*). (**b**) Axial oral and intravenous contrast enhanced CT image through the level of the pancreas shows minute calculi in the head and body of the pancreas and pancreatic duct dilatation (*asterisk*). Diagnosis: Chronic pancreatitis with stones in the head of the pancreas

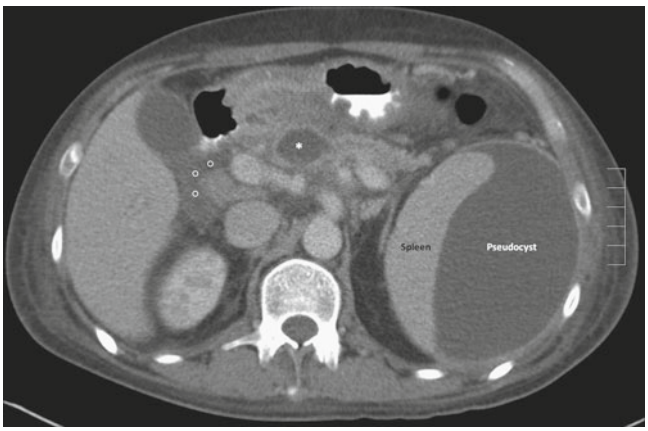

Fig. 25.40 A 65-year-old man with LUQ abdominal pain. Axial oral and intravenous enhanced CT image through the upper abdomen shows subcapsular fluid collection in the spleen and a small fluid collection (*asterisk*) in the body of the pancreas with some inflammatory changes anteriorly. Small amount of fluid (*white circles*) is noted around the head of the pancreas. Diagnosis: Pancreatic pseudocyst

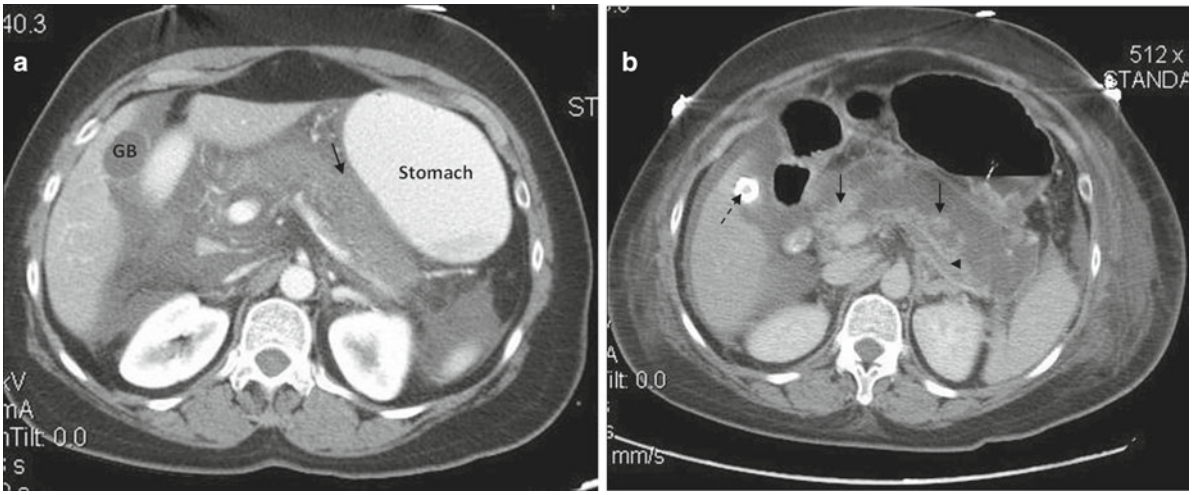

Fig. 25.41 A 69-year-old woman with severe upper abdominal pain and hypotension. (**a**) On day 1: axial oral and intravenous contrast enhanced CT image through the upper abdomen shows relative lack of enhancement of the pancreas (see normal Fig. 25.34). There is peripancreatic fluid and ascites (*solid black arrows*). A gallstone is not visualized within the GB (gallbladder). (**b**) On day 9: axial oral and intravenous contrast enhanced CT image through the upper abdomen shows necrosis of most of the pancreas; only small portions of the pancreas are identifiable (*black arrows*). Fluid density is seen in the pancreatic bed. There is splenic venous thrombosis (*black arrowhead*). On this image a gallstone is visible (*dash black arrow*). Diagnosis: Severe acute necrotizing pancreatitis

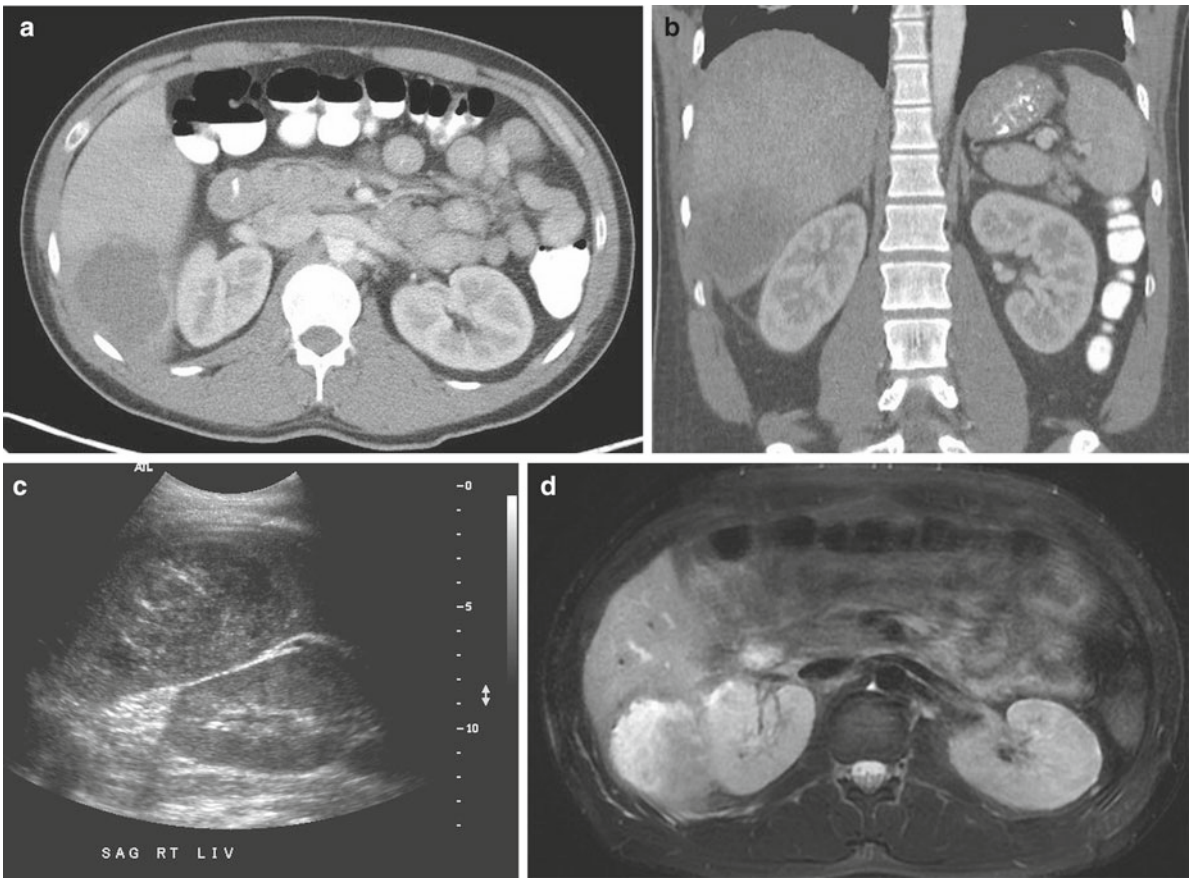

Fig. 25.42 A 65-year-old woman with fever and RUQ abdominal pain. (**a**) Axial oral and intravenous contrast enhanced CT image through the mid abdomen shows a focal mass in the right lobe of the liver with low attenuation and slightly irregular border. (**b**) Coronal reconstructed CT image through the posterior abdomen shows a focal mass in the right lobe of the liver. (**c**) Right upper quadrant ultrasound sagittal image shows a complex mass in the liver. (**d**) Magnetic resonance imaging was done to further clarify the nature of this mass and confirmed an enhancing mass suggestive of an abscess. Diagnosis: Hepatic abscess

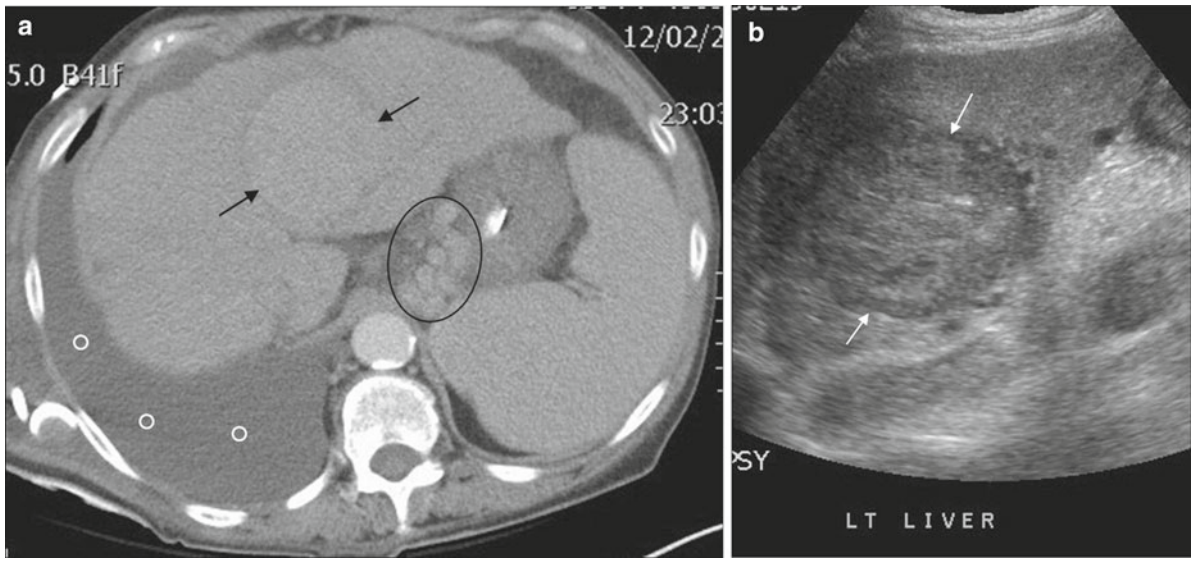

Fig. 25.43 A 69-year-old man with hepatic encephalopathy. (**a**) Axial intravenous contrast enhanced CT image through the upper abdomen shows a mass in the liver (*black arrows*). The liver is small and irregular-cirrhotic. There is splenomegaly; small amount of ascites and large right pleural effusion (*white circles*), and varices (*black circle*). (**b**) Sagittal ultrasound image shows the liver mass (*white arrows*) to be complex consistent with hepatocellular carcinoma. Diagnosis: Hepatic carcinoma

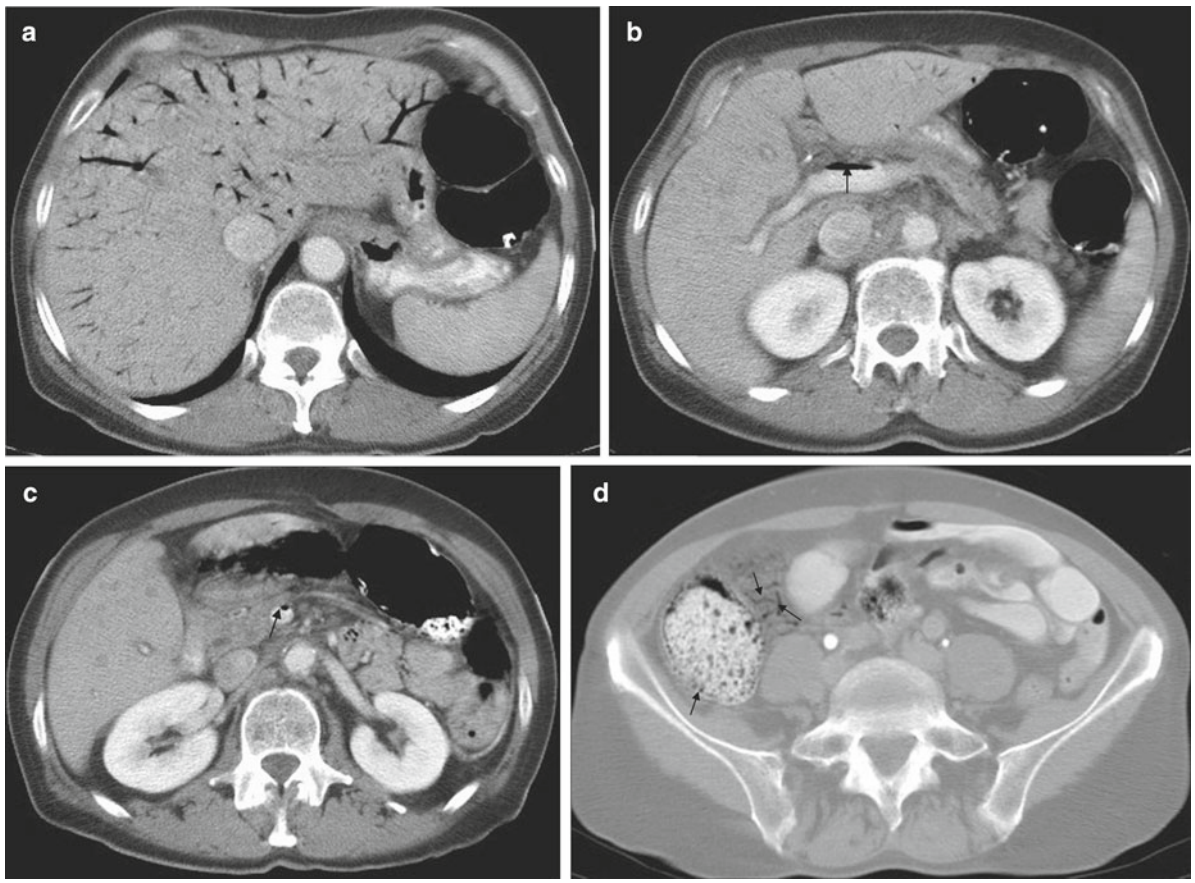

Fig. 25.44 A 72-year-old man with severe abdominal pain and bloody diarrhea. (**a**) Axial oral and intravenous contrast enhanced CT image through the level of the upper abdomen shows air in the portal venous system. (**b**) Axial oral and intravenous contrast enhanced CT image through the level of the portal vein shows air-contrast level in the portal vein (*black arrow*). (**c**) Axial oral and intravenous contrast enhanced CT image through the level of the kidneys shows air in the superior mesenteric vein (*black arrow*). (**d**) Axial oral and intravenous contrast enhanced CT image with pulmonary window setting shows air in the bowel wall, suggesting pneumatosis intestinalis (*black arrows*). Diagnosis: Pneumatosis intestinalis and portal venous air

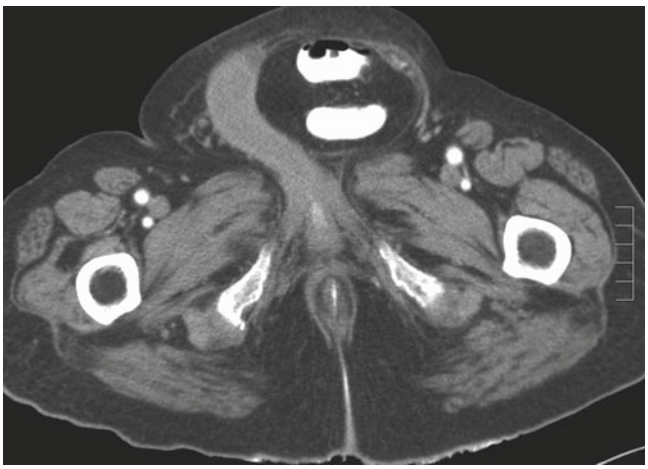

Fig. 25.45 An 84-year-old man with heaviness in the left groin. Axial oral and intravenous contrast enhanced CT image through the level of the ischii demonstrates a left inguinal hernia with bowel content in the scrotum. There is no bowel obstruction to suggest incarceration. Diagnosis: Left inguinal hernia

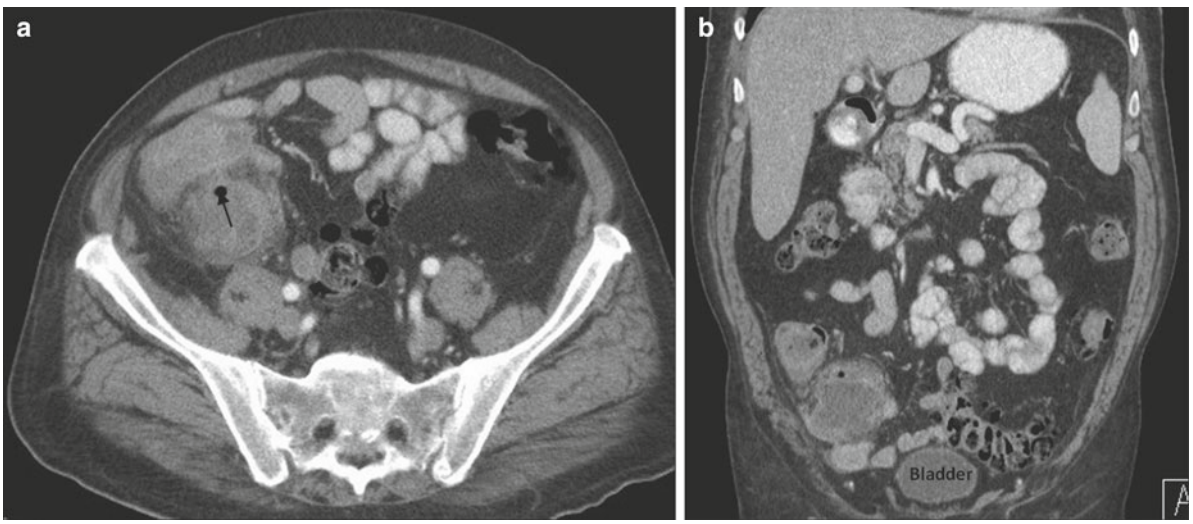

Fig. 25.46 An 89-year-old man presents with fever, nausea, vomiting, and severe RLQ abdominal pain. (**a**, **b**) Axial and coronal oral and intravenous contrast enhanced CT images in the lower abdomen demonstrate a soft tissue mass with fluid and air (*black arrow*) adjacent to the cecum. The features suggest a perforated appendiceal abscess. Diagnosis: Appendiceal abscess

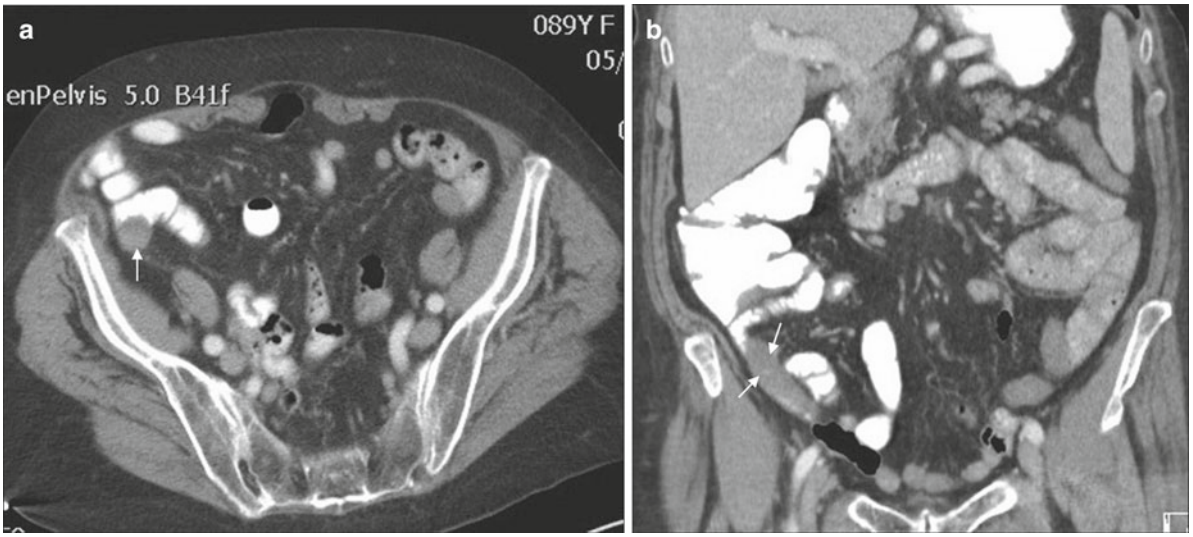

Fig. 25.47 An 89-year-old woman with RLQ abdominal pain and tenderness. (**a**, **b**) Axial and coronal oral and intravenous contrast enhanced CT images through the lower abdomen and pelvis show a dilated appendix, indicative of acute, but not perforated appendicitis (*white arrows*). Diagnosis: Acute appendicitis

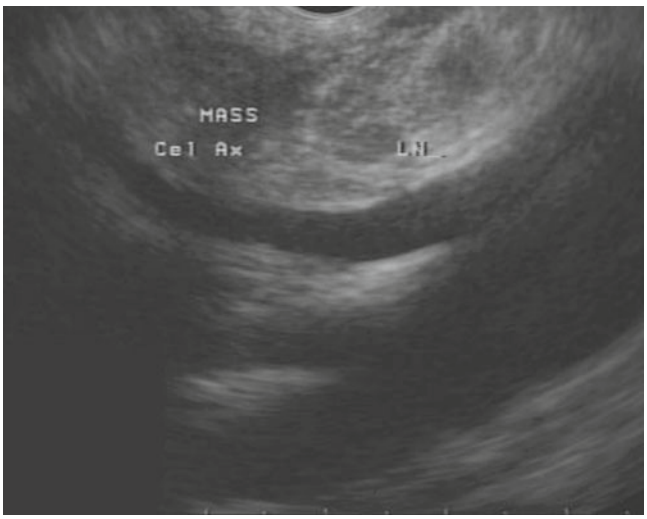

Fig. 25.48 A 69-year-old man presents with mild abdominal pain, loss of appetite, and weight loss. Linear endoscopic ultrasound (EUS) image reveals a hypoechoic mass lesion in the body of pancreas encasing the celiac axis, consistent with periaxial adenocarcinoma. Diagnosis: Pancreatic mass (courtesy of Hazar Michael, MD. Robert Wood Johnson University Hospital)

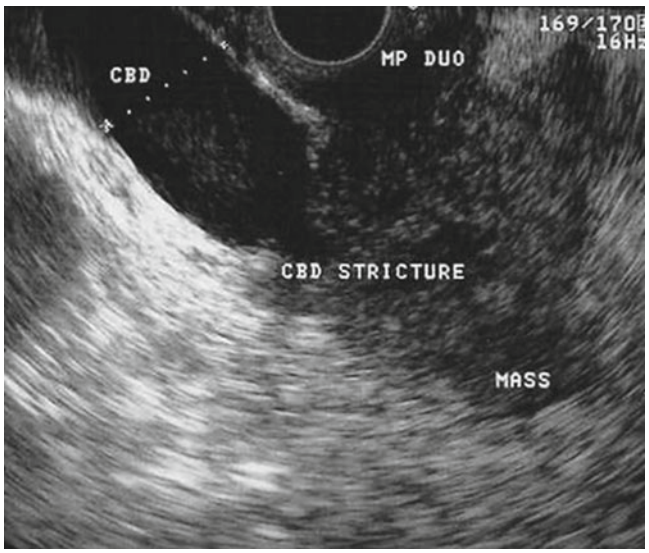

Fig. 25.49 A 70-year-old man presents with jaundice, fatigue, and weight loss. Linear EUS image reveals a hypoechoic mass lesion in the head of pancreas invading the distal CBD and duodenum wall leading to CBD stricture associated with market proximal CBD dilatation. Diagnosis: Pancreatic mass with CBD dilatation (courtesy of Hazar Michael, MD. Robert Wood Johnson University Hospital)

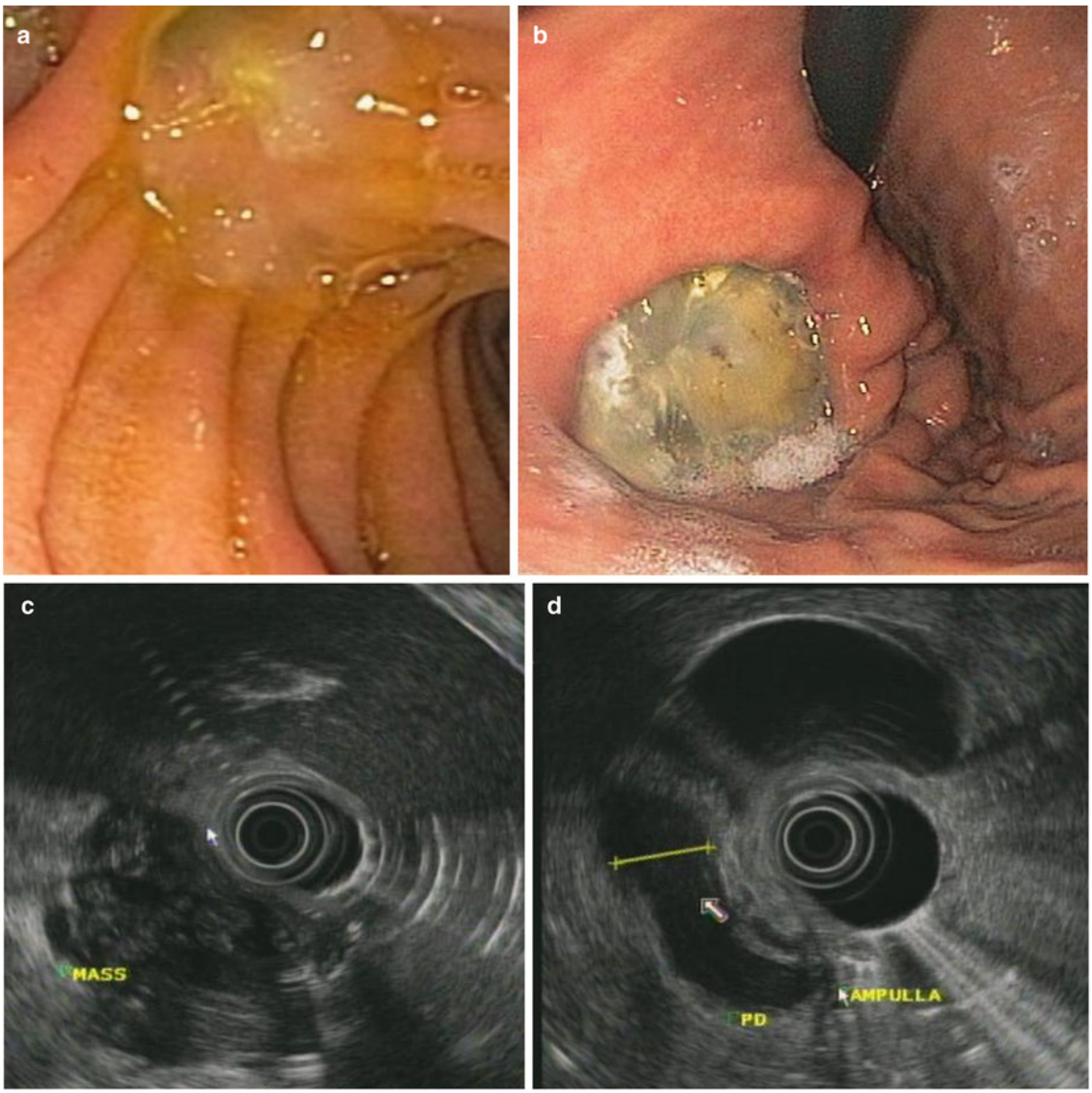

Fig. 25.50 A 74-year-old man presents with chronic relapsing pancreatitis, weight loss, and steatorrhea. (**a**) Endoscopic view of the major papilla shows a fish mouth papilla secreting mucinous material. (**b**) Endoscopic view through retroflexion in the stomach reveals a deep ulcer in the fundus with mucous adherent to the ulcer base. This is secondary to a direct extension to the gastric fold by a malignant intraductal papillary mucinous tumor (IPMT). (**c**) Radio EUS image reveals markedly expanded main pancreatic duct by a heterogeneous head of pancreas mass with irregular borders containing mucinous material. (**d**) Radio EUS image reveals the head of pancreas with markedly dilated main pancreatic duct and echogenic material within the duct consistent with mucin. The duct does not manifest any strictures. Diagnosis: Malignant intraductal papillary mucinous tumor (courtesy of Hazar Michael, MD. Robert Wood Johnson University Hospital)

Acknowledgments We are grateful to Nancy Chen MD for her contributions in completing this chapter.

Advanced Imaging of Geriatric Gastrointestinal Pathology

26

Fernanda Samara Mazzariol

Introduction

This chapter will illustrate the use of magnetic resonance imaging cholangiopancreatography (MRCP), CT colonography (CTC), the imaging and interventional treatment of acute and chronic mesenteric ischemia, and acute gastrointestinal bleeding.

MRCP

MRCP has replaced the more invasive and expensive endoscopic retrograde cholangiopancreatography (ERCP) for diagnostic purposes. ERCP is reserved when intervention or tissue sampling are necessary. MRCP also helps plan ERCP and percutaneous guided interventions in the biliary tree (Fig. 26.1a–c).

CT Colonography

Conventional optical colonoscopy (COC) limitations include the need for sedation, failure to complete the exam in 5–10% of patients, and potential risk of perforation and bleeding (0.1–0.3%). CTC detection rate for medium and large polyps is adequate; however, its accuracy in detecting small lesions (<6 mm) is inferior to COC [1, 2]. An incomplete COC examination is traditionally followed by a double contrast barium enema, which was found to have lower sensitivity and specificity than CTC in detecting colorectal polyps ≥6 mm in a recent study [3].

CTC indications include incomplete COC, evaluation of the colon proximal to an obstructing lesion (Fig. 26.2a–d), screening of patients who refuse COC and utilization in patients unfit for COC due to severe cardiac or pulmonary disease or with bleeding diathesis, typically problems in the old. Two recent studies [4, 5] found CTC to be safe and effective in screening the geriatric population.

Adequate colonic cleansing, fecal tagging, and colonic distention are prerequisites for successful CTC. Bowel cleansing presents a challenge in the elderly, frail patient. CTC in the elderly population with limited colonic preparation to exclude mass and polypoid lesions greater than 1 cm has been reported to be feasible [6]. CTC images are processed into a 3D virtual fly-through used for primary read; 2D images are also used to characterize the lesions (Fig. 26.3a–d).

The adenoma-carcinoma sequence and "de novo" carcinogenesis are two proposed pathways for colorectal cancer development, although controversial in importance [7]. It is estimated that a majority of the cancers follow the adenoma-carcinoma sequence through a series of genetic alterations [8] which occur over a prolonged period of time. Most small polyps are not adenomatous and incidence of cancer in small polyps is rare [9, 10]. Although advanced histology can be found in small lesions [11], a great number of polyps under 1 cm are hyperplastic and believed to have little or no malignant potential. Conversely, a small subset of hyperplastic polyps (<3%) may be in another category, the serrated adenoma, with its own pathway to cancer development [12, 13]. Some estimate that up to 20% of sporadic colorectal cancers develop through the serrated adenoma pathway [13]. CTC cannot differentiate adenomatous from hyperplastic polyps.

Small polyp measurements vary between CTC, COC, and pathology specimens with CTC measurement closest to true dimension of the polyp [14]. There is an ongoing debate between radiologists and gastroenterologists regarding management of small polyps found at CTC [11, 15, 16]. Flat adenomas, lesions with height less than 50% its width and lesions less than 2 mm raised, are more difficult and sometimes impossible to detect on CTC.

CTC screening can detect colonic or extracolonic cancers in addition to other significant diseases in one of 200

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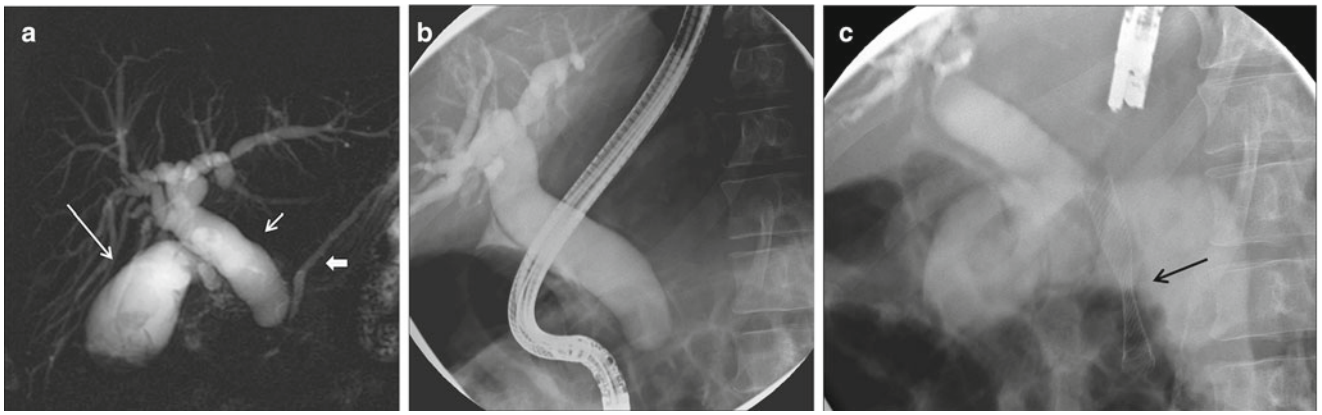

Fig. 26.1 Seventy-one-year-old male presenting with jaundice. (**a**) Magnetic resonance imaging cholangiopancreatography showing dilated intrahepatic ducts and common duct (*short thin arrow*). There is abrupt tapering in the distal portion from benign stricture due to inflammation associated to peptic ulcer disease. The pancreatic duct (*fat arrow*) and gallbladder (*long thin arrow*) are indicated. (**b**) Corresponding endoscopic retrograde cholangiopancreatography image before stent placement. (**c**) Removable stent placed. Note "waist" of the stent at the site of stricture (*black arrow*)

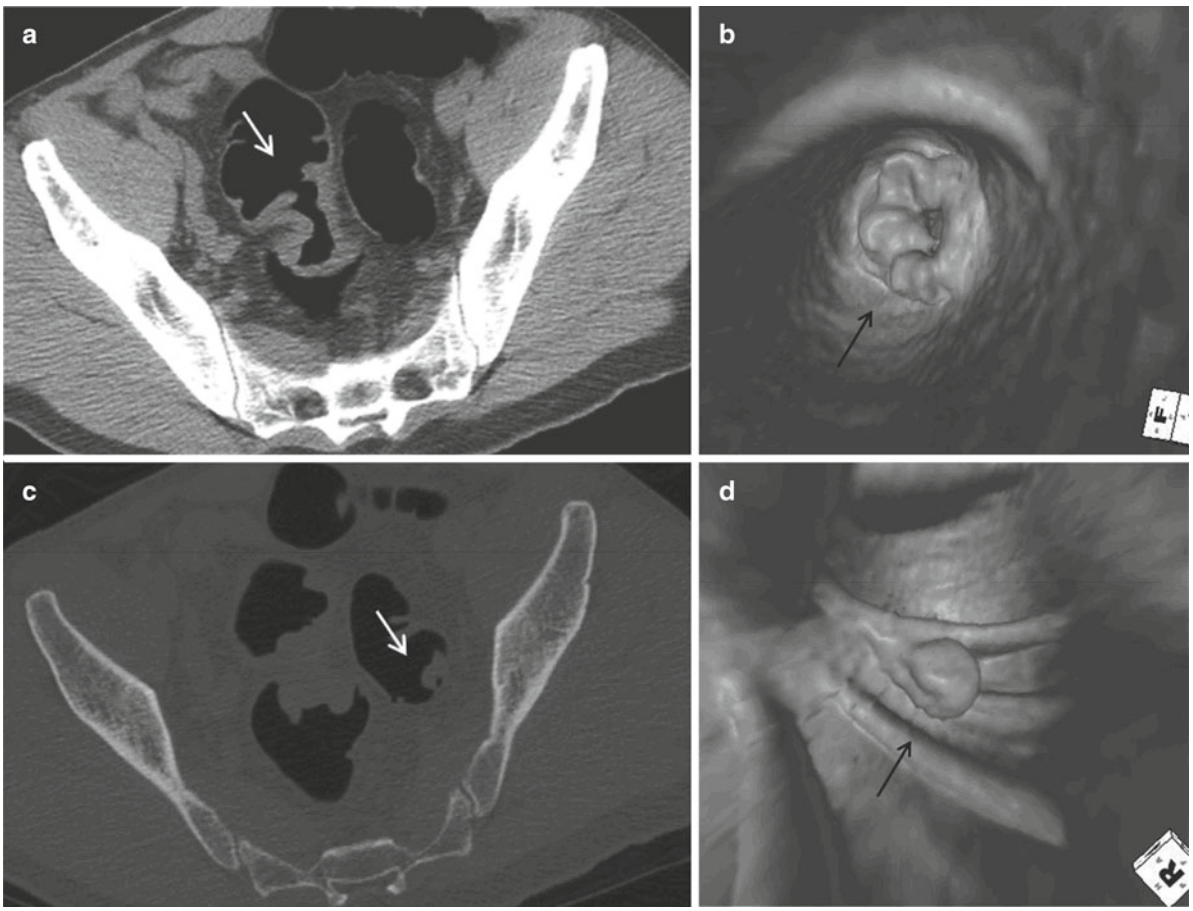

Fig. 26.2 (**a**) CT colonography (CTC) 2D view of 4.5 cm annular constricting mass in the distal sigmoid colon (*white arrow*) on elderly patient. The gastroenterologist was unable to pass colonoscope proximal to mass. (**b**) Corresponding 3D endoluminal view of the mass (*black arrow*). (**c**) CTC found polyp in the proximal sigmoid colon (*white arrow*) which was also included in the resection and confirmed on pathology to represent hyperplastic polyp. (**d**) Corresponding 3D endoluminal view of the polyp (*black arrow*)

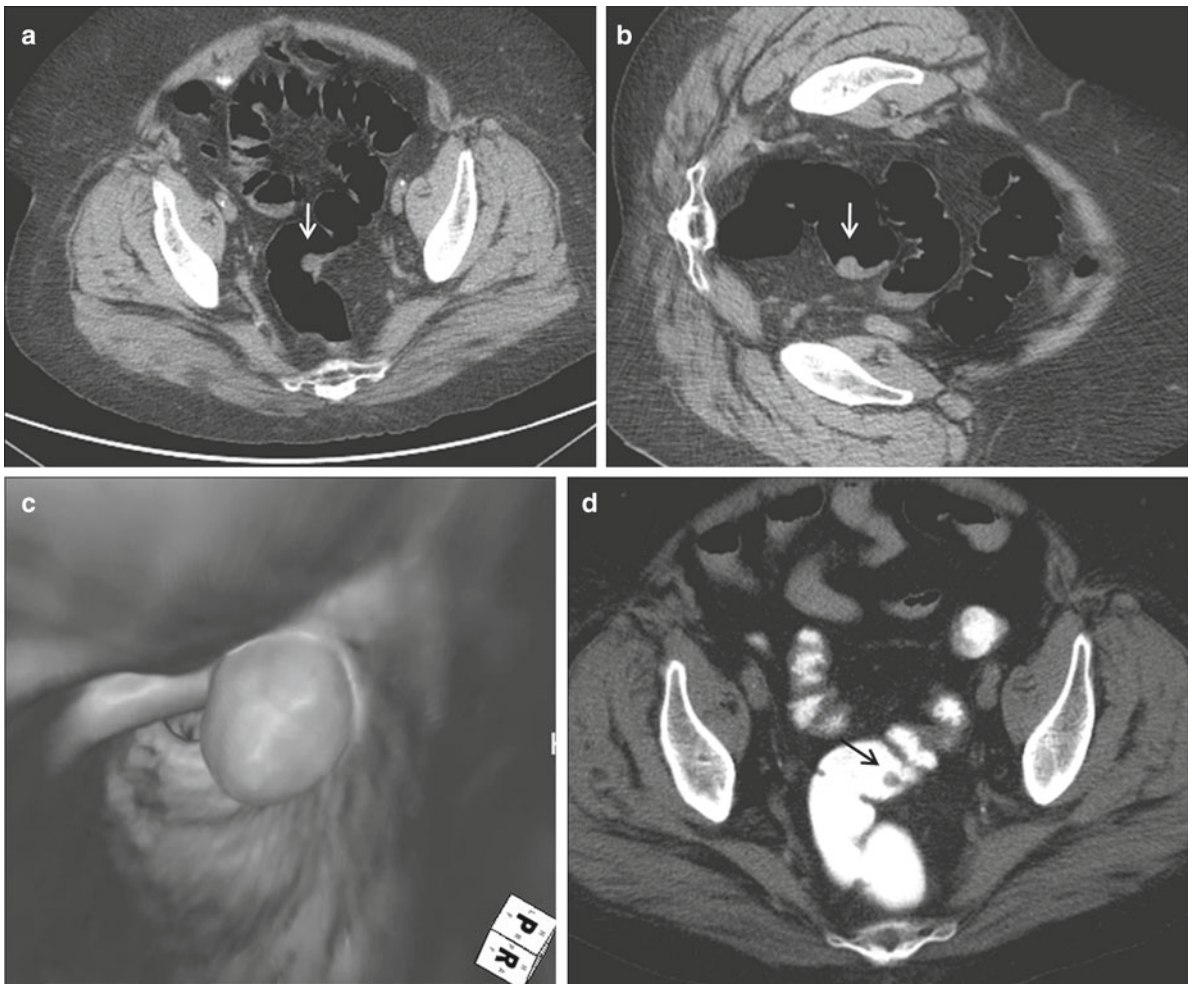

Fig. 26.3 Seventy-three-year-old obese female with contraindication to anesthesia for conventional optical colonoscopy secondary to multiple comorbidities. (**a**) CTC supine scan shows a 1.7 cm polyp in the sigmoid colon (*arrow*). (**b**) The patient was unable to assume prone position. Left lateral decubitus scan was performed showing the same lesion (*arrow*). (**c**) CTC 3D endoluminal view of the polyp. (**d**) CT scan performed for other reasons 1 year prior to CTC. The polyp (*black arrow*) outlined in the barium pool was slightly smaller and inconspicuous, only identified in retrospect

asymptomatic adults [17]. Early detection and treatment of cancers may contribute to favorable outcomes.

COC is the gold standard for colorectal cancer screening allowing for immediate tissue sampling. CTC is an acceptable alternative for colorectal cancer screening when COC is incomplete, cannot be performed or for patients who refuse COC as a screening modality. The choice between COC and CTC should be made by the clinician and patient, especially in geriatric patients with associated comorbidities.

Acute Gastrointestinal (GI) Bleeding

In patients presenting with acute gastrointestinal bleeding, once the measures to achieve hemodynamic stability have been established, radiologic exams can localize, characterize, and treat the bleeding lesion. Acute variceal bleeding in the upper GI tract is usually treated by means of upper endoscopy (EGD) or transhepatic portosystemic shunt (TIPS) placement.

Endoscopy is the initial diagnostic and therapeutic modality in acute GI bleeding [18]. Radiologic exams play a greater role in lower GI bleeding, as colonoscopy is often suboptimal due to inadequate bowel preparation, lesions being obscured by massive bleeding and the inaccessibility of small bowel to conventional endoscopy.

Bleeding must be active at the time of imaging for diagnosis. CT angiography (CTA) and or conventional catheter directed angiography (CA) are initial exams of choice in hemodynamically unstable patients as they can determine the precise anatomic location of hemorrhage and CA can treat the bleeding. Radionuclide imaging is the initial examination for hemodynamically stable patients with slow intermittent bleeding.

Radionuclide Imaging (Scintigraphy)

Scintigraphy can detect bleeding at rates as low as 0.04–0.1 mL/min, is noninvasive, requires little patient preparation, is generally well tolerated and readily available in most institutions. It is possible to perform imaging 18–24 h after injection of labeled RBCs. Positive scintigraphy increases the diagnostic yield of CA [19] and its positive predictive value for diagnostic CA is improved if the test is positive within the first 2 min of injection [20]. Scintigraphy can screen out patients who are not actively bleeding at the time of exam and spare them the risks and cost of a potentially nondiagnostic invasive study.

Diagnosis is made by intraluminal manifestation of radiotracer activity, increased intensity of the radiotracer and movement of the radiotracer demonstrated in real time during dynamic acquisition of data [21] (Fig. 26.4a, b).

Scintigraphy is time consuming and precise anatomic localization is not possible. The reported accuracy varies

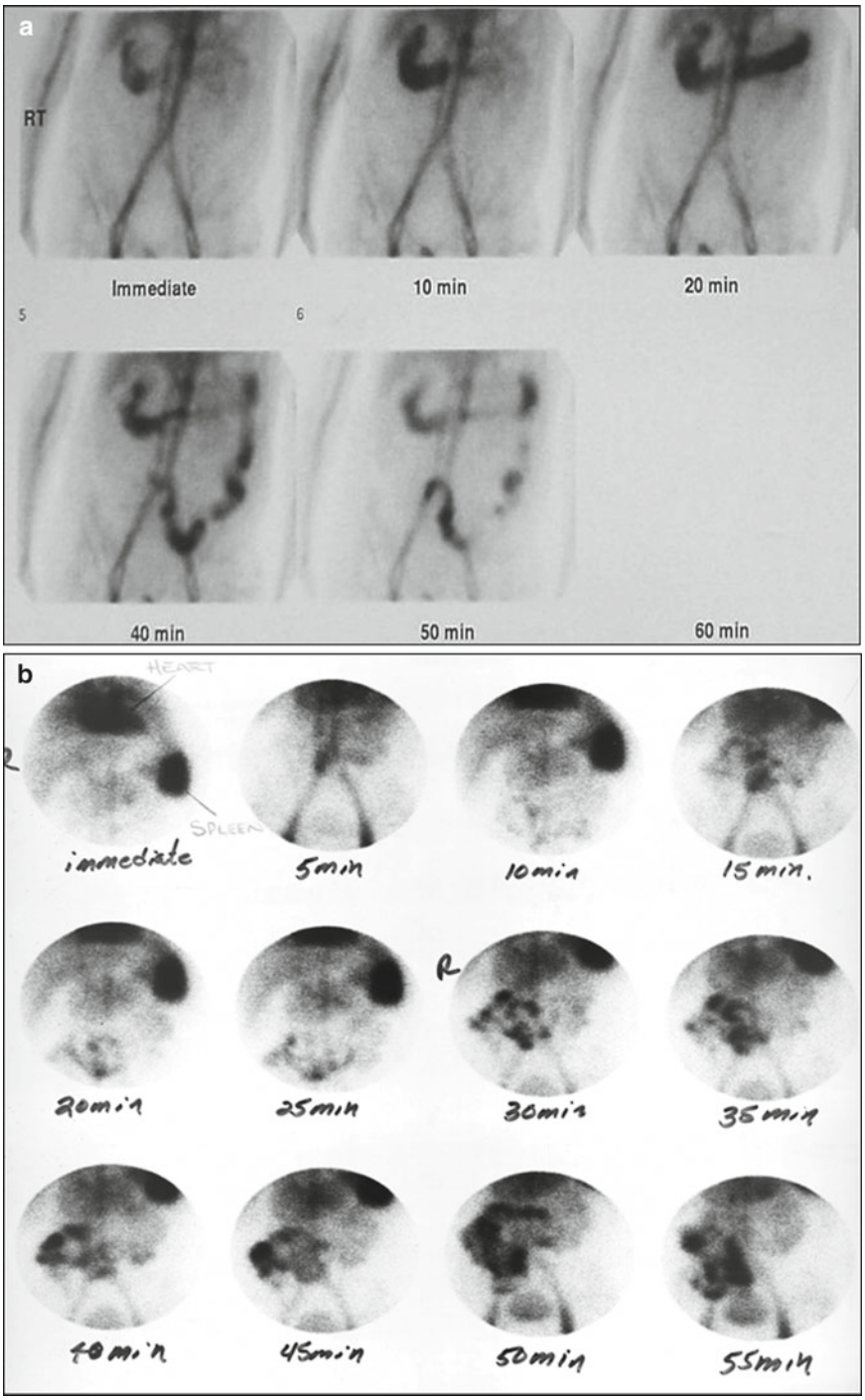

Fig. 26.4 (**a**) Hepatic flexure of the colon bleeding on scintigraphy showing increased accumulation and movement of the radiotracer in the bowel lumen over time. (**b**) Small bowel bleeding on scintigraphy. (Courtesy of Dr. Leonard Freeman, Professor of Nuclear Medicine and Radiology, Montefiore Medical Center, Albert Einstein College of Medicine)

from 40 to 100%, therefore surgical interventions, particularly segmental intestinal resections, are rarely performed on the basis of scintigraphy findings alone [22].

Catheter-Directed Angiography (CA)

Bleeding rates as low as 0.5 mL/min can be detected with accurate anatomic localization; and treatment can be performed with high success rates. CA is used less frequently for upper GI bleeding due to higher yield from traditional EGD [23, 24]. CA is valuable when EGD is not available, if bleeding cannot be stopped using EGD [25] and for poor surgical candidates [18].

The most common causes of lower GI bleeding in the geriatric population are colonic diverticulosis and angiodysplasia. Superselective catheter embolization treatment, usually with microcoil [26, 27], is effective and has low complication rates. Small bowel is a less frequent site of lower GI bleeding with angioectasia representing the most common cause [28] (Fig. 26.5). Sources of bleeding in the small bowel are more difficult to diagnose and patient outcomes are poorer than with upper GI and colonic bleeding [28]. If resection is entertained, microcatheter infusion of methylene blue stain or a microcoil can be used to limit the extent of small bowel resection.

Extravasation of contrast into the bowel lumen is pathognomonic of hemorrhage (Fig. 26.6a–c). Indirect findings of bleeding site are pseudoaneurysm, arterial venous fistula, hyperemia, neovascularity, and extravasation of contrast into a confined space.

Disadvantages of CA include high cost, invasiveness, associated risks of catheter related and vascular access complications, utilization of iodinated contrast material and false negatives related to intermittent bleeding, bleeding below detectable rates and variant vascular anatomy.

CT Angiography

CTA has been performed for the diagnosis of acute GI bleeding with localization accuracy comparable to CA [29, 30]. A study by Yoon et al. [31], reports 91% sensitivity and 99% specificity in localizing massive gastrointestinal bleeding with CTA. In porcine models, bleeding rates as low as 0.3 mL/min [32] and 0.1 mL/min [33] were detected.

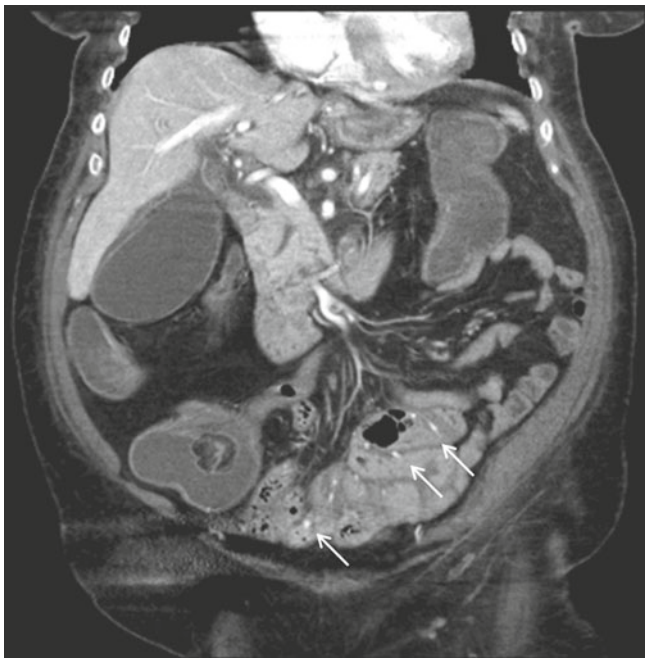

Fig. 26.5 CT angiogram of 76-year-old female with end stage renal disease presenting with massive GI bleed. Coronal reformatted image showing angioectasia of small bowel evidenced by several focally dilated arteries along the small bowel wall (some indicated by *arrows*). No active bleeding was demonstrated during the CT angiography (CTA). Patient recovered with conservative treatment and the diagnosis was confirmed later with double balloon endoscopy

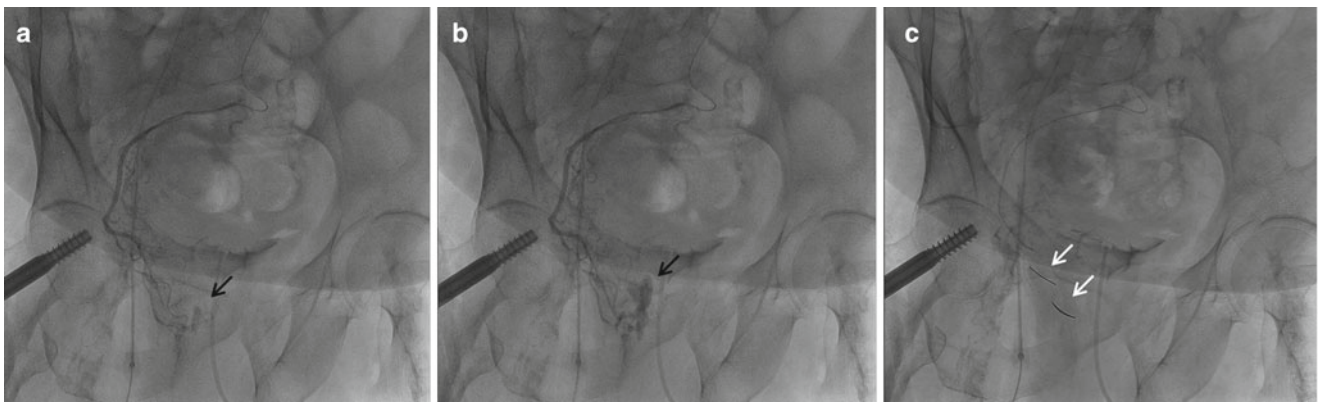

Fig. 26.6 (**a**) Superselective angiography showing contrast extravasation into the rectal lumen (*black arrow*). (**b**) Increased contrast pooling in the rectal lumen (*black arrow*). (**c**) Microcoil embolization of the rectal artery branches feeding the bleeding lesion. The *white arrows* indicate deployed microcoils

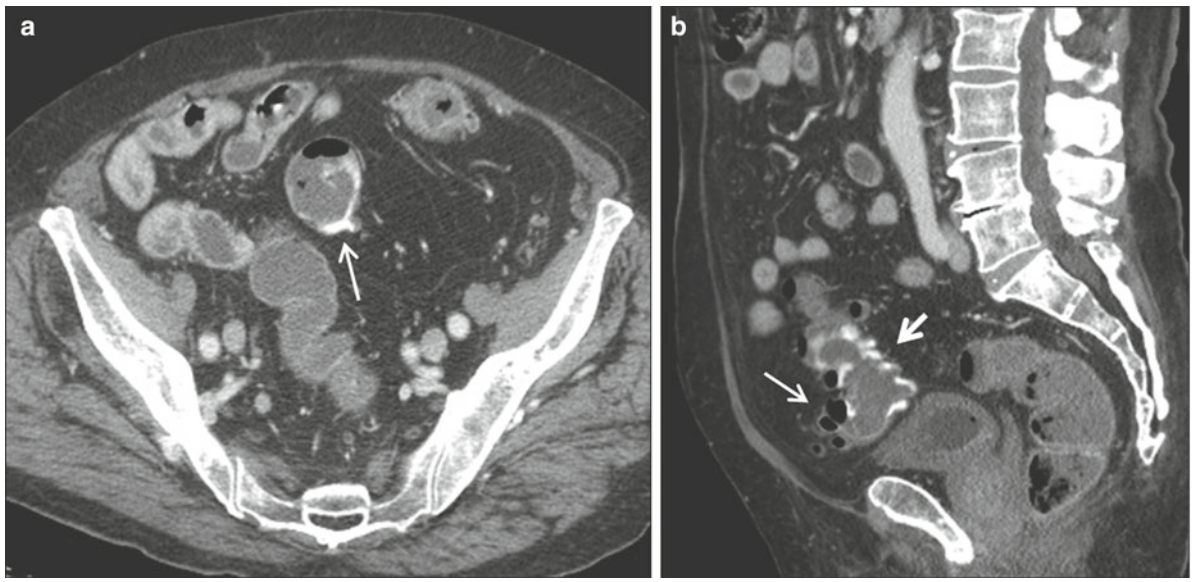

Fig. 26.7 CTA showing acute GI bleed in elderly patient. (**a**) Axial image showing contrast pooling in the lumen of the sigmoid colon (*arrow*) from bleeding diverticulum. (**b**) Sagittal reformation showing several diverticula (*thin arrow*) and contrast pooling in the lumen (*thick arrow*)

A noncontrast CT scan to detect preexisting hyperdense material in the bowel is followed by contrast enhanced CTA. Extravasation of contrast material into the bowel lumen is diagnostic. Pitfalls include poor angiographic technique, enhancement of the bowel mucosa which may be interpreted as bleeding and preexisting high attenuation material in the bowel lumen which decreases CTA diagnostic accuracy. Radiation and iodinated contrast material exposure represent additional disadvantages. However, information regarding the etiology, site of bleeding, and vascular anatomy can positively affect clinical, interventional, and surgical management decisions. A focused interventional approach following CTA results in less digital subtraction exposures, shortened procedure time, and reduces the amount of iodinated contrast used during CA.

CTA is rapid, safe, sensitive, easy to perform, readily available, and allows for precise localization of bleeding site. Some centers have been using it to triage patients who present with significant lower GI bleeding [34–36] (Figs. 26.7a, b and 26.8a–c).

Acute Mesenteric Ischemia and Chronic Mesenteric Insufficiency (CTA and CA)

Acute mesenteric ischemia (AMI) is caused by arterial occlusive disease, venous occlusive disease, strangulation/obstruction and hypoperfusion associated with nonocclusive vascular disease. CT findings vary depending on the cause and underlying physiopathology. In patients with chronic arterial insufficiency of the intestines, known as abdominal angina (AA), CTA is helpful to evaluate the degree of stenosis of the celiac trunk and superior mesenteric artery (SMA), evaluate the collateral circulation and to exclude other causes of intestinal ischemia such as retroperitoneal or celiomesenteric malignancy, median arcuate ligament syndrome, aneurysms, and dissections [37, 38].

CA is the gold standard to evaluate the mesenteric vasculature and the preferred modality for treatment of AA (Fig. 26.9a, b). Usually only one of the compromised arteries (SMA) requires treatment, but if feasible in the presence of high grade stenosis (>70%) both arteries should be treated.

CTA evaluates the bowel wall, mesentery, and the vessels in a single exam (Fig. 26.10a–c). Emboli and thrombi in the mesenteric arteries and veins, degree of arterial stenosis of the celiac trunk and SMA, and status of the collateral circulation are clearly depicted in the postcontrast phase. Precontrast images are useful to evaluate the degree of arterial calcification, hyperattenuating intravascular clot and intramural bowel hemorrhage. The two main limitations of CTA are lack of dynamic visualization of the flow pattern and difficulty in determining the degree of stenosis of heavily calcified vessels.

Bowel wall is thickened when ischemia is caused by venous occlusion, strangulation, ischemic colitis, and arterial occlusion after reperfusion. When exclusive occlusive arterial ischemia with or without bowel infarction is present, the bowel wall may be paper thin due to lack of edema or hemorrhage. Low attenuation of the wall indicates edema and high attenuation indicates intramural hemorrhage or hemorrhagic infarction. After contrast administration, poor enhancement is specific but not sensitive for infarction. Conversely, hyperenhancement of the bowel wall can also be seen in ischemia. Pneumatosis intestinalis and portomesenteric venous gas in

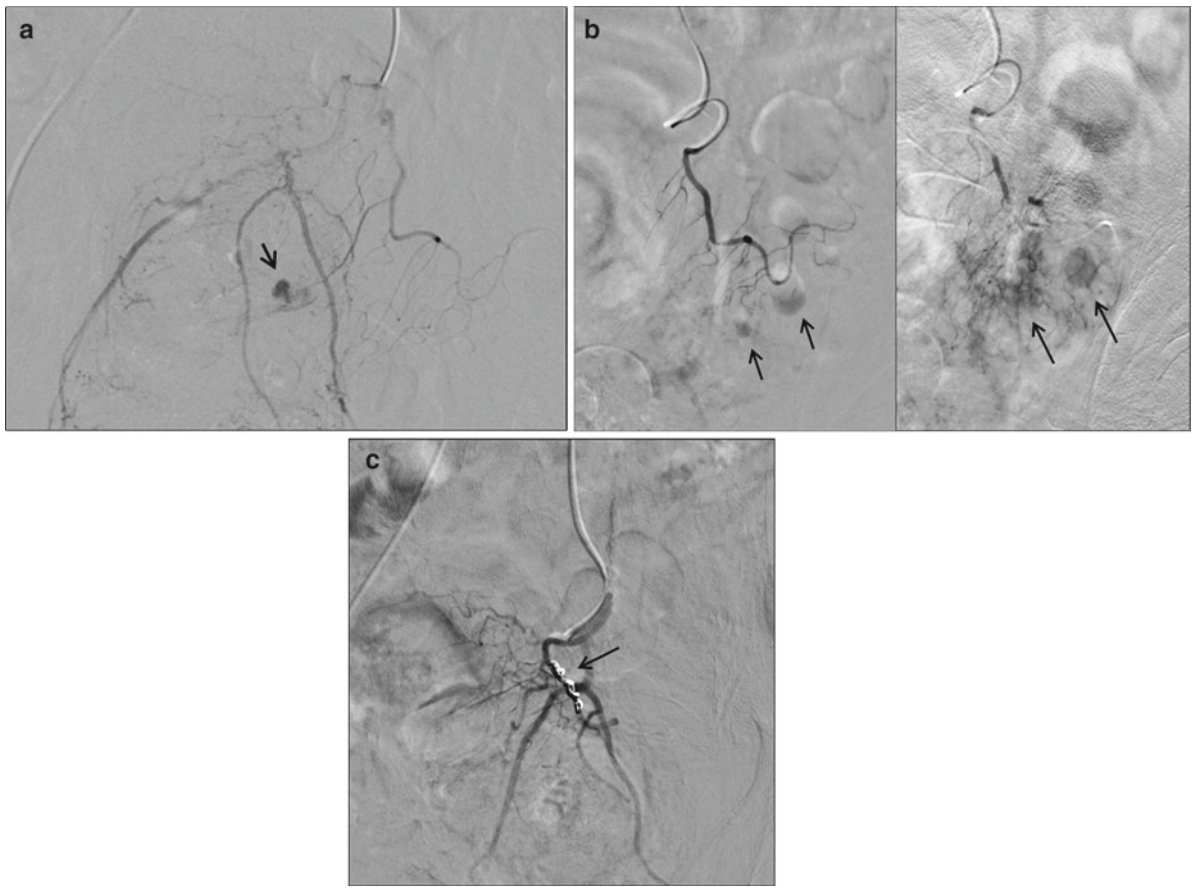

Fig. 26.8 The patient in Fig. 26.7 with bleeding colonic diverticula was treated with coli embolization. (**a**) Corresponding selective angiography shows a pseudoaneurysm (*arrow*). (**b**) Extravasation of contrast into the lumen (*arrows*). (**c**) The bleeding was treated with coil embolization (*arrow*)

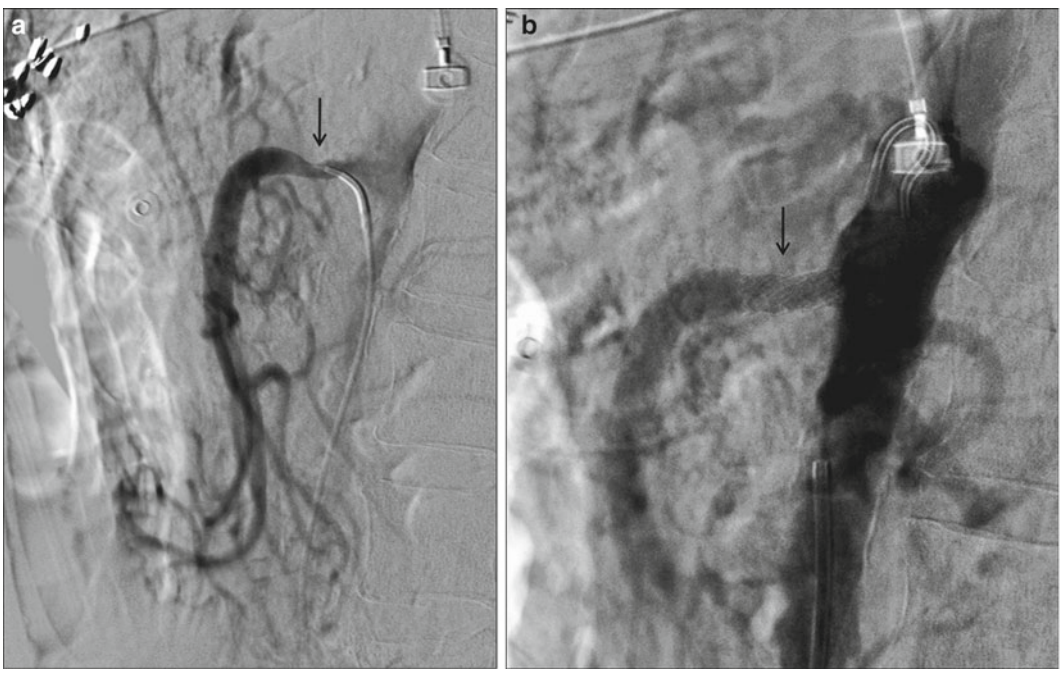

Fig. 26.9 Seventy-five-year-old female with abdominal pain and superior mesenteric artery (SMA) stenosis. (**a**) Stenosis at the origin of the SMA with 40 mmHg pressure gradient across stenosis (*arrow*). (**b**) Good result after angioplasty and stent placement (*arrow*) with resolution of pressure gradient

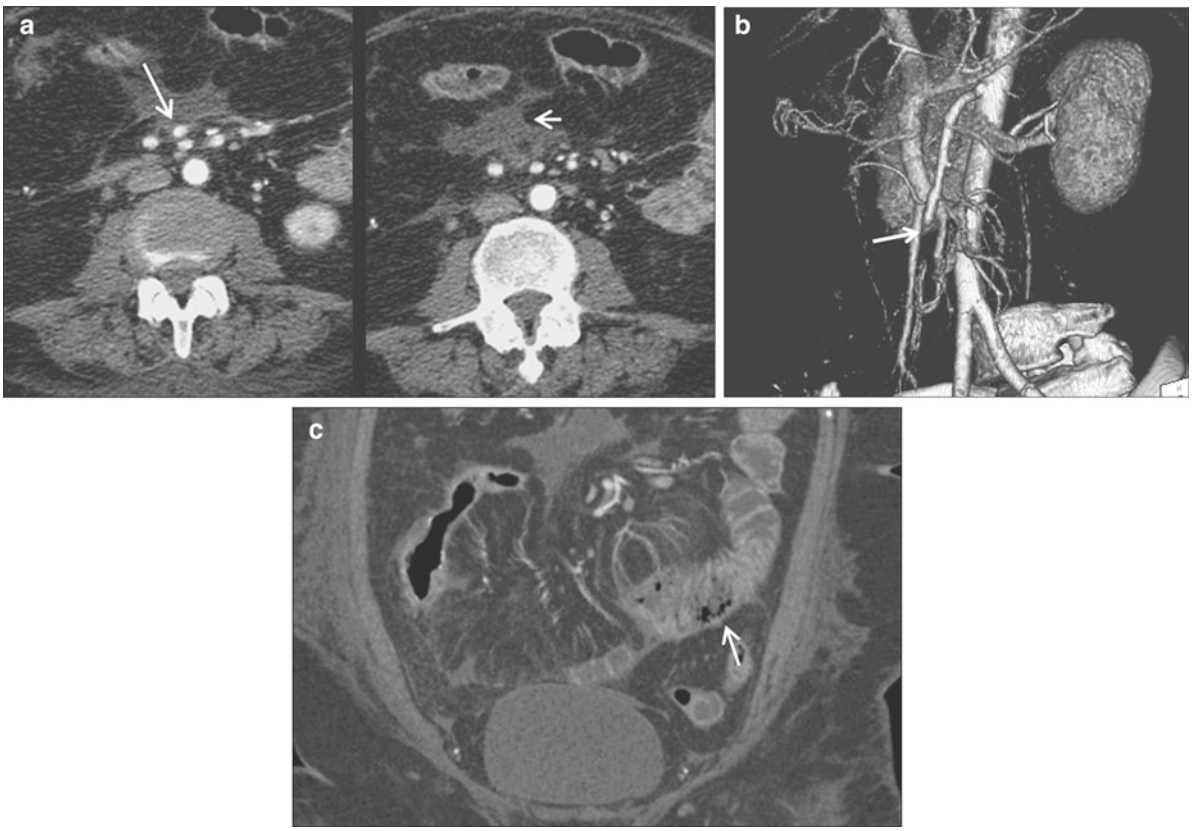

Fig. 26.10 Seventy-three-year old with acute SMA occlusion. (**a**) The SMA is patent (*long arrow*) on the image on the *left* and no longer seen in the next axial CT slice (image on the *right*). *Short arrow* indicates fluid in the mesentery. The other vessels in the images are branches of the superior mesenteric vein. (**b**) 3D reconstruction shows the point of SMA occlusion (*arrow*). (**c**) Coronal reformatted image shows pneumatosis of the small bowel, indicating bowel ischemia. (Courtesy of Dr. Sarah Oh, Assistant Professor of Radiology, Montefiore Medical Center, Albert Einstein College of Medicine)

the presence of bowel ischemia indicates transmural infarction. Bowel lumen is often dilated due to interruption of normal peristalsis and may contain fluid particularly in venous occlusive disease and strangulation. Ascites and mesenteric fat stranding represent transudation of fluid [39, 40].

Once the etiology of AMI and AA have been established, the treatment may be open (surgical) or percutaneous. Percutaneous treatment includes catheter directed thrombolysis, balloon angioplasty, and stent placement.

Key Points

- Magnetic resonance imaging cholangiopancreatography has replaced endoscopic retrograde cholangiopancreatography (ERCP) for diagnostic imaging and is also used for planning of ERCP or percutaneous guided interventions in the biliary tree.
- Conventional optical colonoscopy is the gold standard for colorectal cancer screening allowing for immediate tissue sampling. CT colonography is an acceptable alternative for colorectal cancer screening when optical colonoscopy is incomplete, cannot be performed or for patients who refuse optical colonoscopy as a screening modality.
- In acute lower gastrointestinal bleeding CT angiography (CTA) and/or conventional catheter directed angiography (CA) are initial exams of choice in hemodynamically unstable patients as they can determine the precise anatomic location of hemorrhage and CA can treat the bleeding. Radionuclide imaging is the initial exam for hemodynamically stable patients with slow intermittent bleeding.
- Both CTA and conventional angiography (CA) are used for the diagnosis of acute mesenteric ischemia and abdominal angina. CTA evaluates the bowel wall, mesentery, and vessels in a single exam. Percutaneous balloon angioplasty and stent placement are the preferred treatment of abdominal angina.

References

1. Macari M, Bini E, Hue X, et al. Colorectal neoplasms: prospective comparison of thin-section low-dose multi-detector row CT colonography and conventional colonoscopy for detection. Radiology. 2002;224:383–92.

2. Copel L, Sosna J, Kruskal J, et al. CT colonography in 546 patients with incomplete colonoscopy. Radiology. 2007;244:471–8.
3. Sosna J, Sellac T, Oumar S, et al. Critical analysis of the performance of double-contrast barium enema for detecting colorectal polyps >6 mm in the era of CT colonography. AJR. 2008;190:374–85.
4. Yucel C, Lev-Toaff A, Moussa N, et al. CT colonography for incomplete or contraindicated optical colonoscopy in older patients. AJR. 2008;190:145–50.
5. Kim D, Pickhardt P, Hanson M, et al. CT colonography: performance and program outcome measures in an older screening population. Radiology. 2010;254:493–500.
6. Keeling A, Slattery M, Leong S, et al. Limited-preparation CT colonography in frail elderly patients: a feasibility study. AJR. 2010;194:1279–87.
7. Bedenne L, Faivre J, Boutron MC, et al. Adenoma-carcinoma sequence or "de novo" carcinogenesis. Cancer. 1992;69:883–8.
8. Vogelstein B, Fearon E, Hamilton S, et al. Genetic alterations during colorectal-tumor development. N Engl J Med. 1988;319:525–32.
9. Aldridge AJ, Simson JH. Histological assessment of colorectal adenomas by size: are polyps less than 10 mm in size clinically important? Eur J Surg. 2001;167:777–81.
10. Nusko G, Mansmann U, Altendorf-Hofmann A, et al. Risk of invasive carcinoma in colorectal adenomas assessed by size and site. Int J Colorectal Dis. 1997;12:267–71.
11. Rex DK, Overhiser AJ, Chen SC, et al. Estimation of impact of American College of Radiology recommendations on CT colonography reporting for resection of high-risk adenoma findings. Am J Gastroenterol. 2009;104(1):149–53.
12. O'Brien MJ. Hyperplastic and serrated polyps of the colorectum. Gastroenterol Clin North Am. 2007;36(4):947–68; viii.
13. East JE, Saunders BP, Jass JR. Sporadic and syndromic hyperplastic polyps and serrated adenomas of the colon: classification, molecular genetics, natural history, and clinical management. Gastroenterol Clin North Am. 2008;37(1):25–46; v.
14. Summers R. Polyp size measurement at CT colonography: what do we know and what do we need to know? Radiology. 2010;255:707–20.
15. Kisiel JB, Bruining DH, Fletcher JG, et al. Computed tomographic colonography and high-risk adenomas: a gap in the guidelines? Gastroenterology. 2009;136(7):2395–6; discussion 2396–7.
16. Kim DH, Pickhardt PJ, Taylor AJ. Characteristics of advanced adenomas detected at CT colonographic screening: implications for appropriate polyp size thresholds for polypectomy versus surveillance. AJR. 2007;188:940–4.
17. Pickhardt P, Kim D, Mainers R, Wyatt K, et al. Colorectal and extracolonic cancers detected at screening CT colonography in 10286 asymptomatic adults. Radiology. 2010;255:83–8.
18. Millward S. ACR appropriateness criteria on treatment of acute nonvariceal gastrointestinal tract bleeding. J Am Coll Radiol. 2008;5(4):550–4.
19. Gunderman R, Leef J, Ong K, et al. Scintigraphic screening prior to visceral arteriography in acute lower gastrointestinal bleeding. J Nucl Med. 1998;39:1081–3.
20. Ng DA, Opelka FG, Beck DE, et al. Predictive value of Tc99m-labeled red blood cell scintigraphy for positive angiogram in massive lower gastrointestinal hemorrhage. Dis Colon Rectum. 1997;40:471–7.
21. Holder L. Radionuclide imaging in the evaluation of acute gastrointestinal bleeding. Radiographics. 2000;20:1153–9.
22. Hammond K, Beck D, Hicks T, et al. Implications of negative technetium 99-labeled red blood cell scintigraphy in patients presenting with lower gastrointestinal bleeding. Am J Surg. 2007;193:404–8.
23. Hastings G. Angiographic localization and transcatheter treatment of gastrointestinal bleeding. Radiographics. 2000;20:1160–8.
24. Murata S, Tajima H, Fukunaga T, Abe Y, Niggemann P, Onozawaga S, et al. Management of pancreaticoduodenal artery aneurysms: results of superselective transcatheter embolization. AJR. 2006;187:290–8.
25. Andersen P, Duvnjak S. Endovascular treatment of non variceal acute arterial upper gastrointestinal bleeding. World J Radiol. 2010;2(7):257–61.
26. Funaki B, Kostic J, Lornz J, et al. Superselective microcoil embolization of colonic hemorrhage. AJR. 2001;177:829–36.
27. Funaki B. Superselective embolization of lower gastrointestinal hemorrhage: a new paradigm. Abdom Imaging. 2004;29:434–8.
28. Prakash C, Zuckerman G. Acute small bowel bleeding: a distinct entity with significant different economic implications compared with GI bleeding from other locations. Gastrointest Endosc. 2003;58:330–5.
29. Yoon W, Jeong YY, Kim JK. Acute gastrointestinal bleeding: contrast enhanced MDCT. Abdom Imaging. 2006;31:1–8.
30. Zink SI, Ohki SK, Stein B, et al. Noninvasive evaluation of active lower gastrointestinal bleeding: comparison between contrast-enhanced MDCT and 99mTc-labeled RBC scintigraph. AJR. 2008;191:1107–14.
31. Yoon W, Jeong Y, Shin S, Lim H, Song S, Jang N, et al. Acute massive gastrointestinal bleeding: detection and localization with arterial phase multi-detector row helical CT. Radiology. 2006;239:160–7.
32. Kuhle WG, Sheiman RG. Detection of active colonic hemorrhage with use of helical CT: findings in a swine model. Radiology. 2003;228(3):743–52.
33. Kuhle WG, Shieman RG. The sensitivity of helical CT in detecting active colonic hemorrhage (abstr). J Vasc Interv Radiol. 2000;11(Suppl):208.
34. Laing C, Tobias T, Rosenblum D, et al. Acute gastrointestinal bleeding: emerging role of multidetector CT angiography and review of current imaging techniques. Radiographics. 2007;27:1055–70.
35. Sabharwal R, Vladica P, Chou R, et al. Helical CT in the diagnosis of acute lower gastrointestinal haemorrhage. Eur J Radiol. 2006;58:273–9.
36. Lee S, Welman CJ, Ramsay D. Investigation of acute lower gastrointestinal bleeding with 16 and 64-slice multidetector CT. J Med Imaging Radiat Oncol. 2009;53:56–63.
37. Cademartiri F, Raaijmakers R, Kuipe J, et al. Multi-detector row CT angiography in the patients with abdominal angina. Radiographics. 2004;24:969–84.
38. Cognet F, Ben Salem D, Dranssart M, et al. Chronic mesenteric ischemia: imaging and percutaneous treatment. Radiographics. 2002;22:863–80.
39. Furukawa A, Kanasaki S, Naoaki K, et al. CT findings of acute mesenteric ischemia from various causes. AJR. 2009;192:408–16.
40. Ofer A, Abadi S, Nitecki S, et al. Multidetector CT angiography in the evaluation of acute mesenteric ischemia. Eur Radiol. 2009;19:24–30.

Part VI

Pathology

Laboratory Tests in Older Adults: Indications, Interpretation, Issues

27

T.S. Dharmarajan and C.S. Pitchumoni

Introduction

Laboratory tests play a relevant role in patient care. In today's escalating healthcare environment, providers need to be cognizant of the risks, benefits, and costs of routine or standard batteries of tests. Caution needs to be exercised about age-based criteria as the reason to choose tests in the geriatric age group, especially prior to a surgical procedure. In general, it is more likely that test results may be abnormal in the older population [1]. As more tests are performed, the odds of obtaining abnormal results increases, posing implications for both patient and provider. False positive tests contribute to further escalation of costs. Routine tests based on age alone may no longer be paid for by insurance companies. In the past several years, there have been changes in approach due to economic pressures with a trend towards "indicated" rather than routine testing [2]. Tests do not always provide the information that the physician seeks, and the results may not be relevant to diagnosis or management.

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Is Old Age a Reason to Perform Tests?

It is generally accepted that advancing age is associated with comorbidity. Does this justify routine screening? In a study of 544 surgical patients over age 70, the prevalence of abnormal electrolyte values and thrombocytopenia was small (0.5–5%); the prevalence of abnormal hemoglobin, creatinine, and glucose was higher at 12, 10, and 7%, respectively, but did not predict adverse outcomes [3]. The authors concluded that routine testing for hemoglobin, creatinine, glucose, and electrolytes on the basis of age alone may not be indicated [3]. Laboratory values in screening by insurers were not significantly influenced by age alone; most abnormalities arose from impairments, rather than age [4]. However the cost-effectiveness is greater in older age, as there is a better likelihood of disease being detected [4].These statements must be weighed against the probability that disease detected by testing will modify management [2], justifying the test. Whether a poor history in the cognitively impaired or an atypical presentation in the old justifies the use of tests is debatable [4]. There is also a call for modified biochemical reference values for some tests in the over 65 age group [5]. It may be difficult to determine as to what tests will be significant in the patient who manifests multiple disease processes [6]. A good history of over-the-counter medications including supplement use may be relevant to test results [7].

Manifestations Determine the Need for Testing

In general, tests are done on the basis of symptoms or signs, to rule out underlying disease, to understand the severity of a disorder, to monitor the progress or prognosis of the illness, and assess the effectiveness of treatment. What constitutes normal or a range of accepted values is rarely ideal; the values are determined by a reference population factoring age, gender, race, and other variables [4].

Most laboratory values in older adults fall in the normal range, with significant abnormalities raising suspicion of

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disease [8]. The common abnormalites noted in a study involved alkaline phosphatase, serum phosphorus, low creatinine clearance without an alteration of serum creatinine, abnormalities in glucose, and deficiencies in vitamins and albumin, many indicating disease rather than aging [8]. Interestingly, data from common blood laboratory tests demonstrated that metabolic abnormalities are associated with global cognitive changes in the elderly; they included hyperglycemia, hypernatremia, hyperkalemia, low hemoglobin, and elevated creatinine, blood urea nitrogen (BUN), and white blood cell counts [9].

Unwanted Testing May Carry Risks More Than Benefits

The questions to be asked before requesting a test are: is the test relevant to the patient's health? Is there is a reason for the test? And would the test have potential to alter management? A screening program for the old in a rural practice found that although a few patients benefited, and it was academically stimulating, the benefits were not worth the effort; there was also reservation about the impact of testing on the quality of life [10]. Daily routine testing even in the sick hospitalized older adult may lead to significant blood loss and iatrogenic anemia with hemodynamic changes, requiring transfusions and influencing mortality [11]. Healthcare providers made aware of the cost of phlebotomy did order tests more appropriately to bring about savings for the hospital [12].

Unfortunately, laboratory test results are not always simple to interpret; they may be positive, negative, or inconclusive. A positive or abnormal test indicates that the disorder was present; a negative or normal test means that the disorder is not present; an inconclusive test is neither positive nor negative. A false positive test suggests that a disorder is present, when in reality it is not; a false negative test does not detect the disorder when in reality it is present. Even in the healthy adult, there is a likelihood that 1 in 20 tests ordered may be abnormal (5%) in the absence of an evident underlying abnormality [4]. For a panel of 20 tests, the chances are that there is a 64% chance of at least one abnormal test [13]. Thus more testing has the potential to cause anxiety for the patient (or provider). Interestingly, if anesthesiologists ordered tests prior to a procedure, instead of primary physicians and surgeons, there was a significant reduction in costs without an increase in complications [14].

Is there an increase in liability for requesting or not requesting a test? Legal concerns are often the reason for providers to request routine laboratory tests. Although there may be legal risk for failure to order a test and make a diagnosis in the first place, the risk may be greater for ordering a laboratory test and not following up in a timely fashion with required actions based on the abnormal results [1, 13]. Laboratory test results must be acknowledged, and reports initialed by the provider. Documentation must include negative and positive findings; critical test results warrant immediate action and rapid communication to the patient, along with documentation and actions taken. In summary, it is most desirable that the provider who orders a test follows up with the test results appropriately.

The following discussion arbitrarily divides laboratory tests into those *commonly or routinely* considered in all patients undergoing examination (or a procedure) irrespective of the history and physical examination, as opposed to those tests selected based on a *specific and individualized* reason. The topic does not cover every available test, rather it exemplifies the points made earlier.

Tests Performed Commonly: "Routine" Tests

Hemoglobin and Hematocrit

The pros and cons of routine testing are cited briefly in Table 27.1. Hemoglobin and hematocrit are among the useful routine tests. A study comparing two groups of men and women around 44 ± 0.9 years to 63 ± 0.9 years found significant differences with aging in hemoglobin (decreasing), MCV (increasing) and other indices; there were also differences in ferritin [15]. The most common causes of microcytosis are iron deficiency and thalassemia trait [16]. Anemia is a common multifactorial condition in the geriatric age group. Based on the WHO definition, anemia is present in 10% of those over 65 years and in 20% of the over 85 year group in the community, increasing to 48–63% of nursing home patients [17]. Even more important, based on the National Health and Nutritional Examination Survey (NHANES) data, in two-thirds of anemia there is a discernible cause noted with routine testing; a third of cases has a nutritional basis involving iron, B12, and folate deficiency in variable combinations, a third of anemia is from chronic disease and in a third routine tests do not provide an explanation [18]. The impact of anemia on organ dysfunction cannot be underestimated; it is an additional negative component in heart disease, diabetes, and cerebrovascular disease and a predictor of mortality [17, 19, 20]. A recent study of the 65+ age group revealed 12% to have iron deficiency anemia; many with unexplained anemia were "suspicious for myelodysplastic syndrome" [21]. The association between anemia and gastrointestinal disease is common and well known.

Ferritin, B12, and Folic Acid

While ferritin is a useful marker for body iron stores in the stable community patient, it tends to be elevated in the ill

Table 27.1 Common or "routine" tests [1, 4–6, 8, 10, 26, 53, 73]

Hemoglobin
Anemia: prevalence 10% of community adults over age 65, 20% over 85
Laboratory tests can delineate an etiology in two-thirds of anemics
Creatinine and blood urea nitrogen (BUN)
Renal function declines with age; but serum creatinine may remain normal in spite of decline in kidney function (effect of sarcopenia)
Calculation of renal function entails use of an acceptable formula
BUN is increased by multiple causes: renal failure, volume depletion, heart failure, gastrointestinal bleeding, dietary causes, medication effect, and obstructive uropathy
BUN may be lower in liver disease and malnutrition
Electrolytes
Are commonly abnormal due to the presence of renal disease, gastrointestinal losses, heart failure, and medication effect
Abnormalities also result from hepatic, thyroid, or pulmonary disease
Albumin and prealbumin
Consider liver disease, gastrointestinal or renal losses, and malnutrition
Acute negative phase reactant; deconditioning or illness lower albumin
Cholesterol, total and fractions, triglycerides
Considered as standard screen in all adults
Frequency of testing: dependent on measures used in management
Liver function
Abnormal tests are common, even in asymptomatic adults
Interpretation and further evaluation may need specialist consultation
Medication history is relevant for interpretation
Prothrombin time and APTT
Dictated by bleeding or clotting history and presence of liver disease
Use of anticoagulants or antiplatelet agents, alcoholism
Erythrocyte sedimentation rate
Marginal increase with age, more in females than in males
Nonspecific and increases with many illnesses
Fecal
Fecal occult blood test (needs to be better targeted)

(acute phase reactant) with ferritin values requiring cautious interpretation [22]. Ferritin should be interpreted in conjunction with health status, along with serum iron levels, iron-binding capacity, and transferrin saturation [23]. At times, the markers are inadequate to guide iron therapy [24]. In the NHANES I study, elevated transferrin saturation was associated with elevated mortality in over 2% of adults; but recent data from NHANES III suggest that ferritin and transferrin saturation are not associated with morality in those not taking iron supplements and without a baseline history of cardiovascular disease or cancer [25].

The need to evaluate folic acid and B12 status must be individualized based on clinical manifestations, history of illness, and dietary habits, along with initial hematological indices. Both these nutrients are low in a variety of gastrointestinal disorders affecting sites between the stomach and terminal ileum (detailed in another chapter). At this time they are not recommended among the routine initial panel of tests

Renal Function

Serum creatinine by itself is an unreliable indicator of renal function in the old. Although the creatinine level would be expected to rise with age-related decline in renal function, it may remain normal as a result of age-associated sarcopenia. Thus instead of using the serum creatinine as a marker, an acceptable formula is utilized. Because of the high prevalence of CKD in geriatric age groups, precise estimates of renal function and staging are relevant, especially for appropriate dosing of drugs, when pharmacokinetics are dependent on renal function and further to assess stage of kidney disease. Particularly in the frail elderly, such estimates are invaluable. The choice of formulae include the Cockcroft-Gault equation, Modification of Diet in Renal Disease Study, or the newer Chronic Kidney Disease Epidemiology Collaboration Initiative Equation [26].

BUN levels are influenced by multiple causes. Levels are elevated in acute and chronic renal failure, volume depletion, heart failure, gastrointestinal bleeding, dietary causes, use of medications such as steroids aor diuretics and obstructive uropathy; on the other hand, low levels occur in liver disease. In the presence of renal disease, one must also assess electrolyte status.

Liver Function

Liver function tests (LFTs) include a panel of tests: liver enzymes, bilirubin, and hepatic synthetic measures (prothrombin time and albumin). About 1–4% of asymptomatic patients manifest abnormal tests [27]. As many as 14.7% of a Chinese population had abnormal LFTs, the most common causes being metabolic syndrome, nonalcoholic fatty liver disease, and alcohol [28]. Nonalcoholic fatty liver disease is a common cause of abnormal AST and ALT worldwide, especially in affluent nations, increasing with the growing obesity epidemic [29].

LFTs are a panel and not all are true tests of liver function; further abnormalities may not reflect liver disease [30]. A focused history and physical examination are a foundation for appropriate testing [27]. Enzyme levels vary with gender, ethnicity, and age. Abnormal LFTs are commonly encountered in asymptomatic patients during routine visits and consultations; a cost-effective and systematic approach is recommended for their interpretation [31]. Even the excessive use of vitamins, such as vitamin A, may influence LFTs. Higher mortality has been demonstrated in a study of 560,000 life insurance applicants with higher levels of AST, ALT, and

GGT [32]. On the other hand, low ALT activity was also a predictor of reduced survival, mediated by its association with frailty and increasing age [33].

Serum Albumin

Screening for protein energy malnutrition at an early stage allows interventions to be most successful [34]. The value of serum albumin levels is immense; levels reflect not only nutritional status, but also relate to renal and hepatic function, gastrointestinal disease, and catabolic states. In an orthogeriatric unit, nearly 450 elderly with hip fractures demonstrated better functional independence with normoalbuminemia at admission and at discharge [35]. Hypoalbuminemia is a predictor of poor outcome or mortality in the ill, as e.g., in decompensated heart failure [36] and colon cancer prior to surgery [37].

Serum Lipids

Measurement of total cholesterol and its fractions (high density, low density, very low density) and triglycerides are now considered standard screening tests in adults. While they need to be repeated to monitor impact of therapy, multiple testing in the geriatric population appears associated with multiple providers, independent of indications and comorbidity, as demonstrated in a study of over 1.15 million Medicare beneficiaries [38].

Additional Comments

Routine repeat testing of critical values of hemoglobin, platelet count, white blood cell count, prothrombin time, and activated partial thromboplastin time do not offer advantage over a single run [39]. Erythrocyte sedimentation rate is a useful nonspecific test in several illnesses, with values higher typically in anemia and inflammatory states; low sedimentation rates are also noted in heart failure, common in older adults. Marginal increase in the sedimentation rates occur with age [6].

Individualized or "Specific" Tests

While a provider may not be clear about the need or lack of need for routine testing, specific testing clearly relates to findings in the history and examination. They are hence best individualized (Table 27.2).

Table 27.2 Individualized or "specific" [4, 11, 16–18, 20, 22, 23, 25, 27, 28, 30, 31, 34, 40, 49, 51, 57, 61–63, 65]

Antinuclear antibody
Is positive with illnesses, e.g., systemic lupus, scleroderma, etc.
Can be drug-induced positive (anticonvulsants, hydralazine)
Positive ANA in low titers common in the old
Ferrokinetics
Serum iron, total iron-binding capacity, ferritin
Used in conjunction with transferrin saturation, indicator of iron availability
Ferritin is an acute phase reactant, falsely elevated in inflammation
[a]B12 and folic acid
Deficiencies are common and occur in up to 25% of the older adults
B12 levels in borderline range are hard to interpret and may require homocysteine and methylmalonic acid assays to confirm
Additional tests help determine the specific etiology of B12 deficiency such as intrinsic factor antibodies for pernicious anemia
[a]Vitamin D status
25 hydroxy D levels, low in 40–50% of older adults
Predisposition: diet, restricted mobility, sun exposure, age
If calcium levels are low, may be suggestive of vitamin D deficiency
Vitamin D toxicity may present as hypercalcemia
Tests for pancreatic function
Serum amylase, lipase when specifically warranted
Tests for celiac disease, an entity that is generally underdiagnosed
Anti-TG IgA and anti-enodomysial IgA
Anti-TG IgG if IgA absent
HLA DQ2, HLA DQ8
[a]Thyroid function
Tests are commonly abnormal from thyroid and nonthyroid illness
Initial screen: thyroid-stimulating hormone, free thyroxine
Guidelines as to when to initiate screening and frequency vary
C reactive protein
Nonspecific marker of inflammation
Homocysteine and methylmalonic acid assays: do not provide specific diagnosis in most situations, but are helpful where B12 levels are borderline
Urinalysis and/or culture
With history of diabetes, renal disease, polyuria, suspected infection, abdominal pain, etc.
Fecal tests: examples
Fecal occult blood tests
Fecal DNA testing for colorectal cancer
Clostridium difficile-associated disease
Fecal tests for malabsorption
Tests for parasitic or other bacterial infection

[a]Opinions and guidelines on testing vary

Fecal Occult Blood Testing

Fecal occult blood testing (FOBT) is recommended by national guidelines for colorectal cancer (CRC) screening and is shown to reduce mortality in CRC. Most use standard tests; higher sensitivity guaiac testing and immunochemical tests were reported by only 22 and 8.9%, respectively [40]. Rather than relying on the multiple specimen home test, 74% of physicians perform in-office tests on a single stool specimen collected during digital rectal examination; the in-office test is considered a poor test that misses 95% of advanced neoplasia [41]. Even I-FOBT appears associated with false

negative results [42]. Fecal DNA testing for CRC screening is now available. Improvements in stool DNA tests relating to sensitivity for CRC and the use of fecal immunochemical tests is evolving. Data from a longitudinal cohort of patients over age 70 suggest that the net burden could be decreased by better targeting FOBT screening and follow up to healthy older adults; those with best life expectancy were less likely to experience a net burden [43]. Anticoagulant or aspirin therapy, commonly utilized in older adults, does not affect the positive predictive value of an immunological fecal occult blood test in those undergoing CRC screening as noted in a cohort case-controlled study [44].

Screening for Celiac Disease

This is a common but under-recognized entity in the geriatric population (see chapter on celiac disease). Finding the simplest and most patient-friendly test has impacted clinical practice, along with frustrations attributable to refractory cases [45]. Screening for celiac disease may be a consideration in type 1 diabetes mellitus, autoimmune diseases, inflammatory bowel diseases, and first-degree relatives with the disease. Serum IgA antibodies to tissue transglutaminase (tTG) are increased in active disease (except when IgA-deficient); a related antiendomysial IgA antibody is similar in sensitivity and specificity [46]. Relatives of a patient with celiac disease may be screened through a blood test or cheek swab for HLA DQ2 or HLA DQ8 by polymerase chain reaction; their absence makes celiac disease highly unlikely (negative predictive value 100%) [46, 47].

Screening for Diabetes

Testing for diabetes has increased over the years; HbA1c has largely replaced the glucose tolerance test [48]. With the increasing prevalence of obesity along with increasing life expectancy, diabetes is a common disorder, enhancing the value of HbA1c testing. Screening for prediabetes and diabetes appears cost-effective [49].

Acute Pancreatitis

Data covering 1996–2005 suggest an increase in the incidence of acute pancreatitis, in part because of the increased testing for pancreatic enzymes; the proportion of ED visits resulting in an inpatient discharge diagnosis of acute pancreatitis has been going up [50]. Serum amylase and lipase are relevant here, although both are nonspecific when the elevations are less than three times the upper normal [51]. C reactive protein may be a nonspecific marker for severity.

Testing for Bleeding and Coagulation

Routine coagulation testing may have higher yield if based on increasing risk of coagulopathy in those on warfarin or heparin or with liver disease [50, 52]. In complex conditions such as disseminated intravascular coagulation, although several parameters are abnormal, not a single test appears sufficiently accurate to establish or reject the diagnosis [53]. For coagulation monitoring, an initial questionnaire for bleeding history should be used, followed by coagulation testing should the history be suggestive [54]. The change in paradigm is the increasing use of an evidence-based approach based on bleeding history and awareness of limitations of routine coagulation tests to guide management in the event of massive bleeding [55]. It is essential to obtain a history of herbal or supplement use, as they influence bleeding and clotting parameters; simulataneous use of garlic, ginger, ginkgo biloba, saw palmetto, and ginseng can influence the International Normalized Ratio (INR) [56, 57].

Vitamin D Status

Measurement of 25-hydroxy vitamin D is relevant in those older adults at risk. Included are presence of any of the following: restricted activity to indoors; not on supplements or dairy products; malabsorption or malnutrition; use of medications which metabolize vitamin D (e.g., anticonvulsants); chronic liver and kidney disease; inflammatory bowel disease; and gait abnormalities, falls, and generalized unexplained pain. The test should be used in conjunction with calcium, phosphorus, and alkaline phosphatase levels [31]. Laboratory testing for vitamin D has increased in the U.S. between 2008 and 2009, in part from a greater awareness of vitamin D deficiency [58]. Excessive consumption of "over the counter" remedies with vitamin D can result in high levels and hypercalcemia [59].

Testing for *Clostridium dif cile*

The topic of C. difficile infection is detailed in chapter 54. A meaningful choice has to be made between enzyme immunoassays for toxin A and B, detection of *Clostridium difficile* glutamate dehydrogenase, cell culture cytotoxicity, and PCR-based assays for toxin detection; tests vary in sensitivity and specificity [60–62].

Antinuclear Antibodies

Autoimmune diseases are common with no age group exempt. However the tests lack sensitivity and standardization and include false positives and negatives [63]. In fact,

false positive tests ANA without disease are more common than systemic lupus, a frequent cause being older age. Besides low titer positivity that is common in the geriatric patient, medications such as hydralazine, anticonvulsants, and isoniazid are associated with a positive test, as also certain nonviral hepatitis and primary biliary cirrhosis.

Homocysteine

Homocysteine levels are increased in a variety of situations such as aging, chronic kidney disease, and hypothyroidism, in addition to vitamin B12, folic acid, and B6 deficiencies, indicating that the test is not specific. Routine testing for homocysteine is not warranted including the consideration in inflammatory bowel disease, although 13% of all inflammatory bowel disease patients had elevated levels in a study [64]. The provider should be knowledgeable about the application and interpretation of elevated homocysteine levels [65].

Selecting Tests Prior to a Procedure

In general, the best approach to choosing tests prior to a surgical or gastrointestinal (GI) procedure is to make the selection based on a comprehensive history and physical examination, including an understanding of the current (and recent) prescribed and over-the-counter medications; the list should include herbals and ophthalmic preparations. History is targeted to relevant aspects in light of the procedure to be performed; e.g., is the procedure just endoscopy or endoscopy plus biopsy and excision of a lesion? Will there be blood loss? Is this likely based on the history, comorbidity, and current medication intake?

In a study of 19,557 older adults, over 9,000 patients underwent cataract surgery *without* routine testing, compared to a similar number *on routine* testing. Routine medical testing did not measurably increase the safety of surgery [66]. Although this was not a gastrointestinal procedure, lessons can be learnt from the data. More was expected from the physician's physical assessment compared to the yield from laboratory testing [67]. The results may be extrapolated to other low-risk procedures. More than 30 years of evidence suggests that a focused history and physical examination and minimal selective laboratory tests may be best, with costs optimized by this approach [68]. A healthy older adult in good functional state, undergoing evaluation for hernia surgery, requires little by way of testing; here there is little need for prothrombin time and partial thromboplastin time, as they are clinically insignificant for the concerned procedure and may only delay surgery [1, 67]. On the other hand, after adjustment for age and comorbidities, serum albumin level (along with chest X-ray) was a predictor of postoperative complications in the elderly with hip fracture [69]. As preoperative predictors of mortality, hypoalbuminemia, acute renal impairment and high white cell count were present in 11, 24, and 33% of 70+ year olds tested in a study, where only 47% had all the tests performed [70] (Table 27.3).

Table 27.3 Preprocedure testing[a] [1, 3, 13, 14, 35, 54, 55, 67, 68, 70, 71]

General
Tests are best individualized based on a comprehensive history and physical examination
Full medication review: prescribed, topical, ophthalmic, herbals, and other supplements; include over-the-counter medications
Blood tests do not require repeating if performed in the recent past and the patient's clinical status is unchanged
In the healthy, asymptomatic older adult
Hematological
Hemoglobin level if blood loss is expected
Complete blood count if costs are reasonable
Platelet counts if indicated by history or examination
Renal, electrolyte, and metabolic
Serum creatinine and BUN in those over 40 years
Blood glucose, including screening for prediabetes and diabetes
Electrolytes based on indication (e.g., diuretic use)
Coagulation parameters when suggested by history or examination
In the older adult with comorbidity
Testing is individualized to history and comorbidity; examples
In CKD, tests for renal function and electrolytes (such as sodium, potassium, bicarbonate)
In a diabetic, besides glucose, tests for end organ damage
In cardiac disease, specialized cardiac testing
In the obese, tests for metabolic syndrome and organ dysfunction
Liver function, with a history of alcoholism
With a bleeding history, obtain history of medication use (anticoagulants, aspirin, herbals) and test for liver function, platelet counts, bleeding, and clotting parameters
Blood type and cross match: in anemia and with anticipated blood loss

[a]Chest radiographs, electrocardiogram, and additional tests may warrant consideration, based on age and/or comorbidity

Testing Prior to Endoscopy

Generally follow the guideline suggested above. There is insufficient data to determine the benefit of routine laboratory testing before endoscopy procedures [71]. Without evidence of a bleeding disorder or coagulopathy, the prothrombin time, INR, and partial thromboplastin time neither predicts nor correlates with intra- or postoperative bleeding. In fact, when bleeding does occur, it was more often in those with normal coagulation factors in absence of clinical risk factors [71]. Routine platelet counts are not advised in the absence of history or examination suggestive of thrombocytopenia. The recommendations are clearly stated in a position statement [71].

Table 27.4 Factors that may influence test results

Gastrointestinal surgery in the past
Prescribed and "over the counter" drugs
Supplements
Herbals
Smoking
Fasting or fed state
False negative tests
False positive tests

Table 27.5 Additional concerns about laboratory testing in the elderly

Costs of testing may influence willingness to undergo testing
Repeat testing and inconsistent results
Legal implications of overlooking an abnormal test result
Consequence of unwarranted repeated blood draws: iatrogenic anemia
Fears and emotions associated with testing, especially in dementia
Hematomas, local injuries, associated with fragile skin and veins

Several concerns relating to laboratory testing are commonly encountered by the patient or provider; a partial list is summarized in Tables 27.4 and 27.5. Ordering a test requires assessing the likelihood that a patient has specific conditions prior to the order, along with an understanding of the accuracy of test and as to how it will change management [72]. Speaking with the patient is the first choice and benefits from the test should outweigh risks; no test (not even a noninvasive one) is benign; in this regard, often less is more [72].

Key Points

- Although a large number of laboratory tests are available as screening option, the best approach would be to individualize testing based on history and physical examination.
- Significant abnormalities do not occur solely from aging.
- Abnormal test results in the elderly more likely indicate underlying disease.
- Test results are influenced by several factors, including gender race, fasting or fed state, and medication or herbals.
- The probability of abnormal test results increases in the older adult, in much part due to underlying comorbidity.
- Preprocedure testing is best guided by a focused history and examination, current medications, and planned procedure.
- In the hospital setting, judicious ordering of tests may be associated with lower cost and negative consequences.
- Test results must be followed by providers and abnormal test results addressed.

References

1. Hepner DL. The role of testing in the preoperative evaluation. Cleve Clin J Med. 2009;76(4):S22–7.
2. Fleisher LA. Routine laboratory testing in the elderly: is it indicated? Anesth Analg. 2001;93:249–50.
3. Dzankic S, Pastor D, Gonzalez C, Leung JM. The prevalence and predictive value of abnormal preoperative laboratory tests in elderly surgical patients. Anesth Analg. 2001;93:301–8.
4. Pokorski RJ. Laboratory values in the elderly. J Insur Med. 1990;22(2):117–9.
5. Bourdel-Marchasson I, Laksir H, Puget E. Interpreting routine biochemistry in those aged over 65 years: a time for change. Maturitas. 2010;66(1):39–45.
6. Keiso T. Laboratory values in the elderly. Are they different? Emerg Med Clin North Am. 1990;8(2):241–54.
7. Whitworth A. Micronutrients: to supplement or not to supplement? J Natl Cancer Inst. 2006;98(4):230–2.
8. Coodley EL. Laboratory tests in the elderly. What is abnormal? Postgrad Med. 1989;85(1):333–8.
9. Bruce JM, Harrington CJ, Foster S, Westervelt HJ. Common laboratory values are associated with cognition among older inpatients referred for neuropsychological testing. Clin Neuropsychol. 2009;23(6):909–25.
10. Edwards Y. Usefulness of blood tests carried out during screening of the elderly population in one practice. Br J Gen Pract. 1991;41:496–8.
11. Adiga GU, Dharmarajan TS, Dutcher JP. Iatrogenic anemia in hospitalized older adults: impact on mortality. J Am Geriatr Soc. 2003;51:S212.
12. Stuebing EA, Miner TJ. Surgical vampires and rising health care expenditure: reducing the cost of daily phlebotomy. Arch Surg. 2011;146(5):524–7.
13. Macpherson DS. Preoperative laboratory testing: should any tests be "routine" before surgery? Med Clin North Am. 1993;77(2):289–308.
14. Finegan BA, Rashiq S, McAlister FA, O'Connor P. Selective ordering of preoperative investigations by anesthesiologists reduces the number and costs of tests. Can J Anaesth. 2005;52:575–80.
15. Martin H, Langenhan K, Huth M, et al. Clinical laboratory diagnosis and aging. 3: evaluation of a study of aging—complete blood and urine status. Z Gerontol Geriatr. 2001;3493:183–91.
16. Van Vranken M. Evaluation of microcytosis. Am Fam Physician. 2010;82(9):1117–22.
17. Patel KV. Epidemiology of anemia in older adults. Semin Hematol. 2008;45(4):210–7.
18. Guralnik JM, Eisenstaedt RS, Ferrucci L, et al. Prevalence of anemia in persons 65 years and older in the United States: evidence for a high rate of unexplained anemia. Blood. 2004;104(8):2263–8.
19. Dharmarajan TS, Dharmarajan L. Anemia in older adults: an indicator requiring evaluation. Fam Pract Recert. 2007;29(6):16–26.
20. Dharmarajan TS, Pais W, Norkus EP. Does anemia matter? Anemia, morbidity and mortality in older adults: need for greater recognition. Geriatrics. 2005;60(12):22–9.
21. Price EA, Mehra R, Homes TH, Schrier SL. Anemia in older persons: etiology and evaluation. Blood Cells Mol Dis. 2011;46(2):159–65.
22. Knovich MA, Store JA, Coffman LG, et al. Ferritin for the clinician. Blood Rev. 2009;23(3):95–104.
23. Coyne D. Iron indices: what do they really mean? Kidney Int Suppl. 2006;101:S4–8.
24. Ferrari P, Kulkarni H, Dheda S, et al. Serum iron markers are inadequate for guiding iron repletion in chronic kidney disease. Clin J Am Soc Nephrol. 2011;6(1):77–83.

25. Menke A, Muntner P, Fernandez-Real JM, Gualiar E. The association of biomarkers of iron status with mortality in US adults. Nutr Metab Cardiovasc Dis. 2011; ahead of print.
26. Michels WM, Grootendorst DC, Verduijn M, et al. Performance of the Cockcroft-Gault, MDRD and New CKD-EPI formulas in relation to GFR, age and body size. Clin J Am Soc Nephrol. 2010;5:1003–9.
27. Krier M, Ahmed A. The asymptomatic outpatient with abnormal liver function tests. Clin Liver Dis. 2009;13(2):167–77.
28. Zhang H, He SM, Sun J, et al. Prevalence and etiology of abnormal liver function tests in an adult population in Jilin, China. Int J Med Sci. 2011;8(3):254–62.
29. Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. Aliment Pharmacol Ther. 2011;34(3):274–85.
30. Coates P. Liver function tests. Aust Fam Physician. 2011;40(3):113–5.
31. Kennel KA, Mathew TD, Hurley DL. Vitamin D deficiency in adults: when to test and how to treat. Mayo Clin Proc. 2010;85(8):752–8.
32. Pinkham CA, Krause KJ. Liver function tests and mortality in a cohort of life insurance applicants. J Insur Med. 2009;41(3): 170–7.
33. Le Couteur DG, Blyth FM, Creasey HM, et al. The association of alanine transaminase with aging and morality. J Gerontol A Biol Med Sci. 2010;65(7):712–7.
34. Omran ML, Morley JE. Assessment of protein energy malnutrition in older persons, part II: laboratory evaluation. Nutrition. 2000;16(2):131–40.
35. Mizrahi EH, Fleissig Y, Arad M, et al. Admission testing and functional outcome of elderly hip fracture patients: is it important? Aging Clin Exp Res. 2007;19(4):284–9.
36. Uthamalingam S, Kandala J, Daley M, et al. Serumalbumin and mortality in acutely decompensated heart failure. Am Heart J. 2010;160(6):1149–55.
37. Lai CC, You JF, Yeh CY, et al. Low preoperative serum albumin in colon cancer: a risk factor for poor outcome. Int J Colorectal Dis. 2011;26(4):473–81.
38. Goodwin JS, Asrabadi A, Howrey B, et al. Multiple measurement of serum lipids in the elderly. Med Care. 2011;49(2):225–30.
39. Toll AD, Lir JM, Gulati G, et al. Does routine repeat testing of critical values offer any advantage over single testing? Arch Pathol Lab Med. 2011;135(4):440–4.
40. Nadel MR, Berkowitz Z, Klabuncle CN, et al. Fecal occult blood testing beliefs and practices of U.S. primary care physicians; serious deviations from evidence-based recommendations. J Gen Intern Med. 2010;25(8):833–9.
41. Collins JF, Lieberman DA, Durbin TE, Weiss DG. Veterans Affairs cooperative Study #380 Group. Accuracy of screening for fecal occult blood on a single sample obtained by digital rectal examination: a comparison with recommended sampling practice. Ann Intern Med. 2005;142:81–5.
42. Rozen P, Shabtai EI, Liphshitz I, Barchana M. Risk for colorectal cancer in elderly persons and possible methodologies for their screening. Eur J Gastroenterol Hepatol. 2011;23(5):431–7.
43. Kistler CE, Kirby KA, Lee D, et al. Long term outcomes following positive fecal occult blood test results in older adults: benefits and harms. Arch Intern Med. 2011;171(15):1344–51.
44. Mandelli G, Radaelli F, Paggi S, et al. Anticoagulant or aspirin treatment does not affect the positive predictive value of an immunological fecal occult blood test in patients undergoing colorectal cancer screening: results from a nested in a cohort case-controlled study. Eur J Gastroenterol Hepatol. 2011;23(4): 323–6.
45. Hadithi M, Pena AS. Current methods to diagnose the unresponsive and complicated forms of celiac disease. Eur J Intern Med. 2010;21(4):247–53.
46. van der Windt DA, Jellema P, Mulder CJ, et al. Diagnostic testing for celiac disease among patients with abdominal symptoms, a systematic review. JAMA. 2010;303:1738–46.
47. Rostom A, Dube C, Conney A, et al. The diagnostic accuracy of serologic tests for celiac disease: a systematic review. Gastroenterology. 2005;128:538–46.
48. Wilson SE, Lipscombe LL, Rosella LC, Manuel DG. Trends in laboratory testing for diabetes in Ontario, Canada 1995–2005: a population-based study. BMC Health Serv Res. 2009;9:41.
49. Chatterjee R, Narayan KM, Lipscomb J, Phillips LS. Screening adults for pre-diabetes and diabetes may be cost-saving. Diabetes Care. 2010;33(7):1484–90.
50. Yadav D, Ng B, Saul M, Kennard ED. Relationship of serum pancreatic enzyme testing trends with the diagnosis of acute pancreatitis. Pancreas. 2011;40(3):383–9.
51. Yadav D, Agarwal N, Pitchumoni CS. A critical evaluation of laboratory tests in acute pancreatitis. Am J Gastroenterol. 2002;97:1309–18.
52. Thachil J. Relevance of clotting tests in liver disease. Postgrad Med. 2008;84(990):177–81.
53. Levi M, Meijers JC. DIC: which laboratory tests are most useful. Blood Rev. 2011;25(1):33–7.
54. Heindl B. Perioperative coagulation monitoring—medical and economic aspects. Anasthesiol Intensivmed Norfallmed Schmerzther. 2010;45(5):292–6.
55. Kozek-Langenecker SA. Perioperative coagulation monitoring. Best Pract Res Clin Anaesthesiol. 2010;24(1):27–40.
56. Abad MJ, Bedoya LM, Bermejo P. An update on drug interactions with the herbal medicine ginkgo biloba. Curr Drug Metab. 2010;11(2):171–81.
57. Wittkowsky AK. Dietary supplements, herbs and oral anticoagulants: the nature of the evidence. J Thromb Thrombolysis. 2008;25(1):72–7.
58. Rosen CJ. Vitamin D insufficiency. N Engl J Med. 2011;364: 248–54.
59. Lowe H, Cusano NE, Binkley N, et al. Vitamin D toxicity due to a commonly available "over the counter" remedy from the Dominican Republic. J Clin Endocrinol Metab. 2011;96(2):291–5.
60. Schimidt ML, Gilligan PH. *Clostridium difficile* testing algorithms: what is practical and feasible? Anaerobe. 2009;15:270–3.
61. Cheng AC, Ferguson JK, Richards MJ, et al. Australasian Society for Infectious Diseases guidelines for the diagnosis and treatment of *Clostridium difficile* infection. Med J Aust. 2011;194:353–8.
62. Cohen SH, Gerding DN, Johnson S, et al. Clinical Practice Guidelines for *Clostridium difficile* infection in adults: 2010 Update by the Society for Healthcare (SHEA) Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). Infect Control Hosp Epidemiol. 2010;31(5):431–55.
63. Meroni PL, Schur PH. ANA screening: an old test with new recommendations. Ann Rheum Dis. 2010;69(8):1420–2.
64. Vagianos K, Berstein CN. Homocysteiemia and B vitamin status among adult patients with inflammatory bowel disease: A one year prospective follow-up study. Inflamm Bowel Dis. 2012;18(4): 718–24.
65. Chatthanawaree W. Biomarkers of cobalamin (vitamin B12) deficiency and its application. J Nutr Health Aging. 2011; 15(3):227–31.
66. Schein OD, Katz J, Bass EB, et al. The value of routine preoperative medical testing before cataract surgery. N Engl J Med. 2000;342:168–75.
67. Roizen MF. More preoperative assessment by physicians and less by laboratory tests. N Engl J Med. 2000;342:204–5.

68. Richman DV. Ambulatory surgery: how much testing do we need? Anesthesiol Clin. 2010;28(2):185–97.
69. Lee HP, Chang YY, Jean YH, Wang HC. Importance of serum albumin level in the preoperative tests conducted in elderly patients with hip fracture. Injury. 2009;40(7):756–9.
70. Achuthan S, Smirk A, Keeble A, Leslie K. Perioperative mortality score: data collection and cost. Anaesth Intensive Care. 2011; 39(2):274–8.
71. Levy MJ, Anderson MA, Baron TH, et al. Position statement on routine laboratory testing before endoscopic procedures. Gastrointest Endosc. 2008;68(5):827–32.
72. Redberg R, Katz M, Grady D. Diagnostic tests: another frontier for less is more. Arch Intern Med. 2011;172:619.
73. Martin D, Beardsell I. Is routine coagulation testing necessary in patients presenting to the emergency department with chest pain? Emerg Med J. 2012;29(3):184–7.

Gastrointestinal Pathology in the Older Adult

28

Noam Harpaz, Hongfa Zhu, and Mohammad Raoufi

Introduction

The spectrum of gastrointestinal (GI) pathology in the geriatric individual is diverse and affects all sites in the GI tract. Progress in gastroenterology has been rapid, with histopathology today playing an important role in diagnosis and management. Improvements in diagnostic modalities including high-resolution endoscopy, endoscopic ultrasound, fine needle aspiration, and optically targeted biopsies have enhanced the diagnostic yield and accuracy of histopathological diagnosis in patient care.

This chapter illustrates the role of pathology in the diagnosis of a variety of classical and newer GI disorders in the geriatric population. The chosen disorders are relevant in the elderly and detailed elsewhere in the text.

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Reflux esophagitis (Fig. 28.1a, b)

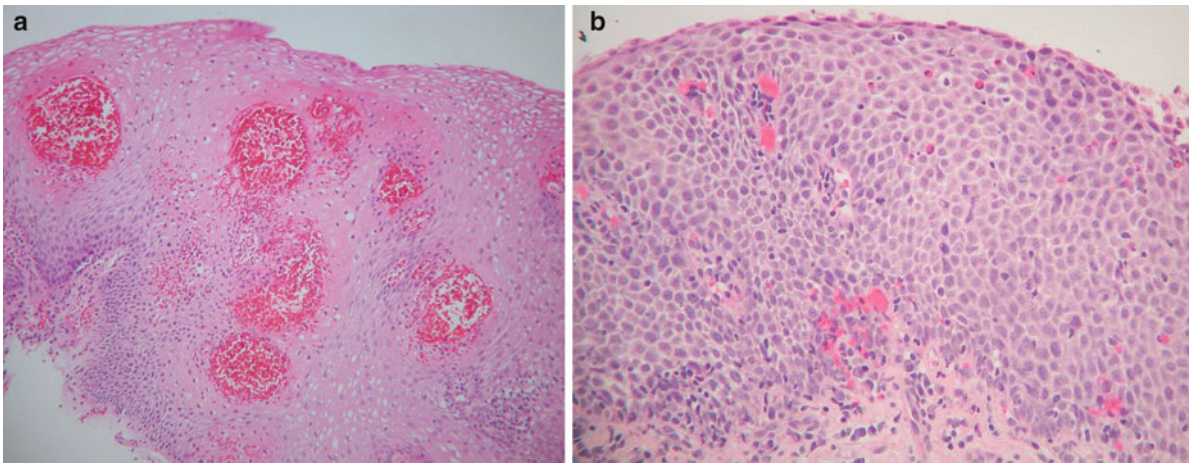


Fig. 28.1

Reflux esophagitis presents a variety of different but overlapping microscopic manifestations. A. In this biopsy, the squamous esophageal mucosa features prominent dilated capillaries, or vascular lakes, corresponding endoscopically to mucosal erythema. The surrounding squamous cells are swollen and contain densely eosinophilic cytoplasm. This squamous "ballooning" is caused by intracellular leakage of plasma protein across chemically injured cell membranes. B. Biopsy of another patient with reflux esophagitis showing basal cell hyperplasia, reflecting increased cell turnover, and scattered eosinophils

Barrett esophagus (Fig. 28.2a, b)

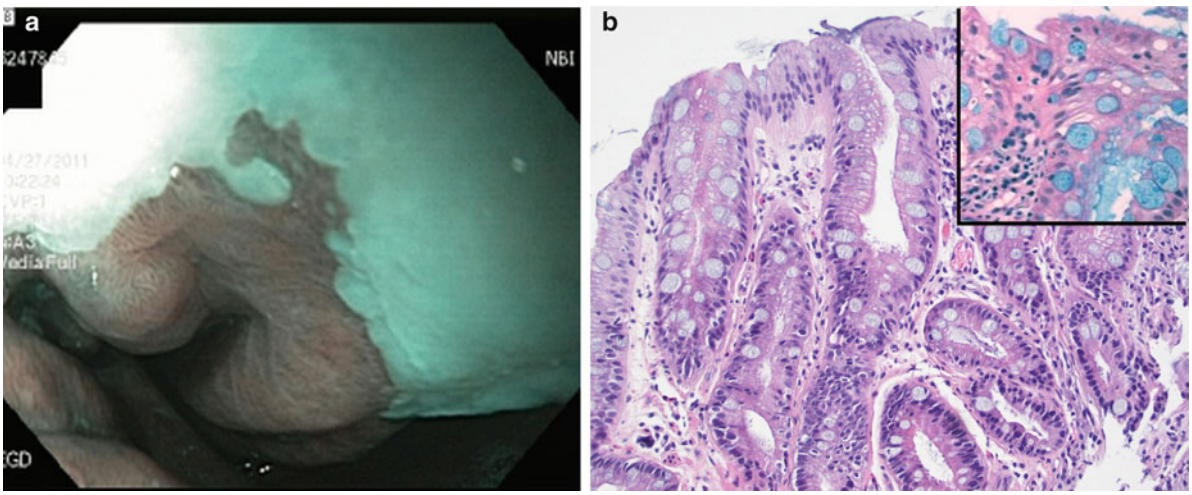


Fig. 28.2

Barrett esophagus, defined as metaplastic replacement of the squamous esophageal mucosa by columnar mucosa, occurs in approximately 10% of individuals with chronic gastroenteric reflux. A. Short-segment Barrett esophagus, observed with narrow band imaging, featuring an irregular tongue of dark mucosa that extends into the tubular esophagus. B. The metaplastic columnar epithelium consists of cells with microvesicular cytoplasm interspersed with goblet cells with a single large mucin vacuole. (Inset) Alcian blue stain highlights the goblet cells, helping distinguish them from gastric surface cells

Barrett dysplasia (Fig. 28.3a, b)

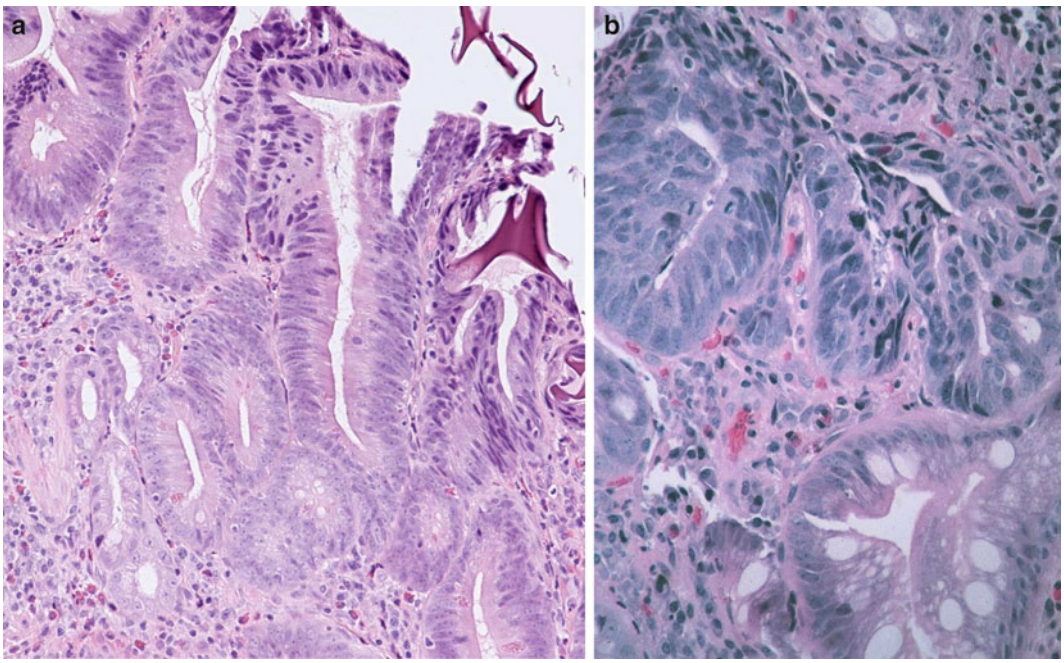


Fig. 28.3

Barrett dysplasia, a neoplastic change that precedes the development of esophageal adenocarcinoma, occurs in up to 20% of patients with Barrett esophagus. A. Low-grade dysplasia is characterized by glandular and surface epithelium with darkly stained, crowded nuclei. The nuclei have a parallel configuration and are mostly confined to the base of the cells. B. High-grade dysplasia features epithelial cells with disorderly, stratified nuclei that occupy a large proportion of the cytoplasm

Barrett adenocarcinoma (Fig. 28.4a, b)

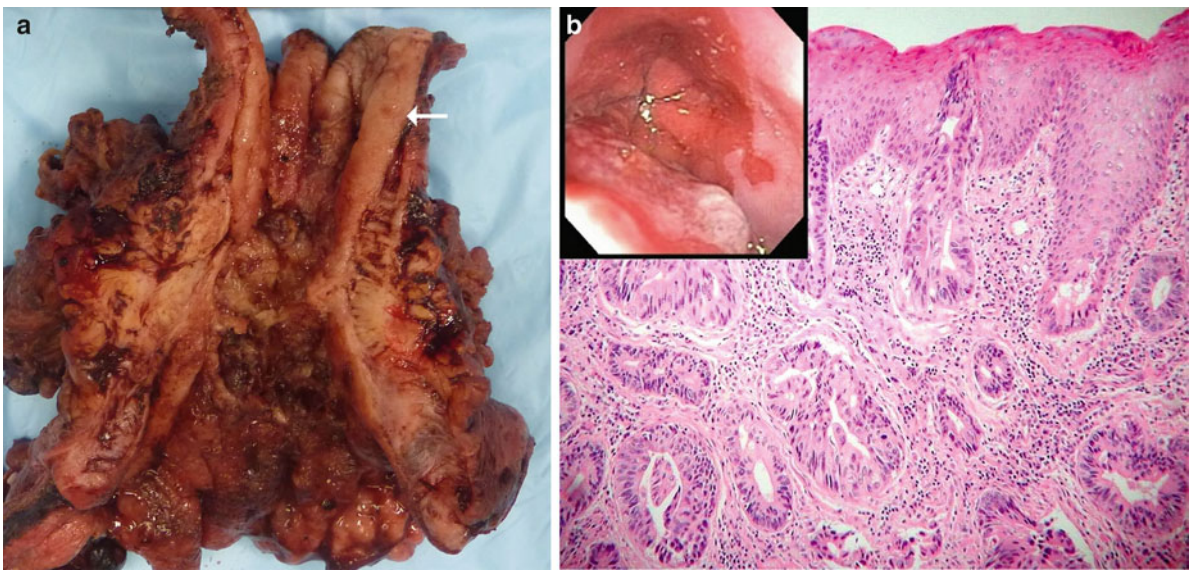


Fig. 28.4

Esophageal adenocarcinoma occurs in a subset of patients with Barrett esophagus at a rate estimated at 5% per decade. A. Esophagectomy specimen containing an ulcerated, stricturing mass which invades transmurally into the surrounding soft tissue. Arrow highlights the squamo-columnar junction. B. Another tumor consisting microscopically of malignant glands invading into the esophageal wall. The overlying squamous mucosa has re-grown following previous ablation of dysplastic Barrett mucosa by photodynamic therapy. (Inset) Protuberant mass arising in partially columnar-lined esophagus

Esophageal squamous cell carcinoma (Fig. 28.5a, b)

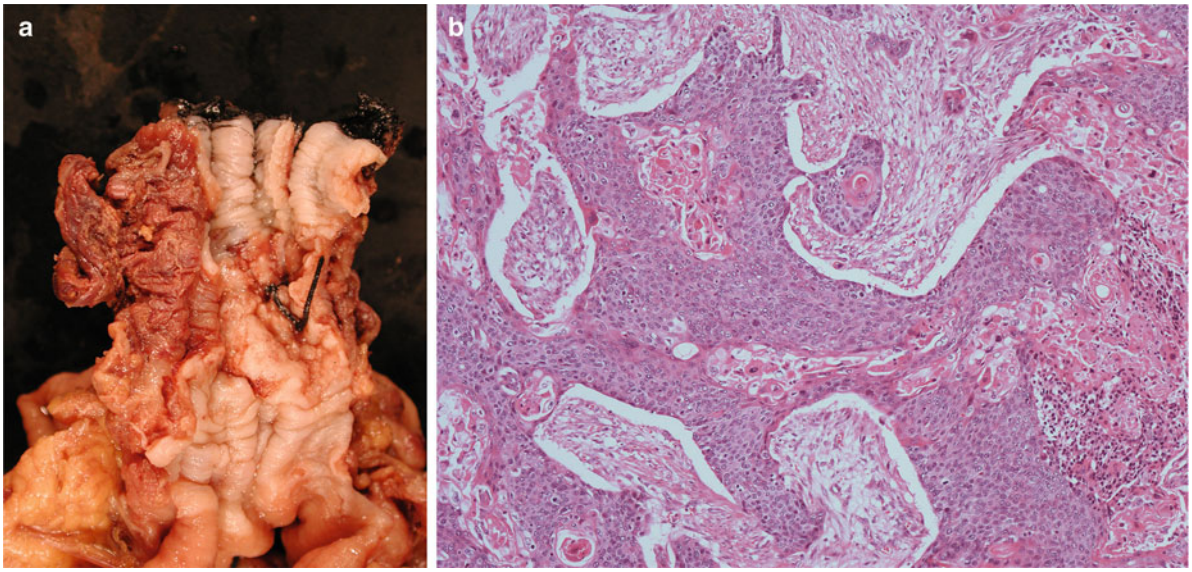


Fig. 28.5

Squamous cell carcinoma in a patient who presented with dysphagia and weight loss. A. Esophagectomy specimen with ulcerated tumor mass surrounded above and below by squamous mucosa. B. Microscopically, the tumor consists of solid sheets of cohesive tumor cells. Scattered groups of keratinized tumor cells appear as dyscohesive eosinophilic cells

Candida esophagitis (Fig. 28.6)

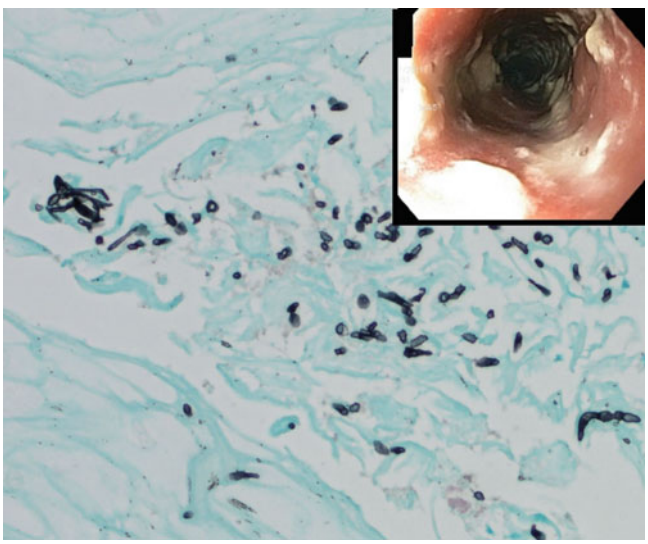


Fig. 28.6

Candida esophagitis presents microscopically as pseudomembranes consisting of fungal spores, pseudohyphae, and desquamated squamous cells. The fungi are best seen with special stains such as this silver impregnation stain. (Inset) Endoscopically, the pseudomembranes present as whitish mucosal plaques

Herpes esophagitis (Fig. 28.7)

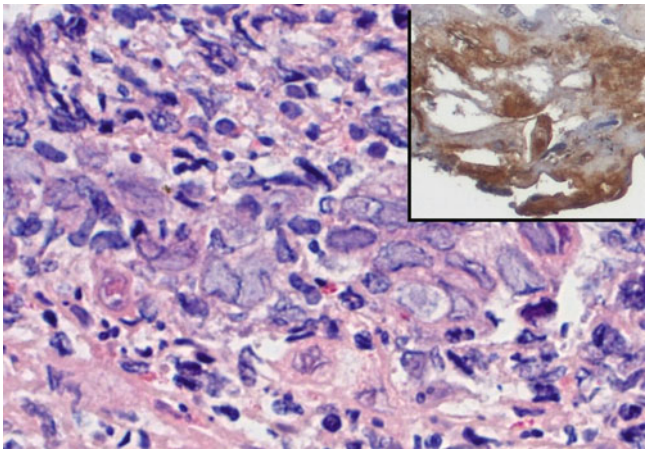


Fig. 28.7

Herpes esophagitis presents endoscopically as mucosal vesicles and erosions. Microscopically, one observes desquamated squamous cells with single or multiple "ground glass" nuclei characterized by grayish central pallor. (Inset) Immunoperoxidase stain for Herpes antigen

Eosinophilic esophagitis (Fig. 28.8)

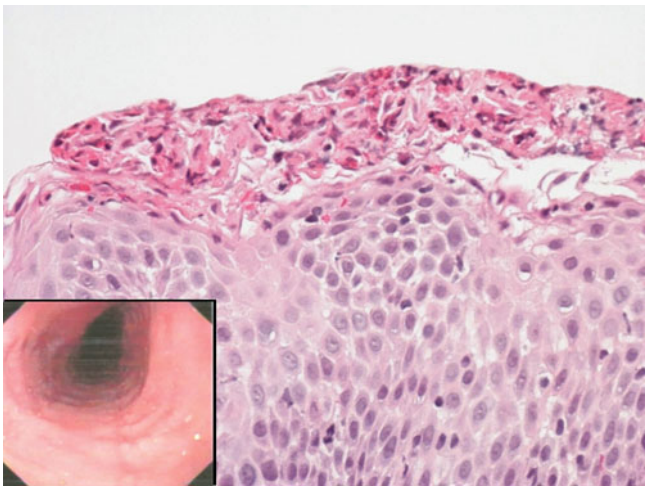


Fig. 28.8

Eosinophilic esophagitis has distinctive microscopic features, among which are collections of intramucosal eosinophils layered near the surface, sometimes admixed with desquamating squamous cells as shown in this example. (Inset) Endoscopically, the mucosa may appear ringed and may also feature vertical furrows and tiny white mucosal patches that correspond to desquamative foci

Hypergastrinemia (Fig. 28.9a, b)

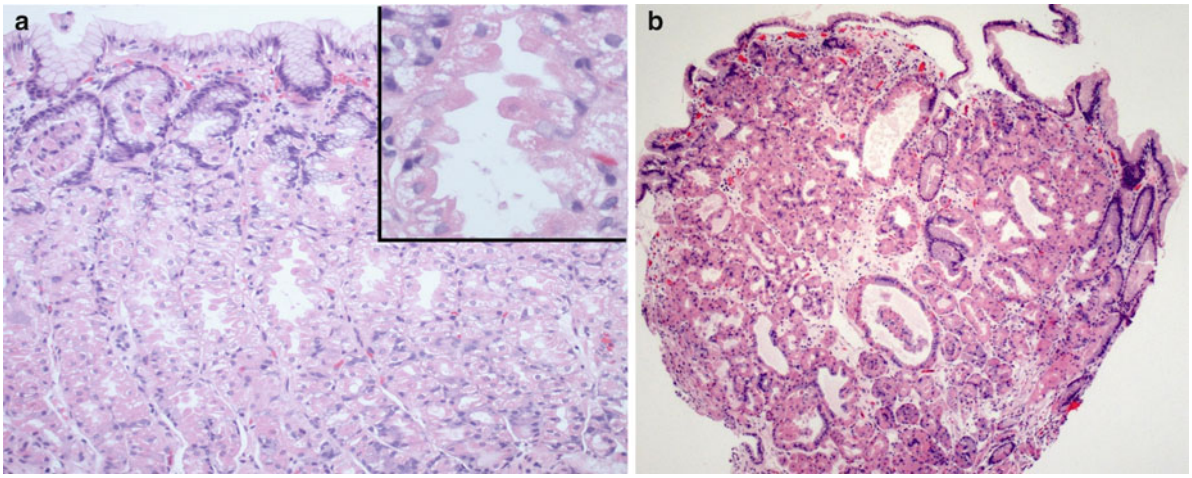


Fig. 28.9

Hypergastrinemia, usually associated with chronic use of proton pump inhibitors or less commonly with Zollinger–Ellison syndrome, causes striking hyperplasia of the gastric parietal cells. A. The oxyntic glands have dilated lumens lined by abundant parietal cells. (Inset) The parietal cells are enlarged, vacuolated, and protrude into the lumen, producing a sawtooth profile. B. Chronic use of PPIs also results in single or multiple gastric fundic gland polyps that consist of cystically dilated foveolar and oxyntic-lined glands with increased parietal cells

Iron pill gastropathy (Fig. 28.10)

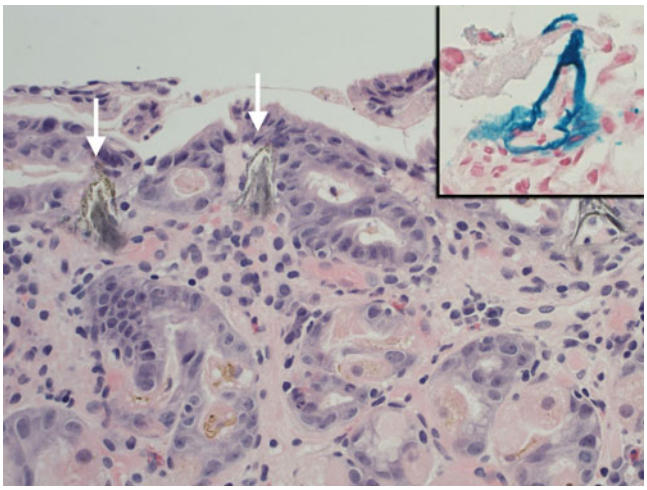


Fig. 28.10

Deposition of therapeutic iron, a potential cause of erosive gastritis, presents microscopically as subsurface basophilic- and gold-colored deposits (arrows). (Inset) The iron particles can be highlighted with Perl's Prussian blue stain

Other chemical gastropathies (Fig. 28.11a, b)

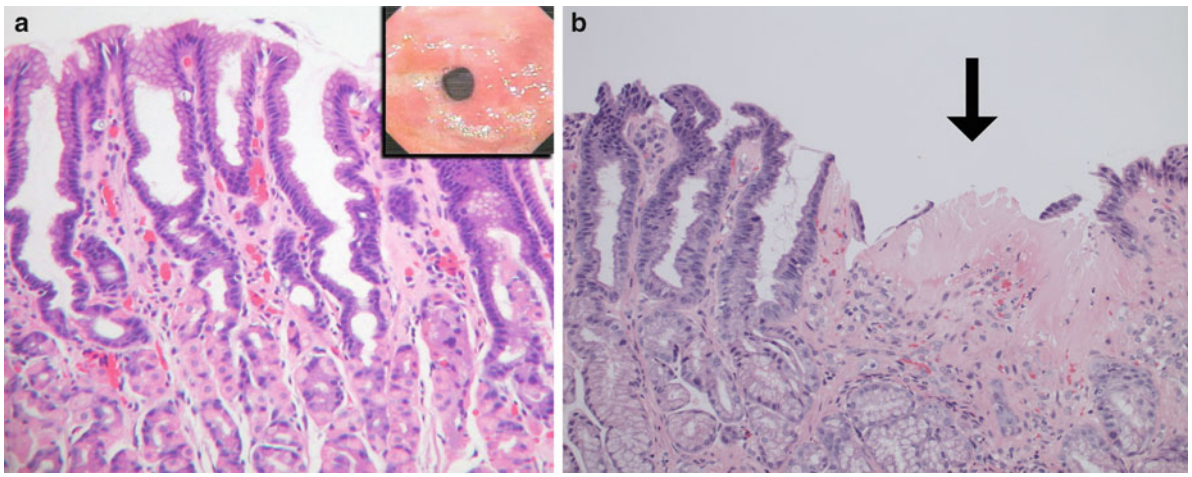


Fig. 28.11

A. Bile reflux gastropathy presents microscopically with corkscrew-shaped foveolae lined by mucin-deficient, basophilic columnar epithelium. (Inset) Endoscopically, the gastric mucosa is erythematous and covered with bile-tinged secretions. B. NSAID-associated erosive gastritis. The mucosa contains a discrete erosion covered by fibrinous exudate (arrow). The adjacent intact foveolae are similar to those in bile reflux gastropathy

Chronic gastritis (Fig. 28.12a, b)

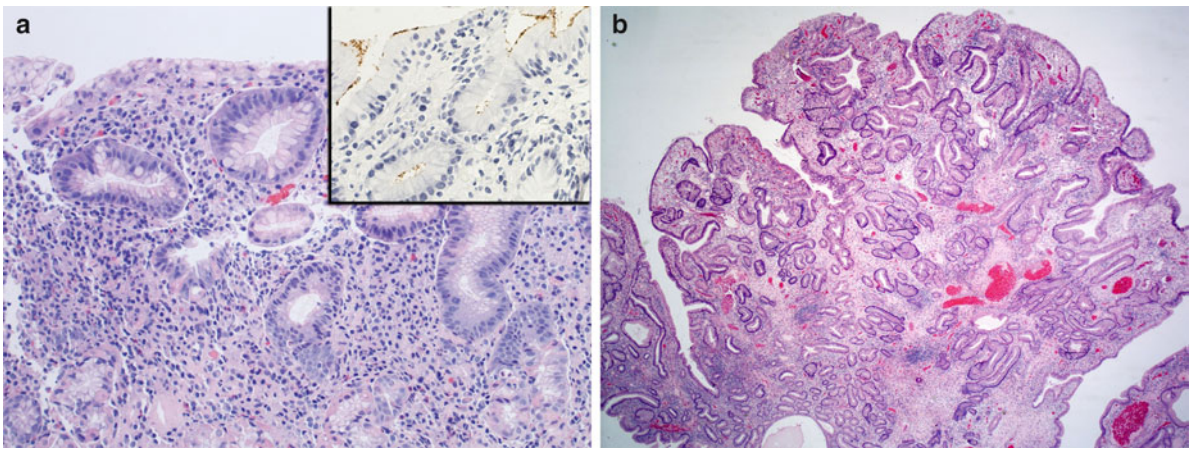


Fig. 28.12

A. *Helicobacter pylori*-associated gastritis featuring dense mononuclear inflammatory cell infiltrates. (Inset) Immunoperoxidase stain highlights the slender bacilli attached to the gastric surface epithelium. B. Hyperplastic gastric polyp. These polyps occur singly or multiply in the setting of chronic gastritis. They consist microscopically of tortuous, dilated gastric foveolae surrounded by expanded, chronically inflamed stroma

Gastric adenoacarcinoma (Fig. 28.13a, b)

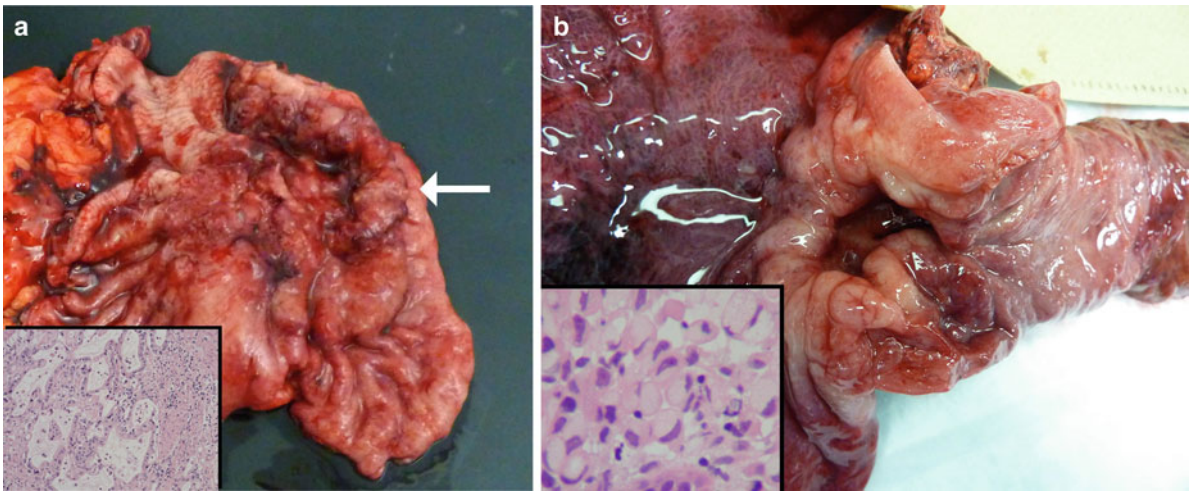


Fig. 28.13

A. Large, ulcerated tumor occupying the gastric antrum. (Inset) Microscopically, the tumor consists of malignant, partially formed glands and is classified as "intestinal" (Lauren classification). B. Ulcerated tumor occupying the pylorus. (Inset) Microscopically, the tumor consists of signet ring cells, i.e., dyscohesive cells with mucin vacuoles and peripherally displaced crescentic nuclei, and is classified as "diffuse"

GIST (Fig. 28.14a, b)

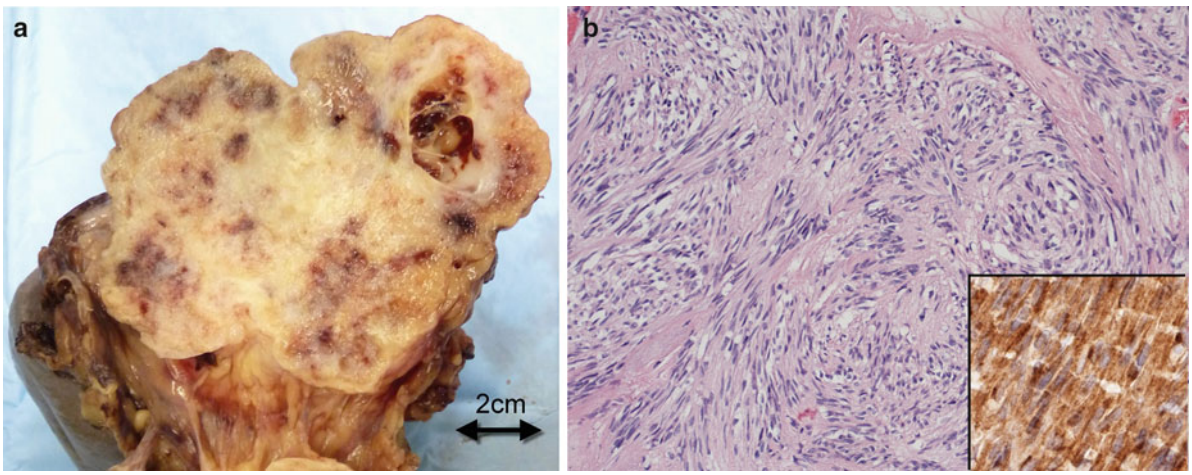


Fig. 28.14

Gastrointestinal stromal tumors (GIST) may arise throughout the gastrointestinal tract or abdomen. They vary with respect to malignant potential from essentially benign to highly malignant, the distinction depending mainly on location, size, and mitotic activity. A. 8 cm GIST of low malignant potential protruding from the serosal aspect of the stomach. The cut surface reveals a well-circumscribed, grey-white, mostly solid mass. B. Microscopically, the tumor consists of whorls of uniform spindle cells with absent mitotic figures. (Inset) Immunohistochemical expression of the c-Kit tyrosine protein kinase (CD117) occurs in the great majority of GISTs and helps distinguish them from other spindle cell tumors

NSAID-associated enteropathy (Fig. 28.15a, b)

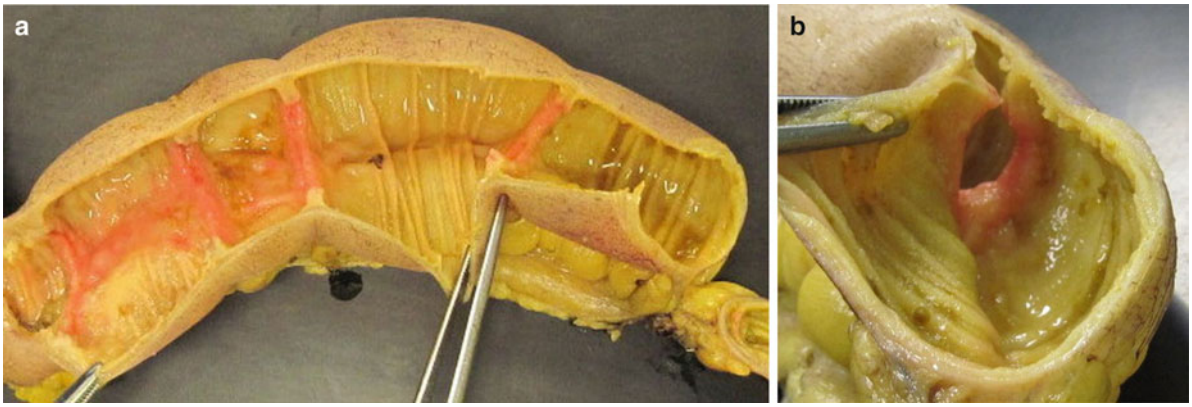


Fig. 28.15

Excessive use of NSAIDs may result in enteric erosions or, less commonly, formation of intestinal diaphragms. A. Segment of small intestine with multiple transverse septa. B. Close-up view of diaphragm with central lumen

Celiac disease (Fig. 28.16)

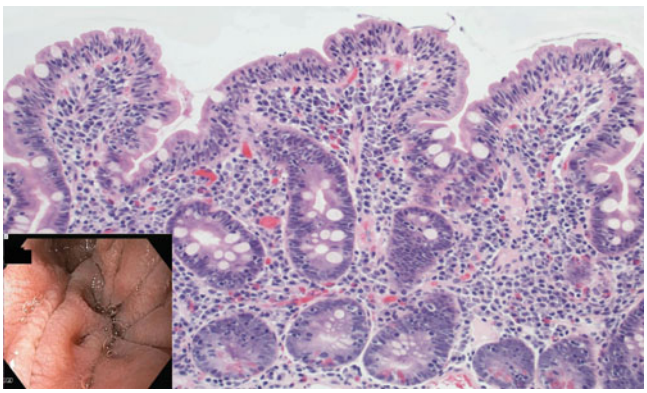


Fig. 28.16

Celiac disease featuring numerous intraepithelial lymphocytes, villous blunting, and elongated crypts. Of these characteristics, the most sensitive, though not necessarily specific, is intraepithelial lymphocytosis. The other features are absent in some patients, especially those with mild symptoms. (Inset) Endoscopically, scalloping of the small intestinal mucosa is a clue to the diagnosis of celiac disease, albeit not a specific feature

Small intestinal diverticulosis (Fig. 28.17)

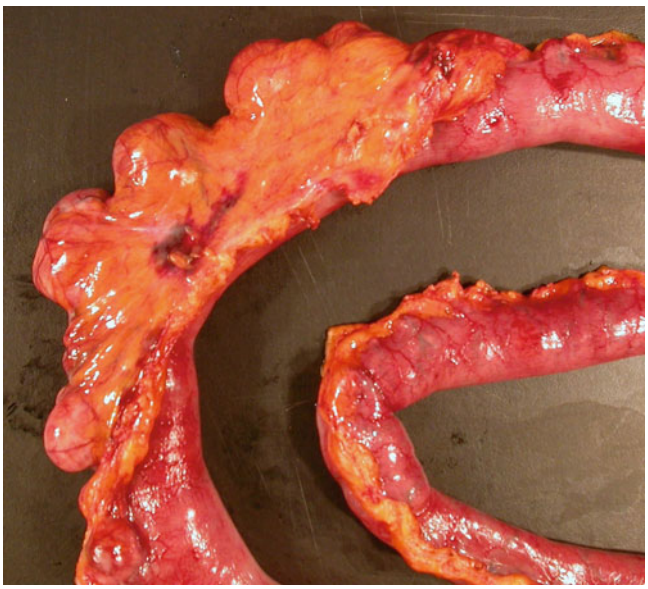


Fig. 28.17

Small intestinal diverticulosis, a potential cause of bacterial overgrowth and malabsorption syndrome, usually occurs in elderly patients. Multiple bulging diverticula are seen along the mesenteric insertion

Ulcerative colitis (Fig. 28.18a, b)

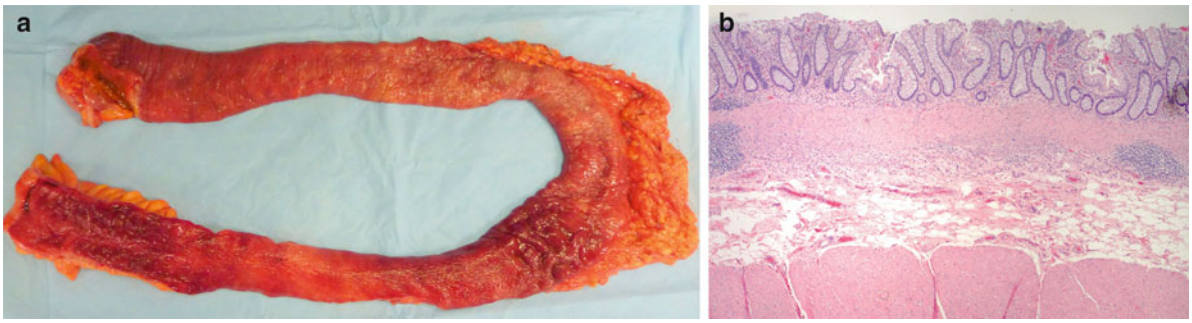


Fig. 28.18

Ulcerative colitis. A. Colectomy specimen (top, cecum; bottom, rectum) with mildly active pancolonic disease manifested by diffuse attenuation of the normal mucosal folds and patchy erythema in areas of active inflammation. B. Microscopically, the mucosa features disorganized crypt architecture and a thickened muscularis mucosae, but no inflammation of the deeper layers

Crohn's disease (Fig. 28.19a, b)

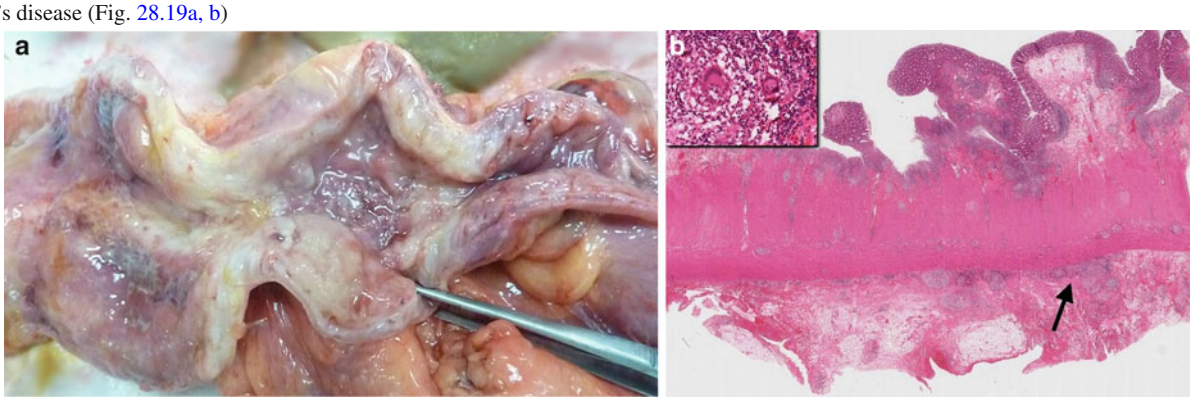


Fig. 28.19

Crohn's disease. A. Resected small intestine featuring mural thickening, multiple inflammatory strictures, and ulcerated mucosa. B. Microscopic features of Crohn's disease including inflammatory polyps, transmural lymphoid aggregates, and chronic subserosal inflammation with granulomas (arrow) (Inset) Epithelioid cell granuloma at high magnification.

Ischemic colitis (Fig. 28.20a, b)

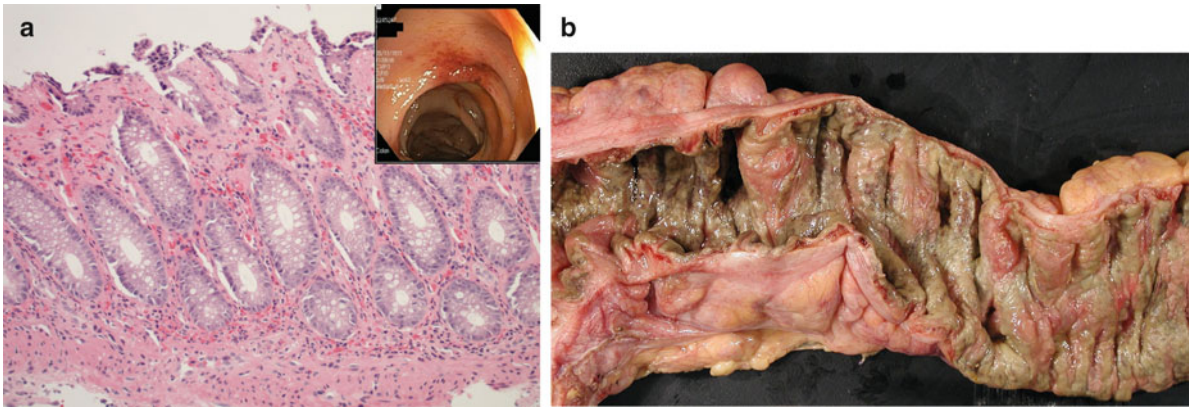


Fig. 28.20

Ischemic colitis can vary greatly in clinical severity, mild cases affecting the mucosa and more severe cases involving progressively deeper layers of the colonic wall. A (Inset). Mild ischemia in a patient with abdominal pain and rectal bleeding presenting endoscopically with mucosal petechia and red-brown discoloration. Microscopically, the colonic crypts, especially near the surface, are narrowed and depleted of goblet cells and the lamina propria is eosinophilic due to leakage of plasma protein from damaged capillaries. B. Moderately severe ischemic colitis with extensive ulceration but no evidence of peritonitis

Antibiotic-associated colitis (Fig. 28.21)

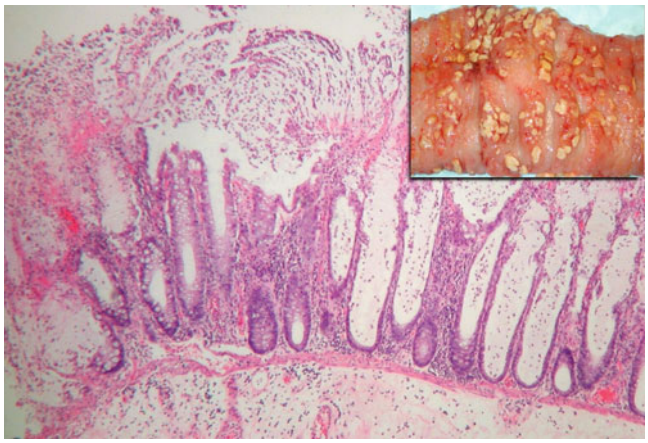


Fig. 28.21

Pseudomembranous colitis, the most severe manifestation of antibiotic-associated colitis, presents microscopically with dilated, mucin-filled colonic crypts, and overlying mucosuppurative exudates that appear to spew forth from a necrotic surface. On the far left, nearly the entire thickness of the mucosa has been effaced by necrosis. (Inset) Resected colon containing tan, plaque-like pseudomembranes each surrounded by a halo of erythema. Although *Clostridium difficile* accounts for most cases of pseudomembranous colitis, other bacterial pathogens including *Shigella*, enterohemorrhagic *Escherichia coli,* and *Klebsiella oxytoca* can have similar manifestations

Melanosis coli (Fig. 28.22)

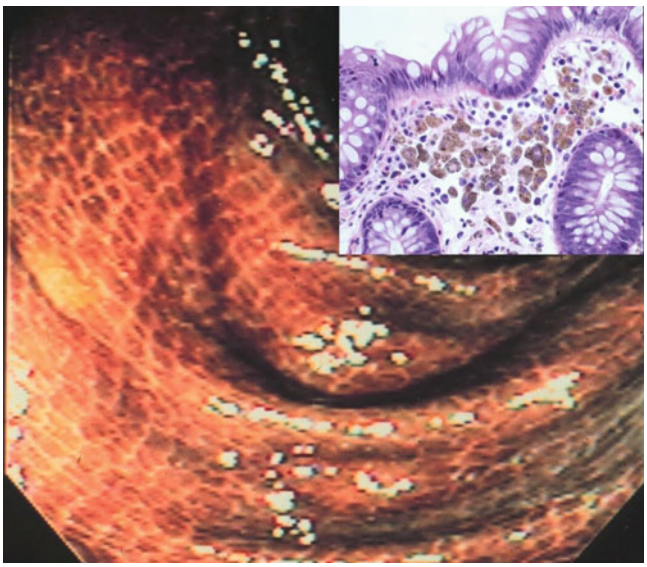


Fig. 28.22

Abuse of laxatives may result in melanosis coli, a dark brown mucosal pigmentation, manifested in this case by a "leopard skin" pattern. (Inset) Microscopically, the mucosa contains clusters of histiocytes with brown cytoplasmic lipofuscin pigment, a breakdown product of apoptotic epithelial cells

Radiation proctitis (Fig. 28.23a, b)

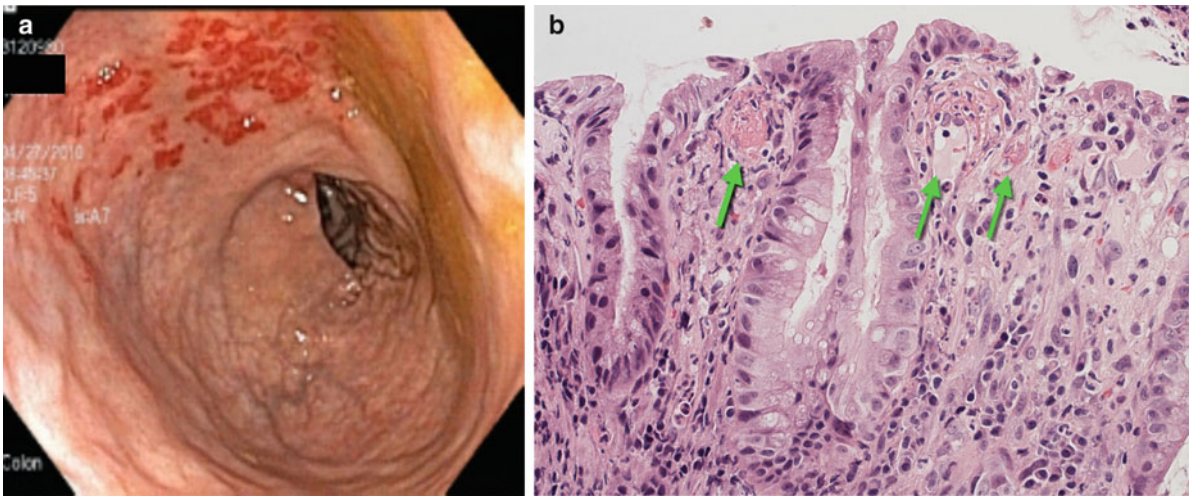


Fig. 28.23

Radiation proctitis following pelvic radiotherapy in a patient presenting with rectal pain and bleeding. A. Endoscopic findings include localized or diffuse hyperemia, petechia, or telangiectasias. B. Microscopically, the mucosa contains dilated, thrombosed subsurface capillaries (arrows)

Serrated colorectal polyps (Fig. 28.24a, b, c)

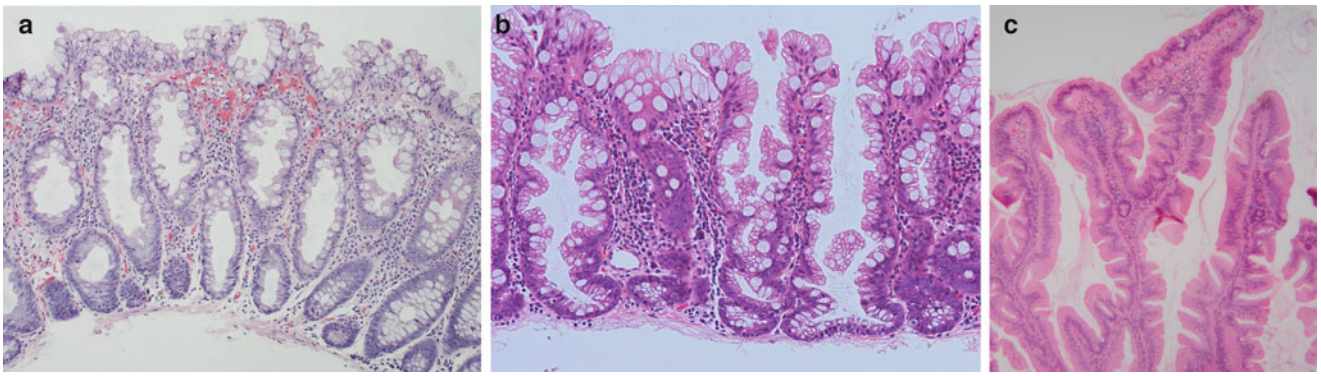


Fig. 28.24

Serrated colorectal polyps affect similar demographic groups as conventional colorectal polyps, the great majority arising in middle age and beyond. A. Hyperplastic polyp. This tends to be quite small and is usually situated in the distal colorectum. Microscopically, the upper portion of the crypts is expanded and has a serrated luminal profile but the basal portion is tapered and has a circular lumen. B. Sessile serrated polyp, also known as sessile serrated adenoma. This polyp tends to be larger and more frequently right-sided than hyperplastic polyps. Microscopically, the crypts are hyperserrated along their entire length and some have a flat base that extends laterally forming an inverted T. C. Traditional serrated adenoma. This polyp also tends to be large and occurs anywhere in the colorectum. The epithelium is dysplastic and features eosinophilic cytoplasm and crowded, elongated nuclei. Sessile serrated polyps and traditional serrated polyps are both considered precancerous lesions

Colorectal adenoma (Fig. 28.25a, b)

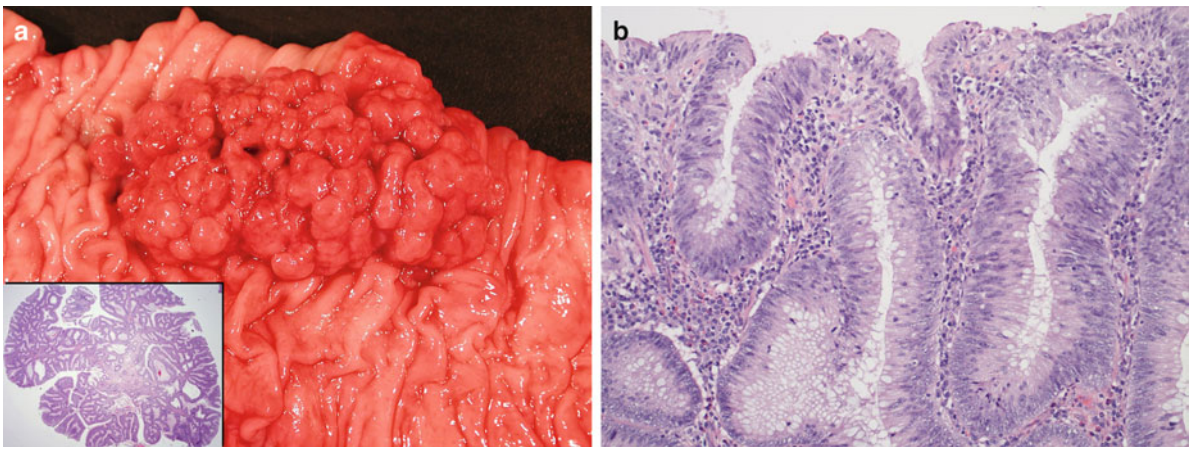


Fig. 28.25

Colorectal adenomas occur anywhere in the colorectum and vary greatly in size and configuration. The likelihood of harboring cancer is directly related to their size, multiplicity, and severity of histologic dysplasia. A. Large, sessile colorectal adenoma. (Inset) Microscopically, this portion of the adenoma consists of crowded tubular structures. B. The lining epithelium, seen at high magnification, consists of dysplastic columnar epithelial cells with crowded, elongated, dark-staining nuclei

Colorectal cancer (Fig. 28.26a, b)

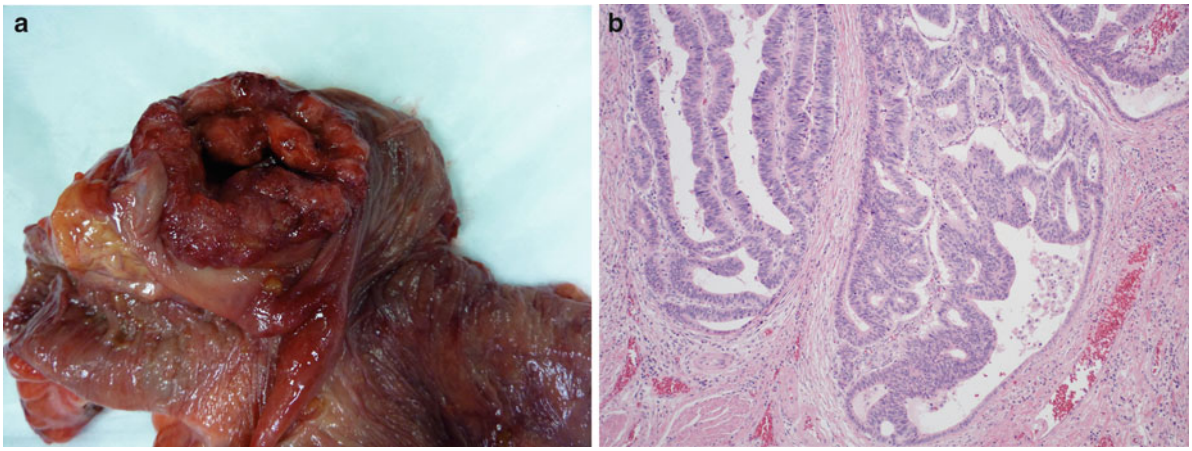


Fig. 28.26

A. Protuberant cecal adenocarcinoma with granular, hemorrhagic surface. B. Typical histological appearance of colorectal cancer featuring columnar cells with a gland-within-gland arrangement and surrounding fibrotic stroma.

Diverticulitis (Fig. 28.27)

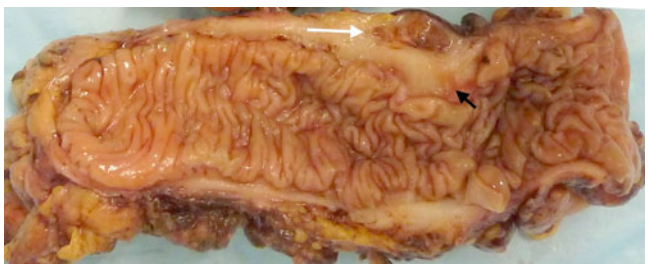


Fig. 28.27

Diverticulitis of the sigmoid colon complicated by a mesenteric abscess (white arrow)

Extranodal lymphoma (Fig. 28.28a, b)

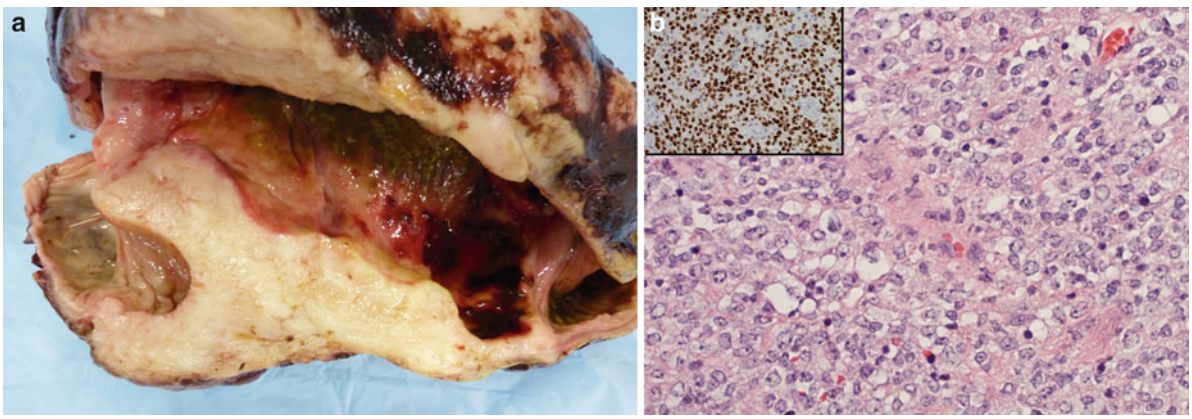
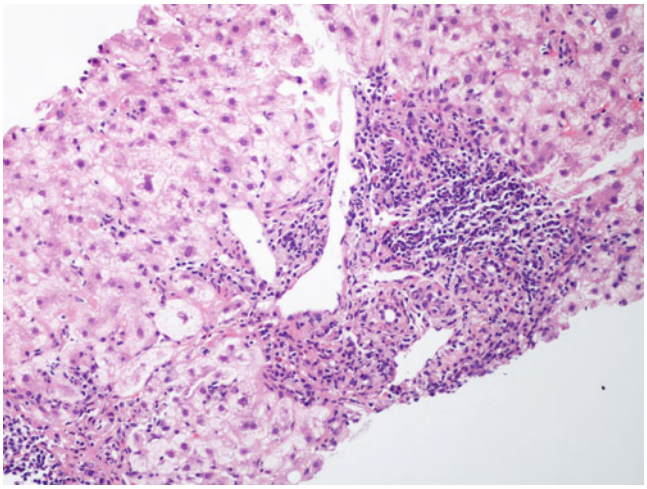


Fig. 28.28

Extranodal lymphomas arise most frequently in the gastrointestinal tract. A. Small intestine with diffuse large B cell lymphoma presenting as an ileal tumor mass. Cut section reveals fleshy tan ("fish flesh") parenchyma that replaces the intestinal wall. B. Microscopically, the tumor consists of large, atypical monomorphous cells. (Inset) Immunostain for Pax-5, a transcription factor specific for B lymphocytes

Autoimmune hepatitis (Fig. 28.29)



Autoimmune hepatitis. Liver needle biopsy with lobular and portal lymphoplasmocytic inflammatory cell infiltrates, interface hepatitis, and hepatocyte necrosis

Hepatocellular carcinoma (Fig. 28.30)

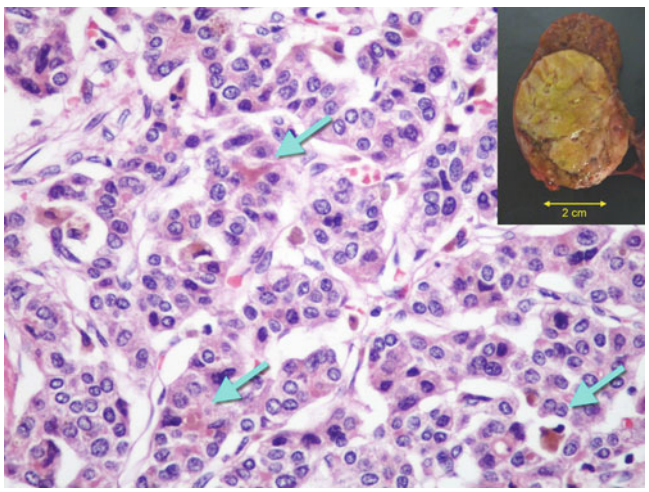


Fig. 28.30

Hepatocellular carcinoma may present diverse histological appearances. This example features trabecular architecture and bile secretions (arrows). (Inset) Caudate lobectomy specimen with well-demarcated, slightly green tumor nodule that is grossly diagnostic of HCC

Steatohepatitis (Fig. 28.31)

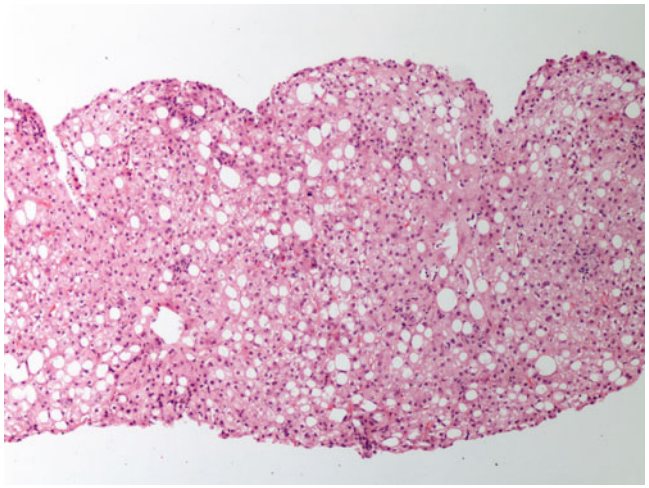


Fig. 28.31

Steatohepatitis is characterized microscopically by large droplet steatosis, ballooning hepatocyte degeneration, and mild lobular inflammation

Primary sclerosing cholangitis (Fig. 28.32)

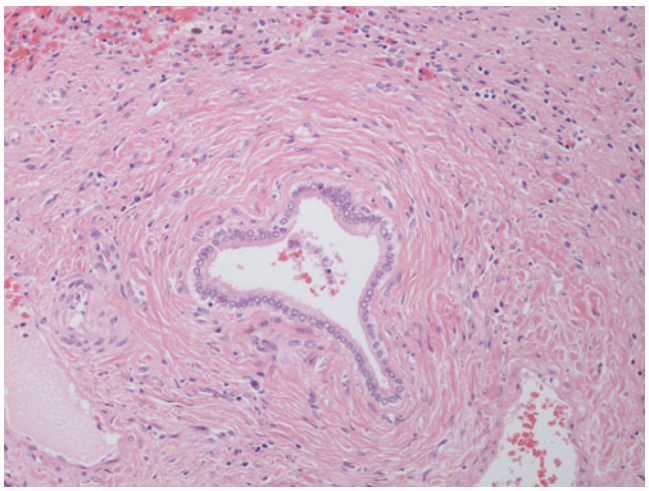


Fig. 28.32

Biliary tract in primary sclerosing cholangitis shows periductal “onion-skin” fibrosis

Gallbladder adenocarcinoma (Fig. 28.33a, b)

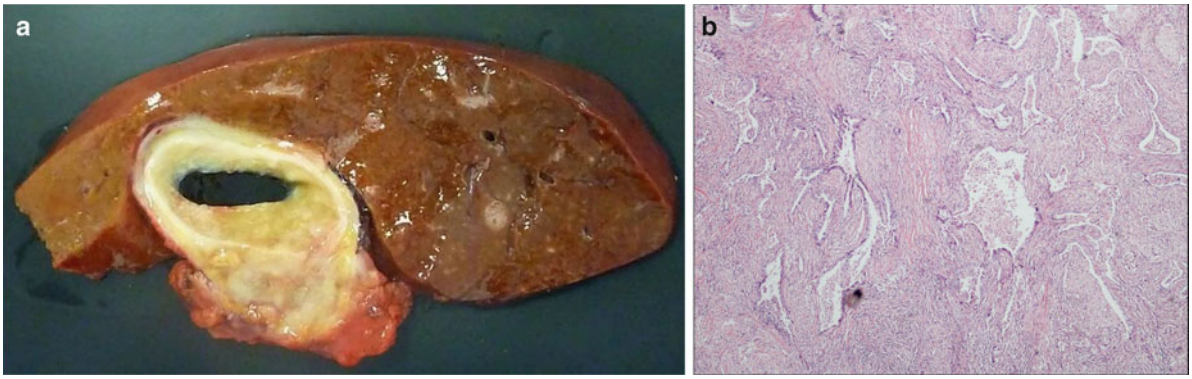


Fig. 28.33

A. Liver with cholangiocarcinoma of gallbladder. The wall is circumferentially thickened and replaced by a scirrhous, white tumor. B. Microscopically, the tumor consists of large, irregularly-shaped glands surrounded by reactive fibrous stroma

Metastatic colon cancer (Fig. 28.34)

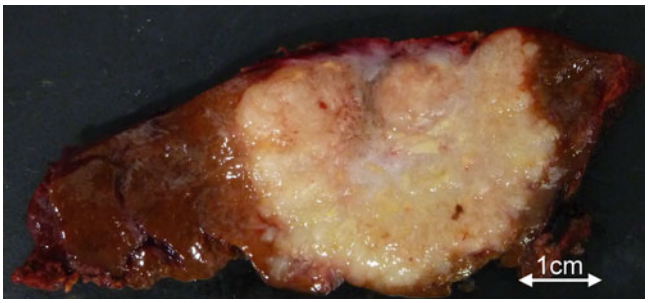


Fig. 28.34

Segmental liver resection with isolated metastasis of colonic adenocarcinoma. Macroscopically, the yellow-grey color, central fibrosis, and irregular, infiltrative borders are typical of such lesions

Primary biliary cirrhosis (Fig. 28.35)

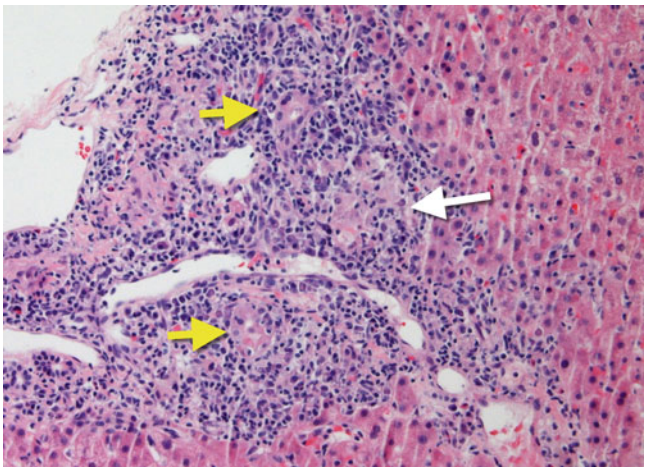


Fig. 28.35

Primary biliary cirrhosis. This liver biopsy shows lymphoplasmocytic inflammation of portal tracts, bile ductular damage (yellow arrows) and periductular granulomatous reaction (white arrow)

Pancreatic cancer (Fig. 28.36a, b)

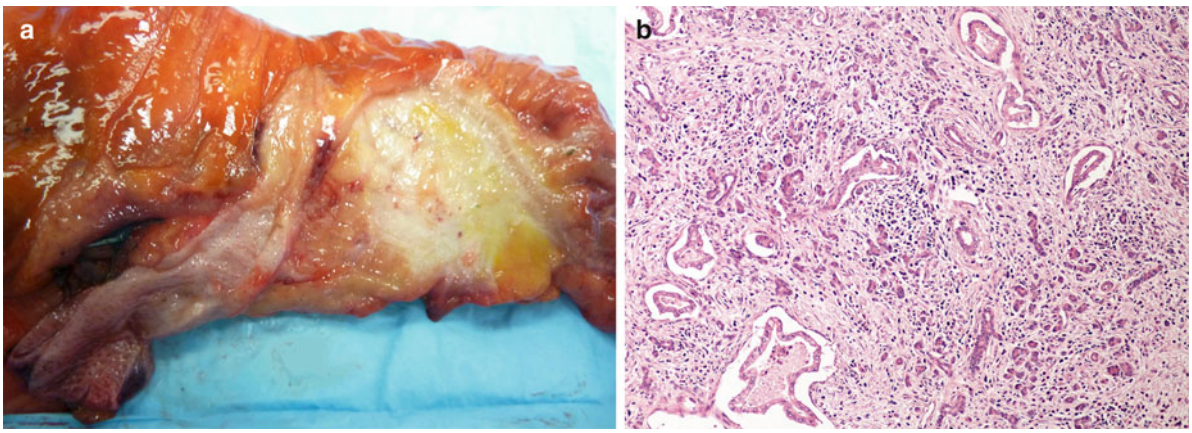


Fig. 28.36

A. Whipple resection specimen with pancreatic adenocarcinoma. An ill-defined firm, white tumor mass has replaced the normal lobulated pancreatic parenchyma. The distal bile duct is dilated as a result of tumor compression, accounting for the patient's clinical presentation with painless jaundice. B. Microscopically the tumor consists of well-differentiated glands infiltrating atrophic pancreatic parenchyma

Pancreatic serous cystadenoma (Fig. 28.37)

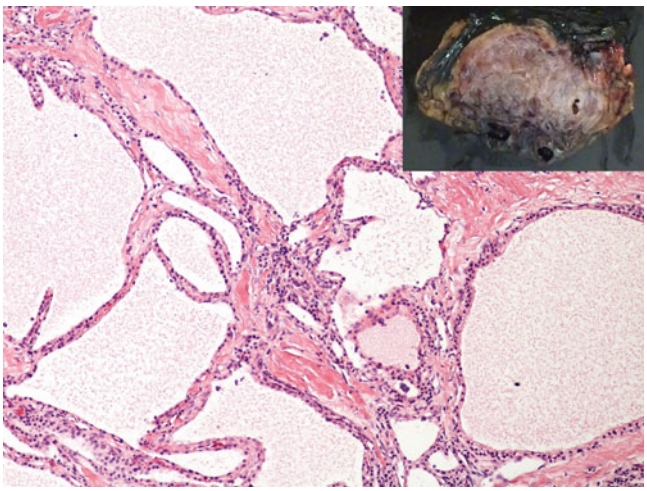


Fig. 28.37

Pancreatic serous cystadenoma is slow-growing and almost invariably benign and usually arises in the pancreatic tail, thus rarely causing jaundice. Microscopically, it consists of numerous small cysts of fibrous tissue sepata lined by a single layer of cuboidal or flat epithelial cells with clear cytoplasm and small, uniform nuclei. (Inset) Grossly, the tumor presents as a grayish, well-circumscribed microcystic mass

Intraductal papillary mucinous neoplasm (IPMN) (Fig. 28.38a, b)

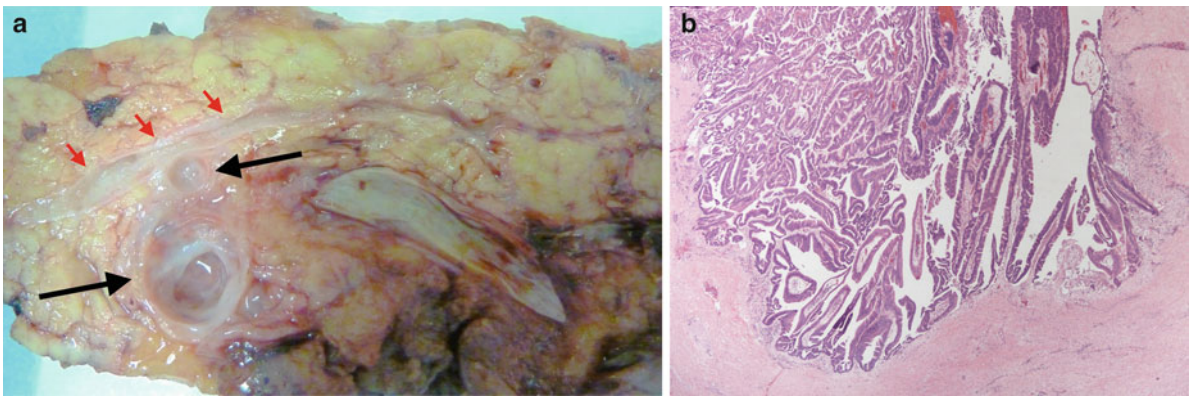


Fig. 28.38

Pancreatic intraductal papillary mucinous neoplasm (IPMN). A. Pancreas sectioned to reveal the main duct (red arrows) and cystically dilated branch ducts with mucinous contents (black arrows). B. Microscopically, the duct is lined by neoplastic fronds and tubules and surrounded by atrophic fibrotic parenchyma

Chronic pancreatitis (Fig. 28.39)

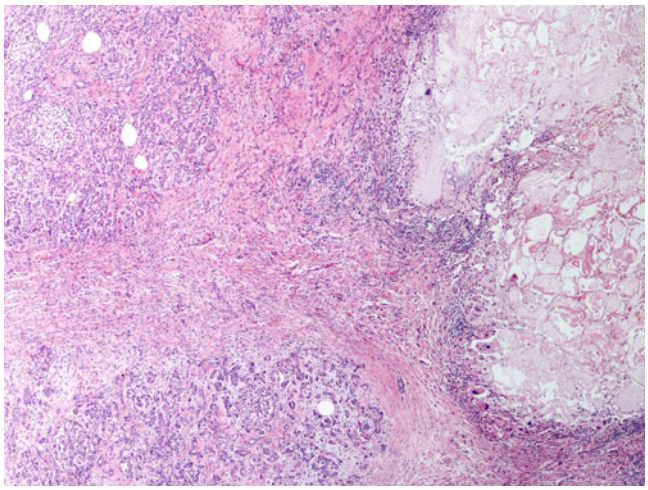


Fig. 28.39

Chronic pancreatitis is manifested microscopically by atrophy of the acinar and ductal pancreatic tissues associated with chronic inflammation and fibrosis. The pale regions on the right correspond to fat necrosis

Pancreatic pseudocyst (Fig. 28.40)

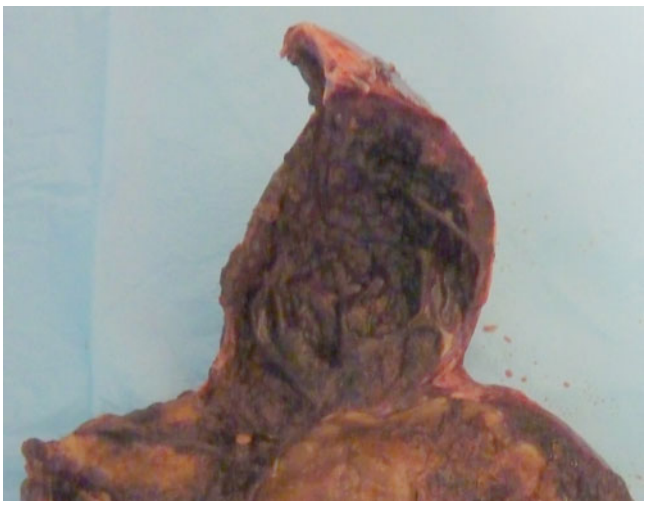


Fig. 28.40

Pancreatic pseudocyst, consisting of a fibrous wall without any epithelial lining, results from cystic necrosis of pancreatic and surrounding soft tissues in the setting of acute pancreatitis. The inner surface of this resected cyst is blood-stained due to intracystic hemorrhage

Part VII

Motility Disorders

Dysphagia

29

James C. Reynolds and Bassem R. George

Introduction

Dysphagia is common in older patients requiring prompt evaluation [1]. The differential diagnosis in patients with dysphagia is broad because the mechanisms involved are varied (Fig. 29.1). The tests available to evaluate dysphagia are associated with both risks and costs, not to mention inconvenience and discomfort, particularly in the geriatric patient. It is therefore incumbent on clinicians who care for the elderly to have a well-organized diagnostic strategy that will lead to the diagnosis with the least amount of testing and discomfort.

While dysphagia can be caused by devastating diagnoses such as a massive cerebrovascular accident or cancer, many causes are acute or subacute conditions for which effective treatments are available and can result in significant improvements in quality of life. Dysphagia may be the first symptom of a systemic disorder that would benefit from an early diagnosis. Furthermore, dysphagia may be iatrogenic.

Dysphagia is categorized by location and cause (Fig. 29.1). Diagnostic evaluation begins by determining whether the problem is associated with difficulty in transferring oral contents through the pharynx and into the esophagus or within the esophagus. While this sounds simple, patients are commonly referred for the wrong test and the wrong specialist. Oropharyngeal (or transfer) dysphagia (OPD) and esophageal dysphagia can be further categorized as inflammatory, mechanical, or functional.

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Functional causes of oropharyngeal or esophageal dysphagia present the greatest challenge to the clinician. Unlike many other gastrointestinal symptoms, dysphagia is rarely due to psychopathology. In fact, the one diagnosis that had frequently been attributed to anxiety, globus "hystericus," is now known to be caused by gastroesophageal reflux in the vast majority of patients. On the other hand, many disorders that cause dysphagia can be considered "functional" because they are due to disorders of extrinsic or intrinsic nerves or muscular disorders that cannot be appreciated by standard radiographic, endoscopic, or blood tests. Many are unable to benefit from effective treatment because they were led to believe that their problem was "all in the head." It is important therefore for physicians who care for the elderly to be well informed of the benefits, limitations, and risks of tests used to evaluate dysphagia.

Dysphagia is common in the elderly. Up to 50% of nursing home residents manifest dysphagia. Furthermore, even in elderly patients who deny dysphagia, functional studies of swallowing are abnormal in 63% [2]. In addition to impaired quality of life, dysphagia predisposes to risk of aspiration pneumonia, chronic cough, and malnutrition.

Diagnosis

Diagnostic Approach

The initial diagnostic approach must be to determine the urgency in pursuing the diagnosis and to effectively locate the site of the disorder causing dysphagia. The urgency of the evaluation is determined by the presence of alarm symptoms and signs. Several disorders lead to dysphagia including central nervous system disease, disorders of the peripheral nerves or neuromuscular apparatus, oral lesions, pharyngeal pathology, upper, mid, and lower esophageal dysfunction, impairment of the lower esophageal sphincter, and gastric causes. Dysphagia all too often results from primary or

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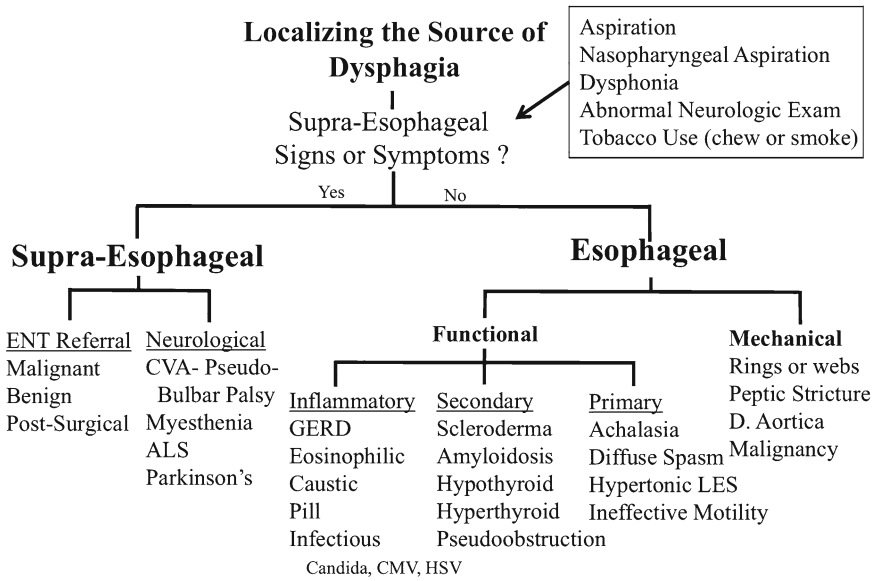

Fig. 29.1 Localizing the cause of dysphagia

secondary malignancies of the oropharynx or esophagus or, much less commonly, from masses external to the pharynx, esophagus, or stomach.

Alarm Signs and Symptoms

Dysphagia in any patient over the age of 40 should be considered an alarm symptom. Associated symptoms that are imperative for more diagnostic studies include weight loss, blood loss, progressively severe symptoms, symptoms that awaken the patient from sleep, and odynophagia. Odynophagia, or pain associated with swallowing, results when there is a break in the mucosa protecting the esophagus. While most commonly the manifestation is due to benign causes such as esophagitis from acid reflux, infections, eosinophilic infiltrate, or pills, it may also result from malignant invasion. Esophageal disorders that cause dysphagia rarely present with overt bleeding such as hematemesis, melena, or hematochesia. In contrast, occult bleeding from the esophagus may be rarely a cause of iron deficiency. Therefore, evidence of occult blood loss should be sought by fecal occult blood testing and a blood count.

In addition to weight loss, any other information from history or physical examination that raises the probability of cancer risk should warrant immediate, thorough evaluation. Anorexia, dysgeusia, and early satiety often precede weight loss. Symptoms of dysphagia associated with chronic acid reflux including heartburn, regurgitation, and chest pain are most commonly due to benign disorders but should also heighten the concern for malignancy, particularly in the elderly, because the most common esophageal cancer develops in patients with Barrett's metaplasia [3]. The duration and extent of tobacco and alcohol use potentiate each other to increase the risk for esophageal squamous cell cancer (SCCa) [4]. Alcohol and tobacco use also increase the risk for head and neck SCCa that can cause OPD. Extra-esophageal malignancies, especially lung, breast, melanoma, or lymphoma, rarely cause dysphagia.

Table 29.1 Etiologies of transfer dysphagia

Central and peripheral nervous system disorders
Cerebrovascular accident with pseudobulbar palsy
Dementia
Multiple sclerosis
Amyotrophic lateral sclerosis
Parkinson's disease
Brainstem tumors (primary or metastatic)
Tabes dorsalis
Bulbar poliomyelitis
Peripheral neuropathies (botulism, diphtheria, diabetes)
Diseases of the motor end-plate
Myasthenia gravis
Myopathies
Polymyositis
Upper esophageal sphincter (UES) disorders
Cricopharyngeal achalasia
Zenker's diverticulum

New onset of neurologic symptoms or signs warrants evaluation. Neurologic disorders lead to oropharyngeal and esophageal dysphagia. Thus every patient with dysphagia requires a thorough neurologic examination. The early detection of cranial nerve disorders can be lifesaving. Dysphagia is a common early symptom of neurologic disorders including multiple sclerosis, myasthenia gravis, and amyotrophic lateral sclerosis (Table 29.1). Cerebrovascular accidents (CVAs), particularly brain stem involvement, commonly cause dysphagia. While this may result from an obvious acute stroke, it may also result from multiple small vessel infarcts that may evade easy diagnosis.

Distinguishing Esophageal from Oropharyngeal Dysphagia

The challenge in localizing the source of dysphagia results from the frequency of referred symptoms. Most patients with esophageal dysphagia refer their symptom to the suprasternal notch or even the neck, when the obstruction is much lower in the chest. Therefore, any patient presenting with dysphagia referred to the lower neck or suprasternal notch should be considered non-informative. In contrast, dysphagia described as inferior to the suprasternal notch, in the substernal area, reliably localizes the source.

Other symptoms may help localize the cause of dysphagia. OPD is suggested by nasopharyngeal regurgitation, aspiration, cough while eating, dysphonia, drooling, and presence of neurologic symptoms. Recurrent aspiration pneumonia or unexplained interstitial pneumonia also suggests a disorder that causes transfer dysphagia. Physical findings of OPD include the presence of oropharyngeal mass, ulceration, neck mass, or cervical adenopathy. Detection of a gurgling sound by placing a stethoscope on the neck suggests a Zenker's diverticulum.

Other historical features or symptoms may identify dysphagia to the esophagus (Table 29.2). The most common associations with esophageal dysphagia are gastroesophageal reflux including heartburn, regurgitation, and chest pain. Every patient with dysphagia should be enquired about Raynaud's phenomenon (alteration in color of their fingers on cold exposure). Findings of sclerodactyly, telengiectasia, calcinosis, or ulcerations of the digits or ears should raise concerns for secondary dysphagia from connective tissue disorders such as scleroderma, CREST syndrome, mixed connective tissue disease, or overlap syndrome (Table 29.3). Symptoms of allergies, hay fever, asthma, and eczema are associated with eosinophilic esophagitis (EoE). A history of a compromised immune system raises the risk for infectious esophagitis.

Sold food dysphagia is detailed in Table 29.4. History of prescription and over-the-counter medications is essential in all patients with dysphagia. Medications that lead to esophageal injury are listed in Table 29.5.

Table 29.2 Primary disorders of esophageal motility

Hyper-contractile state
Achalasia
Secondary achalasia
Chagas disease
Paraneoplastic
Diffuse esophageal spasm (DES)
Isolated hypertonic LES (nutcracker esophagus)
Impaired contractile states
Ineffective esophageal motility (IEM)
Isolated hypotensive LES
Diffuse motility disorder

Table 29.3 Secondary motility disorders of the esophagus

Connective tissue disorders
Progressive systemic sclerosis (scleroderma)
CREST syndrome
Systemic lupus erythematosus (SLE)
Mixed connective tissue disorder (MCTD)
Overlap syndromes
Metabolic disorders
Diabetes
Hypothyroidism
Hyperthyroidism
Amyloidosis
Chronic idiopathic pseudo-obstruction
Gastric causes
Benign
Paraesophageal hernia
Gastric torsion
Gastric carcinoma
Gastric lymphoma
Malignancies
Pseudo achalasia
Paraneoplastic syndrome
Miscellaneous
Oropharyngeal abscess
Cervical osteophytes

Table 29.4 Etiology of solid food dysphagia

Esophagitis
Peptic stricture, including GERD
Barrett's esophagus
Prolonged use of nasogastric tubes
Caustic stricture
Pill esophagitis
Iatrogenic injury
Radiation
Endoscopy
Surgery
Infections
Candida
Cytomegalovirus (CMV)
Herpes simplex virus (HSV)
Human immunodeficiency virus (HIV)
Extrinsic compression
Vascular
Dysphagia aortica
Dysphagia lusoria
Mediastinal mass (benign, malignant, infections such as tuberculosis)
Inflammatory
Eosinophilic esophagitis
Pemphigus
Pemphigoid
Stevens–Johnson syndrome
Webs and rings
Schatzki's ring
Plummer–Vinson syndrome

Table 29.5 Medications that cause esophageal injury

Doxicycline
Alendronate
Potassium chloride
Ascorbic acid
Aspirin
NSAIDs
Quinidine
Phenytoin
Iron tablets

Common Causes of Dysphagia

In a review of patients presenting with esophageal dysphagia in a primary care setting, the most common diagnoses were esophageal reflux (44%), benign strictures (36%), esophageal motility disorder (11%), neoplasm (6%), infectious esophagitis (2%), and achalasia (1%) [5].

Functional Transfer Dysphagia

Most patients with normal anatomic evaluation but who still have transfer dysphagia suffer from neuromuscular disorders. Videofluoroscopy is the standard for evaluating such disorders. The quality of this subjective study is dependant on the skill of the speech language pathologist and supervisor. Functional endoscopic evaluation of swallowing (FEES) by a skilled otorhinolaryngologist may also be effective. High-resolution impedance manometry may offer quantitative bedside diagnostic analysis in the future [6]. Since all muscles involved with the transfer of oral contents to the esophagus are striated and under the control of cranial nerves the differential diagnosis includes disorders that require evaluation by a neurologist. A partial listing of such disorders is provided in Table 29.1.

Mechanical Causes of Transfer Dysphagia

Head and neck cancers are common mechanical causes of transfer dysphagia in elderly patients. A history of tobacco and alcohol use is common. Hence, patients who do not have a proven neurologic cause of transfer dysphagia warrant evaluation by a otorhinolaryngologist. The prognosis of head and neck malignancies is determined by the size of the tumor and the extent of its metastatic extension characterized by TNM staging. The otorhinolaryngologist can also perform a FEES.

Benign mechanical causes of dysphagia may not be easy to diagnose. Laryngoscopy and frontal and lateral barium swallow should be performed to identify the etiology. Causes include enlarged thyroid gland, cervical osteophytes, oropharyngeal abscesses, and surgical scarring [7]. Hypertrophic osteophytes are common, but seldom cause dysphagia. Osteophytes at C5–7 levels are most commonly implicated.

Zenker's diverticulum is a common benign mechanical cause of dysphagia that develops when there is bulging of the Killian's triangle from dysfunctional contractions of the pharynx and incomplete relaxation of the upper esophageal sphincter. The cause of Zenker's diverticula continues to be debated. The current theory is that the diverticulum is created by incomplete relaxation of a fibrotic persistently constricting UES causing a bulge of the mucosa over Killian's triangle to create a diverticulum. The diagnosis is made commonly by a speech pathologist or radiologist performing a barium esophagogram that includes cervical views. A small Zenker's diverticulum may be an incidental finding requiring no treatment. Consultation with a speech pathologist may be beneficial to help alter diet consistency. A related condition is cricopharyngeal achalasia caused by hypertrophy, incoordination, and/or incomplete opening of the upper esophageal sphincter, which is primarily composed of the cricopharyngeus muscle. The diagnosis is relevant because treatment can be provided with minimally invasive procedures such as injection of botulinum toxin. In more advanced cases, myotomy is required. Caution must be used, however, in overdiagnosing or overtreatment because the UES provides an important secondary barrier to acid reflux reaching the airway in appropriately diagnosed patients; however, the risk of myotomy is acceptable [8]. Most patients diagnosed with a "hypopharyngeal bar" on barium swallow do not have symptoms from this finding and should not be treated. When a hypertrophic cricopharyngeus is the cause of symptoms, dilation can often be beneficial. Rarely surgery is necessary.

Functional Esophageal Dysphagia

Esophageal dysphagia is often due to disordered motility of the esophagus. The principal function of the esophagus is to transport fluids and solids from the oral cavity to the stomach. This seemingly simple task is actually complex due to changes in the neuromuscular apparatus that occur during this transit. It requires precise but brief opening and closure of the upper esophageal sphincter followed by a single peristaltic contraction that must transit from ambient pressure to negative intrathoracic pressure to positive intra-abdominal pressure. It occurs as the lining of the tube transitions from stratified squamous epithelium to columnar epithelium with their distinct sensory and secretory differences. Perhaps most importantly this transition changes from striated muscles controlled by the central nervous system to smooth muscle that is controlled by intrinsic (enteric) nerves located in the myenteric and submucosal nerves that are modified by

autonomic nerves and hormones. Hence motility abnormalities are common. While dysphagia results from disruption of motor or neuronal function of the pharynx and UES, other disorders such as Parkinson's disease, ALS, and polymyositis also alter esophageal dysfunction.

Intrinsic neuromuscular or functional disorders can be characterized by increased or impaired muscular contractions (Table 29.2). Nearly half the patients will have non-obstructive dysphagia related to acid reflux-induced esophagitis with or without ulceration [9]. Empiric dilation with rigid dilators has been recommended in patients who present with solid food, but not liquid food dysphagia. This recommendation is based on both retrospective and prospective data [10, 11]. In a prospective randomized trial of through the scope (TTS) balloon dilation, there was no benefit to balloon dilation of the distal esophagus in patients who did not have an obstruction by endoscopy [12]. Non-obstructive dysphagia is more common in patients with ineffective esophageal motility (IEM). These patients are at great risk for esophageal stricture, a finding difficult to appreciate with modern, narrow endoscopes. Prokinetic agents that might improve impaired esophageal motility are being tested, but not currently available.

In contrast, there are several modalities available to treat esophageal disorders characterized by increased contractility. These include medications (anticholinergics, calcium channel blockers, and nitrates); injection therapy (botulinum toxin); mechanical treatment such as balloon dilation in patients with hypertensive LES, diffuse esophageal spasm (DES), or achalasia [13]; and surgery. For patients with serious concurrent illnesses endoscopic botulinum toxin injection can provide effective, low-risk relief for 6–9 months. With the availability of laparoscopic techniques, Heller myotomy is increasingly used in the treatment of achalasia [14]. Long-term retrospective [15, 16] and prospective [17] studies show equivalent benefits and lower risk from pneumatic dilation as with surgical myotomy. The treatment chosen is based on availability of local expertise and the patient's preference.

Inflammatory Causes of Dysphagia

Inflammation is the most common cause of esophageal dysfunction leading to dysphagia. Hence, endoscopy should be performed in all patients with esophageal dysphagia. Acid reflux is the most common cause of esophageal inflammation [9]. Other inflammatory conditions are often attributed to reflux, escaping diagnosis and treatment if endoscopy with biopsy is not performed. Causes of esophagitis associated with dysphagia include infections, radiation, caustic ingestion, and pill esophagitis (Tables 29.4 and 29.5).

The importance of inflammation as a common cause of dysphagia and food impaction, even in the absence of ulceration or stricture, is demonstrated by EoE [18]. Recently, EoE has become the most common cause of food impaction. While EoE is readily included in the differential diagnosis of dysphagia in younger men, this immune disorder can occur at any age and is well documented in octogenarians. EoE must enter the differential diagnosis because of the increased risk of perforation in such patients with vomiting and forceful dilation [19]. Inflammation due to radiation, infections, and pill injury can also cause motility dysfunction leading to dysphagia that is in excess of the mucosal injury.

Gastroesophageal reflux and its complications have increased in frequency [3]. Mucosal injury, dysphagia, and Barrett's esophagus all occur more frequently in the elderly. Diagnosis and treatment are obvious in the presence of the most complications of GERD including erosive esophagitis, Barrett's associated neoplasms, and esophageal strictures. GERD frequently causes dysphagia even in the absence of endoscopic evidence of esophagitis [9]. Effective therapy of acid reflux can often relieve dysphagia in such patients. Fundoplication is rarely needed and may worsen dysphagia [20].

Mechanical Causes of Esophageal Dysphagia

Malignant Mechanical Obstruction

The majority of patients who present with esophageal cancer complain of dysphagia; however, 4–7% of patients present only with dyspepsia, and not dysphagia [21]. The patients with esophageal cancer who have the best prognosis are those diagnosed during surveillance for Barrett's metaplasia. Most patients with malignant mechanical causes of dysphagia have a primary esophageal cancer. Rarely neoplasms may metastasize to the esophageal wall or invade the esophagus locally from malignancies in the lung or mediastinum. Invasion by lung cancers into the esophagus may mimic transfer dysphagia by creating a tracheo-esophageal fistula that leads to aspiration, chronic coughing, and pneumonia. A videofluoroscopic barium swallow will usually clarify the diagnosis.

Primary Esophageal Cancer

Esophageal adenocarcinoma has increased in incidence and now exceeds that of SCCa in all age groups [3]. SCCa occurs most commonly in patients who have abused alcohol, tobacco, or both. Other risk factors for esophageal SCCa have been well described [4].

Metaplastic epithelium covering the distal esophagus for variable lengths with specialized (Goblet Cell) changes defines Barrett's esophagus. This histological finding is clearly a premalignant lesion. Patients followed over time have a risk of developing esophageal adenocarcinoma, especially males with chronic heartburn [22]. Fortunately in

an individual patient, the risk is small. Prospective studies estimate that 1:35 will develop high-grade dysplasia and 1:125 will develop adenocarcinoma [23]. Epidemiologic studies suggest that the risk is substantially less [24, 25]. Dysphagia is a common symptom in both benign metaplasia and adenocarcinoma. Unfortunately, it is this feared symptom that may be associated with malignant transformation. Dysphagia may also develop in patients with Barrett's esophagus who are treated with ablation therapies.

Benign Mechanical Causes of Dysphagia

Fortunately, benign mechanical causes of dysphagia are nearly three times more common than esophageal cancer [26] and can be effectively treated (Table 29.4). Esophageal strictures have an incidence of 1.1/10,000 person years and increase markedly with age [26]. The vast majority are peptic strictures. Proximal esophageal webs associated with iron deficiency are known as Plummer–Vinson or Paterson–Brown Kelly syndrome. These proximal strictures are associated with atrophic glossitis, iron deficiency anemia, and dysphagia referred to the cervical area. Dysphagia is usually attributed to the stricture but may also result from muscular dysfunction related to the iron deficiency itself [27]. Iron replacement will improve the symptoms.

Benign narrowing of the esophagus may also be caused by vascular compression of the esophagus by the aorta, an aberrant subclavian artery, or the right atrium. In the elderly, this is most commonly due to dysphagia aortica resulting from extrinsic compression of the esophagus by a tortuous or aneurysmal aorta. Dysphagia lusoria, another well-recognized vascular cause of dysphagia, results from an aberrant right subclavian artery. While the diagnosis of this disorder increases with age, it is almost always diagnosed before the age of 60 or remains asymptomatic [28].

Benign Esophageal Strictures

Peptic esophageal stricture is the diagnosis often sought by the gastroenterologist because of its prevalence and response to treatment. Peptic strictures are more common in men than women and almost always present with dysphagia. Benign esophageal strictures develop from chronic inflammation causing fibrous formation and collagen deposition. It is estimated that 65–70% of all benign strictures are peptic in origin and result from chronic uncontrolled gastroesophageal reflux. Heartburn occurs in most patients with peptic strictures but may be absent in 25%. Atypical symptoms associated with GERD including chronic cough, regurgitation, and asthma are also common. Schatzki's ring is common in the elderly and impairs quality of life; it is easily treated by dilation. Other inflammatory conditions, surgery, endoscopic therapies, radiation, and congenital lesions can also lead to solid food dysphagia (see Table 29.4). Esophageal webs associated with iron deficiency are an uncommon but treatable benign obstruction of the esophagus [29, 30].

Endoscopic esophageal dilation techniques can effectively eliminate symptoms of dysphagia in nearly all patients without the need for surgical intervention. Effective management of the stricture includes both dilation and addressing the underlying cause [3].

Diagnostic and Therapeutic Options

Diagnostic options other than the all-important history and physical exam include radiographic, endoscopic, and functional tests (Fig. 29.1). Testing must include the triple-phase barium swallow, evaluation by a speech pathologist, FEES, laryngoscopy, esophagogram, videofluoroscopic barium swallow, and CT scans. A common mistake is to get only the cervical esophagogram and thus miss treatable lesions or malignancy at a treatable stage in the distal esophagus. When evaluating esophageal dysphagia, barium swallow has been the traditional test of first choice. Since peptic strictures are nearly three times as common as malignant ones, currently endoscopy should be considered as the first test in most patients with esophageal dysphagia [31].

Motility studies are cost-effective in the evaluation of dysphagia. Common motility disorders that lead to dysphagia include achalasia, DES, hypertonic lower esophageal sphincter, IEM, and scleroderma. Manometry is cost-effective, since each of these diagnoses leads to specific and often effective intervention.

Dilation of Esophageal Strictures

Prior to performing endoscopic dilation, the endoscopist should fully characterize the cause of the stricture, risk inherent to this specific patient, and complexity of the lesion. A thorough evaluation of the esophagus should be performed prior to esophageal dilation. While previously dilation was recommended at the initial endoscopy in most patients, biopsies of the esophagus should be considered when the cause of the esophageal narrowing is unknown to ensure that EoE is excluded [19]. A barium esophagogram can clarify the length of the stricture, presence of a diverticulum, size of the hiatal hernia, and severity of the tortuosity. Endoscopy should be performed to determine the presence of Candida esophagitis, esophageal ulceration, EoE, Barrett's esophagus, or cancer by evaluation and biopsies.

Contraindications to dilation include severe coagulopathy, active bleeding, an ulcerated stricture, or an inability to tolerate the chosen sedation. Patients with tight strictures, gastroparesis, or esophageal diverticulum should consume only

clear liquids on the day before the procedure. Prior to beginning the procedure, the endoscopist should decide whether a Savary, guide wire dilation, or balloons TTS dilators are to be used. It is important to determine whether fluoroscopy is needed. Using the double hemostat technique, however, fluoroscopy is needed in only the most complicated strictures. A consistent consensus regarding the superiority of one dilator over the other is not apparent [32]. Dysphagia will typically resolve when the esophagus can be effectively dilated to greater than 18 mm. Providing effective acid suppression in all patients with peptic strictures, especially those that are complicated, is clearly important in management [33, 34].

Key Points

- Dysphagia is common in older adults and always warrants evaluation.
- History and physical examination should include a review of medications, history of smoking and alcoholism, and evaluation of neurological status.
- Neuromuscular disorders that commonly cause dysphagia are cerebrovascular disease, Parkinson's disease, and dementia.
- Mechanical causes include benign and malignant disorders such as esophageal strictures, Zenker's diverticulum, and tumors of head and neck and esophagus.
- Functional causes of dysphagia affect the ability to swallow solids and liquids simultaneously.
- Inflammatory causes of dysphagia include esophagitis due to acid reflux, radiation, and infections and pill esophagitis.
- EoE is being increasingly diagnosed as a reversible cause of solid and liquid dysphagia.
- Schatzki's ring causes intermittent dysphagia.
- Dysphagia results in poor quality of life, aspiration, and weight loss.
- Evaluation and management of dysphagia is a multidisciplinary approach.

References

1. Siebens H, Trupe EH, Siebens AA. Prevalence of feeding and swallowing disorders in a nursing home. Arch Phys Med Rehabil. 1984;65:651.
2. Ekberg O, Feinberg MJ. Altered swallowing function in elderly patients without dysphagia: radiologic findings in 56 cases. Am J Roentgenol. 1991;156:1181–4.
3. Reynolds JC, Rahimi P, Hirschl D. Barrett's esophagus: clinical characteristics. Gastroenterol Clin North Am. 2002;31(2):441–60.
4. Ribeiro U, Vaz Safatle-Ribeiro A, Reynolds JC, et al. Risk factors for developing squamous cell cancer of the esophagus. Br J Surg. 1996;83(93):1174–85.
5. Esfandyari T, Potter JW, Vaezi MF. Dysphagia: a cost analysis of the diagnostic approach. Am J Gastroenterol. 2002;97:2733–7.
6. Omari TI, Papathanasopoulos A, Dejaeger E, et al. Reproducibility and agreement of pharyngeal automated impedance manometry with videofluoroscopy. Clin Gastroenterol Hepatol. 2011;9:862–7.
7. Ladenhime SE, Marlow FI. Dysphagia secondary to cervical osteophytes. Am J Otolaryngol. 1999;20:184–9.
8. Williams RB, Ali GN, Hunt DR, et al. Cricopharyngeal myotomy does not increase the risk of esophagopharyngeal acid regurgitation. Am J Gastroenterol. 1999;94:3448–54.
9. Triadofilopoulos G. Nonobstructive dysphasia in reflux esophagitis. Am J Gastroenterol. 1989;84:614–8.
10. Marshall JB, Chowdhury TA. Does empiric esophageal dilation benefit dysphasia when endoscopy is normal? Dig Dis Sci. 1996;41:1099–101.
11. Colon CJ, Young MA, Ramirez FC, et al. The short and long term efficacy of empirical esophageal dilation in patients with nonobstructive dysphasia: a prospective, randomized study. Am J Gastroenterol. 2000;95:910–3.
12. Scolapio JS, Gostout CJ, Schroeder KW, et al. Dysphagia without endoscopically evident disease: to dilate or not? Am J Gastroenterol. 2001;96:327–30.
13. Dempsey DT, Kalan MM, Gerson RS, et al. Comparison of perioperative outcomes following open and laparoscopic esophagomyotomy for achalasia. Surg Endosc. 1999;13:747–50.
14. Wang YR, Dempsey DT, Friedenberg FK, et al. Am J Gastroenterol. 2008;103:2454–64.
15. Parkman HP, Reynolds JC, Ouyang A, et al. Pneumatic dilatation or esophagomyotomy treatment for idiopathic achalasia: clinical outcomes and cost analysis. Dig Dis Sci. 1993;38(1):75–85.
16. Chan KC, Wong SKH, Lee DWH, et al. Short-term and long-term results of endoscopic balloon dilation for achalasia: 12 years' experience. Endoscopy. 2004;36:690–4.
17. Hulselmans M, Vanuytsel T, Degreef T, et al. Long-term outcome of pneumatic dilation in the treatment of achalasia. Clin Gastroenterol Hepatol. 2010;8:30–5.
18. Kapel RC, Miller JK, Torres C, et al. Eosinophilic esophagitis: a prevalent disease in the United States that affects all age group. Gastroenterology. 2008;5:1569.
19. Schoepfer AM, Gonsalves N, Bussmann C, et al. Esophageal dilation in eosinophilic esophagitis: effectiveness, safety and impact on the underlying inflammation. Am J Gastroenterol. 2010;105:1062–70.
20. Richter JE, Dempsey DT. Laparoscopic antireflux surgery: key to success in the community setting. Am J Gastroenterol. 2008;103:289–91.
21. Canga III C, Vakil N. Upper GI malignancy, uncomplicated dyspepsia, and the age threshold for early endoscopy. Am J Gastroenterol. 2002;97:600–3.
22. Lagergren J, Bergstrom R, Lindgren A, et al. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med. 1999;340:825–31.
23. Shaheen N, Ransohoff DF. Gastroesophageal reflux, Barrett esophagus, and esophageal cancer: scientific review. JAMA. 2002;287:1972–81.
24. Pohl H, Welch G. The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. J Natl Cancer Inst. 2005;97:142–6.
25. Hvid-Jensen F, Pedersen L, Drewes AM, et al. Incidence of adenocarcinoma among patients with Barrett's esophagus. N Engl J Med. 2011;365:1375–83.
26. Ruigomez A, Rodriguez LAG, Wallander M, et al. Esophageal stricture: incidence, treatment patterns and recurrence rate. Am J Gastroenterol. 2006;101:2685–92.

27. Miranda ALM, Dantas RO. Esophageal contractions and oropharyngeal and esophageal transits in patients with iron deficiency anemia. Am J Gastroenterol. 2003;98:1000–4.
28. Janssen M, Baggen MGA, Veen HF, et al. Dysphagia lusoria: clinical aspects, manometric findings, diagnosis and therapy. Am J Gastroenterol. 2000;95:1411–6.
29. Dickey W, McConnell B. Celiac disease presenting as the Paterson-Brown Kelly (Plummer-Vinson) syndrome. Am J Gastroenterol. 1999;94:527–9.
30. Maleki D, Cameron AJ. Plummer-Vinson syndrome associated with chronic blood loss anemia and large diaphragmatic hernia. Am J Gastroenterol. 2002;97:190–3.
31. Ahmad A, Palletsky F, Reynolds J. Management of esophageal strictures. In: Bayless TM, Diehl AM, editors. Advanced therapy in gastroenterology and liver disease. 5th ed. Hamilton: BC Decker; 2004.
32. Scolapio JS, Pasha TM, Gostout CJ, et al. A randomized prospective study comparing rigid to balloon dilators for benign esophageal strictures, and ring. Gastrointest Endosc. 1999;50:13–7.
33. Said A, Brust DJ, Gaumnitz EA, et al. Predictors of early recurrence of benign esophageal strictures. Am J Gastroenterol. 2003;98:1252–6.
34. Guda NM, Vakil N. Proton pump inhibitors and the time trends for esophageal dilation. Am J Gastroenterol. 2004;99:797–800.

Gastroparesis in Older Adults

30

Richard W. McCallum and Ashish Malhotra

Gastroparesis is a chronic symptomatic disorder characterized by evidence of gastric retention or delayed emptying in the absence of mechanical obstruction [1].

Epidemiology

The true prevalence of gastroparesis is difficult to ascertain given the relatively poor correlation of symptoms with gastric emptying (GE) [2], the need to apply a diagnostic test in a community setting [3], and the fact that many patients with gastroparesis may not even seek health care or be referred to gastroenterologists. In a recent study out of Olmsted County, USA, the age-adjusted incidence per 100,000 person-years of definite gastroparesis was 2.5 for men and 9.8 for women and the age-adjusted prevalence was 9.6 and 37.8 for men and women, respectively [4]. The incidence of definite gastroparesis increased significantly with advancing age with a peak incidence of 10.5 per 100,000 in patients ≥60 years of age.

The overall survival for gastroparesis patients is significantly reduced when compared to their age/gender-specific expected survival. The hospitalizations related to gastroparesis have been increasing in the United States, with economic impact [5].

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Normal Gastric Motility

The proximal portion of the stomach (fundus, cardia) mainly serves as the reservoir for food. Nutrients can be ingested without a rise in the intragastric pressure [6]. Three main mechanisms involved in the regulation of this function are the receptive relaxation, accommodation, and enterogastric reflexes [7]. The distal part of the stomach (primarily the antrum) acts as the "grinder." To achieve this function, the slow waves, controlled by the interstitial cells of Cajal, also known as the pacemaker cells, coordinate the postprandial fed pattern that leads to emptying of digestive solids. Contractions associated with the migrating motor complex (MMC) empty indigestible solids immediately after solid food digestion is completed and during fasting between meals and at night [8, 9]. The physical nature of the food, such as the particle size, fat, and calorie content, and various neurohumoral factors influence the rate of GE. The glucose-regulating hormones such as glucagon-like peptide (GLP-1), hormones released with fat and protein intake such as cholecystokinin (CCK), peptide YY, and secretins slow GE while motilin and ghrelin levels are increased with meals and augment gastric motility [10, 11]. Solid particles empty in three phases over 3–4 h. An initial lag phase, where food is stored in the proximal stomach; next it gets triturated and churned, as the antral contractions propel particles against a closed pylorus [9], and finally is followed by the propellant phase of relatively constant emptying where food particles are pushed out of the stomach once the particle size is <5–6 mm [12, 13]. Noncaloric and minimally caloric liquids empty faster, but increased caloric content may slow down the emptying rate [14]. For example, the calories supplement "Ensure" (1 cal/cc) empties very similarly to a standardized eggbeater meal.

Effects of Aging on Gastric Motility

In general, gastric motility is relatively preserved during healthy aging. However, studies on the effect of aging on GE

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have yielded some conflicting results [15–18]. This is largely due to various study limitations, such as, choice of tests for GE being less than ideal, and heterogeneous study population including those with significant comorbidities. Despite these shortcomings, the overall evidence suggests that healthy aging is associated with minimal slowing of GE, as well as less hunger, delayed proximal gastric accommodation, and increased postprandial antral volume [19]. Thus older adults may experience less fullness, discomfort, and bloating, in response to proximal gastric distention when compared with the young [20]. Although the age-dependent slowing of GE is not profoundly meaningful on a clinical level, an awareness of this phenomenon is important for a better understanding of certain observations such as diminished/delayed pharmacologic effect of orally administered drugs.

The mechanisms underlying the slowing of GE with aging are uncertain. Autonomic nerve dysfunction is more common in the older subjects, but its correlation with slower GE is poor [21]. It remains unclear if there is derangement of gastric electrical rhythm with aging. Neurohumoral changes such as increased plasma CCK (both fasting and postprandial), decreased plasma ghrelin, decreased mucosal prostaglandins, pepsin and bicarbonate levels have been reported in the elderly [19], which may affect gastric motility and digestive function. A decrease in gastric acid secretion associated with aging may decrease the efficiency of trituration of solids and hence will mildly and subtly slow gastric emptying.

Etiology

The potential underlying causes for gastroparesis are numerous (Table 30.1). Any disease that can alter motor or sensory pathways of the stomach can potentially cause or contribute to gastroparesis. Idiopathic, diabetic, and postsurgical/vagotomy are the three main etiologies for gastroparesis, accounting for almost 80% of the cases [3].

Certain common disorders in the geriatric population warrant special emphasis:

1. *Neurological diseases*: The most common central nervous system disorder that affects GE is Parkinson's disease (PD). In a prospective study, it was shown that 88% of patients with PD have delayed GE [22]. There are two components of gastrointestinal (GI) dysfunction in PD. First, it causes striatal muscle dysfunction, affecting primarily the oropharynx, proximal esophagus, and the anal canal. Second, dysfunction can involve the smooth muscle and autonomic and/or enteric nervous system (ENS) with a more global adverse impact on GI motility [23].
   Although there are a large number of peripheral neuropathies, few affect the stomach (Table 30.1). Amyloidosis is one entity to consider. In a large retrospective series of patients with primary amyloidosis, only 0.4%, however, were found to have delayed GE [24].
2. *Endocrine disorders*: The prevalence of diabetes mellitus (DM) increases with age and is one of the most common causes of impaired gastric motility. Normal aging is associated with impaired glucose tolerance. This is considered secondary to increased peripheral insulin resistance,

Table 30.1 Etiology of gastroparesis

Neuromuscular disorders
Central nervous system disorders: *Parkinson's disease*, brain-stem tumors, multiple sclerosis
Peripheral neuromuscular disorders: Muscular dystrophy, Guillian–Barre syndrome, acute dysautonomia
Others: *Amyloidosis*, visceral neuropathies, visceral myopathies
Endocrine disorders
Diabetes mellitus[a]
Hypothyroidism
Hypoparathyroidism
Metabolic disorders
Uremia
Chronic liver disease
Paraneoplastic/cancer-related syndromes
Gastrointestinal disorders
Gastroesophageal reflux disease
Atrophic gastritis with or without pernicious anemia
Acute viral gastroenteritis (cytomegalovirus)
Acute/chronic gastritis
Idiopathic intestinal pseudo-obstruction
Pancreatitis
Mesenteric ischemia
Autoimmune/collagen vascular disorders
Systemic sclerosis/scleroderma
Dermatomyositis
Polymyositis
Mixed connective tissue disease
Systemic lupus erythematosus
Postsurgical disorders[a]
Vagotomy
Anti-reflux operations
Roux-en-Y syndrome
Gastrectomy
Pancreatectomy
Organ transplantation (combined heart–lung transplantation)
Trauma
Head injury, spinal cord injury
Psychogenic disorders
Anorexia nervosa, stress
Medications (Table 30.2)
Idiopathic/infectious[a]
Viral (Cytomegalovirus, Epstein Barr, Norwalk and Herpes simplex virus)
Parasitic (*Trypanosoma cruzi*)

Italicized causes are common in older adults
[a]Represents most common causes of gastroparesis

decreased beta cell function, and possibly delayed postprandial suppression of hepatic gluconeogenesis [19]. In the western world, it is estimated that at least 20% of the population aged 65 and above have DM, with the majority being type 2 [19]. Furthermore, disordered gastric motor function may affect nutrient delivery to the small bowel and thus cause fluctuations in blood glucose levels [23]. Between 20 and 40% of patients with DM develop dysfunction of the autonomic nervous system, contributing to delay in GE [19]. Hyperglycemia causes acute disruption of gastric motility even when the autonomic nervous is intact, as in diabetic ketoacidosis [14]. Motor abnormalities in diabetic gastroparesis include abnormal intragastric distribution of food, reduced occurrence of the antral component of the MMC, antral dilation, and electrical dysrhythmias [19]. These abnormalities may be secondary to extrinsic autonomic denervation (as above), hyperglycemia per se, and/or direct involvement of the ENS and enteric muscle [25]. Hormonal factors including CCK, peptide YY, and amylin and secritin tightly regulate GE and their upregulation could contribute to retardation of gastric motility [19]. Hypothyroidism increases with old age and may affect GI motility. Hypothyroidism may be associated with pernicious anemia and decreased gastric acid secretion with further decrease in gastric motility. Hypothyroidism is associated with slowing of motor activity throughout the GI tract [26]. This alteration is clinically more significant in the small and large bowel than in the stomach [26].

3. *Renal disease*: The prevalence of chronic kidney disease (CKD) increases exponentially in older adults [27]. CKD, regardless of its etiology, is associated with symptoms of impaired gastric motility such as bloating, nausea, and vomiting. Patients with diabetic nephropathy, however, have increased predilection for gastroparesis [28].
4. *Paraneoplastic/cancer-related syndromes*: The prevalence of cancer is high in older adults [29]. Paraneoplastic syndrome caused by cancer cells that express antigens mimicking the neuronal tissues results in an autoimmune/inflammatory neuropathy of the ENS. Another report showed that sera containing antineuronal antibodies inhibited muscle contractions of the circular muscle [30, 31]. Small cell cancer of the lung is the most common cause, with cancer of the prostate, pancreas and breast, lymphoma, and melanoma less common [30, 31]. Neuronal invasion by tumor and side effects of chemotherapy may also contribute to delayed GE [31]. Occult malignancy should be suspected in the presence of anti-Hu antibodies and unexplained gastroparesis, particularly in an elderly individual with accompanying weight loss.
5. *Achlorhydria*: Elderly patients may have decreased gastric acid secretion, chronic atrophic gastritis, and pernicious anemia [32]. Atrophic gastritis may be the final stage of Helicobacter pylori infection with diffuse gastritis involving the proximal stomach and antrum; patients with atrophic gastritis can have delayed GE. The two main mechanisms hypothesized are: (1) decreased trituration from low gastric acid and pepsin secretion; and (2) thinner smooth muscle, reported in pernicious anemia [14, 33]. A study with dual-isotope technique in patients with achlorhydria due to atrophic gastritis and pernicious anemia showed that GE of solids was delayed but liquid emptying was preserved [34]. Excessive gastric acid as in Zollinger–Ellison syndrome is associated with accelerated GE [14].
6. *Iatrogenic disorders*: The geriatric population often receives multiple medications [35]. Thus, drug-induced alterations in gastric motility, due to polypharmacy or drug interactions, are a possible etiology in this population. Table 30.2 illustrates common medications that could retard gastric motility.

Table 30.2 Medications causing delayed gastric emptying

Cardiovascular/respiratory drugs
Calcium channel antagonists (nifedipine, diltaizem, verapamil)
Dopamine
Potassium
Beta-adrenergic agonists
Gastrointestinal drugs
Aluminum hydroxide
Anticholinergics/antispasmodics (hyoscyamine, dicyclomine)
Psychiatric/neurologic drugs
Opioids (morphine, codeine, etc.)
Tricyclics (amitriptylline, nortriptylline, etc.)
Phenothiazines
Levodopa
Hormonal drugs
Synthetic estrogen
GLP analog (exenatide or pramlintide)

Clinical Presentation

Gastroparesis may present with constellation of symptoms. Some patients may present with debilitating nausea and vomiting, and in others, it may be a more indolent disease with early satiety, postprandial fullness, and abdominal distention [36].

In one study, nausea, vomiting, bloating, and early satiety were reported by 92, 84, 75, and 60%, respectively, [3] and abdominal pain in 46%. A succession splash may be elicited as a sign of retained gastric contents (solid and liquid). Heartburn may be the main symptom of gastroparesis. Reflux is facilitated by fundic distention which increases the rate of transient lower esophageal sphincter relaxations [36]. Although some patient with gastroparesis with frequent

vomiting lose weight and develop malnutrition, others are overweight or obese through consumption of liquid diet [37]. Phytobezoars may complicate gastroparesis and an early sign may be retained food seen during an upper endoscopy. Gastric ulcer and pyloric outlet obstruction are complications of bezoars. Elimination of bezoars is accomplished by endoscopic destruction and lavage; enzymatic digestion; and dietary exclusion of foods rich in indigestible residue. Variably delayed GE in diabetics may lead to unpredictable nutrient delivery to the small bowel, with erratic glycemic control; this can be a clinical "tip-off" to consider gastroparesis [19].

Differential Diagnosis

Vomiting associated with gastroparesis must be differentiated from regurgitation due to reflux disease or rumination syndrome, episodic vomiting seen in cyclic vomiting syndrome, and abdominal pain with vomiting in superior mesenteric artery syndrome [38]. Vomiting typically occurs 1–2 h or longer following the meal, with older food contents being identified. Since functional dyspepsia and rapid GE may have similar clinical manifestations; a standardized 4-h GE scintigraphy test may help differentiate these disorders [39]. The symptomatic spectrum of small intestinal bacterial overgrowth (SIBO) and gastroparesis has significant overlap. Patients may have bloating, early satiety, and upper abdominal discomfort in both. The two disorders can coexist in the elderly due to hypoacidity promoting bacterial colonization of the small bowel; awareness of this relationship helps management [40].

Diagnostic Approach

Initial evaluation: A detailed history and physical examination are critical to understand the severity of the disease, underlying etiologies and exclude disorders with similar presentation. A review of medications that exacerbate or delayed GE is important (see Table 30.2).

Evaluate for etiologies and complications: Blood tests for diabetes, uremia, thyroid or parathyroid disease, and pernicious anemia and serologic studies for connective tissue diseases (anti-nuclear antibodies, sedimentation rate), and serum protein electrophoresis for amyloidosis may all help identify potential causes of gastroparesis. Especially with new onset symptoms of gastroparesis and weight loss, serologic markers for paraneoplastic syndrome should be considered. These include type 1 antineuronal nuclear antibody (specifically), anti-Hu antibodies, anti-Purkinje cell cytoplasmic antibody, and ganglionic nicotinic acetylcholine receptor antibody [41]. Serum electrolytes to rule out hypokalemia and contraction alkalosis, a complete blood count to exclude anemia and serum protein/albumin as a nutritional marker, are indicated.

Exclude mechanical obstruction: Most patients with suspected gastroparesis require upper endoscopy or radiographic imaging to exclude mechanical obstruction, such as compression of the distal duodenum, adhesions due to prior surgery, or ulcer disease. The presence of retained food in the stomach after overnight fasting in the absence of mechanical obstruction on endoscopy is suggestive of gastroparesis.

Confirm delayed GE: A gastric emptying test is required to establish a definite diagnosis of gastroparesis. GE of a solid-phase meal by scintigraphy is considered the gold standard as it quantifies the emptying of a physiologic, caloric meal that can assess the motor function of the stomach. An international scintigraphy method has been established with 99mTc-sulfur colloid-labeled, low-fat meal consisting of scrambled egg substitute, two slices of bread, strawberry jam, and water [42, 43]. Images are taken at 0, 1, 2, 3, and 4 h after the test meal ingestion. The 4-h method is accepted to be most sensitive and specific. Gastric retention of more than 10% at the end of 4 h would be consistent with gastroparesis. In diabetics, the blood glucose should be measured prior to the test and recorded in the report. If glucose level is >275 mg/dL, it should be lowered with insulin and/or the test be rescheduled. Ideally, patients should also be instructed to stop anti-secretory drugs such as proton-pump inhibitors for 5–7 days, prokinetics at least for 72 h, and narcotics for at least 12 h prior to the test. Smoking may delay GE.

Other tests that can be used to assess for myoelectric function of the stomach are listed in Table 30.3, but their role at this time is limited. Routine evaluation of gastroparesis should include the scintigraphic assessment, with endoscopic, ultrasound, and CT as additive measures to exclude other diagnoses.

Treatment

Diet and Lifestyle Modifications

Although there are no prospective, randomized controlled trials comparing dietary treatments in gastroparesis, a low-fat, low-fiber diet of small portions and frequent feedings are often recommended [44]. This makes physiologic sense as studies have shown that fat slows GE [45]; fiber can increase the risk for bezoar formation [46, 47], and large volumes not only slow GE but aggravate the early satiety often present. Patients are advised to chew foods well since the antrum's grinding capability is compromised. Patients should remain upright in an effort to use the effect of gravity to move food from fundus to antrum and to decrease postprandial reflux [44].

Table 30.3 Tests to assess gastric motor function

Test	Advantages	Disadvantages
Tests to assess GE		
Upper gastrointestinal barium radiograph	Provides information regarding mucosal abnormalities	Nonphysiologic Moderate radiation exposure
^{13}C Breath test	Noninvasive Do not involve ionizing radiation, has role in community or even bedside where gamma camera is not available	Requires normal small bowel, pancreas, liver, and pulmonary functions
Scintigraphy	Gold standard Noninvasive Can assess both liquid and solid-phase emptying	Radiation exposure (minimal)
Ultrasonography for serial changes in antral area	Noninvasive Physiologic	Needs expertise for imaging and interpretation Primarily measures liquid emptying
Magnetic resonance imaging	Noninvasive	Expensive, time-consuming Needs specialized center/software/personnel
Tests to assess gastric myoelectric function		
Electrogastrography (EGG)	Noninvasive	Movement artifact may make recording difficult to interpret Research technique, limited clinical utility
Antroduodenal manometry	Can differentiate between neuropathic and myopathic disorders	Invasive Needs expertise to perform and interpret, thus limited availability
Tests to assess for gastric accommodation		
Gastric barostat	Measures proximal gastric accommodation response	Invasive Balloon may interfere with accommodation reflex Mainly used as a research tool
Satiety test	Simple and easy to perform Measures combination of accommodation and sensitivity	Not well standardized

Source: Parkman et al. [1]

Pharmacological Therapy

Drugs to control symptoms: Antiemetics: Antiemetic therapy may help to achieve rapid symptomatic relief [48] (Table 30.4). It is prudent to start with less expensive agents (e.g., phenothiaxines); if ineffective, escalate to newer, more expensive therapies (such as 5HT3 antagonists). Scopolamine patch or promethazine, either oral or rectal suppository, may alleviate continuous nausea.

Pain control and psychopharmacology: Mechanisms involved in the pathogenesis of pain include (but not limited to) visceral hyperalgesia, coexistent inflammatory/cytokine reactions, and dysmotility [44]. A logical step would be to empathize with the patient. NSAIDs like ketorolac and indomethacin may have a role [49], but given their ulcerogenic potential, require caution. Tricyclic antidepressants (amitriptyline), selective serotonin reuptake inhibitors (paroxetine), and anti-epileptics (gabapentin) help control neuropathic pain and reduce visceral perception [48]. Tramadol, an opioid antagonist, with limited effect on mu receptors has little impact on gastric transit [50]. It also has the added benefit of lack of addictive potential with prolonged use. Acupuncture and biofeedback should also be considered can help, with very side effects [51, 52]. Narcotics may be condoned in the name of quality of life.

Exacerbating factors: Restoration of euglycemia and correction of electrolytes and fluid balance help GE. Medications that retard GE (Table 30.2) should be discontinued or limited if possible.

Drugs to augment GE/prokinetics (Tables 30.5 and 30.6): Prokinetic agents mainly used to treat gastroparesis are metoclopramide and domperidone [53]. Both agents are equally effective in reducing the symptoms of diabetic gastroparesis, particularly nausea and vomiting. Adverse CNS effects are more severe and more common with metoclopramide and include somnolence and confusion [54]. Chronic use of metoclopramide has been linked to tremor and rigidity referred to as a "Parkinson's like effect" and tardive dyskinesia, which includes involuntary and repetitive movements of the face, tongue, and body. Those prone include diabetics, female gender, and older adults [55]. Metoclopramide has received a black-box warning in the PDR. Although the original Food and Drug Administration (FDA) approval of medication was for up to 6 weeks, chronic use entails monitoring for adverse events.

Table 30.4 Classification, doses, and adverse reactions of commonly used antiemetic agents in gastroparesis

Class name	Agent	Mode of action	Usual dose	Side effects
Phenothiazine	Prochlorperazine	D2 receptor antagonist	Start with 5–10 mg thrice daily or 5–25 mg as required every 12 h as rectal suppository	Extrapyramidal effects; rarely jaundice
Anti-serotonergic	Ondansetron (others: Granisetron, Dolasteron)	Serotonin 5HT3 receptor antagonist	4–8 mg Thrice daily as required	Constipation with regular use
Anticholinergics	Scopolamine	Muscarinic M1 receptor antagonist	1 mg Every 3 days	Drowsiness, headache, dry mouth, CI-Glaucoma or bladder dysfunction
Phenothiazine	Promethazine	Histamine H1 receptor antagonist	12.5–25 mg Thrice daily as required, or intramuscular	Drowsiness, headache, dry mouth, CI-Glaucoma or bladder dysfunction
Benzodiazepine	Lorazepam	Anti-GABA effect	0.5–1 mg as Required	Sedation
Neurokinin antagonist	Aprepitant	Neurokinin receptor-1 antagonist	40 mg Once daily as required	Weakness, bowel dysfunction, reduced efficacy for OCP
Cannabinoids	Dronabinol	Acts on cannabinoid receptors with multiple central nervous system effects	2.5–5 mg Twice a day as required	Dependence/abuse potential, somnolence, euphoria

Table 30.5 Classification, doses, and adverse reactions of commonly used prokinetic agents in gastroparesis

Name of the drug	Mode of action	Dose	Adverse effects
Metocloporamide	D2 dopamine receptor antagonist Antiemetic action also contributes to relief	Start with 5 mg orally t.i.d., usual 15–20 mg t.i.d., 15 min before meals Can be used IM, SC, or IV	Anxiety, depression, galactorrhea, extrapyramidal side effects, and tardive dyskinesia
Domperidone	D2 dopamine receptor antagonist	Start with 5 mg t.i.d., usual 15–20 mg t.i.d., 15 min before meals	Anxiety, depression, galactorrhea, extrapyramidal side effects, and tardive dyskinesia (less common than metocloporamide)
Erythromycin	Motilin receptor agonist	40–250 mg t.i.d.; 15 min before meals	Abdominal cramping, loss of appetite, potential for many drug interactions Tachyphylaxis develops rapidly
Cisapride	5HT4 serotonin receptor agonist	10–20 mg t.i.d., 15 min before meals	Diarrhea, potential for cardiac dysrhythmia Under strict compassionate use protocol approved by IRB as otherwise not available in the US
Bethanecol	Muscarinic receptor agonist	10–20 mg t.i.d., 15 min before meals	Cholinergic side effects Efficacy against symptoms unclear Side effects are dose limiting
Pyridostigmine	Acetylcholinestrase inhibitors	30 mg q.i.d.	Cholinergic side effects Unclear efficacy

Table 30.6 List of prokinetic agents under investigation

Prokinetic class	Name of the agent
Motilin receptor agonist	Mitemcinal
5HT4 agonist	Renzapride (Alizyme) Mosapride
Ghrelin agonist	EX-1314 (Elixir pharmaceuticals) BIM-28131 (Ipsen pharmaceuticals) TZP-101 (Tranzyme pharmaceuticals)
Cholecystokinin (CCK) antagonists	Loxiglumide Dexloxiglumide
Cholinesterase inhibitors	Acotiamide: Z-338 (Zeria pharmaceuticals) YM443 (Astellas pharmaceuticals)

Domperidone is not approved in the US, but can be obtained by filing for an investigational new drug application to the FDA and obtaining local IRB approval. The responsibility for initiating this agent focuses on the electro-cardiogram where the QT interval needs to be <475 ms for females and <450 ms in males and K^+ levels to be maintained in the normal range. Some compounding pharmacies in the US provide the drug. The usual effective dose is 20 mg four times per day before meals and bed, but sometimes the maximal dose of 30 mg four times per day is necessary. Domperidone has no or minimal penetration of the blood brain barrier and hence the only real side effects relate to

elevation of prolactin-induced breast enlargement and/or tenderness in approximately 5% of patients.

Erythromycin, a motilin receptor agonist, is the most effective intravenous prokinetic agent. It can be given in a low dose orally, preferably as a liquid, in a dose of 150–250 mg up to three times a day to minimize concern for tachyphylaxis [48], which develops with chronic use.

Histamine-2 receptor antagonists, particularly nizatidine, are also partial cholinesterase inhibitors and accelerate gastric emptying and thus can be used to augment emptying of meals at night particularly in patients with severe gastroesophageal reflux symptoms [48].

Role of Botulinum Toxin

Although safe, endoscopic injection of botulinum toxin type-A into the pylorus has shown little effect for symptom relief [56, 57].

Role of Feeding/Venting Tubes

Although medical therapy is effective in most of the patients with gastroparesis, 10–20% of patients are refractory to pharmacological therapy and require hospitalizations [58]. Endoscopic therapy or surgical procedures for establishing a feeding jejunostomy may be required. Feeding jejunostomy in upper GI motility disorders reduces hospitalization rate during the first year after placement [59].

Gastric Electrical Stimulation

Open-label studies suggest that gastric electrical stimulation (GES) therapy leads to improvement in symptoms in idiopathic, diabetic, and postsurgical gastroparesis [60–64]. The mechanism of symptom relief is through activation of afferent pathways controlling CNS centers for nausea and vomiting. Gastric emptying, in many patients, is unchanged. Three clinical parameters have been shown to predict a favorable clinical response with GES: (1) diabetic and past gastric surgery or past vagotomy settings rather than idiopathic gastroparesis, (2) nausea/vomiting rather than abdominal pain as the primary symptom, and (3) independence from narcotic analgesics prior to stimulator implantation [65]. In the report of the most extensive series to date where patients were followed up to 10 years with GES in gastroparesis, many patients were in the 60–70 years age range and were successfully managed with the Enterra neurostimulation device [64]. Complications included infection of the subcutaneous pocket in about 5% of patients over time, electrode dislodgement, electrode erosion into the stomach, and bowel obstruction from the wires [66, 67].

Key Points (Table 30.7)

- The gut ages well and in most cases gastric motility is preserved.
- Gastroparesis is a motor disorder of the stomach with a myriad of clinical manifestations.

Table 30.7 Practical approach to gastroparesis management in the elderly

	Mild gastroparesis	Moderate gastroparesis	Severe gastroparesis
Criteria	Symptoms relatively easily controlled Able to maintain weight and nutrition Gastric retention: 11–20%	Moderate symptoms with partial control with pharmacological agents Able to maintain nutrition with dietary adjustments Rare hospital admissions Gastric retention: 21–40%	Refractory symptoms despite medical therapy Inability to maintain nutrition via oral route Frequent ER visits or hospitalizations Gastric retention: >40%
Dietary modification	Homogenized food, frequent small feedings, decreased fat content, decreased fiber content	As in Mild + rare use of nutrition/caloric supplementation (“ensure/boost”)	As in Mild + routine use of nutrition/caloric supplementation (“ensure/boost”)
Enteral access	Never	Rarely	Usually required for venting/feeding purposes
Pharmacologic treatment	Antiemetic (promethazine) or prokinetic (metoclopramide before meals) required on as needed basis, i.e., when symptomatic	May require daily therapy with prokinetics and symptomatic PRN management with antiemetics; if nausea/vomiting severe may need drugs in suspension form (metoclopramide) or rectal suppositories (such as phenergan supp.)	Usually daily metoclopramide therapy 10 mg ½ h before each meal or domperidone 10–20 mg thrice daily ½ h before each meal; daily antiemetic and may require intravenous forms (such as ondansetron) during severe symptom attacks
Nonpharmacologic treatment	Not needed	Not needed	Gastrostomy tube decompression, parenteral nutrition, and/or compassionate use of gastric neurostimulation device

Modified from data found in Abell et al. [43], Camilleri, [68]

- The "gold-standard" for the diagnosis is confirmation of delayed GE, defined as >10% retention, on a standardized 4-h scintigraphic test utilizing a low-fat (2%) egg beater meal, after careful exclusion of mechanical obstruction.
- Medication-induced effects on gastric motility must be a consideration.
- Treatment warrants cautious selection of pharmacological agents because of concern for an increased likelihood of adverse events.
- Atrophic gastritis and hypochlorhydria could explain mild gastroparesis symptoms with aging.

References

1. Parkman HP, Hasler WL, Fisher RS. American Gastroenterological Association technical review on the diagnosis and treatment of gastroparesis. Gastroenterology. 2004;127:1592–622.
2. Talley NJ, Locke III GR, Lahr BD, et al. Functional dyspepsia, delayed gastric emptying, and impaired quality of life. Gut. 2006;55:933–9.
3. Soykan I, Sivri B, Sarosiek I, et al. Demography, clinical characteristics, psychological and abuse profiles, treatment, and long-term follow-up of patients with gastroparesis. Dig Dis Sci. 1998;43:2398–404.
4. Jung HK, Choung RS, Locke III GR, et al. The incidence, prevalence, and outcomes of patients with gastroparesis in Olmsted County, Minnesota, from 1996 to 2006. Gastroenterology. 2009;136:1225–33.
5. Wang YR, Fisher RS, Parkman HP. Gastroparesis-related hospitalizations in the United States: trends, characteristics, and outcomes, 1995–2004. Am J Gastroenterol. 2007;103:313–22.
6. Ahluwalia NK, Thompson DG, Barlow J. Effect of distension and feeding on phasic changes in human proximal gastric tone. Gut. 1996;39:757–61.
7. Mizumoto A, Monchiki E, Suzuki H, Tanaka T, Itoh Z. Neuronal control of motility changes in the canine lower esophageal sphincter and stomach in response to meal ingestion. J Smooth Muscle Res. 1997;33:211–22.
8. Hinder RA, Kelly K. Human gastric pacesetter potential. Site of origin, spread, and response to gastric transection and proximal gastric vagotomy. Am J Surg. 1977;133:29–33.
9. Meyer JH, Ohashi H, Jehn D, Thomson JB. Size of liver particles emptied from the human stomach. Gastroenterology. 1981;80:1489–96.
10. Morgan KG, Szurszewski JH. Mechanisms of phasic and tonic actions of pentagastrin on canine gastric smooth muscle. J Physiol. 1980;30:229–42.
11. Hirst GD, Edwards FR. Role of interstitial cells of Cajal in the control of gastric motility. J Pharmacol Sci. 2004;96:1–10.
12. Camilleri M. Integrated upper gastro-intestinal response to food intake. Gastroenterology. 2006;131:640–58.
13. Hunt JN, Pathak JD. The osmotic effects of some simple molecules and ions on gastric emptying. J Physiol. 1960;154:254–69.
14. McCallum RW. Motor function of stomach in health and disease. In: Sleisenger MH, Fordtran JS, editors. Gastrointestinal disease: pathophysiology, diagnosis, management, vol. 1. 4th ed. Philadelphia: Saunders; 1989. p. 675–713.
15. Evans MA, Triggs EJ, Cheung M, et al. Gastric emptying rate in the elderly: implications for drug therapy. J Am Geriatr Soc. 1981;29(5):201–5.
16. Horowitz M, Maddern GJ, Chatterton BE, et al. Changes in gastric emptying rates with age. Clin Sci (Lond). 1984;67(2):213–8.
17. Madsen JL, Graff J. Effects of ageing on gastrointestinal motor function. Age Ageing. 2004;33(2):154–9.
18. Kupfer RM, Heppell M, Haggith JW, et al. Gastric emptying and small-bowel transit rate in the elderly. J Am Geriatr Soc. 1985;33(5):340–3.
19. Kuo P, Rayner CK, Horowitz M. Gastric emptying, diabetes and aging. Clin Geriatr Med. 2007;23:785–808.
20. Rayner CK, MacIntosh CG, Chapman IM, et al. Effects of age on proximal gastric motor and sensory function. Scand J Gastroenterol. 2000;35(10):1041–7.
21. Clarkston WK, Pantano MM, Morley JE, et al. Evidence for the anorexia of aging: gastrointestinal transit and hunger in healthy elderly vs. young adults. Am J Physiol. 1997;272:R243–8.
22. Goetze O, Nikodem AB, Weizcorek J, et al. Predictors of gastric emptying in Parkinson's disease. Neurogastroenterol Motil. 2006;18:369–75.
23. O'Mahony D, O'Leary P, Quigley EMM. Aging and intestinal motility: a review of factors that affect intestinal motility in the aged. Drugs Aging. 2002;19(7):515–27.
24. Menke DM, Kyle RA, Fleming CR, et al. Symptomatic gastric amyloidosis in patients with primary systemic amyloidosis. Mayo Clin Proc. 1993;68:763–7.
25. Quigley EMM. Gastric motility and sensation in health and disease. In: Feldman M, Friedman L, Sleisenger M, editors. Sleisenger and Fortran's gastrointestinal and liver disease. 14th ed. New York: Mosby; 2002.
26. Ebert EC. The thyroid and the gut. J Clin Gastroenterol. 2010;44(6):402–6.
27. Lindeman RD. Overview: renal physiology and pathophysiology of aging. Am J Kidney Dis. 1990;16:275–82.
28. Dumitrascu DL, Barnet J, Kirschner T, et al. Antral emptying of semisolid meal measured by real-time ultrasonography in chronic renal failure. Dig Dis Sci. 1995;40:636–44.
29. Smith BD, Smith GL, Hurria A, et al. Future of cancer incidence in the United States: burdens upon an aging, changing nation. J Clin Oncol. 2009;27:2758–65.
30. Lucchinetti CF, Kimmel DW, Lennon VA. Paraneoplastic and oncologic profiles of patients seropositive for type 1 antineuronal nuclear autoantibodies. Neurology. 1998;50:652–7.
31. Hejazi RA, Zhang D, McCallum RW. Gastroparesis, pseudoachalasia and impaired intestinal motility as paraneoplastic manifestations of small cell lung cancer. Am J Med Sci. 2009;338(1):69–71.
32. Carmel R, Aurangzeb I, Qian D. Associations of food-cobalamin malabsorption with ethnic origin, age, *Helicobacter pylori* infection, and serum markers of gastritis. Am J Gastroenterol. 2001;96:63–70.
33. Minami H, McCallum RW. The physiology and pathophysiology of gastric emptying in humans. Gastroenterology. 1984;86(6):1592–610.
34. Halvorsen L, Dotevall G, Walan A. Gastric emptying in patients with achlorhydira or hyposecretion of hydrochloric acid. Scand J Gastroenterol. 1973;8(5):395–9.
35. Giron MS, Wang HX, Bernsten C, et al. The appropriateness of drug use in an older non-demented and demented population. J Am Geriatr Soc. 2001;49:277–83.
36. Hasler WL. Gastroparesis: symptoms, evaluation and treatment. Gastroenterol Clin North Am. 2007;36(3):619–47.
37. Bizer E, Harrell S, Koopman J, et al. Obesity is common in gastroparesis despite nausea, vomiting, and early satiety. Gastroenterology. 2005;128:M1895.
38. Park MI, Camilleri M. Gastroparesis: clinical update. Am J Gastroenterol. 2006;101:1129–39.
39. Delagado-Aros S, Camilleri M, Cremonnini F, et al. Contributions of gastric volumes and gastric emptying to meal size and post meal symptoms in functional dyspepsia. Gastroenterology. 2004;127(6):1685–94.

40. Reddymasu SC, McCallum RW. Small intestinal bacterial overgrowth in gastroparesis: are there any predictors? J Clin Gastroenterol. 2010;44:e8–13.
41. De Giorgio R, Guerrini S, Barbara G, et al. Inflammatory neuropathies of the enteric nervous system. Gastroenterology. 2004;126(7):1872–83.
42. Tougas G, Eaker EY, Abell TL, et al. Assessment of gastric emptying using a low fat meal: establishment of international control values. Am J Gastroenterol. 2000;95:1456–62.
43. Abell TL, Camilleri M, Donohoe K, et al. Consensus recommendations for gastric emptying scintigraphy: a joint report of the American Neurogastroenterology and Motility Society and Society of Nuclear Medicine. Am J Gastroenterol. 2008;103:753–63.
44. Parkman HP, Camilleri M, Farrugia G, et al. Gastroparesis and functional dyspepsia: excerpts from the AGA/ANMS meeting. Neurogastroenterol Motil. 2010;22:113–33.
45. Parrish CR. Nutrition concerns for the patient with gastroparesis. Curr Gastroenterol Rep. 2007;9:295–302.
46. Sanders MK. Bezoars: from mystical charms to medical and nutritional management. Pract Gastroenterol. 2004;XXVIII:37.
47. Whitson BA, Kandaswamy R, Sutherland DER. Diabetic gastroparesis associated bezoar resolution via cola-lysis. Clin Transplant. 2008;22:242–4.
48. Reddymasu SC, McCallum RW. Pharmacotherapy of gastroparesis. Expert Opin Pharmacother. 2009;10(3):469–84.
49. Hasler WL, Soudah HC, Dulai G, et al. Mediation of hyperglycemia-evoked gastric slow-wave dysrhythmias by endogenous prostaglandins. Gastroenterology. 1995;108(3):727–36.
50. Mauer AH, Krevsky B, Knight LC, et al. Opioid and oipoid like drug effects on whole-gut transit measured by scintigraphy. J Nucl Med. 1996;37(5):818–22.
51. Takahashi T. Acupuncture for functional gastrointestinal disorders. J Gastroenterol. 2006;41:8–17.
52. Chiarioni G, Whitehead WE. The role of biofeedback in the treatment of gastrointestinal disorders. Nat Clin Pract Gastroenterol Hepatol. 2008;5:371–82.
53. McCallum RW, Ricci DA, Rakatansky H, et al. A multicenter placebo controlled clinical trial of oral metoclopramide in diabetic gastroparesis. Diabetes Care. 1983;6:463–7.
54. Patterson D, Abell T, Rothstein R, et al. A double-blind multicenter comparison of domperidone and metoclopramide in the treatment of diabetic patients with symptoms of gastroparesis. Am J Gastroenterol. 1999;94:1230–4.
55. Pasricha PJ, Pehlivanov A, Sugumar A, et al. Drug insight: from disturbed motility to disordered movement—a review of the clinical benefits and medicolegal risks of metoclopramide. Nat Clin Pract Gastroenterol Hepatol. 2006;3:138–48.
56. Arts J, Holvoet L, Caenepeel P, et al. Clinical trial: a randomized-controlled crossover study of intrapyloric injection of botulinum toxin in gastroparesis. Aliment Pharmacol Ther. 2007;26:1251–8.
57. Friedenberg FK, Palit A, Parkman HP, Hanlon A, Nelson D. Botulinum toxin A for the treatment of delayed gastric emptying. Am J Gastroenterol. 2008;103:416–23.
58. Syed AA, Rattansingh A, Furtado SD. Current perspectives on management of gastroparesis. J Postgrad Med. 2005;51:54–60.
59. Colemont LJ, Camilleri M. Chronic intestinal pseudo-obstruction: diagnosis and treatment. Mayo Clin Proc. 1989;64:60–70.
60. Familoni BO, Abell TL, Voeller G, et al. Electrical stimulation at a frequency higher than basal rate in human stomach. Dig Dis Sci. 1997;42:885–91.
61. McCallum RW, Chen JD, Lin Z, et al. Gastric pacing improves emptying and symptoms in patients with gastroparesis. Gastroenterology. 1998;114:456–61.
62. Abell TL, Van Cutsem E, Abrahamsson H, et al. Gastric electrical stimulation in intractable symptomatic gastroparesis. Digestion. 2002;66:204–12.
63. Forster J, Sarosiek I, Delcore R, et al. Gastric pacing is a new surgical treatment for gastroparesis. Am J Surg. 2001;182:676–81.
64. McCallum RW, Lin Z, Forster J, et al. Gastric electrical stimulation improves outcomes in patients with gastroparesis for up to 10 years. Clin Gastroenterol Hepatol. 2011;9:314–9.
65. Maranki JL, Lytes V, Meilahn JE, et al. Predictive factors for clinical improvement with Enterra gastric electric stimulation treatment for refractory gastroparesis. Dig Dis Sci. 2008;53(8):2072–8.
66. Anand C, Al-Juburi A, Familoni B, et al. Gastric electric stimulation is safe and effective: a long-term study in patients with refractory gastroparesis in three regional centers. Digestion. 2007;75:83–9.
67. Abell T, McCallum RW, Hocking M, et al. Gastric electrical stimulation for medically refractory gastroparesis. Gastroenterology. 2003;125:421–8.
68. Camilleri M. Clinical Practice. Diabetic gastropareisis. New Eng J Med. 2007;356:820–9.

Esophageal Reflux Disease and Its Complications

31

Missale Solomon and James C. Reynolds

The prevalence of gastroesophageal reflux disease (GERD) is increasing across all ages. Older individuals are more likely to develop severe disease as a result of several factors including age-related physiologic changes, medication effects, and a higher prevalence of hiatal hernia. Typical symptoms of heartburn are less common in older adults and the disorder may be silent or present atypically with dysphagia, vomiting, or extraesophageal symptoms. The severity of inflammation increases with age, with the elderly at highest risk of complications of GERD including Barrett's esophagus and esophageal adenocarcinoma (EAC). Proton pump inhibitor (PPI) therapy is the cornerstone of treatment and provides a safe and cost-effective modality of treatment in the majority of geriatric patients. However, potential complications of PPI therapy and their management should be well recognized by primary care physicians and gastroenterologists.

Epidemiology

The prevalence of GERD worldwide is increasing with higher rates in North America and Europe [1]. Population studies estimate that more than 20% of persons over age 65 years in the western hemisphere have GERD defined as at least weekly heartburn [2]. Recently, several large population studies have demonstrated that there is no significant increase in GERD symptoms with age; despite that fact, the frequency of esophagitis is significantly higher in older than in younger subjects [3]. The actual prevalence of GERD in the elderly is probably higher given the inaccuracy of symptoms. Epidemiologic data consistently support the view that as people age the severity of reflux esophagitis increases, whereas symptoms are attenuated and become less typical [2]. Moreover, a large epidemiological study from the US reported that age was an important risk factor for the development of severe forms of GERD, in addition to male gender, white ethnicity, and hiatus hernia [4].

Pathophysiology

GERD results when the reflux of stomach contents, and rarely, duodenogastric reflux of bile lead to troublesome symptoms and/or complications [5]. Gastroesophageal reflux (GER) is a normal physiologic event which leads to disease with excessive exposure. This occurs commonly as a result of decreased lower esophageal sphincter (LES) pressure and transient episodic LES relaxations (tLESRs) unaccompanied by swallowing. Physiologic studies reveal that the length of the abdominal LES and the amplitude of peristaltic contractions decrease with age leading to diminished ability to clear material refluxed from the stomach [6]. Furthermore, there is impaired esophageal peristalsis and decreased salivary production with significantly reduced salivary bicarbonate response to acid perfusion in the aged [7–9]. Gastric acid secretion does not decrease with aging unless there is *Helicobacter pylori*-associated atrophic gastritis. However, slowing of gastric emptying that is observed with aging plays an important role in the pathogenesis of GERD [10].

Hiatal hernia (HH), a common anatomic abnormality in older adults, predisposes to the development of GERD [11]; HH refers to the herniation of abdominal contents through the esophageal hiatus of the diaphragm. Normally, the distal most end of the esophagus resides in the abdominal cavity with the crus of the diaphragm providing an extrinsic component to the gastroesophageal barrier. With HH, this antireflux mechanism is lost, compromising the process of acid clearance after a reflux episode. The increase in HH seen with

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age is thought to result from fibromuscular degeneration compounded by episodes of raised intra-abdominal pressure, as seen in kyphosis associated with osteoporosis and obesity. Not surprisingly, the presence and the size of the hernia are strongly associated with the severity of reflux esophagitis. In one study, HH larger than 3 cm was strongly associated with greater risk of severe erosive esophagitis [3, 12].

The antireflux barrier can be further jeopardized by the concurrent use of medications. Smooth muscle relaxants such as calcium channel blockers, nitrates, and anticholinergics impair sphincter function and peristalsis. Other drugs such as NSAIDs, potassium chloride tablets, tetracycline, methotrexate, and bisphosphonates may injure the esophageal mucosa [13]. Superimposed ill effects of lifestyle and diet that include smoking, large fatty meals, caffeine, and obesity common in the geriatric population can further increase the risk of reflux and are targets of intervention [14] (Fig. 31.1).

The aerodigestive apparatus is a secondary defense against pulmonary aspiration of GER and includes the pharynx, upper esophageal sphincter (UES), esophageal body, glottis, and vocal cords [15]. Esophageal distention by either air or a balloon evokes a glottal closure mechanism, an esophagoglottal reflex, which is more prominent in the proximal esophagus and plays an important role in preventing laryngeal aspiration of acid due to GER accompanied by acid regurgitation into the pharynx. On the other hand, these events may also lead to esophageal peristalsis resulting in relaxation of the LES, facilitating reflux of gastric content into the esophagus. In older individuals, the UES resting pressure is elevated and the UES opening is narrowed which is compensated by increased hypopharyngeal pressure as compared to younger subjects, and as a result, the response to esophageal distension is preserved even with advanced aging [16].

Obesity and being overweight have been positively related to GERD. Data from 8,936 older adults suggest that body mass index is related positively to GERD and this relationship is a consequence of an increased gastric acid reflux, caused by enhanced intra-abdominal pressure impacting the reflux [17].

The relationship between GERD and *H. pylori* is complex and controversial. Prevalence studies indicate an inverse pattern and in some studies the prevalence and severity of reflux esophagitis were shown to increase after successful eradication of *H. pylori* [18]. Furthermore, the decline in the incidence of *H. pylori* infection has been linked to the increased prevalence of Barrett's esophagus and esophageal adenocarcinoma [19]. This suggests that *H. pylori* infection may be protective against GERD mainly by causing atrophic gastritis and intestinal metaplasia which leads to reduced gastric output especially with the cagA + virulent strain. When *H. pylori* is eradicated, the gastric mucosa returns to normal increasing acid secretion and possibly leading to GERD symptoms in susceptible patients. Several meta-analyses, however, have failed to confirm these associations [20].

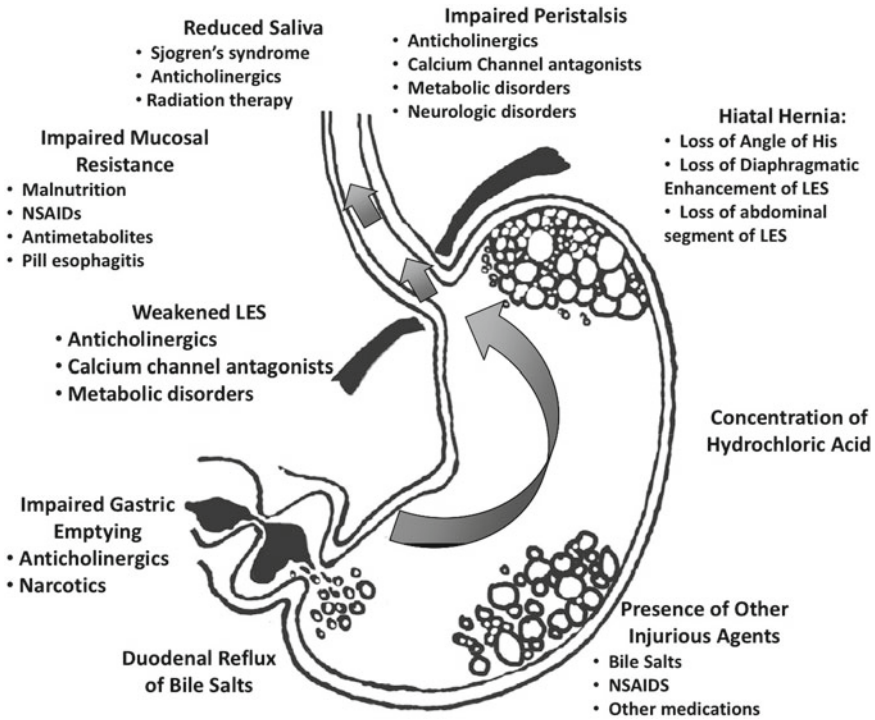

Fig. 31.1 Factors which influence gastrointestinal reflux

Clinical Features

The classical symptom of GERD is heartburn, a burning feeling, rising from the stomach or lower chest and radiating toward the neck, throat, and occasionally the back [21]. The clinical presentation of GERD differs significantly between the old and the young. The typical symptom complex of heartburn and acid regurgitation routinely used to screen and diagnose GERD is often absent in the older group, who instead more likely report dysphagia, vomiting, and respiratory difficulties [22]. Even of more concern, a significant number remain asymptomatic despite the presence of advanced esophageal erosions. In a large US multicenter study, close to a third of the patients aged over 70 who were diagnosed with severe esophagitis were asymptomatic. In the same study, the prevalence of severe esophagitis increased with age, but did not correlate with increased symptom severity [4]. Not surprisingly, complications such as hemorrhage, Barrett's esophagus, and strictures may present with mild or no symptoms. However, data from 14,521 Russian respondents of different age groups suggested that heartburn is the prevalent symptom and its prevalence in those 60 and older is higher than in the young, clearly affecting the quality of life [23]. Increasing insulin resistance and the metabolic syndrome appears associated with greater severity and prevalence of GERD; whether reducing insulin resistance will improve symptoms requires study [24].

Extraesophageal Manifestations

Extraesophageal manifestations of GERD are common in older adults. They include noncardiac chest pain (NCCP), dental erosions, ENT manifestations such as pharyngitis, hoarseness, and pulmonary manifestations including wheezing, cough, and aspiration pneumonia [22]. The pathophysiology involves microaspiration of acid into the larynx and pharynx, and vagally mediated bronchospasm and laryngospasm [25].

The role of reflux in such disorders is underestimated due to atypical symptoms and difficulty in confirming the diagnosis with endoscopy and pH monitoring. Antisecretory therapy can be used for a diagnostic trial and therapy in the majority of cases. This is true in NCCP, commonly a result of GERD, where empiric use of PPIs is recommended as the initial approach to diagnosis [26]. However, in older persons with new onset heartburn or chest pain, it is essential to request an initial electrocardiogram and further testing to exclude coronary artery disease, prior to proceeding with evaluation for GERD. While GERD is not immediately lethal, coronary artery disease may be.

Not all extraesophageal symptoms respond to PPI therapy. Laryngitis improves with treatment of GERD in only those patients where the manifestations are due to reflux [27]. In the absence of GERD symptoms, however, it is unlikely to respond to GERD treatment. Similarly several large RCTs have recently shown that despite a high prevalence of asymptomatic GERD among patients with poorly controlled asthma, treatment with PPI does not improve the asthma [28, 29].

Diagnosis

The diagnosis of GERD is usually based on the occurrence of heartburn on 2 or more days a week; however, the absence of these symptoms does not exclude the disease [5]. An empiric trial of acid suppression is a simple and cost-effective method of diagnosing GERD. High-dose PPI given for at least 2 weeks has a sensitivity of over 80% and should be considered in a subset of patients [30]. The standard of care in patients with "new onset" or persistent GERD who are over 50 years of age and in anyone presenting with alarm symptoms is endoscopic examination, the gold standard for detection of mucosal disease. However, the lack of a strong correlation between symptoms and the severity of disease in older patients makes the role of symptom-based endoscopic screening challenging [4]. Therefore, there should be a high index of suspicion and a low threshold to perform endoscopy in older individuals. While the finding of linear mucosal damage extending from the GEJ is highly specific, the absence of erosive disease in no way excludes the diagnosis. Endoscopy also permits opportunity for mucosal biopsies necessary to exclude the diagnosis of eosinophilic esophagitis.

Several conditions in older individuals present with symptoms that mimic GER. Candida esophagitis and other forms of infectious esophagitis should be considered not only in the immune compromised, but also in those on broad-spectrum antibiotics, diabetics, and the malnourished. Pill esophagitis is common in the geriatric population, in those on alendronate, potassium, chloride, doxycycline, quinidine, and nonsteroid anti-inflammatory drugs, among others. The ulcers often occur at the junction of smooth and striated muscles in the upper third of the esophagus and require careful endoscopic evaluation of the entire esophagus. Inlet patch mucosa, a form of gastric mucosa heterotopias, may present with respiratory complications, globus, heartburn, and regurgitation. Pemphigus, pemphigoid, epidermolysis bullosa, and Steven Johnson syndrome are esophageal disorders that cause burning pain, dyspepsia, and dysphagia. Rarely these disorders affect the esophagus unaccompanied by or precede the skin involvement. Mechanical disorders of the esophagus including intrinsic occlusions, extrinsic compression, strictures, webs and rings, and cancer can present with symptoms that mimic esophageal reflux.

Esophageal 24 h pH testing is useful in those who do not respond to medical therapy. A normal study in the presence

of erosive disease may indicate an alternate etiology such as pill-induced esophagitis or duodenogastric reflux. The addition of impedance pH monitoring in the latter group is useful in differentiating between acid and nonacid reflux. On the other hand, negative endoscopy in a patient with abnormal esophageal pH test suggests the need for more aggressive drug therapy, whereas a normal test points toward a functional disorder. Esophageal manometry is reserved for the localization of the LES before pH testing and for evaluating esophageal peristalsis before surgery.

Management

The goals of treatment of GERD in the elderly are essentially the same as in all adults and include symptom relief, healing of erosive esophagitis, and prevention and management of complications. Lifestyle modification is an important first step in management of GERD. Foods rich in fat increase esophageal exposure by delaying gastric emptying and increasing frequency of tLES relaxation. Similarly, peppermint and chocolate can induce reflux symptoms by reducing the LES pressure. Beverages such as coffee, tea, soda, tomato, and citrus juice, which are either acidic or can stimulate gastric acid production, contribute to heartburn [14]. Spicy food is often incriminated in the precipitation of GERD symptoms. Smoking has been shown to increase distal esophageal exposure time through the effect on the LES, while alcohol may precipitate GERD by increasing acid secretion, reducing LES pressure, increasing spontaneous LES relaxations, and impairing esophageal motility and gastric emptying [31]. However, a systemic review that evaluated the literature from 1975 to 2004 revealed showed no evidence supporting an improvement in GERD measures after cessation of smoking, alcohol, and the other dietary interventions [32]. In the same study, only reduction of excess weight and elevation of the head of the bed were shown to benefit patient symptoms, but neither prevent complications. Therefore, a more aggressive therapeutic approach is often recommended. The approach should include a careful review of the patient's current medications, and where possible, avoidance of drugs known to worsen GERD (Table 31.1).

Table 31.1 Commonly used medications that worsen gastroesophageal reflux disease (GERD) and their mechanisms

Decrease LES pressure
Anticholinergics
Barbiturates
Benzodiazepines
Beta-agonists
Caffeine
Calcium channel blockers
Dopamine
Ethanol
Estrogen
Nitrates
Progestrone
Theophylline
Directly injure esophageal mucosa
Antiretroviral agents
Ascorbic acid
Aspirin
Bisphosphonates
Doxicyline
Ferrous sulfate
Phenytoine
Potassium chloride
Propranolol
NSAIDs
Tetracycline
Trimethoprine–sulfamethoxazole
Quinidine
Decrease gastric emptying
Anticholinergics
Calcium channel blocker
Clonidine
Dopamine agonists
Lithium
Narcotics
Nicotine
Progestrone

Antacids

Antacids are available over-the-counter and promptly act by neutralizing gastric acid. Simethacone is added to many formulations and provide an additional physical barrier to acid. These measures help self-treat mild, infrequent heartburn symptoms and provide rapid relief; however, they do not heal erosive esophagitis, nor prevent complications [33]. Furthermore, antacids require frequent dosing and should be used with caution in older adults due to the potential risk of salt overload, calcinosis and calcium nephrolithiasis, constipation, diarrhea, and drug interactions.

Histamine-2-Receptor Antagonists

Acid secretion by gastric parietal cells is stimulated by acetylcholine, histamine, and gastrin. Histamine-2-Receptor Antagonists (H_2RAs) reduce acid secretion by competing for histamine receptors on parietal cells. They are more effective in controlling nocturnal, as compared with meal-related, acid secretion because the parietal cell is stimulated postprandially by gastrin and by acetylcholine [34]. Compared to placebo, H_2RAs significantly decreased heartburn, although symptoms are rarely abolished. The overall esophagitis healing rates with H_2RAs rarely exceeds 60% following up to 12 weeks of

treatment, even when higher doses were used [35]. H_2RAs are relatively safe with a side effect rate of about 4%, most being minor and reversible. However, cimetidine and to a lesser degree ranitidine can inhibit the P450 cytochrome system causing drug interactions, which requires monitoring of other medications taken simultaneously. When used intermittently, H_2RAs can be effective in blocking nocturnal acid reflux. When used daily, however, tolerance develops and the benefit diminishes.

Proton Pump Inhibitors

PPIs provide meal-stimulated and nocturnal gastric acid inhibition of the parietal cell regardless of any stimuli and to a significantly greater degree than H_2RAs and are currently the cornerstone of treatment of GERD. Compared to H_2RAs, PPIs promote a greater degree and more sustained duration of acid suppression. In a recent Cochrane review involving 4,032 patients in 26 RCT trials, PPIs were superior to H_2RAs in healing esophagitis at 4–8 weeks with a number-to-treat of 3 [36]. Currently, there are seven PPIs available on the market with similar therapeutic efficacies; however, large studies comparing PPIs found a greater therapeutic advantage to using esomeprazole in severe LA grade C/D esophagitis [37]. A recommended regimen in patients with confirmed esophagitis is a 2-month course of daily PPI with expected cure rates over 90%. However, GERD is a chronic disease and most elderly will require long-term maintenance therapy. The relapse rate can be as high as 90% annually after discontinuation of PPIs [38]. Relapse rates increase following the abrupt discontinuation of a PPI due to oxyntic cell hyperplasia [39]. Tapering off the PPI over 3–4 weeks may reduce relapses. PPIs are widely used with high effectiveness and safety in the old. Common side effects include diarrhea, abdominal pain, constipation, and headache which are rarely limiting and typically respond to dose reduction or discontinuation of the medication. However, more than the aforementioned, long-term use is associated with serious complications from PPI use as a consequence of profound acid suppression and has received much attention of late. When PPIs are ineffective, an alternated diagnosis should be sought for (Table 31.2).

Table 31.2 Potential reasons for proton pump inhibitor (PPI) failure and recommended approach

Symptoms are not a result of acid reflux
Seek an alternate diagnosis
Nonacid reflux
Perform impedance pH monitoring
Resistant reflux
High-dose PPI therapy needed
Cost of medical therapy prohibitive
Nocturnal acid breakthrough
Persistent regurgitation

PPI–Clopidogrel Interaction

Following widespread use of antiplatelet therapy, upper gastrointestinal bleeding (UGI) has emerged as a common and often life-threatening complication. Prophylactic coadministration of PPIs significantly reduces bleeding risk; however, recent studies have questioned the safety of this approach. Clopidogrel, a prodrug, undergoes CYP2C19-dependent activation in the liver. Ex vivo studies suggest that PPIs, such as omeprazole, competitively inhibit the CYP2C19 enzyme, thereby interfering with activation of clopidogrel and decrease its antiplatelet effect [40]. The FDA has issued a warning regarding the concomitant use of clopidogrel and PPIs. An alternative approach used by some is to dose clopidogrel 12 h apart from the PPI, but this approach may not be effective (based on pharmacokinetics) [41]. Until the potential interaction is better understood, caution is advised with coadministration. In patients at high risk for GI bleeding, especially the older adults on aspirin or NSAIDs, the risk of reduced activity of clopidogrel must be weighed against bleeding risks and decisions taken on case-by-case basis. Other drug–drug interactions are mentioned in Table 31.3.

PPI Use and Pneumonia

Gastric acid is an important barrier to colonization and infection by invading pathogens. Attenuation of this acidity results in increased bacterial colonization of the upper aerodigestive tract, providing a plausible mechanism as to why patients on PPIs or H_2RAs might be at increased risk of pneumonia. Studies designed to clarify this risk show contradictory results. A recent large US-based population study did not observe an increased risk of community-acquired pneumonia in older adults on PPI and H_2RA [42]. On the other hand, several studies demonstrate a slight trend toward an association between PPI use and pneumonia, with a higher risk for PPIs over H_2RAs [43, 44]. Therefore, the use of PPIs should

Table 31.3 Potential complications of PPIs

Osteoporosis
Small intestinal bacterial overgrowth
Increased susceptibility to enteric pathogens
Traveler's diarrhea
Clostridium difficile
Drug–drug interactions
Cytochrome P450 interaction with Clopidogrel
Reduced absorption of Atazanavir
Increased susceptibility to aspiration pneumonia
Vitamin B12 and iron malabsorption
Increased *Helicobacter pylori* gastritis
Acute interstitial nephritis

be limited to situations where the indications are clear, and in such cases, they must be used in the lowest effective dose and for the shortest duration.

PPI Therapy and Enteric Infections

Potent inhibition of gastric acid can reduce the antiseptic benefit of gastric acid and lead to a proliferation and increased enteric exposure to ingested pathogenic bacteria. Enteric infections including *Salmonella*, *Campylobacter,* and *Shigella* are more prevalent in those on PPIs [45]. More importantly, an increased incidence of *Clostridium difficile* infections has been reported with PPI administration, with a doubling in the incidence of infections [46, 47]. The duration of PPI treatment was found to be an independent risk factor in one study, with the incidence of infection increasing from 5 to 23% in those on PPI therapy for over 6 months [48]. Therefore, a risk-benefit evaluation is necessary prior to initiating antisecretory therapy in those at high risk of developing enteric infections (e.g., hospitalized patients on antibiotics, frail and elderly, immunosuppressed). In such patients, preventative measures may be utilized.

PPIs, Osteoporosis, and Fractures

PPIs may interfere with calcium absorption, a process dependent on gastric acidity. In turn, this leads to a decline in bone loss and increased risk of fractures [47]. Several retrospective studies suggest that a higher dose and duration of PPI use conferred an increased risk, the largest odds ratio being 1.92 (1.16–3.18) after 7 years of PPI use [49].

Nevertheless, the FDA has recently issued a warning regarding the possible link between PPI use and increased fracture risk. In those who require high-dose, long-term PPIs, osteoporosis and fall risk should be assessed and the use of medications revised as appropriate. This includes the use of calcium supplements, vitamin D, and/or bisphosphonates.

Antireflux Surgery

Performed in expert hands, antireflux surgery can potentially eliminate the GER by increasing basal LES pressure, decreasing episodes of tLESRs, and inhibiting complete LES relaxation. Long-term maintenance studies comparing medical therapy with antireflux surgery have demonstrated either similar clinical efficacy or significantly better control of GERD symptoms postsurgery [50, 51]. Therefore, patients with typical or atypical GERD symptoms well controlled on PPIs desiring alternative therapy or patients with volume regurgitation and aspiration symptoms not controlled on PPIs may benefit from the surgery. Currently, the two most popular procedures, performed laparoscopically through the abdomen, are the Nissen 360° fundoplication and the Toupet partial fundoplication. Postoperative mortality is rare (<1%), but a variety of complications occur with relative frequency after antireflux surgery, including: dysphagia, gas-bloat syndrome, and postvagotomy symptoms. Perhaps far more concerning is the high recurrence rate of GERD symptoms after antireflux surgery [51]. Several studies have observed that laparoscopic fundoplication does not increase the mortality or morbidity in older adults compared to younger counterparts [52, 53] Therefore, the healthy older adult should not be refused antireflux surgery solely on the basis of age. Best results are obtained by experienced surgeons in high-volume centers who report recurrence of symptoms in only 10–15% of patients; long-term studies suggest that 60% of patients are back on acid-suppressive medication 5–15 years later.

Prior to antireflux surgery, endoscopy must be performed to identify Barrett's esophagus and exclude stricture, dysplasia, or carcinoma. Motility studies in selected patients can identify ineffective esophageal peristalsis or diagnose a motility disorder which may alter management. Although not routinely indicated, barium esophagogram can help define a nonreducible hiatal hernia and a shortened esophagus which may entail additional surgical maneuvers. In the subset of patients with erosive esophagitis not responding to PPI therapy or those with nonerosive GERD, 24-h pH testing is necessary to confirm the diagnosis.

Overall, PPIs seem to be safe therapy in the elderly, while antireflux surgery may be safe and effective in a subset of older adults with GERD [54].

Complications of GERD

Chronic untreated GERD can lead to ulceration, bleeding, peptic strictures, Barrett's esophagus, and adenocarcinoma. All complications are more common in the geriatric population [4]. Similar to the young, the most common complication of GERD in older adult is esophagitis, ranging in severity from mild inflammation to severe ulceration. Chronic reflux leads to ulceration in up to 50% of patients' aged 60 or above, compared to only 20% in those younger than 40 years. Esophageal strictures occur as a result of untreated ulcerative esophagitis which contributes to 60–70% of benign strictures in the distal esophagus [55]. Simple strictures are best treated with dilation via a balloon or bougie and adjunctive use of acid-suppressing medications (see related Chap. 29). In a third of these patients, repeated dilation is necessary to relieve dysphagia. Patients with refractory strictures may benefit from placement of self-expanding plastic stents and rarely surgery [56].

Barrett's Esophagus

An important and increasingly common complication of GERD is Barrett's esophagus (BE). Here, premalignant, specialized columnar epithelium replaces the normal squamous epithelium of the distal esophagus in reaction to chronic exposure of stomach contents. The actual prevalence of BE is difficult to ascertain since it is often asymptomatic, but it is undoubtedly more common in Caucasian men over age 60 [57]. Ten to fifteen percent of patients over 50 who undergo upper endoscopy for GERD have BE as compared to only 0.3–5% of all patients undergoing endoscopy [58]. The AGA recommends screening upper endoscopy for patients with well-established risk factors for Barrett's esophagus; they include age over 50 years, male sex, white race, chronic GERD, hiatal hernia, elevated body mass index, and intra-abdominal distribution of body fat. The risk of malignant progression is approximately 0.5% per year [59]. Patients with BE must be evaluated with endoscopy and multiple biopsies obtained to look for presence of dysplasia. Treatment includes use of acid-suppressive medications, but there are no convincing data that the therapy alters the natural history of the disease. Antireflux surgery can reduce both acid and nonacid reflux, but again there is no definitive data that it decreases the progression to dysplasia or cancer. Recently, several ablative endoscopic therapies have emerged, with radiofrequency suggesting most promise.

GERD and Esophageal Adenocarcinoma

EAC has recently emerged as a cancer that is increasing in incidence faster than any other in the US and western world. While the reasons are largely unknown, strong associations have been drawn with increasing presence of GERD and decreasing prevalence of *H. pylori* [59]. As with BE, EAC is more prevalent in White men with a three to fourfold increase in the rate of incidence in men 65 or older since the 1980s [60]. When patients present with dysphagia and weight loss, the cancer is usually incurable with poor 5-year survival. Treatment depends on the location and stage of the cancer and includes surgery combined with radiation and chemotherapy. In a large data base from 154,406 endoscopies, reflux esophagitis and its complications including BE and benign esophageal stricture increased with age; the prevalence in the elderly was similar in both sexes [61, 62].

Key Points

- While the frequency and severity of heartburn does not increase with age, the severity of inflammation does and so do the complications of gastroesophageal reflux disease (GERD) including ulcerations, bleeding, strictures, Barrett's esophagus, and esophageal adenocarcinoma.
- Heartburn as a manifestation warrants exclusion of coronary heart disease in the old, especially in presence of risk factors.
- Use of multiple medications that diminish esophageal clearance or cause mechanical obstruction, altered esophageal motility, altered lower esophageal sphincter (LES) function, and delay in gastric emptying explain the increased severity of GERD in the elderly.
- Symptoms of GERD in the older adult are often absent or atypical; manifestations include those related to aspiration, vomiting, and dysphagia.
- Proton pump inhibitor (PPI) therapy remains the cornerstone of therapy with favorable short-term side effect profile and few drug interactions.
- Long-term PPI therapy has been associated with several adverse effects.

References

1. Pandolfino JE, Kwiatek MA, Kahrilas PJ. The pathophysiologic basis for epidemiologic trends in gastroesophageal reflux disease. Gastroenterol Clin North Am. 2008;37(4):827–43, viii.
2. Becher A, Dent J. Systematic review: ageing and gastro-oesophageal reflux disease symptoms, oesophageal function and reflux oesophagitis. Aliment Pharmacol Ther. 2011;33(4):442–54.
3. Pilotto A, Franceschi M, Leandro G, et al. Clinical features of reflux esophagitis in older people: a study of 840 consecutive patients. J Am Geriatr Soc. 2006;54(10):1537–42.
4. Johnson DA, Fennerty MB. Heartburn severity underestimates erosive esophagitis severity in elderly patients with gastroesophageal reflux disease. Gastroenterology. 2004;126(3):660–4.
5. Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol. 2006;101(8):1900–20; quiz 1943.
6. Lee J, Anggiansah A, Anggiansah R, et al. Effects of age on the gastroesophageal junction, esophageal motility, and reflux disease. Clin Gastroenterol Hepatol. 2007;5(12):1392–8.
7. Andrews JM, Heddle R, Hebbard GS, et al. Age and gender affect likely manometric diagnosis: audit of a tertiary referral hospital clinical esophageal manometry service. J Gastroenterol Hepatol. 2009;24(1):125–8.
8. Bitar K, Greenwood-Van Meerveld B, Saad R, Wiley JW. Aging and gastrointestinal neuromuscular function: insights from within and outside the gut. Neurogastroenterol Motil. 2011;23(6):490–501.
9. Urita Y, Domon K, Yanagisawa T, et al. Salivary gland scintigraphy in gastro-esophageal reflux disease. Inflammopharmacology. 2007;15(4):141–5.
10. Kamiya T, Adachi H, Joh T. [Relationship between gastric motility and the pathophysiology of GERD]. Nihon Rinsho. 2007;65(5):836–9.
11. Koek GH, Sifrim D, Lerut T, et al. Multivariate analysis of the association of acid and duodeno-gastro-oesophageal reflux exposure with the presence of oesophagitis, the severity of oesophagitis and Barrett's oesophagus. Gut. 2008;57(8):1056–64.
12. Patti MG, Goldberg HI, Arcerito M, et al. Hiatal hernia size affects lower esophageal sphincter function, esophageal acid exposure, and the degree of mucosal injury. Am J Surg. 1996;171(1):182–6.

13. Pilotto A, Franceschi M, Vitale D, et al. Drug use by the elderly in general practice: effects on upper gastrointestinal symptoms. Eur J Clin Pharmacol. 2006;62(1):65–73.
14. Dore MP, Maragkoudakis E, Fraley K, et al. Diet, lifestyle and gender in gastro-esophageal reflux disease. Dig Dis Sci. 2008; 53(8):2027–32.
15. Jadcherla SR, Hogan WJ, Shaker R. Physiology and pathophysiology of glottic reflexes and pulmonary aspiration: from neonates to adults. Semin Respir Crit Care Med. 2010;31(5):554–60.
16. Shaker R, Hogan WJ. Normal physiology of the aerodigestive tract and its effect on the upper gut. Am J Med. 2003;115(Suppl 3A):2S–9.
17. Gao L, Weck MN, Rothenbacher D, Brenner H. Body mass index, chronic atrophic gastritis and heartburn: a population-based study among 8936 older adults from Germany. Aliment Pharmacol Ther. 2010;32(2):296–302.
18. Hamada H, Haruma K, Mihara M, et al. High incidence of reflux oesophagitis after eradication therapy for *Helicobacter pylori*: impacts of hiatal hernia and corpus gastritis. Aliment Pharmacol Ther. 2000;14(6):729–35.
19. Wang C, Yuan Y, Hunt RH. *Helicobacter pylori* infection and Barrett's esophagus: a systematic review and meta-analysis. Am J Gastroenterol. 2009;104(2):492–500; quiz 491, 501.
20. Qian B, Ma S, Shang L, et al. Effects of *Helicobacter pylori* eradication on gastroesophageal reflux disease. Helicobacter. 2011;16(4):255–65.
21. Berstad A, Hatlebakk JG. The predictive value of symptoms in gastro-oesophageal reflux disease. Scand J Gastroenterol Suppl. 1995;211:1–4.
22. Raiha IJ, Impivaara O, Seppala M, Sourander LB. Prevalence and characteristics of symptomatic gastroesophageal reflux disease in the elderly. J Am Geriatr Soc. 1992;40(12):1209–11.
23. Morozov SV, Stavraki ES, Isakov VA. [The prevalence of heartburn in the elderly patients in urban outpatient clinics in Russia]. Eksp Klin Gastroenterol. 2010;12:17–23.
24. Hsu CS, Wang PC, Chen JH, et al. Increasing insulin resistance is associated with increased severity and prevalence of gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2011; 34(8):994–1004.
25. Gastal OL, Castell JA, Castell DO. Frequency and site of gastroesophageal reflux in patients with chest symptoms. Studies using proximal and distal pH monitoring. Chest. 1994;106(6):1793–6.
26. Pandak WM, Arezo S, Everett S, et al. Short course of omeprazole: a better first diagnostic approach to noncardiac chest pain than endoscopy, manometry, or 24-hour esophageal pH monitoring. J Clin Gastroenterol. 2002;35(4):307–14.
27. Vaezi MF, Richter JE, Stasney CR, et al. Treatment of chronic posterior laryngitis with esomeprazole. Laryngoscope. 2006;116(2):254–60.
28. Kiljander TO, Junghard O, Beckman O, Lind T. Effect of esomeprazole 40 mg once or twice daily on asthma: a randomized, placebo-controlled study. Am J Respir Crit Care Med. 2010;181(10):1042–8.
29. Mastronarde JG, Anthonisen NR, Castro M, et al. Efficacy of esomeprazole for treatment of poorly controlled asthma. N Engl J Med. 2009;360(15):1487–99.
30. Giannini EG, Zentilin P, Dulbecco P, et al. Management strategy for patients with gastroesophageal reflux disease: a comparison between empirical treatment with esomeprazole and endoscopy-oriented treatment. Am J Gastroenterol. 2008;103(2):267–75.
31. Festi D, Scaioli E, Baldi F, et al. Body weight, lifestyle, dietary habits and gastroesophageal reflux disease. World J Gastroenterol. 2009;15(14):1690–701.
32. Kaltenbach T, Crockett S, Gerson LB. Are lifestyle measures effective in patients with gastroesophageal reflux disease? An evidence-based approach. Arch Intern Med. 2006;166(9):965–71.
33. Behar J, Sheahan DG, Biancani P, et al. Medical and surgical management of reflux esophagitis. A 38-month report of a prospective clinical trial. N Engl J Med. 1975;293(6):263–8.
34. Lipsy RJ, Fennerty B, Fagan TC. Clinical review of histamine2 receptor antagonists. Arch Intern Med. 1990;150(4):745–51.
35. Wang WH, Huang JQ, Zheng GF, et al. Head-to-head comparison of H2-receptor antagonists and proton pump inhibitors in the treatment of erosive esophagitis: a meta-analysis. World J Gastroenterol. 2005;11(26):4067–77.
36. Khan M, Santana J, Donnellan C, et al. Medical treatments in the short term management of reflux oesophagitis. Cochrane Database Syst Rev. 2007;(2):CD003244.
37. Metz DC, Pratha V, Martin P, et al. Oral and intravenous dosage forms of pantoprazole are equivalent in their ability to suppress gastric acid secretion in patients with gastroesophageal reflux disease. Am J Gastroenterol. 2000;95(3):626–33.
38. Pilotto A, Leandro G, Franceschi M. Short- and long-term therapy for reflux oesophagitis in the elderly: a multi-centre, placebo-controlled study with pantoprazole. Aliment Pharmacol Ther. 2003; 17(11):1399–406.
39. Niklasson A, Lindstrom L, Simren M, et al. Dyspeptic symptom development after discontinuation of a proton pump inhibitor: a double-blind placebo-controlled trial. Am J Gastroenterol. 2010;105(7):1531–7.
40. Gilard M, Arnaud B, Cornily JC, et al. Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin: the randomized, double-blind OCLA (Omeprazole CLopidogrel Aspirin) study. J Am Coll Cardiol. 2008;51(3):256–60.
41. Laine L, Hennekens C. Proton pump inhibitor and clopidogrel interaction: fact or fiction? Am J Gastroenterol. 2010;105(1):34–41.
42. Dublin S, Walker RL, Jackson ML, et al. Use of proton pump inhibitors and H2 blockers and risk of pneumonia in older adults: a population-based case-control study. Pharmacoepidemiol Drug Saf. 2010;19(8):792–802.
43. Fohl AL, Regal RE. Proton pump inhibitor-associated pneumonia: not a breath of fresh air after all? World J Gastrointest Pharmacol Ther. 2011;2(3):17–26.
44. Laheij RJ, Sturkenboom MC, Hassing RJ, et al. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. JAMA. 2004;292(16):1955–60.
45. Leonard J, Marshall JK, Moayyedi P. Systematic review of the risk of enteric infection in patients taking acid suppression. Am J Gastroenterol. 2007;102(9):2047–56; quiz 2057.
46. Dial S, Alrasadi K, Manoukian C, et al. Risk of *Clostridium difficile* diarrhea among hospital inpatients prescribed proton pump inhibitors: cohort and case-control studies. CMAJ. 2004;171(1):33–8.
47. Wright MJ, Proctor DD, Insogna KL, Kerstetter JE. Proton pump-inhibiting drugs, calcium homeostasis, and bone health. Nutr Rev. 2008;66(2):103–8.
48. Dalton BR, Lye-Maccannell T, Henderson EA, et al. Proton pump inhibitors increase significantly the risk of *Clostridium difficile* infection in a low-endemicity, non-outbreak hospital setting. Aliment Pharmacol Ther. 2009;29(6):626–34.
49. Kaye JA, Jick H. Proton pump inhibitor use and risk of hip fractures in patients without major risk factors. Pharmacotherapy. 2008;28(8):951–9.
50. Oelschlager BK, Quiroga E, Parra JD, et al. Long-term outcomes after laparoscopic antireflux surgery. Am J Gastroenterol. 2008;103(2):280–7; quiz 288.
51. Galmiche JP, Hatlebakk J, Attwood S, et al. Laparoscopic antireflux surgery vs esomeprazole treatment for chronic GERD: the LOTUS randomized clinical trial. JAMA. 2011;305(19):1969–77.
52. Brunt LM, Quasebarth MA, Dunnegan DL, Soper NJ. Is laparoscopic antireflux surgery for gastroesophageal reflux disease in the elderly safe and effective? Surg Endosc. 1999;13(9):838–42.
53. Wang W, Huang MT, Wei PL, Lee WJ. Laparoscopic antireflux surgery for the elderly: a surgical and quality-of-life study. Surg Today. 2008;38(4):305–10.

54. Poh CH, Navarro-Rodriguez T, Fass R. Review: treatment of gastroesophageal reflux disease in the elderly. Am J Med. 2010; 123(6):496–501.
55. Spechler SJ. AGA technical review on treatment of patients with dysphagia caused by benign disorders of the distal esophagus. Gastroenterology. 1999;117(1):233–54.
56. Repici A, Hassan C, Sharma P, et al. Systematic review: the role of self-expanding plastic stents for benign oesophageal strictures. Aliment Pharmacol Ther. 2010;31(12):1268–75.
57. Reynolds JC, Rahimi P, Hirschl D. Barrett's esophagus: clinical characteristics. Gastroenterol Clin North Am. 2002;31(2):441–60.
58. Hayeck TJ, Kong CY, Spechler SJ, et al. The prevalence of Barrett's esophagus in the US: estimates from a simulation model confirmed by SEER data. Dis Esophagus. 2010;23(6):451–7.
59. Spechler SJ, Sharma P, Souza RF, Inadomi JM, Shaheen NJ. American Gastroenterological Association technical review on the management of Barrett's esophagus. Gastroenterology. 2011;140(3): e18–52; quiz e13.
60. Devesa SS, Blot WJ, Fraumeni Jr JF. Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. Cancer. 1998;83(10):2049–53.
61. Menon S, Jayasena H, Nightingale P, Trudgill NJ. Influence of age and sex on endoscopic findings of gastrooesophageal reflux disease: an endoscopy database study. Eur J Gastroenterol Hepatol. 2011;23(5):389–95.
62. Bytzer P, Christensen PB, Damkier P, et al. Adenocarcinoma of the esophagus and Barrett's esophagus: a population-based study. Am J Gastroenterol. 1999;94(1):86–91.

Part VIII

Signs and Symptoms

Abdominal Pain

32

C.S. Pitchumoni and T.S. Dharmarajan

Introduction

Older adults frequently suffer both acute and chronic abdominal pain. Nearly half the over-65-year age group presenting to the emergency department with abdominal pain require hospitalization and as many as a third require surgical intervention [1–3]. Geriatric patients differ in that the majority of older individuals manifest comorbidity; a smaller number are incapable of expressing themselves adequately or describe their complaints to the physician to facilitate assessment, evaluation, and execute diagnostic procedures [4].

Pain is also a "sixth sense" apart from the five senses of sight, sound, smell, taste, and touch whereby the faculty of pain warns the patient of impending danger or presence of injury [5]. The patient deprived of the ability to perceive pain may be in grave peril. Sadly this may be the situation in some elderly patients. On the other hand, appropriate assessment of pain by the provider is now considered routine in healthcare and important enough to be termed a fifth vital sign (along with temperature, pulse, blood pressure, and respiratory rate) and has been signed into law in the state of California, effective the year 2000 [6].

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Abdominal pain similar to other painful disorders, negatively impairs the older patients' quality of life. Impaired cognitive function, sleep disturbance, impaired functional abilities, and diminished socialization are some factors affecting quality of life. Further, abdominal pain in the older adult may be ominous; the overall mortality for elderly patients attending the emergency department with the chief complaint of abdominal pain exceeds 10% [1, 4].

Addressing the special concerns of pain in general in older adults, the American Geriatrics Society published clinical practice guidelines specific for the assessment and management of pain, and the American Medical Doctors Association published clinical practice guidelines for the management of pain in long-term care settings [7–9].

Assessment of Pain

There may be a misconception among some patients and providers that aches and pains are a part of aging. It is also erroneous to believe that older individuals perceive less pain than the young. It is important that providers understand the barriers in the assessment of pain in geriatric patients. The older patient and caregiver may dismiss pain for several reasons: belief that is a natural consequence of aging; the desire not to be a burden to the caregiver, family, or nursing staff; fear of dreadful disease and impending death; fear of hospitalizations, diagnostic studies; and finally costs of health care [10–16]. The current best indicator of the pain experience is the patient's own report, including the intensity of pain and its impact on daily function [7].

Communication barriers add to the burden in evaluating pain. Many elderly suffer from diminished cognitive, sensory-perceptual and motor abilities posing difficulty in communication. Patients with dementia, delirium, stroke, and aphasic syndromes encounter communication barriers; language and cultural background may compound difficulties in pain assessment.

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Abdominal pain in the geriatric age group is frequent in occurrence and potentially serious, besides being an underrecognized problem. Comprehensive assessment of abdominal pain in the older adult is a clinical art that cannot be replaced by endoscopic or imaging procedures and finding an "incidentaloma." Recognition and proper understanding of pain is often a key to diagnosis. A focused history from the patient and/or caregiver is the most important initial step to determine the choice of diagnostic studies that may be cost effective and useful, taking into account the unique problems in obtaining a history in the cognitively impaired. The approach should be to not only look, but also to listen to the patient, as in the case of gastroesophageal reflux disease (GERD), and use validated scales as indicated [17–19].

Several instruments or tools have been tested and used for pain assessment, including the Visual Analog Scale, Faces Pain Scale, Short-Form McGill Pain questionnaire, Pain Assessment in Advanced Dementia Tool; these can help in practice and improve pain assessment and management [17]. On the other hand, assessment of pain in the demented older adult is different. Patients with early Alzheimer's disease may have pain discriminatory capacity and weaker emotional and affective experience of pain, but in advanced cases it may be very difficult to even determine the presence of pain [18]. Here, a systematic approach requires three steps: direct questioning (self-report), direct behavioral observation and interview with caregiver/informant [18]. In the nursing home residents with dementia, the use of a Certified Nursing Assistant Pain Assessment Tool (CPAT) has proved useful and observes five categories of facial expression, behavior, mood, body language, and activity tool to arrive at a score of 0–5 [5]. Pain perception can also vary with the type of dementia and criteria adopted [20]. A multidisciplinary role may be required to deal with demented patients presenting with abdominal pain.

Several of the challenges encountered in the diagnosis of abdominal pain in the older are listed in Table 32.1. An approach to the evaluation and the importance of history are cited in Tables 32.2 and 32.3 [1–4, 10–16, 21].

Table 32.1 Challenges in the diagnosis of abdominal pain in older adults [1–16, 21, 46–55]

Physiological changes
Decrease in pain perception
Delayed presentation to ED
History taking
Decreased hearing
Impaired memory
Dementia
Decreased ability to speak
Fear of diagnosis
Fear of losing independence
Fear of financial loss
Psychiatric disorders
Comprehension difficulties
Language barriers
Effect of concurrent medications
NSAIDs: blunting of pain, risk of peptic ulcer, anemia
Narcotic use: blunting of pain and sensorium
Digoxin, colchicine, metformin, aspirin, NSAIDs cause abdominal pain
Beta blockers: blunt cardiac response and mask tachycardia
Physical examination
Normothermic/hypothermic in the presence of infection
Tachycardia may be blunted
Tachypnea disproportionate to pain
Decreased pain perception/tenderness
Decreased rebound and guarding
Comorbid conditions
Diabetes may blunt pain
May mask the acute problem
Rapid deterioration in the presence of organ dysfunction
Laboratory values
May be normal even in the presence of infection
Imaging studies
Plain X-ray abdomen: general usefulness is limited but needed for evaluation of free air and intestinal obstruction
Ultrasound: useful to diagnose abdominal aortic aneurysm (AAA), gallstones
Findings may be obscured by body habitus, bowel gas
CT: useful, but incidental findings may lead to overdiagnosis

Causes of Abdominal Pain

It is beyond the scope of this chapter to discuss individual conditions causing abdominal pain; causes may be gastrointestinal or nongastrointestinal. Nongastrointestinal causes may be genito-urinary, musculoskeletal, skin, metabolic, thoracic causes, or spinal; they must be part of the differential diagnosis of abdominal pain in the older adult (Table 32.4).

Biliary tract disease accounts for almost 25% of cases in the older adult with abdominal pain followed by nonspecific pain, malignancy, intestinal obstruction, complicated peptic ulcer, incarcerated hernias, diverticulitis, and appendicitis. Chronic disorders may also present with intermittent exacerbations. Internal hernia, adhesion, volvulus, Crohn's disease, porphyria, diabetic neuropathy, irritable bowel syndrome (IBS), chronic mesenteric ischemia, metastatic cancer, chronic pancreatitis, psychiatric causes, and the effects of medications are examples. Organizing the differential diagnosis into categories (inflammatory, obstructive, vascular, and other) provides a framework for history, physical examination, and diagnostic studies [22]. Despite the difficulties in evaluating abdominal pain (in the elderly) for the primary care physician and the subspecialists, the goals of clinical assessment are similar and are detailed in several excellent reviews [13–29].

Table 32.2 Suggested steps in the evaluation of abdominal pain [4, 10–16]

Expect the history to be incomplete
Additional history from family members or caregivers may be helpful
Repeat vital signs often
Auscultation of abdomen before percussion/palpation
Listen to bowel sounds/bruits
Perform all of the following routine tests
CBC
Electrolytes
LFTs
Amylase/lipase
Imaging studies—select the study based on need
Plain film of abdomen (KUB)
Abdominal sonography
CT of abdomen
Chest X-ray
Cardiac evaluation
EKG
Second line tools
Blood gas
Blood and urine culture
Angiography
Nuclear scan
MRI

Table 32.3 Points to elicit in the history of abdominal pain

Location
Character
Radiation
Onset
Duration
Periodicity
Tempo/chronology
Aggravating factors
Relieving factors
Associated features
Past medical/surgical history
Family and social history
Detailed medication history
History of occult or evident alcohol consumption

Table 32.4 Nongastrointestinal causes of abdominal pain as part of differential diagnosis [43, 46–55]

Genito-urinary	Kidney stones
	Pyelonephritis
	Acute urinary retention
Cardiovascular	Aortic dissection
	Aortic aneurysm
	Unstable angina
	Acute myocardial infarction
	Pulmonary embolism
Respiratory	Pneumonia
Gynecological	Ovarian rupture
Musculoskeletal	Inguinal/ventral hernia, strangulated
	Osteomyelitis
	Radiculitis
	Disorders of vertebra
	Muscle injury
Metabolic	DKA
	Uremia
	Hyperparathyroidism
	Porphyria
	Addison's disease
Heavy metal poisoning	Lead poisoning with herbal medicines
Neuro-cutaneous	Herpes zoster
	Injection abscess (in diabetics)

An experience with the *acute abdomen* in subjects of mean age 78 years over 4 years revealed that the most common reasons for emergency surgery in the group were mechanical bowel obstruction (45%), perforation (18%), and strangulated hernia (18%); mesenteric ischemia was the most important cause of fatal outcome; the study concluded that acute abdomen is a frequent cause of death requiring vigilance and early attention [30]. The following summarizes selected painful abdominal disorders in the geriatric patient.

1. Cholecystitis: Cholelithiasis increases with age, with the severity of gallstone disease much higher with age. Unlike in the young, more than half the elderly patients with acute cholecystitis do not have nausea, vomiting, or fever [10]. Even with complications such as gall bladder empyema, gangrene, or frank perforation, a third may be afebrile [31]. Leukocytosis is absent in 30–40% along with normal liver function tests. The accuracy of sonographic Murphy's sign does not decline even with premedication with opioid drugs [32]. There is an increased incidence of acalculous cholecystitis, a fact not appreciated readily on ultrasound [33]. With a high clinical suspicion of cholecystitis, and a negative ultrasound, HIDA scan is to be performed.
2. Peptic ulcer disease: There is an increased incidence of NSAID induced peptic ulcer disease in the elderly, particularly in women who tend to consume more analgesics than men for back pain. NSAID induced peptic ulcers are likely to be painless because of the analgesic property of the medication but often cause low grade bleeding resulting in iron deficiency anemia. Perforated peptic ulcer may be the initial manifestation of the disease. The onset of abdominal pain may not be acute, and abdominal rigidity may be absent [34]. Plain radiograph of the abdomen may not show free intraperitoneal air in nearly 40% of patients unless a lateral film is obtained [35].
3. Pancreatitis: The incidence of pancreatitis increases as age advances, with the most common etiology being gallstone disease. The mortality increases as age advances.

The disease may present initially solely with systemic inflammatory response syndrome. Although an early CT scan in the younger patient with acute pancreatitis may not be necessary, the threshold for performing a CT scan in the older patient should be low [10].

4. Diverticular disease: The incidence increases with age. Diverticulitis manifests as left lower quadrant pain, along with fever and leukocytosis. Diverticulitis may be complicated by fistula to the bladder or uterus. Free perforation, rare in the younger population, occurs more often in the elderly.
5. Appendicitis: The incidence of appendicitis in older adults is much lower than in the young, but the mortality ranges from 4 to 8%. The diagnosis of appendicitis in the elderly is often missed, with half of all cases already perforated at time of diagnosis. Fever, anorexia, right lower quadrant pain, and leukocytosis are evident in less than a third, and one-quarter may have no right lower quadrant tenderness. CT scan of the abdomen is mandatory in the evaluation of a patient with suspected appendicitis, along with early surgical consultation [35–37].
6. Mesenteric ischemia: The symptoms of acute mesenteric ischemia are nonspecific. The classic triad of abdominal pain, gut emptying, and underlying cardiac disease is found in the minority of cases. Leukocytosis is notable along with some degree of metabolic acidosis and elevated lactate. Physical examination is often nonrevealing. Abdominal tenderness, peritoneal signs, and bloody stools are late occurrences. Hyperamylasemia should not be mistaken for acute pancreatitis. CT is the imaging test of choice. However, angiography is the gold standard [38, 39].
7. Splenic infarction: This entity is a rare cause of acute abdominal pain in the old, and especially seen in those with primary antiphospholipid antibodies syndrome; CT scan of the abdomen helps diagnosis [40].
8. Ruptured abdominal aortic aneurysm (AAA): Because of sudden onset of back pain radiating toward the groin associated with microscopic hematuria, AAA is often confused with renal colic. Other conditions which mimic ruptured AAA include diverticulitis, GI bleeding from aortoenteric fistula, and acute coronary syndrome. The diagnosis of AAA should be excluded in any patient who has syncope or hypertension in combination with abdominal or back pain [10]. The U.S. Preventive Services Task Force (USPSTF) recommends a one-time screening for AAA by ultrasonography in men aged 65–75 years who have ever smoked [41]; patients with peripheral arterial disease and peripheral aneurysms with abdominal pain deserve consideration for dissecting aneurysm. Hypotension is absent in nearly 65% of cases. Atypical presentations of ruptured AAA are common [42, 43].
9. Bowel obstruction: Small bowel obstruction (SBO) occurs secondary to adhesions consequent to prior abdominal surgery. SBO is characterized by sudden, sharp, periumbilical pain, bilious vomiting suggestive of high gut obstruction, and feculent emesis low gut obstruction. Hyperactive bowel sounds and audible rushes are suggestive physical examination findings. Large bowel obstruction is often a consequence of left sided colon cancer, diverticulitis, or volvulus.
10. Hernia: Femoral and inguinal hernia tend to be overlooked. In particular, in older obese women, the inguinal regions escape physical examination; hence examination for hernias should in the supine and if possible, the upright position; CT or MRI scan can establish the diagnosis [44].
11. Drug induced pain is associated with a high prevalence of polypharmacy. Commonly incriminated drugs include NSAIDs, aspirin, erythromycin, colchicines, drugs associated with acute pancreatitis, and antibiotics associated with *Clostridium difficile* colitis [45].
12. Unusual causes: The physical examination should include the abdomen, inguinal regions, and the back in evaluation of abdominal pain. Herpes zoster as the cause of pain may be evident by the presence of vesicles or crusting. Pain in herpes can precede the onset of rash, making it a difficult diagnosis, and be concurrent with or appear after the rash subsides, the last one termed postherpetic neuralgia. Older adults may be unaware of the rash as they do not routinely look at the back, emphasizing the importance of a thorough physical examination. Besides herpes, causes of abdominal pain encountered in the geriatric patient include pyelonephritis, renal colic, and hepatic or subphrenic abscess. Hence the need for physicians to entertain a broad differential diagnosis, in the background of inadequate to no history [46–55].

Dealing with Abdominal Pain

As the geriatric patient may be hypotensive, obtunded or even hypothermic, portending a serious illness, speed of diagnosis is vital in managing abdominal pain. In addition to routine pulse oximetry, oxygen, and cardiac monitoring in those with acute abdominal pain, intravenous access is essential. Surgical consultation is best entertained early rather than too late. As already stated, the liberal utility of ultrasound and CT may be a consideration [45]. Further, the patient may have to be placed on "nothing by mouth orders" until a diagnosis is apparent.

Pain management is multifactorial and involves psychological and physical methods, and drugs (including NSAIDs, opioids, antispasmodics, regional, and epidural analgesia), in conjunction with risk-benefit assessment [15]. A detailed

approach to pharmacology of pain is essayed in a guideline from the American Geriatrics Society [7]. Although older adults are generally at higher risk of adverse drug reactions, analgesics and pain-modulating drugs are still safe and effective, when comorbidities are carefully considered [7]. Age-associated differences in effect, sensitivity, pharmacokinetics and dynamics, and adverse effects must be understood by the provider with regard to use of analgesics.

A study on the influence of gender on emergency department management and outcomes in geriatric abdominal pain in those aged 70 years and over demonstrated no difference in diagnoses and management between men and women; however, men had a higher rate of death within 3 months [56]. Further, patients over age 80 years appear 17% less likely than the <65 year group to receive analgesia for abdominal pain in the emergency department, and also less likely to receive opioids [57]. A systematic PubMed and Cochrane analysis of data over 18 years suggests a dearth of data on the effect of pain treatment in those with dementia and agitation [58], indicating the need for more studies.

Key Points

- Abdominal pain in the elderly is a challenging problem in view of its common occurrence and difficulty in diagnosis.
- Nearly 50% of older adults with abdominal pain at the ED require hospitalization; surgical intervention is required in about a third.
- Abdominal pain is not a natural consequence of aging.
- Difficulties in obtaining an adequate history, medication effect, and communication barriers confound the pathology and interfere with early diagnosis of the etiology.
- Physical examination findings may be absent or not evident.
- Comorbid diseases, especially dementia, may blunt or confuse the clinical picture.
- Pain assessment in dementia should depend on observations and examination rather than the patient's complaints.
- Laboratory values may not be abnormal despite a critical illness.
- Patients with appendicitis may not manifest leukocytosis and elevated amylase may not mean pancreatitis.
- More than half the elderly with acute cholecystitis do not have nausea, vomiting, or fever.
- NSAID induced peptic ulcers are common in the elderly and associated with no pain, rather may present with severe anemia.
- Appendicitis, although rare, may present with no fever, anorexia, right lower quadrant pain, or leukocytosis.
- CT scan of the abdomen has to be liberally used in the evaluation of abdominal pain.

References

1. Yeh E, McNamara RM. Abdominal pain. Clin Geriatr Med. 2007;23:255–70.
2. Kizer KW, Vassar MJ. Emergency department diagnosis of abdominal disorders in the elderly. Am J Emerg Med. 1998;16:357–62.
3. Brewer BJ, Goldern GT, Hitch DC, Rudolf LE, Wangensteen SL. Abdominal pain. An analysis of 1,000 consecutive cases in a University Hospital emergency room. Am J Surg. 1976;131:457–78.
4. Herr KA, Garand L. Assessment and measurement of pain in older adults. Clin Geriatr Med. 2001;17:457–78.
5. Cervo FA, Bruckenthal P, Chen JJ, et al. Pain assessment in nursing home residents with dementia: psychometric properties and clinical utility of the CAN Pain Assessment Tool. J Am Med Dir Assoc. 2009;10:505–10.
6. Pain assessment: the fifth vital sign. http://www.rn.ca.gov/pdfs/regulations/npr-b-27.pdf. Accessed 17 July 2011.
7. AGS Panel on pharmacological management of persistent pain in older persons. J Am Geriatr Soc. 2009;57:1331–46.
8. Hanlon JT, Perers S, Sevick MA, et al. Pain and its treatment in older nursing home hospice/palliative care residents. J Am Med Dir Assoc. 2010;11:579–83.
9. AGS Clinical Practice Committee: management of cancer pain in older patients. J Am Geriatr Soc. 1997;45:1273.
10. Martinez JP, Mattu A. Abdominal pain in the elderly. Emerg Med Clin North Am. 2006;74:371–88.
11. Lyon C, Clark DC. Diagnosis of acute abdominal pain in older patients. Am Fam Physician. 2006;74:1537–44.
12. Burg M, Francis L. Acute abdominal pain in the elderly. Emerg Med. 2005;37:8–12.
13. Bjoro K, Herr K. Assessment of pain in the nonverbal or cognitively impaired older adult. Clin Geriatr Med. 2008;24:237–62.
14. McCleane G. Pain perception in the elderly patient. Clin Geriatr Med. 2008;24:203–11.
15. Makhana GK. Understanding and treating abdominal pain and spasms in organic gastrointestinal diseases: inflammatory bowel diseases and biliary diseases. J Clin Gastroenterol. 2011;45 (Proceedings from the Pan-European conference on irritable bowel syndrome, 10 Dec 2010, Vienna, Austria):S89–93.
16. Dempsey DT. Chapter 26: Stomach. In: Brunicardi FC, Andersen DK, Billiar TR, Dunn DL, Hunter JG, Matthews JB, Pollock RE, editors. Schwartz's principles of surgery. 9th ed. http://www.accessmedicine.com/content.aspx?aID=503024.
17. Manias E, Gibson SJ, Finch S. Testing an educational nursing intervention for pain assessment and management of older people. Pain Med. 2011;12(8):1199–215.
18. Andrade DC, Faria JW, Caramelli P, et al. The assessment and management of pain in the demented and non-demented elderly patient. Arq Neuropsiquiatr. 2011;69(2-B):387–94.
19. Bardhan KD, Berghofer P. Look-but also listen! ReQuest: an essay on a new validated scale to assess the outcomes of GERD treatment. Digestion. 2007;75 Suppl 1:87–100.
20. Carlino E, Benedetti F, Rainero I, et al. Pain perception and tolerance in patients with frontotemporal dementia. Pain. 2010;151(3):783–9.
21. Bruckenthal P. Assessment of pain in the elderly adult. Clin Geriatr Med. 2008;24:213–6.
22. Ragsdale L, Southerland L. Acute abdominal pain in the older adult. Emerg Med Clin North Am. 2011;29(2):429–48.
23. Crane SJ, Talley NJ. Chronic gastrointestinal symptoms in the elderly. Clin Geriatr Med. 2007;23:721–34.
24. Barie PS, Eachempati SR. Acute acalculous cholecystitis. Gastroenterol Clin North Am. 2010;39:343–57.

25. Morley JE. Constipation and irritable bowel syndrome in the elderly. Clin Geriatr Med. 2007;23:823–32.
26. Ozden N, Gurses B. Mesenteric ischemia in the elderly. Clin Geriatr Med. 2007;23:871–87.
27. Cangemi JR, Picco MF. Intestinal ischemia in the elderly. Gastroenterol Clin North Am. 2009;38:527–40.
28. Touzios JG, Dozois EJ. Diverticulosis and acute diverticulitis. Gastroenterol Clin North Am. 2009;38:513–25.
29. Cartwright SL, Knudson MP. Evaluation of acute abdominal pain in adults. Am Fam Physician. 2008;77:971–8.
30. Costamagna D, Pipitone Federico NS, Erra S, et al. Acute abdomen in the elderly. A peripheral general hospital experience. G Chir. 2009;30(6–7):315–22.
31. Morrow DJ, Thompson J, Wilson SE. Acute cholecystitis in the elderly. Arch Surg. 1978;113:1149–52.
32. Nelson BP, Senecal EL, Prak T, et al. Opioid analgesia in the elderly: is the diagnosis of gallbladder pathology hindered. Ann Emerg Med. 2004;44(S4):S89.
33. Shuman WP. Low sensitivity of sonography and cholescintigraphy in acalculous cholecystitis. Am J Roentgenol. 1984;143(3):531–4.
34. Fenyo G. Acute abdominal disease in the elderly: experience from two series in Stockholm. Am J Surg. 1982;143:751–4.
35. McNamara RM. Acute abdominal pain. In: Sanders AB, editor. Emergency care of the elder person. St. Louis: Beverly Cracom Publications; 1996. p. 219–43.
36. Gupta H, Dupuy DE. Advances in imaging of the acute abdomen. Surg Clin North Am. 1997;77:1245–63.
37. Storm-Dickerson TL, Horratas MC. What have we learned over the past 20 years about appendicitis in the elderly? Am J Surg. 2003;185:198–201.
38. Meyer T, Klein P, Schweiger H, et al. How can the prognosis of acute mesenteric artery ischemia be improved? Results of a retrospective analysis [German]. Zentralbl Chir. 1998;123:230–4.
39. Glenister KM, Corke CF. Infarcted intestine: a diagnostic void. ANZ J Surg. 2004;74:260–5.
40. Rossato M, Paccagnella M, Burei M, et al. Splenic infarction: a rare cause of acute abdominal pain presenting in an older patient with primary antiphospholipid antibodies syndrome. Intern Emerg Med. 2009;4(6):531–3.
41. U.S. Preventive Services Task Force. Screening for abdominal aortic aneurysm: recommendation statement. Ann Intern Med. 2005;142:198–202.
42. Marston WA, Ahlquist R, Johnson Jr G, et al. Misdiagnosis of ruptured abdominal aortic aneurysms. J Vasc Surg. 1992;16:859–68.
43. Salkin MS. Abdominal aortic aneurysm: avoiding failure to diagnose. ED Legal Lett. 1997;8:67–78.
44. van de Langenberg R, Scheltinga MR, Streukens SA, et al. Elderly women with abdominal pain due to an incarcerated "femoral hernia". Ned Tijdschr Geneeskd. 2008;152(29):1597–601.
45. Dang C, Aguilera P, Dang A, Salem L. Acute abdominal pain. Geriatrics. 2002;57:30–42.
46. Chang C, Wang S. Acute abdominal pain in the elderly. Int J Gerontol. 2007;1:77–82.
47. Sanson TG, O'Keefe KP. Evaluation of abdominal pain in the elderly. Emerg Med Clin North Am. 1996;14:615–27.
48. Bugliosi TF, Meloy TD, Vukov LF. Acute abdominal pain in the elderly. Ann Emerg Med. 1990;19:1383–6.
49. Rothrock SG, Greenfield RH. Acute abdominal pain in the elderly: clue to identify serious illness. Part 2: diagnosis and management of common disorder. Emerg Med Rep. 1992;13:185–92.
50. Telfer S, Fenyo G, Holt PR, de Dombal FT. Acute abdominal pain in patients over 50 years of age. Scand J Gastroenterol Suppl. 1998;144:47–50.
51. de Dombal FT. Acute abdominal pain in the elderly. J Clin Gastroenterol. 1994;19:331–5.
52. Birnbaum BA, Jeffrey Jr RB. CT and sonographic evaluation of acute right lower quadrant abdominal pain. AJR Am J Roentgenol. 1998;170:361–71.
53. Frauenfelder T, Wildermuth S, Marineck B, Boehm T. Nontraumatic emergent abdominal vascular conditions: advantages of multidetector row CT and three-dimensional imaging. Radiographics. 2000;24:481–96.
54. Glasgow RE, Mulvihill SJ. Acute abdominal pain. In: Fledman M, Friedman LS, Brandt LJ, editors. Sleisenger and Fordtran's gastrointestinal and liver disease. 8th ed. Philadelphia: Saunders Elsevier; 2010. p. 87–98.
55. Cotton D, Taichman D, Williams S. In the clinic: herpes zoster. Ann Intern Med. 2011;154:ITC-1–14.
56. Gardner RL, Almeida R, Maselli JH, Auerbach A. Does gender influence emergency department management and outcomes in geriatric abdominal pain? J Emerg Med. 2010;39(3):275–81.
57. Mills AM, Edwards JM, Shofer FS, et al. Analgesia for older adults with abdominal pain or back pain in the emergency department. West J Emerg Med. 2011;12(1):43–50.
58. Husebo BS, Ballard C, Aarsland D. Pain treatment of agitation in patients with dementia: a systematic review. Int J Geriatr Psychiatry. 2011;26(10):1012–8.

Intestinal Gas

33

Debra R. Goldstein and C.S. Pitchumoni

For millennia, physicians and laymen alike have been intrigued by intestinal gas. The topic of gaseousness, familiar to all, has perhaps gained inadequate scientific respect. In the past century, though, many analyses have been made of the sources and composition of intestinal gas, with some excellent publications over 20 years old [1]. The relationship between intestinal gas and symptom production is poorly defined. Rarely have studies been done when symptoms and diseases are active. As new data emerge, our knowledge in this field will undoubtedly grow [2–4].

Problems pertinent to belching, bloating, and flatulence are commonly brought up to the primary physician or gastroenterologist. Proper characterization of these clinical syndromes carries unique pathophysiology and implications for management.

Belching occurs when air from a distended esophageal body causes relaxation of the upper esophageal sphincter and escape of gas into the pharynx. Belching can be either gastric or supragastric, the latter occurring in patients, but not in healthy subjects [5]. Normal belching occurs frequently after meals, when gastric distension results in transient lower esophageal sphincter (LES) relaxation. Chronic excessive belching is almost always supragastric belching or aerophagia.

Bloating refers to the subjective sensation of abdominal swelling. It is associated both with visceral hypersensitivity and impaired transit. Bloating is not always correlated with distension or actual increase in abdominal girth.

Flatulence is the volitional or involuntary release of gas from the anus as well as the perception of excessive expulsion of gas.

The management of intestinal gas in the older population is even more challenging than in the younger population. Communication of complaints may be compromised; signs and symptoms are frequently the result both of polypharmacy and of underlying chronic illnesses; and pharmacologic intervention may be limited by a greater proclivity to untoward effects. Therefore, it is an appropriate topic in a text dedicated to geriatrics, with attention given to factors in the older population. A brief look at the passage of gas through the various segments of the intestinal tract will be followed by a review of the components of intestinal gas.

Passage of Gas Through the Gastrointestinal Tract

The volume of gas in the intestinal tract at any one time is relatively small. Using argon washout technique, Levitt demonstrated the total volume of intestinal gas to be 200 mL [6]. This technique, however, measured gas only from the jejunum to the rectum, omitting more proximal gas, and therefore yielding falsely low values. Most current investigators, however, believe that approximately 100 mL of gas is present in the intestinal tract in the fasting state, distributed equally in stomach, small intestine, ascending colon, transverse colon, descending colon, and pelvic colon. This volume, however, may increase postprandially by 65%, particularly in the pelvic colon [7]. Average daily anal expulsion of gas, on the other hand, is 600–700 mL, of which over 50% is swallowed air [8]. Nitrogen (N_2), oxygen (O_2), carbon dioxide (CO_2), hydrogen (H_2), and methane (CH_4) comprise over 99% of intraluminal gas. Gastric principle gases include N_2, O_2, and CO_2, whereas flatus also includes H_2 and CH_4. In each segment of the intestine, the volume and composition of gas are determined by chemical reactions, bacterial fermentation

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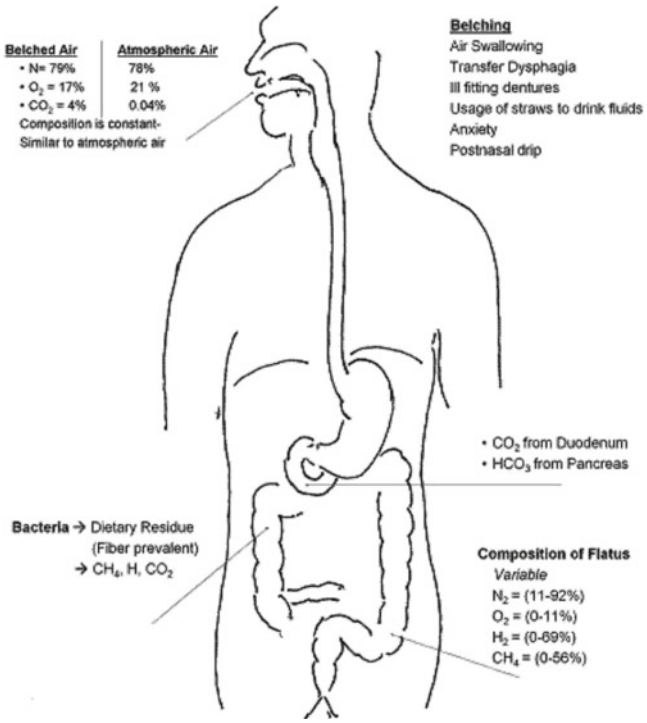

Fig. 33.1 Intestinal gas: composition, formation, and disposition

and consumption, diffusion between luminal and blood compartments, all in the setting of swallowing and belching, gut motility, and anal evacuation. In the healthy state, food substrate and bacterial populations contribute to individual variation; in disease, enzyme deficiencies, malabsorption, mucus secretion, and a host of other factors play additional role.

Virtually all gas in the stomach comes from swallowed air (atmospheric air 78% N_2, 21% O_2, 0.9% argon, 0.04% CO_2), most of which is eructated. The large quantity of nitrogen represented in atmospheric air is less represented further along the gastrointestinal tract. As swallowed air contains very little carbon dioxide, CO_2 diffuses from blood into the stomach bubble. Much of the oxygen of swallowed air is absorbed from the stomach into the blood along its pressure gradient (Fig. 33.1).

In the upper small intestine, bicarbonate and acid combine to produce CO_2. Bicarbonate is present in salivary, biliary, pancreatic, and small bowel secretions, and hydrochloric acid is secreted by the stomach (about 30 mEq/h after meals). Fatty acids are released from the digestion of triglycerides (about 100 mEq acid/30 g fat) [9]. Although CO_2 diffuses rapidly into the blood, in the postprandial state the high pCO_2 causes luminal pN_2 to fall below that of blood, and N_2 diffuses from the blood to the intestine. Both CO_2 and N_2 are propelled into the colon.

Colonic bacterial flora, the product of early environmental exposures, antibiotic usage, and dietary habits, is highly variable with each individual [10]. Acting upon delivered substrate, bacteria in the colon both produce and consume various gases. It is primarily here that the content of flatus is determined. Large numbers of bacteria, fermenting undigested carbohydrates and proteins, produce H_2 and CO_2. The substrate that is delivered to the colon is also highly variable. Lactose malabsorption, as a result of insufficient lactase synthesis, is a common problem. Overconsumption of fructose-containing beverages may overwhelm digestive capabilities. Many fruits and vegetables, particularly legumes, contain undigestible oligosaccharides such as raffinose and stachyose; these become substrate for colonic bacteria (see Chap. 21). Small quantities of starches present in wheat, oats, corn, and potatoes are resistant to digestion, a resistance enhanced by the refrigeration and reheating of food products [11]. Fiber in a meal can decrease starch absorption [12], and beans contain an amylase inhibitor that interferes with starch digestion [13]. The high correlation between hydrogen gas and carbon dioxide concentrations in flatus suggests a similar mechanism for their production.

Components of Intestinal Gas

The nitrogen (N_2) content of the GI tract approximates that of swallowed air (78%), with only small amounts represented by bacterial metabolism. A relatively insoluble gas, N_2, diffuses poorly into the bowel lumen, but will do so if the pNO_2 falls below that of blood. This can occur following a bean meal, for example, when the delivery of undigestible oligosaccharides to intestinal bacteria results in the rapid production of CO_2, H_2, and CH_4 [14, 15].

Carbon dioxide (CO_2) is liberated from the interaction of bicarbonate and acid. Acid is delivered via gastric acid secretion after a meal may result in the production of over 600 mL of CO_2 [16], while fatty acid hydrolysis of 30 g of fat can produce several liters of CO_2 from the large quantities of bicarbonate secreted in saliva, mucus, bile, and pancreatic juice. Carbon dioxide is also produced as a direct metabolic product of bacterial fermentation; most of this CO_2 is absorbed as it passes down the intestinal tract and does not appear in flatus. Were this not the case, the quantity of CO_2 generated would be intolerable. Rapid transit states can overwhelm the system.

The percentage of hydrogen gas (H_2) present in the GI tract is highly variable and dependent in part upon the bacterial population [17]. Entirely a bacterial metabolic product, the presence of hydrogen gas fluctuates with availability of substrate, such as undigestible disaccharides and oligosaccharides, as well as products of malabsorption states. Colonic bacteria containing alpha-D-galactopyanosidase, an enzyme absent in humans, readily digest the oligosaccharides stachyose and raffinose, liberating hydrogen gas [18]. Other colonic bacteria rapidly consume the H_2 liberated by these organisms. Hydrogen which is not consumed is either

excreted per rectum or absorbed in the portal circulation and excreted by the lungs.

Methane gas (CH_4), interestingly, is not present in all individuals. Its production depends upon both highly anaerobic conditions and favored bacterial flora. Two-thirds of adults over 10 years of age are CH_4 "non-producers" [18]. The production of CH_4 is dependent more upon the concentration of methanobacteria in the gut than upon a particular substrate. Recent literature supports a reciprocal relationship between the presence of CH_4 and delayed transit states [19]. In fact, the excretion of methane alone in constipation-predominant irritable bowel syndrome (IBS) patients has been demonstrated in breath testing with a positive predictive value of 100%, with diarrhea-predominant IBS patients found to be mainly hydrogen excreters [20].

Both CH_4 and H_2 are combustible gases that may be explosive when present with oxygen. Interestingly, mannitol, once used to prepare patients for colonoscopy, was reported to cause accumulation of potentially explosive concentrations of hydrogen (>4.1%) and/or methane (>5%), producing a combustible mixture [21].

Oxygen contained in swallowed air is utilized by bacteria along the entire course of the intestinal tract. Diffusing readily into the circulation where it is bound by hemoglobin, little backward diffusion takes place. The resulting pO_2 in flatus is only 1–2 mmHg. With the pO_2 of feces even less than that of flatus, an environment favoring growth of fastidious anaerobic bacteria is thus formed.

Since N_2, CO_2, H_2, CH_4, and O_2 are all odorless gases, there must be other trace gases to account for the odor of flatus. Less than 1% of flatus is composed of ammonia, hydrogen sulfide, methanethiol, dimethylsulfide, indole, skatole, mercaptans, volatile amines, and short chain fatty acids. Notably, though, the human nose is able to detect gases in concentration as low as 1:100,000,000 [22]. As some of these gases are absorbed from the bowel lumen and then excreted by the lungs, they may contribute to the characteristic and individual odor of breath, and also to the phenomenon of the so-called extra-oral halitosis [23].

Clinical Gas Syndromes

Belching and passing flatus are generally normal, not pathologic, events.

Belching that is chronically repetitive, so-called malignant belching, is the result of inappropriate aerophagia or swallowing of air into the hypopharynx, with immediate expulsion [5]. The behavior of chronic repetitive belching is often a manifestation of emotional stress; it may also, however, be precipitated by the discomfort of an underlying organic or functional problem that needs attention. Excessive salivation, often the result of painful mouth conditions, may incite aerophobia and belching. After each belch, a portion of the aspirated air passes into the stomach, increasing the size of the gastric air bubble. The temporary relief of belching encourages repetition, but the expanding gastric bubble causes added discomfort, and the behavior can become a vicious cycle. Repeated belching over time may also widen the diaphragmatic hiatus, and lead to hiatal hernia.

More air is normally swallowed in the supine than in the upright position, and the bed-ridden elderly often swallow air and belch in much the same fashion as the infant. In some cases, excessive belching is caused by consuming large amounts of gas-containing foods, such as carbonated drinks, apples, breads, and whipped foods; in these situations, dietary manipulations will be curative. The ingestion of foods that reduce LES pressure, such as caffeine, fats, and mints, can also exacerbate belching. A myriad of medications, including beta-agonists for asthma, calcium channel blockers, anti-depressants and anti-psychotics, also lower LES pressure. Although there are no scientific studies to support or refute, it is reasonable to believe that eating rapidly, chewing gum, sucking on hard candy, drinking through a straw, and smoking may increase air swallowing and excessive belching. In the older adult, chewing and swallowing problems can result from neurologic deficits, ill-fitting dentures, and drugs that affect normal salivation.

Bloating is the sensation of retained excess gas within the lumen of the intestine and has been associated with both visceral hypersensitivity [24, 25] and dysfunctional motility. The association of bloating with actual increased abdominal girth is variable. Although not included in the Rome III criteria [26], bloating is a common symptom of IBS, shared by up to 92% of patients carrying this diagnosis [27]. Bloating may be more commonly seen in the setting of constipation, but it is common to all subtypes of IBS. Although the IBS patient need not produce more gas to have gas-related symptoms [28], recent studies are addressing the role of small intestinal bacterial overgrowth (SIBO) and bacterial fermentation as etiologic in the bloating symptom of IBS [29–31]. The hypothesis is not validated as neither culture nor breath testing has been endorsed as a gold standard measurement of SIBO.

Many patients who complain of bloating have normal amounts of gas in the GI tract, as demonstrated by argon gas washout studies [32]. The concept of impaired reflex control of gas transit, which initially led to coining the term "splenic flexure syndrome," is perhaps re-illustrated by abdominal CT studies showing increased lateral girth along with diaphragmatic descent, also suggesting a dyssynergia of diaphragm contraction and abdominal wall muscle relaxation. Thus, bloating may result from the perception of excess gas, the production of excess gas, impaired transit of intestinal gas, or any of these factors in combination.

Functional gastrointestinal disorders of the bowel are common in older adults and can be diagnosed after excluding organic disorders such as malignancy or mesenteric ischemia [33].

SIBO can result from a number of pathophysiologic conditions and play an important role in the prevalence of bloating. SIBO can cause not only bloating but also abdominal pain, diarrhea, and macrocytic anemia. The disorder is detailed in chapter 46. While the definitive test for SIBO is culture of small bowel aspirate, it is invasive, time consuming, difficult, and insensitive [34]. Lactulose breath testing is inexpensive, and easier but may be inaccurate [35, 36].

Maldigestion and malabsorption of both simple and complex carbohydrates and dietary fiber are a common cause of excess gas production. Flatulence is usually the first reported symptom, with bloating ensuing later. Lactose intolerance is the most common cause of simple carbohydrate maldigestion. Insufficient amount of enterocyte brush border lactase to hydrolyze lactose into glucose and galactose occurs in 21% of Caucasians, 75% of African Americans, 51% of Hispanics, 79% of the Native Americans, and 60–80% of Asians. Other simple carbohydrates can also lead to gas and bloating. Fructose is variably absorbed in the gastrointestinal tract. A monosaccharide, it is found in three basic forms in the diet: as free fructose, in fruits and honey; as a component of sucrose; and in fructans, a polymer of fructose, found in oligosaccharides of some vegetable and wheat. Fructose is present more in some fruits (apples, pears, grapes, mango, and watermelon) than others (berries, citrus fruits, bananas, and pineapples) [37]. As a component of sucrose and honey, its importance in malabsorption has become more common with the advent of high fructose corn syrup (HFCS), an additive to most drinks and many commercial desserts. Fructose malabsorption is a less well-understood disorder, as the absorptive capacity of fructose in "normal" individuals is not known. Like other carbohydrates, fructose fermentation by colonic bacteria can result in H_2, CO_2, methane, and short chain fatty acids with resulting flatulence, bloating, and abdominal pain [38–40]. Patients with IBS appear to have more symptoms, but not more malabsorption by breath testing, than normal controls [41]. Most importantly, withdrawal of fructose from the diet results in high rates of symptom resolution. Because of numerous false positive and negative results, hydrogen breath testing has had limited usefulness. Hence diagnosis is often based upon history alone.

Sorbitol, another sugar found in fruit and a common sweetener used in "sugar-free" candy and other diet foods, is malabsorbed by 43% of Caucasians and 55% of non-Caucasians and causes a similar clinical syndrome [42].

The average amounts of malabsorbed complex carbohydrate per 100 g meal are 20 g for beans; 7–10 g for wheat, oats, potatoes, and corn; and 0.9% for rice [43]. The undigestible oligosaccharides stachyose and raffinose are abundant in beans and other legumes. Whole grains generate five times more hydrogen gas than refined flours. In the older population, radiation, chemotherapy, and transient viral infections can precipitate disaccharidase deficiency.

Flatulence is the sum of gases which is produced throughout the intestinal tract. Although one focuses initially on the abundance of bacteria producing CO_2, H_2, and methane in the large bowel and by diet rich in fermentable substrate, flatus also includes air that is swallowed; CO_2 formed in the upper intestine as a product of digestion; and gases which diffuse along their concentration gradient from the blood stream into the bowel lumen. This amount may be further increased by conditions of excessive mucous secretion interfering with CO_2 and H_2 diffusion; bacterial overgrowth conditions; rapid small intestinal transit, as well as conditions of maldigestion and malabsorption, all leading to increased substrate availability for bacterial fermentation in the colon.

Although insufficient data has been gathered regarding the "normal" volume and composition of flatus, an elegant study noted that the volume of gas expelled by volunteers may range from 200 to 2,400 mL/24 h [8]. Interestingly, there was no consistent relationship between flatus volume and dietary fiber volume, likely reflecting bacterial adaptation to dietary intake.

With air passing through the intestine much more rapidly than liquids or solids, once introduced into the stomach, air can be passed as flatus in as little as 20–35 min, with postprandial flatus noticeable approximately 1 h after eating. The size of a single expulsion of gas varied from 25 to 100 mL, with hydrogen and CO_2 the predominant gases expelled, and a third of participants expelling methane [8, 44]. One third of expelled gas was unidentified, representing most likely the nitrogen of both swallowed air and diffusion throughout the intestinal tract. The average volume of flatus passage per hour is 100 mL, volume per 24 h 400–2,400 mL, and fewer than 25 times per day considered normal. Large volumes of flatus are expelled after a meal, illustrating both the greater interaction between substrate and bacteria after eating, and the impact of the well-known gastro-colic reflex. This explains why flatus production is decreased during sleep.

Although there is no good treatment for flatulence other than dietary manipulation, various remedies are suggested [45, 46]. Most interventions aimed at altering the normal colonic bacterial milieu with luminal antibiotics have not proved very successful in altering flatus production. A recent randomized double-blind study, however, has reported the value of rifaximin therapy for abdominal bloating and flatulence [47]. On the other hand, flatus volume, as well as degree of bloating, will improve by reducing the poorly digested disaccharides in the diet—lactose, fructose, and sorbitol. Similar benefits can be seen with reductions in dietary soluble fiber: legumes (beans, peas, soybeans), onions, celery, carrots, cruciferous vegetables (kale, collard greens, cabbage, brussels sprouts, cauliflower, bok choy, radish, broccoli, arugula), raisins, apples, pears, grapes, and prune juice; and complex starches such as wheat and potato [45, 48]. Dietary modification for symptom amelioration,

however, must be balanced by the broad health benefits of short-chain fatty acids, the major metabolic product of bacterial fermentation in the colon. These benefits include key roles in glucose and cholesterol regulation, colonocyte nutrition and blood flow, and gut immune function [49].

In addition to being the fermentable substrates which yield H_2 and CO_2, most of these gas-forming foods contain sulfur moieties. In the presence of sulfur-reducing bacteria, these sulfate-containing foods result in excessively odoriferous flatus. Moreover, the sulfide ion itself inhibits carbonic anhydrase enzymes, active transporters of CO_2 across luminal membranes, and its presence, therefore, contributes to increased flatus volume. Men produce more aromatic flatus than women, and the utility of activated charcoal-lined undergarments remains a matter of debate.

Finally, many types of colitidies, and parasitic diseases in particular, are associated with increased flatulence [50]. Clearly, these entities need to be considered and excluded.

Challenges Unique to the Elderly

In spite of our knowledge of definitions, per se, of belching, bloating, and flatulence, patients group their complaints by saying "I am suffering from excessive gas or indigestion." Good history taking, therefore, is essential in diagnosis and management. Do the elderly inherently have more belching, bloating, and passage of flatus than the younger population? Certain conditions associated with aging do result in increased intestinal gas. The condition of "lactase nonpersistence" is a well-known example of an age-related phenomenon, and in fact may affect certain populations well before old age. In the majority of settings, however, it is the non-gastrointestinal medical disorders, seen in the aged populations, which secondarily cause belching, bloating, and flatus.

Why might the elderly have more issues with belching? An older individual with ill-fitting dentures might experience mouth pain, excessive salivation, and air swallowing. Geriatric patients are generally required to swallow more medications, and in doing so, significant quantities of air are swallowed as well. Further, for reasons of illness or diminished stamina, they may spend proportionately more time in the supine rather than the upright position, with two to three times more air swallowed in the supine position. More likely to have encountered serious illness, an elderly person postlaryngectomy, for example, may utilize a devise that generates phonation by swallowing of air.

There are several reasons for a higher prevalence of bloating in the elderly. Constipation is far more common in the older population. Endocrine and neurologic diseases, medications, and poor nutrition are all contributory. Advised by physicians and media to take a daily soluble fiber product, this fermentable substrate is delivered to the large bowel, where H_2 and CO_2 are produced. If the patient is impacted, only bloating and discomfort result.

Bloating can be the result of both overproduction and defective transport of intestinal gas. Diabetes mellitus, more common in the old, is a disorder where both mechanisms are operational. Decreased mid-gut motility may cause stasis and bacterial overgrowth, with fermentation of substrate and gas production in the small intestine. At the same time, increased motility may result in the delivery of partially digested, malabsorbed substrate to bacteria in the colon. A host of factors, cumulative with age, can cause relative obstructive processes in the bowel, leading to bacterial overgrowth. Adhesions from surgery or radiation, strictures following diverticulitis, and malignancy are other examples. To manage constipation, many older adults will increase their ingestion of high fiber foods, and in so doing, become quite flatulent.

Treatment of Intestinal Gas

Non-pharmacologic therapy is usually the appropriate first step in intervention.

Emotional factors and other underlying diseases should be identified and addressed. Habits and behavior patterns should be examined for possible contribution to symptoms (gum chewing, rapid eating "on the run," consumption of large quantities of carbonated beverages or diet candies) with reevaluation after a period of abstinence. Diet must be thoroughly evaluated. To this end, it is helpful to have patients keep a daily record of what they are eating and when they are symptomatic. A trial of a targeted elimination diet can very quickly provide the diagnosis. Often, it is necessary to reduce lactose, fructose, complex carbohydrates, or fruits and vegetables in the diet. Malabsorption of complex carbohydrates is highly variable based on the food item [43]. Tables 33.1 and 33.2 provide a list of lactose containing foods and non-lactose sources of calcium. Small bowel gas propulsion may be impaired by lipids in IBS patients [51], requiring lipids to be adjusted accordingly. Food preparation itself can affect digestion: soaking legumes increases oligosaccharide digestion by significantly decreasing concentrations of raffinose and stachyose [52]. Refrigeration and reheating of starches decreases digestion; fiber and legumes in a meal can interfere with starch digestion. Although the concepts are basic, the subtleties of diet manipulation require an individualized approach. Tables 33.3 and 33.4 provide a list of gas-producing foods and helpful hints in controlling gas production. Success is reached by trial, and with patience.

Pharmacological therapy intervention often begins by examining the side effect profile of medications taken for other conditions, eliminating unnecessary drugs, and decreasing doses where possible. Attention must be paid to pitfalls,

Table 33.1 List of lactose-free foods

Dairy
Lactose-free milk
Nondairy creamers
Soy milk and rice milk
Yogurt containing live bacterial cultures may be well tolerated, as the cultures convert lactose into lactic acid[a]
Avoid yogurt without live cultures, milk, cheese, cream, butter, hot chocolate mixes, evaporated and condensed milks
Breads/starches
French and Italian breads
Saltines and whole grain crackers
Pasta and noodles
Rice, potatoes, and barley
Read labels: Avoid instant potato and rice mixes, prepared bread products made with milk, pancakes and waffles made with milk
Fats
Oils and shortening
Margarine
Many salad dressings
Read labels: Some margarines and salad dressings contain lactose. Avoid butter, cream cheese, and party dips
Fruits and vegetables
All fresh fruits and vegetables
Fruit and vegetable juices
Avoid creamed vegetables, batter-coated vegetables, fruit smoothies made with milk
Proteins
All meat, fish, poultry, and eggs
Legumes, nuts, and seeds
Peanut butter
Soy and tofu products
Read labels: Processed meats, prepared casseroles may contain milk
Soups and sauces
Broth, bouillon, and consommé
Avoid chowders, cream soups, and gravies made with milk
Desserts
Angel food cake, sorbets, and jams/jellies
Any baked good prepared without milk, butter, or cheese
Avoid pudding, custard, ice cream, fudge, and chocolates

[a]Lactose maldigestion occurs on a continuum. Many medicines may contain small amounts of lactose that is clinically unimportant
Data adapted from http://www.ehow.com

Table 33.2 Nondairy food sources of calcium

Nuts, including almonds and Brazil nuts
Broccoli, spinach, kale, rhubarb
Pinto beans
Tofu and other soy products
Canned salmon and sardines
Oranges

Table 33.3 Gas-producing foods

Foods which produce a normal amount of gas:
Meat, fish, poultry, and eggs
All nuts
Vegetables: lettuce, peppers, tomatoes, zucchini, asparagus, avocado, olives, okra
Fruits: cantaloupe, pineapple, berries, grapes, stone fruits
Carbohydrates: white rice, chips, popcorn, graham crackers
Foods which produce a moderate amount of gas:
Vegetables: potatoes and eggplant
Fruits: citrus fruits, apples, and pears
Carbohydrates: pastries and bread
Major gas producers:
Root vegetables: onions, carrots, radishes, leeks, parsnips, celery, cucumbers, collard greens, bok choy, arugula
Legumes: beans, peas, lentils, soybeans
Fruit: bananas, dried fruit (raisins, prunes, apricots)
Carbohydrates: brown rice, pretzels, bagels, wheat germ, bran

Everyone tolerates foods differently: this list should serve as a guideline only
Foods high in fiber are usually major gas producers: they are important for healthy bowel function and should not be eliminated entirely

Table 33.4 Helpful tips for controlling gas

Avoid spicy foods and caffeine, both of which stimulate rapid transit
Avoid beer and other carbonated beverages
Soak dried beans overnight and rinse prior to cooking
Eat slowly and chew food thoroughly
Avoid talking and drinking while eating to prevent air swallowing
Eat smaller, more frequent meals; avoid overeating
Avoid drinking through straws, chewing gum, sucking hard candy and smoking
Maintain well-fitting dentures
Avoid both constipation and excessive use of laxatives
Try to remain calm: anxiety causes air swallowing
Use Beano and lactase products when indicated

Data adapted from University of Michigan Health System MB

such as gluten-containing drugs in the celiac patient; bicarbonate-based, CO_2-generating antacids in the bloated patient.

Probiotics can be used in a pulsed fashion for achlorhydria, scleroderma, and blind loop syndromes, where SIBO may be ever present. Their use to alter microflora and achieve control of pain and bloating in the IBS patient is being studied [53]. Antibiotics are beneficial in bacterial overgrowth and have addressed the prevalence of SIBO in IBS patients through symptom improvement with "antibiotic decontamination" [54, 55]. The antibiotic role in modification of small bowel and colonic microflora in IBS is under investigation [56].

Recent attention has turned to rifaximin, a nonabsorbable bactericidal antibiotic providing targeted results without entering the systemic circulation.

Prokinetic agents such as metaclopramide and domperidone, both dopamine receptor antagonists, provide theoretical benefit in gastroparesis with generalized symptoms of nausea and bloating; however, their use is limited by irreversible extrapyramidal sequelae. Since the disappearance of cisapride from the prokinetic arena, a safe alternative is awaited. Neostigmine, a cholinesterase inhibitor used for myasthenia gravis, has short-term utility in the treatment of ileus. Its poor oral absorption and short duration of action, along with undesirable side effects in those with asthma, peptic ulcer disease, and bradycardia limit its utility. Prokinetic studies in functional bloating have demonstrated symptom improvement in the absence of decline in gas volume, suggesting that motor stimulation alters symptom perception [57, 58].

Anticholinergic, or ant-spasmodic, agents such as dicyclomine and glycopyrrolate are used to decrease bowel motility. In the elderly, however, their efficacy is limited by a myriad of side effects such as drowsiness, blurred vision, confusion, orthostatic hypotension, urinary retention, and constipation. The drug class is contraindicated in narrow angle glaucoma.

Several categories of antidepressants—specifically TCAs, SSRIs, and SNRIs—exert an anti-nociceptive effect on the efferent nerves of the intestine while generally decreasing bowel motility as well. As agents that address gut hypersensitivity, they have been a mainstay of treating IBS for many years.

Gas and bloating may be decreased by using pancreatic enzymes for both primary and secondary pancreatic insufficiency states such as post-gastrectomy, short bowel syndrome, gastric bypass, and rapid transit states. Their demonstrated efficacy in controlling symptoms in healthy subjects after a high fat meal is in some fashion analogous to rapid transit states [59]. Beta-galactosidases (lactase) are therapeutic in the setting of lactose intolerance, and alpha-glycosidase (Beano), harvested from *Aspergillus niger*, decreases the flatulence resulting from ingesting legumes, but not cruciferous vegetables and other poorly digestible fiber [60].

Agents such as simethicone and charcoal have a minor role in decreasing the volume of gas present within the lumen of the intestine.

Key Points

- Belching, bloating, and flatulence are ubiquitous, with the pathogenesis involving a complex interplay of diet, bacterial gut flora, and basic metabolic pathways.
- Belching occurs when air from a distended esophageal body causes relaxation of the upper esophageal sphincter.
- Belching can be supragastric or gastric.
- Belched air is nearly atmospheric in composition.
- Bloating is the subjective sensation of abdominal distension.
- Bloating may be the result of small intestinal bacterial overgrowth (SIBO).
- Flatulence is the sum of gases produced throughout the intestinal tract. There is no good treatment for flatulence except dietary manipulation.
- Therapeutic interventions should be focused first on dietary modifications. Pharmacologic modalities are imperfect, and untoward side effects are common.
- Rifaximin therapy, activated charcoal, avoidance of lactose and fructose-rich foods are strategies to be tried.
- When treating quality of life issues such as flatulence or bloating, caution and patience must be the cornerstone of care.

References

1. Berk JE, Haubrich WS, editors. Gastrointestinal symptoms clinical interpretation. Philadelphia: B.C. Decker; 1991. p. 209–29.
2. Sachdeva S, Rawat AK, Reddy RS, et al. Small intestinal bacterial overgrowth (SIBO) in irritable bowel syndrome: frequency and predictors. J Gastroenterol Hepatol. 2011;26 Suppl 3:135–8.
3. Shah ED, Basseri RJ, Chong K, et al. Abnormal breath testing in IBS: a meta-analysis. Dig Dis Sci. 2010;55:2441–9.
4. Ford AC, Spiegel BM, Talley NJ, et al. Small intestinal bacterial overgrowth in irritable bowel syndrome: systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2009;7:1279–86.
5. Bredenoord AJ, Weusten BLA, Sifrim D, et al. Aerophagia, gastric, and supragastric belching: a study using intraluminal electrical impedence monitoring. Gut. 2004;53:1561–5.
6. Levitt MD. Volume and composition of human intestinal gas determined by means of an intestinal washout technique. N Engl J Med. 1971;284:1394–8.
7. Azpiroz F, Levitt MD. Intestinal gas. In: Feldman M, Friedman L, Brandt L, editors. Schlesinger and Fortran's gastrointestinal and liver disease. 9th ed. Philadelphia: Saunders Elsevier; 2010. p. 233–40.
8. Tomlin J, Lowis C, Read NW. Investigation of normal flatus production in healthy volunteers. Gut. 1991;32:665–9.
9. Rune SJ. Acid-base parameters of duodenal contents in man. Gastroenterology. 1972;62:533–9.
10. Stephen AM, Cummings JH. Mechanism of action of dietary fibre in the human colon. Nature. 1980;284:283–4.
11. Scheppach W, Bach M, Bartam P, et al. Colonic fermentation of potato starch after a freeze-thaw cycle. Dig Dis Sci. 1991;36:1601–5.
12. Hamburg O, Rumessen JJ, Gudmand-Hoyer E. Inhibition of starch absorption by dietary fibre. A comparative study of wheat bran, sugar-beet fibre, and pea fibre. Scand J Gastroenterol. 1989;24:103–9.
13. Perman JA, Modler S. Glycoproteins as substrates for production of hydrogen and methane by colonic bacterial flora. Gastroenterology. 1982;82:911–6.
14. Steggerda FR. Gastrointestinal gas following food consumption. Ann N Y Acad Sci. 1968;150:57–66.
15. Levitt MD, Bond JH. Volume, composition and source of intestinal gas. Gastroenterology. 1970;59:921–9.

16. Fortran JS, Walsh JH. Gastric acid secretion rate and buffer content of the stomach after eating: results in normal subjects and in patients with duodenal ulcer. J Clin Invest. 1973;52:645–57.
17. Levitt MD, Ingelfinger FJ. Hydrogen and methane production in man. Ann N Y Acad Sci. 1968;150:75–81.
18. Calloway DH, Murphy EL. The use of expired air to measure intestinal gas formation. Ann N Y Acad Sci. 1968;150:82–95.
19. Kunkel D, Basseri RJ, Makhani MD, et al. Methane on breath testing is associated with constipation: a systematic review and meta-analysis. Dig Dis Sci. 2011;56:1612–8.
20. Pimental M, Mayer A, Park S, et al. Methane production during lactulose breath test is associated with gastrointestinal disease presentation. Dig Dis Sci. 2003;48:86–92.
21. Avgerinos A, Kalantzis N, Rekoumis G, et al. Bowel preparation and the risk of explosion during colonoscopic polypectomy. Gut. 1984;25:361–4.
22. Hibbard JS. Gaseous distension associated with mechanical obstruction of the intestine. Arch Surg. 1936;33:146–67.
23. Tangerman A, Winkel EG. Extra-oral halitosis: an overview. J Breath Res. 2010;4:017003.
24. Ritchie J. Pain from distension of the pelvic colon by inflating a balloon in the irritable colon syndrome. Gut. 1973;14:125–32.
25. Mertz H, Naliboff B, Munakata J, et al. Altered rectal perception is a biologic marker of patients with irritable bowel syndrome. Gastroenterology. 1995;109:40–52.
26. Drossman DA. The functional gastrointestinal disorders and the Rome III process. Gastroenterology. 2006;130:1377–90.
27. Lin H. Small intestinal bacterial overgrowth. A framework for understanding irritable bowel syndrome. JAMA. 2004;292: 852–8.
28. Simren M. Bloating and abdominal distension: not so poorly understood anymore! Gastroenterology. 2009;136:1487–505.
29. Pimental M, Park S, Mirocha J, et al. The effect of a non-absorbed antibiotic (rifaximin) on the symptoms of the irritable bowel syndrome. A randomized trial. Ann Intern Med. 2006;145:557–63.
30. Koide A, Yamaguchi T, Odaka T, et al. Quantitative analysis of bowel gas using plain abdominal radiograph in patients with irritable bowel syndrome. Am J Gastroenterol. 2000;95:1735–41.
31. Yamini D, Pimentel M. Irritable bowel syndrome and small intestinal bacterial overgrowth. J Clin Gastroenterol. 2010;44:672–5.
32. Lasser RB, Bond JH, Levitt MD. The role of intestinal gas in functional abdominal pain. N Engl J Med. 1975;293:524–6.
33. Bharucha AE, Camilleri M. Functional abdominal pain in the elderly. Gastroenterol Clin North Am. 2001;30:517–29.
34. Lieb JG, Draganov PV. The lacunose breathe test (LBT): modified but still a lot of hot air? J Clin Gastroenterol. 2008;42:1067–9.
35. King CE, Toskes PP. Comparison of the 1-gram (14C) xylose, 10-gram lacunose-H_2, and 80-gram glucose-H_2 breath tests in patients with small intestinal bacterial overgrowth. Gastroenterology. 1986;91:1447–51.
36. Kerckhoffs AP, Visser MR, Samsom M, et al. Critical evaluation of diagnosing bacterial overgrowth in the proximal small intestine. J Clin Gastroenterol. 2008;42:1095–102.
37. Shepherd SJ, Gibson PR. Fructose malabsorption and symptoms of irritable bowel syndrome: guidelines for effective dietary management. J Am Diet Assoc. 2006;106:1631–9.
38. Kyaw MH, Mayberry JH. Fructose malabsorption. True condition or a variance from normality. J Clin Gastroenterol. 2011;45: 16–21.
39. Stone-Dorshow T, Levitt MD. Gaseous response to ingestion of a poorly absorbed fructose oligosaccharide sweetener. Am J Clin Nutr. 1987;46:61–5.
40. Rumessen JJ, Gudmand-Hoyer E. Malabsorption of fructose-sorbitol mixtures. Interaction causing abdominal distress. Scand J Gastroenterol. 1987;22:431–6.
41. Skoog SM, Bharucha AE, Zinsmeister AR. Comparison of breath testing with fructose and high fructose corn syrups in health and IBS. Neurogastroenterol Motil. 2008;20:505–11.
42. Jain NK, Rosenberg DB, Ulahannan MJ. Sorbitol intolerance in adults. Gastroenterology. 1985;80:678–81.
43. Levitt MD, Hirsh P, Felzer CA, et al. H_2 excretion after ingestion of complex carbohydrates. Gastroenterology. 1987;92:383.
44. Pitt P, de Bruija KN, Beeching MF, et al. Studies on breath methane: the effect of ethnic origins and lactulose. Gut. 1980;21: 951–9.
45. Price KR, Lewis J, Wyatt GM, et al. Flatulence-causes, relation to diet and remedies. Nahrung. 1988;32:609–26.
46. Rao SS. Belching, bloating, and flatulence. How to help patients who have troublesome abdominal gas. Postgrad Med. 1997; 101(263–9):275–8.
47. Sharara AI, Aoun E, Abdul-Baki H, et al. A randomized double-blind placebo-controlled trial of rifaximin in patients with abdominal bloating and flatulence. Am J Gastroenterol. 2006;101: 326–33.
48. Rackis JJ, Honig DJ, Sessa DJ, et al. Flavor and flatulence factors in soybean protein products. Food Chem. 1970;18:977–82.
49. Scheppach W. Effects of short chain fatty acids on gut morphology and function. Gut. 1994;35:S35–8.
50. Wolfe MS. Giardiasis. JAMA. 1975;253:1362–5.
51. Salvioli B, Serra J, Azpiroz F, et al. Impaired small bowel gas propulsion in patients with bloating during intestinal lipid infusion. Am J Gastroenterol. 2006;101:1853–7.
52. Nwinuka NM, Abbey BW, Ayalogu EO. Effect of processing flatus-producing oligosaccharides in cowpea (*Vigna unguiculata*) and the tropical African yam bean (*Sphenostylis sternocarpa*). Plant Foods Hum Nutr. 1997;51:209.
53. Nobaek S, Johansson ML, Molin G, et al. Alteration of intestinal micro flora is associated with reduction in abdominal bloating and pain in patients with irritable bowel syndrome. Am J Gastroenterol. 2000;95:1231–8.
54. Pimental M, Chow EJ, Lin HC. Eradication of small intestinal bacterial overgrowth reduces symptoms of irritable bowel syndrome. Am J Gastroenterol. 2000;95:3503.
55. Pimental M, Chow EJ, Lin HC. Normalization of lactulose breathe testing correlates with symptom improvement in irritable bowel syndrome. A double-blind, randomized, placebo-controlled study. Am J Gastroenterol. 2003;98:412–9.
56. Gasbarrini A, Lauritano EC, Garcovich M, et al. New insights into the patho-physiology of IBS: intestinal micro flora, gas production and gut motility. Eur Rev Med Pharmacol Sci. 2008;12:111–7.
57. Accarino A, Perez F, Azpiroz F, et al. Intestinal gas and bloating: effect of prokinetic stimulation. Am J Gastroenterol. 2008;103: 2036–42.
58. Serra J, Azpiroz F, Malagelada JR. Mechanisms of intestinal gas retention in humans: impaired propulsion versus obstructed evacuation. Am J Physiol Gastrointest Liver Physiol. 2001;281: G138–43.
59. Suarez F, Levitt MD, Adshead J, et al. Pancreatic supplements reduce symptomatic response of healthy subjects to a high fat meal. Dig Dis Sci. 1999;44:1317–21.
60. Ganiats TG, Norcross WA, Halverson AL, et al. Does Beano prevent gas? A double-blind crossover study of oral alpha-glycosidase to treat dietary oligo-saccharide intolerance. J Fam Pract. 1994;39:441–5.

Constipation

34

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Introduction

Constipation is a common syndrome in the geriatric age group in all settings, and often poses a management enigma; the disorder has been well reviewed in several position papers [1–7]. The prevalence of constipation is significantly higher in the geriatric age group, compared to those younger, regardless of the methodology of data collection, self-reporting or use of the Rome criteria [8–13]. The disorder is more common in older women than men [3]. It is more prevalent in nursing home residents compared to community adults [14], a finding perhaps relating to differences in comorbidity and medication use [15–17].

The direct Medicare costs for constipation are significant. In 2001, of 5.7 million ambulatory visits that carried a diagnosis of constipation, 2.7 million listed constipation as the primary diagnosis; of these >1.8 million were outpatients and >0.5 million were patients in the emergency department (ED) [18]. Of the total cost incurred at $235 million/year, 55% was for inpatient care, 23% in the ED, and 16% involved outpatient visits to physicians [18]. The in-hospital constipation related complications such as intestinal obstruction, anal fissures, impaction, volvulus, and stercoral ulcers entailed much Medicare and Medicaid costs [19].

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Definition

Because clinicians and patients differ in their views on constipation, consensus criteria have helped in defining the diagnosis of constipation. Rome III criteria (Table 34.1) [20] have standardized the definition of functional constipation [14] and help differentiate functional constipation from constipation predominant irritable bowel syndrome.

Rather than a disease entity, constipation is a term that describe difficulties experienced by a patient in moving the bowels [21]. In practice, clinicians use the frequency of defecation episodes, stool weight, colonic transit time, and anorectal manometry as proxy measures for constipation [22]. Frequency of defecation fewer than three times per week is considered as constipation [23]; however, this may be normal if it does not represent a deviation from baseline defecation practice and there is no associated discomfort [24]. Furthermore, patients often perceive constipation differently from the physician, with many defining constipation as just the presence of hard stools, infrequent evacuation, excessive straining, a sense of incomplete evacuation, excessive time spent on the toilet, and unsuccessful evacuation [25].

Relevant Age-Related Physiological Changes

The input of water into the gastrointestinal (GI) tract is about 9.0 L/day [26]. About 1.5–2.0 L of water enter the colon, with only 100–200 mL in feces [26]; higher water content makes stool softer [27]. Aging does not significantly reduce saliva production, pancreatic, and gastric juice secretion [28, 29].

Colonic motility plays a role in formation of stool. Aging is associated with enteric neurodegeneration and significant decline in cell number and density throughout the GI tract

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Table 34.1 Rome III criteria for functional constipation [20]*

Must include two or more of the following:
Straining during at least 25% of defecations
Lumpy or hard stools in at least 25% of defecations
Sensation of incomplete evacuation for at least 25% of defecations
Sensation of anorectal obstruction/blockage for at least 25% of defecations
Manual maneuvers to facilitate at least 25% of defecations (e.g., digital evacuation, support of the pelvic floor)
Fewer than three defecations per week
Loose stools are rarely present without the use of laxatives
There are insufficient criteria for irritable bowel syndrome

*Diagnostic criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

[30–34]. Smooth muscle relaxation remains normal, but cholinergic neurons are reduced in number [32]. The functional consequence is delayed transit in the large bowel because there is less contraction with the bolus, leading to inefficient peristalsis [32, 35]. A study of extrinsic colonic nerves in rodents have shown a dramatic age-related degeneration of sympathetic motor neurons of the myenteric plexus and decline in colonic transit [36], but there is paucity of data on age-related changes of the extrinsic innervation of the human colon, and regarding degenerative process of interstitial cells of Cajal (intestinal pace maker) as potential cause of constipation with age [35].

Gastric distension and chemical stimulation by nutrients can stimulate peristaltic contractions in the colon to propel material towards the rectum via a neural reflex arc, commonly termed the gastrocolic reflex [35]. The reflex also stimulates colonic motility. The efficiency of gastrocolic reflex with age is not clear.

Endogenous opioids inhibit enteric nerve activity and inhibit both propulsive motor and secretory activities [37, 38]. Three major, distinct classes of opioid receptors are located in the enteric nervous system: delta, kappa, and mu [39, 40]. The enteric mu-opioid receptor is the principal mediator of opioid agonist effects on the GI tract [39]. When opioid agonists bind to these receptors, the release of excitatory and inhibitory neurotransmitters are inhibited, interrupting coordinated rhythmic contractions required for intestinal motility, along with reduction in mucosal secretions [41].

Aging in asymptomatic women is associated with reduced anal resting and squeeze pressures, reduced rectal compliance, reduced rectal sensation, and perineal laxity [42]. Reduced rectal sensation may lead to stool impaction in the rectum [43]. In addition, sarcopenia of aging [44] leads to weak abdominal musculature, which in turn decreases intra-abdominal pressure during straining, creating difficulty in evacuation.

Table 34.2 Common disorders with colonic dysfunction constipation [69, 158–161]

Endocrine or metabolic disorders
Diabetes mellitus
Hypothyroidism
Hypercalcemia
Hypocalcemia
Hypokalemia
Hypermagnesemia
Hyperparathyroidism
Hypoparathyroidism
Neurological disorders
Parkinson's disease
Cerebrovascular disease
Dementia
Spinal cord lesions
Autonomic neuropathy
Neoplasms with paraneoplastic syndromes
Small cell lung cancers
Pulmonary carcinoid
Musculoskeletal or connective tissue disorders
Amyloidosis
Dermatomyositis
Systemic sclerosis
Psychogenic disorders
Anxiety
Depression
Somatization

Pathogenesis

Motility and structural abnormalities are two factors contributing to pathogenesis of constipation. Motility abnormalities include colonic and pelvic floor dysfunction. Colonic motor dysfunction is associated with dietary, medication, and disease factors [21]. Contributing diseases are listed in Table 34.2. In Parkinson's disease, constipation may be evident a mean 10 years (range 5 months to 19 years) prior to motor symptoms [45]. A complex neurohormonal mechanism involving the dorsal vagal nucleus in the brain, vasoactive intestinal peptide (VIP) and gut appear involved [46].

Many medications lower colonic motility and are associated with constipation; a partial list is shown in Table 34.3. Opioid-induced constipation occurs in 40% of patients on opioids, through interference with GI motility by delaying transit, stimulating nonpropulsive motility, segmentation and tone, and inhibition of colonic transit, intestinal, and colonic secretion [4]; inhibition of acetylcholine release from the myenteric plexus and binding to opioid receptors in the intestine decreases intestinal motility and fluid secretion [47, 48]. Drugs with anticholinergic effects decrease intestinal tone and motility [49]; iron and calcium slow intestinal transit

Table 34.3 Medications associated with constipation [17, 49, 52, 69, 162–167]

Aluminum antacids
Anticholinergics
Anticonvulsants
Anti histamine-1 receptor antagonist
Antiparkinsonian drugs
Antipsychotics
Antispasmodics
Beta-adrenergic blockers
Calcium channel blockers
Calcium supplements
Cisplatin
Clonidine
Disopyramide
Diuretics
Fiber (with inadequate fluid intake)
Furosemide
Iron supplements
Nonsteroidal anti-inflammatory drugs
Opioid analgesics
Selective serotonin reuptake inhibitors
Sucralfate
Tricyclic antidepressants

[50]; dehydration may be the basis with furosemide [17]; inhibition of prostaglandins occurs with ibuprofen (prostaglandin analogues cause diarrhea) [51]. With thalidomide, cisplatin, and vinca alkaloids, the mechanism is unclear [52].

The term of idiopathic slow-transit constipation is a clinical syndrome characterized by intractable constipation and delayed colonic transit [53]. The diagnosis is made after excluding colonic obstruction, metabolic disorders (e.g., hypothyroidism, hypercalcemia), drug-induced constipation, and pelvic floor dysfunction [53]. The pathophysiology of ineffective colonic propulsion is incompletely understood, with potential mechanisms reduced colonic contractile response to a meal, fewer colonic high amplitude propagated contractions, and disturbed visceral perception [54, 55]. As the result of abnormal colonic activity, the bowel content remains in ascending or transverse colon, without advancing to the rectosigmoid colon.

Pelvic floor dysfunction or disorders of the anorectum and pelvic floor create outlet dysfunction and inability to adequately evacuate rectal contents [21]. Terms used to describe these disorders include anismus, pelvic floor dyssynergia, paradoxical pelvic floor contraction, obstructed defecation, and functional rectosigmoid obstruction [56]. Pelvic floor dysfunction is most commonly due to dysfunction of the pelvic floor muscles or anal sphincters [57]. In the majority, it results from faulty toilet habits, painful defecation, obstetric or back injury, and brain-gut dysfunction [58, 59]. These patients are unable to coordinate abdominal, rectoanal, and pelvic floor muscle during defecation [60, 61]. This failure of rectoanal coordination may be impaired rectal contraction (61%), paradoxical anal contraction (78%), or inadequate anal relaxation [59]. Thus, incoordination or dyssynergia of involved muscles is primarily responsible [59]. Further, up to half the patients may have rectal hyposensitivity [60, 62].

Structural abnormalities causing constipation include nonobstructive and obstructive lesions. Anal fissure, a cut or split in the epithelial lining of the anal canal distal to the dentate line, is a nonobstructive cause of constipation. Anal fissure creates tearing pain and spasms with defecation for hours after defecation [63, 64]. The pain results in fear of the defection process, resulting in constipation and even fecal impaction. Other painful anorectal lesions include abscess, hemorrhoids, proctalgia fugax, fistula, and levator ani syndrome [65]. Rectal prolapse, rectocele, and prolapsed hemorrhoids create obstructed defecation syndrome [66, 67]. With colon cancer, the location and depth of lesions determine the presentation of obstructive symptoms; the sites for greatest risk for obstruction are the splenic flexure and descending colon [68]. Patients with obstructed defecation have a significant reduction in the amplitude of propagating pressure waves throughout the entire colon [21].

Risk factors implicated in pathogenesis include aging, depression, inactivity, low caloric intake, low income, low education, number of medications taken (independent of adverse effect profile), physical and sexual abuse, and female gender [1].

Evaluation

History

A thorough medical history helps in identifying the etiology and in management of constipation. History should elicit the patient's perceptions of normal bowel habits; onset and duration of symptoms; defecation frequency; color, size, and volume of stool; rectal bleeding or pain; weight loss; straining with passage of stool; abdominal pain or bloating; fecal soiling or diarrhea; and need for digital manipulation during defecation [69]. In addition, older adults should be encouraged to describe ability to sense complete evacuation, stool size using the Bristol Stool Scale, and provide information about their cultural beliefs and expectations [70]. Stool diaries and questionnaires help explore the bowel movement history, and minimize patient embarrassment [22, 71].

Patient perception of normal bowel habits is a relevant initial question. Among persons without apparent GI motility disorders and not on relevant medications, 98% had frequency of movement between three stools per day and three per week [23]. Using Rome criteria, those with fewer than

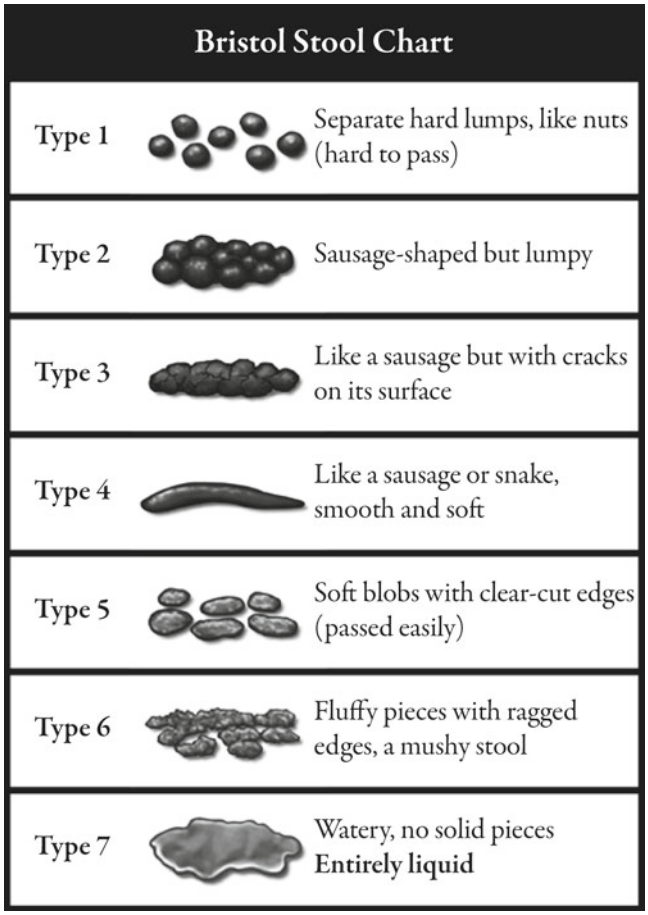

Fig. 34.1 Bristol stool chart (reproduced with kind permission from: Olsen AE, Drewes AM. Validated tools for evaulating opioid-induced bowel dysfunction. Adv Ther. 2011;28(4):279–94

three bowel movements per week may not have constipation if there is no straining, lumpy or hard stool, or sensation of incomplete evacuation. Some degree of urgency, straining, and incomplete evacuation should be considered normal [23]. Excessive straining, feeling of incomplete evacuation, and abdominal bloating were reported by the majority with dyssynergic defecation [71].

Onset and duration of symptoms determine the chronicity in relation to etiologies and complications. Recent alarm symptoms like rectal bleeding, anemia, guaiac-positive stool or mass in the abdomen are red flags prompting enquiry to exclude organic illness and neoplastic disease; recurring problems of a long duration, poorly relieved with dietary measures or laxatives suggest a functional colorectal disorder [70]. About 45% of patients with functional constipation report abdominal pain [72].

Stool form is commonly recorded by using Bristol stool chart [73] (Fig. 34.1). In clinical practice, stool form and frequency are often used as surrogate markers of intestinal and colonic transit [74]. Stool form and shape correlates better than stool frequency with whole-gut transit time [73–75]. Furthermore, fecal incontinence in older adults may be a presenting feature of severe constipation [76].

Careful attention must be paid to the identification of prescriptions and over-the-counter preparations (Table 34.3). In general, older adults use opioids for cancer related or back pain [77], and many develop constipation [78].

Lifestyle, especially diet and physical activity, are associated with bowel movements. A food diary helps assess fiber and fluid intake, frequency of meals, and nutrient content [70]. Difficulties with chewing, swallowing, diet, and mobility are common in the old [69]. In addition, screening for cognitive function, depression, anxiety, and systemic diseases may uncover contributing factors [69].

Physical Examination

Physical examination should be focused towards systemic diseases associating with constipation. Neurological examination uncovers common disorders such as spinal cord lesions, prior stroke, and Parkinson's disease. Poor dentition or oral lesions should be identified [69]. Gait and mobility are assessed as older adults may require help for bowel movements.

Abdominal examination evaluates distention, presence or absence of mass, and bowel sounds. Intestinal dilatation above an obstruction, with no peristalsis below the obstruction suggests fecal impaction (Schlange's sign) [79]. A mass in the left lower quadrant suggests a colonic lesion or stool in the left colon [70, 79]. Discomfort in the left lower quadrant on palpation suggests constipation or diverticular disease [79]. Pelvic examination in women detects internal prolapse or rectocele.

An adequate perianal and digital rectal examination may be the most revealing part of clinical evaluation and dictates subsequent investigation [64, 70, 80]. Digital rectal exam is reliable in detecting normal, but not abnormal, sphincter tone [80]. A simple 10-step approach on performing a rectal examination has been well outlined by Talley [64]; the basics are provided in Table 34.4.

Diagnostic Tests

After the history and examination, several tests may be considered; the basics include a complete blood cell count, serum glucose, creatinine and calcium, primarily to serve a screening function [6]. Hypothyroidism is a rare cause; we believe thyroid function testing is useful in the initial evaluation of constipation. In chronically constipated patients without alarm symptoms or signs, there is inadequate data to make recommendations for routine blood or other diagnostic

Table 34.4 The basics of rectal examination [64, 79, 168]

Prepare the patient by providing an understanding of the procedure and reasons to undergo the examination
The left lateral decubitus position is most suitable, with the knees pulled up [79]
Inspect the perineum; request the patient to strain; observe the perianal region for warts, fecal soiling, prolapsed hemorrhoids, or fistulae [168]
The anal wink is tested by stroking a cotton swab around the anus: its absence indicates disrupted sacral nerve pathways
Digital examination using lubrication: check anal sphincter pressure; pain on examination may indicate anal fissure, inflamed hemorrhoids, or ischio-rectal abscess; palpate the rectal walls to assess the prostate in men and cervix in women; the examination helps exclude a rectal mass and impacted stool
The finger in the rectum gauges resting tone of the internal anal sphincter, which correlates with absent, decreased or normal resting, and squeeze pressures [168]
Evaluate for pelvic floor dysfunction by asking the patient to strain. Normally, the anal sphincter and puborectalis relax, with the perineum descending by 1–3.5 cm. Absence of a descent along with tight muscles supports the diagnosis of paradoxical external anal sphincter and puborectalis contraction (pelvic floor dysfunction or dyssynergia)
Examine the gloved finger for features of the stool and blood, mucus or pus

Modified from [64]

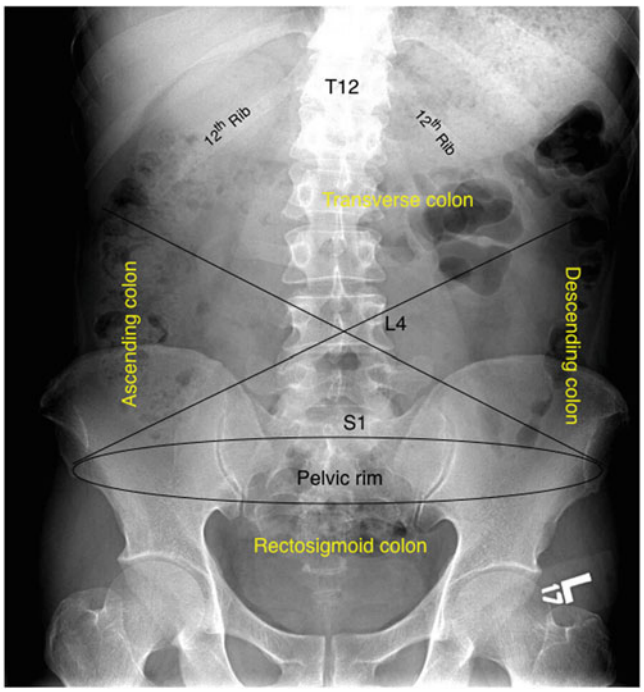

Fig. 34.2 Diagnostic landmarks on abdominal radiograph in patient with constipation

tests including flexible sigmoidoscopy, colonoscopy, and barium enema [2, 81]. Diagnostic studies are indicated in patients with alarm symptoms and signs [2]. Plain abdominal radiography is often helpful, although controversial [69, 82]. Figure 34.2 illustrates the diagnostic landmarks of an abdominal radiograph in a patient with constipation [83]. Routine screening colonoscopy is recommended for all patients with chronic, uncomplicated constipation in the over-50-year olds who have not undergone screening for colorectal cancer [2, 6]. Abdominal sonogram or computed tomography scan of abdomen is indicated when a space occupying lesion is suspected [83].

Specialized tests of colonic transit or pelvic floor function are considered only with severe, intractable constipation with no secondary cause apparent and in whom an adequate trial of high-fiber diet and laxatives is unsuccessful [69]. In older patients with a defecatory disorder, anorectal manometry and balloon expulsion tests are considered only if they will affect management decisions [69].

Transit studies enable a distinction between patients with slow and normal colonic transit times. Presently, colonic transit studies can be performed at every unit with X-ray or fluoroscopy equipment and require a short time at relatively low cost. They can be preliminary means to evaluate constipation, although over half of those with dyssynergic defecation have excessive retention of markers. The radio-opaque marker test is performed by administering a single capsule containing 24 plastic markers on day 1 and by obtaining plain abdominal radiographs on day 6 (120 h later) [70]. Retention of at least 20% of markers (more than six markers) on day 6 (120 h) is considered abnormal and is indicative of Slow-Transit Constipation [70]. The median colonic transit time is 1.5 (1.0–3.7) days for women, and 1.3 (0.8–1.9) days for men [84].

Other modalities for colonic transit study are colonic transit scintigraphy and the wireless motility capsule. Colonic transit scintigraphy is a noninvasive and quantitative method of evaluation of total and regional colonic transit by using an isotope (^{111}In or ^{99}Tc) [70]. Recently, a wireless motility capsule has been found useful and safe in the elderly [14].

Sixty percent of patients with dyssynergic defecation have abnormal radio-opaque marker test with excessive retention of markers [60]. It is important to exclude dyssynergic defecation before making a diagnosis of slow-transit constipation [85, 86]. In older adults, the presence of dyssynergic defecation can be detected by anorectal manometry and balloon expulsion tests. Anorectal manometry is performed by inserting pressure sensitive catheters to provide an assessment of pressure activity in the anorectum and to provide comprehensive information regarding rectal sensation, rectoanal reflexes, and anal sphincter function, at rest and during

defecatory maneuvers [87–89]. Normally when healthy subjects attempt to defecate they generate an adequate propulsive force synchronized with relaxation of the puborectalis and the external anal sphincter. The inability to perform this coordinated maneuver represents the chief pathophysiological abnormality in dyssynergic defecation [60, 86].

The balloon expulsion test is a simple, physiologic assessment of simulated defecation dynamics, by assessing a participant's ability to expel an artificial stool and is often conducted together with anorectal manometry [90]. This test is performed by inserting an empty 10-cm-long latex condom covered with lubricating jelly and tied to a catheter into the rectum of a patient lying in the left lateral position [91]. Water at a temperature of 36°C is instilled into the balloon through the catheter with a 60-mL syringe. The total volume introduced is the minimum to induce a sustained desire to defecate [91]. Patients are asked to sit on a toilet and expel the balloon. Asymptomatic persons can expel the balloon in a median 50 s (range 10–90 s), and always within 5 min [90]. In a large study, the balloon expulsion test had a sensitivity of 88%, positive predictive value of 64% for diagnosing pelvic floor dysfunction; the specificity was 89%, with a negative predictive value of 97% for excluding pelvic floor dysfunction, suggesting that this may be a useful screening test for dyssynergic defecation [91]. Although the failure to expel a balloon strongly suggests dyssynergic defecation, a normal test does not exclude this possibility [90].

Defecography or pelvic magnetic resonance imaging is indicated if the results of anal manometry or balloon expulsion tests are equivocal, or if there is a clinical suspicion of a structural rectal abnormality that hinders defecation [89, 92]. Defecography involves filling the rectum with contrast media and observing the act of defecation with fluoroscopy or magnetic resonance imaging. Currently, magnetic resonance imaging is the only imaging modality that simultaneously can evaluate global pelvic floor anatomy and dynamic motion [93]. Magnetic resonance imaging defecography of the pelvic floor may detect rectoceles, cystoceles, enteroceles, intussusceptions, a dyskinetic puborectalis muscle (in males), changes in the anorectal angle, presence of paradoxical sphincter contraction, and additional pelvic floor abnormalities [94, 95]. A study showed that the sensitivity of magnetic resonance defecography for the diagnosis of dyssynergic defecation is 100%, but with a specificity of only 23% [94]. At this time, limitations of MRI defecography include its high cost, lack of standardization, and availability [96].

Management

Prevention of constipation involves primarily life style measures, with medications utilized when nonpharmacological approaches fail. The prophylactic use of stool softeners and/or laxatives is appropriate, however, in patients on opioids [4, 97]. The goals of treatment of constipation are to relieve symptoms, to restore normal bowel habits (i.e., passage of soft, formed stools at least thrice weekly without straining, and to improve quality of life) [69]. The management strategy includes life style modification, the use of fiber, pharmacologic measures, and miscellaneous modalities such as surgery. Nonpharmacologic approaches are outlined in Table 34.5.

Table 34.5 Nonpharmacological management [69, 83, 97, 98, 101, 103, 105]

Counseling
On the range of variations in bowel habits accepted as normal
On the need for regular bowel habits
Diet
Adequate meals, including recommended fiber content
Adequate fluids daily
Prune juice or prunes may be a helpful measure
Habits
Scheduled toileting around the same time daily, responding to the natural urge to defecate
Utilization of gastrocolic reflex 15–20 min prior to scheduled toileting
Optimal sitting position on toilet during defecation
Avoid distractions (such as reading) while defecating
Fluids
Encourage adequate fluid consumption especially with fiber intake or when at risk for dehydration
Activity
Mild or moderate physical activity daily, ideally 30–60 min after a meal
Medications
Review medications regularly; be aware of adverse drug effects involving the GI tract and interactions
Revise drug regimens or limit use of those that predispose to constipation
Special caution required for patients initiated on opioids
Discourage routine and excessive use of laxatives
Fiber
Encourage intake of fresh vegetables and fruits daily
Utilize fiber rich food with a combination of soluble and insoluble fiber regularly
Commercial fiber formulas are an option when dietary fiber intake is inadequate

Lifestyle Modification

Bowel Training and Education

Regular habits go a long way in the management of constipation. Bowel evacuation is best attempted at a regular time daily. Utility of the gastrocolic reflex is recommended, typically between 5 and 30 min after breakfast, or consumption of warm liquids [83]. Sitting position on toilet must be optimal for defecation. The older person should be educated to sit on the toilet seat with legs apart, and lean forward with

elbows [98]. Sensation of satisfactory bowel emptying in sitting defecation posture necessitates excessive expulsive effort compared to the squatting posture [99]. Bed-bound older adults may experience position related pelvic dyssynergia and difficulty in evacuating stool [100]. Prolonged straining is discouraged, as is a distractive behavior such as reading, while attempting to defecate [83, 101].

Exercise and Diet

Low physical activity is a risk factor for constipation [102]. It is hence logical to include physical training as a treatment measure; multicomponent interventions, including exercise in older nursing home residents significantly increased bowel movements [103]. Where possible, walking is the ideal exercise in older adults, for 30 min most days a week; abdominal and pelvic floor exercises may be additive in effect [97]. The effect of exercise on bowel transit time is probably through stimulation of colonic transit [104].

A minimum of 1.5 L of fluid daily, perhaps more, is recommended especially with high fiber intake [105]; in dehydrated, febrile states, heavy exertion, excessively hot weather, and for frequent flyer seniors, before long-distance air flights large quantities of fluid intake are essential [106]. However, in the healthy, encouraging fluids above usual recommendations do not serve additional benefit to relieve constipation [107]. Caffeinated beverages (coffee, tea, colas) are not considered as part of this quota of fluid consumption [83]. Even so, it is worth emphasizing that the preached trio of diet (fiber), fluid intake and exercise is not supported adequately by science and awaits more data [108].

Fiber

A low fiber diet should not be assumed to be the cause of constipation. In general, dietary fiber plays a role in management of constipation by increasing stool mass, decreasing intestinal transit time, and increasing GI motility [109, 110]. Based on an average from several studies, bulk laxatives or fiber increase bowel movement frequency by an overall weighted average of 1.4 bowel movements/week [111]. Fiber and bulk laxatives decreased abdominal pain and improved stool consistency compared with placebo [111]. However, many patients with slow colonic transit and dyssynergic defecation do not respond well to dietary fiber intake of 30 g/day [112]. In contrast, most constipated patients without an underlying motility disorder improve or became symptom free with this amount of supplemental fiber [112]. A systematic review, which included six RCTs suggested the benefits of soluble fiber in chronic idiopathic constipation, while data for insoluble fiber was conflicting [113].

Dietary Reference Intakes recommend consumption of 14 g dietary fiber/1,000 kcal, or 25 g for adult women, and 38 g for adult men, preferably as dietary form, with adequate water [114], with gradual increase in foods rich in residual fiber [69]. A recent RCT demonstrated dried plums (prunes) to be more effective than psyllium in the management of mild to moderate constipation [115]. Dietary fiber is discussed in chapter 21.

The effect of increasing dietary fiber is not immediate; patients should observe a gradual increase in bowel movement frequency over weeks. Bloating and flatulence may be an adverse effect, but usually resolve with continued use. To minimize this problem, fiber supplementation is commenced in small doses of 5–10 g/day and gradually titrated to the full dose of 20–35 g/day [83, 114]. Fecal impaction should be treated before increasing dietary fiber [69]. Fiber supplementation should be avoided in patients with idiopathic megacolon, megarectum or bowel obstruction, and in the hospitalized ill; these patients require a fiber-restricted diet with laxatives or enemas to prevent fecal retention and impaction [116]. Fiber supplements interfere with drug absorption and hence are best not administered with medications.

Pharmacotherapy of Constipation

Unfortunately, prescribing of medications increasingly has replaced nonpharmacological therapies for outpatient treatment of constipation in the U.S., with hyperosmolars used most frequently and increasingly [117]. Examples, mechanism of actions, and side effects of available pharmacological agents are listed in Table 34.6. Lactulose, sorbitol, senna compound, and bisacodyl may be the initial choice in older adults [14], with polyethylene glycol (PEG) an option for the unresponsive [14, 118]. Newer agents are a consideration when conventional laxatives are ineffective. In general, the effectiveness of treatment remained similar when RCTs at low risk of bias were analyzed [119], but modes of action differ. Costs of laxatives vary; senna and bisacodyl are least expensive, while lactulose and polyethylene glycol incur costs. High-quality trials are needed in the old to make definitive recommendations; an individualized approach is suggested with regard to laxative therapies [120].

Stool Softeners and Emollients

Data on the effectiveness of stool softeners in chronic constipation are limited. A study on 170 patients revealed that docusate was less effective than psyllium, a bulk laxative, in increasing stool water content and overall laxative efficacy [121].

Similar to stool softeners, there is insufficient evidence for the use of paraffin oil, also known as mineral oil, to treat chronic constipation [122]. Mineral oil decreases water absorption and softens the stool, thereby allowing easier passage [123]. It is no longer recommended in the old, as it may cause anal seepage, reduces absorption of fat-soluble vitamins, and predisposes to aspiration lipoid pneumonia [123, 124].

Table 34.6 Pharmacological management [2, 69, 83, 118, 123, 169, 170]

Bulk forming laxatives	
Examples	Psyllium (natural fiber), methylcellulose (modified cellulose), calcium polycarbophil (synthetic)
Actions	Increase water content and stool bulk, with better stool consistency. In the colon, they are fermented by bacteria to produce short chain fatty acids that increase luminal osmolarity and water retention, potentiating laxative effect
Dose	Psyllium: start 3.4 g PO daily, increase dose gradually to 3.4 g PO three times a day
	Methylcellulose: 1 g PO daily, increase gradually to three times a day
Adverse effects	Bloating, flatulence, and abdominal discomfort; fecal impaction with inadequate fluid intake. Esophageal obstruction in those with dysphagia
Stool softeners	
Examples	Docusate, mineral oil
Actions	Softens the stool as a surfactant and causes stool wetting
	Mineral oil acts as an emollient
Dose	Docusate: 100–600 mg PO daily, divided into 1–3 doses
	Mineral oil: 15–45 mL/day PO divided into 1–2 doses daily or 118 mL/rectal daily PRN
Adverse effects	Mineral oil causes lipid pneumonia, malabsorption of fat soluble vitamins, anal seepage. Docusate may impair liver function
Saline laxatives	
Examples	Magnesium salts, sodium phosphate, sodium sulfate
Actions	Through osmotically mediated water retention and stimulation of peristalsis. Magnesium salts release cholecystokinin and activate constitutive nitric oxide synthase causing fluid secretion
Dose	Magnesium citrate: 8.725–17.45 g/day PO divided into 1–2 doses
Adverse effects	Magnesium salts cause hypermagnesemia, especially impaired renal function. Sodium phosphate causes hypocalcemia, hyperphosphatemia, hypernatremia. Sodium and potassium losses may result via stool
Osmotic laxatives	
Examples	Lactulose, sorbitol, polyethylene glycol, glycerin rectal suppository
Action	Neither digested nor absorbed in the small intestine; act through osmotic properties. Lactulose is broken down by bacteria in the colon to lactic and acetic acids to lower colonic pH, favoring formation of less absorbable NH_4^+ from NH_3, effectively trapping ammonia in the colon
Dose	Lactulose: 10–20 g PO daily, 1–2/day, maximum 60 g/day
	Polyethylene glycol (PEG) 3350: 17 g (1 capful) PO daily PRN; need to dissolve in 4–8 oz of liquid
	Glycerin: 5.6 g (1 unit) rectal suppository daily PRN
Adverse effects	Lactulose and sorbitol cause flatulence, abdominal cramps, and diarrhea
Stimulant laxatives	
Examples	Bisacodyl, anthraquinone derivatives (senna, cascara)
Action	Stimulate intestinal motility and reduce absorption of water and electrolytes in the colon. Anthraquinone becomes active on being metabolized by colonic bacteria
Dose	Bisacodyl: 5–15 mg PO daily, oral or suppository. Maximum 30 mg/day
	Senna: 17.2–34.4 mg PO at night PRN
Adverse effects	Bisacodyl causes rectal irritation, abdominal cramps, and colitis. Anthraquinones may cause melanosis coli and urine discoloration

Bulk Laxatives

Bulk laxatives may help manifestations, such as abdominal pain, defecation effort, and painful defecation [122]. Bulk laxatives are most effective in normal transit constipation; the majority of patients with slow-transit constipation or disordered defecation will have a poor response [112]. Effect takes several days [69]. Bulk laxatives must not be prescribed unless fiber cannot be increased in diet [69, 125]. The American College of Gastroenterology Chronic Constipation Task Force (ACG-CCTF) found that psyllium was the only bulking agent with sufficient data for an evidence-based recommendation [2]. The frail old should maintain adequate fluid intake while on bulk laxatives to avoid worsening constipation due to mechanical obstruction. Compared to natural fiber, synthetic compounds undergo less bacterial fermentation and cause less bloating and flatulence [97].

Saline Laxatives

Saline laxatives are not recommended for treatment of chronic constipation as data are inadequate for these agents in any age. Magnesium, sodium, and phosphate containing laxatives are usually well tolerated, but are risky in the presence of renal and cardiac disease, both common in the old. Excessive absorption of sodium, phosphorus, or magnesium may lead to electrolyte and volume overload; saline laxatives cause dehydration when excessively used [126].

Stimulant Laxatives

In general, stimulant laxatives do not produce electrolyte disturbance when used in appropriate dosage [127]. The development of tolerance to stimulant laxatives may occur in slow colonic transit [128]. Sodium picosulphate should be used with caution in those with renal impairment or cardiac failure, for fear of electrolyte disturbance [123]. Castor oil should no longer be used as it causes significant abdominal cramping and nutrient malabsorption [122, 129]. However, recent study involving institutionalized older individuals with chronic constipation showed application of topical castor oil to abdominal wall (castor oil pack) helped fecal consistency, and minimized straining and incomplete evacuation [130]. Oral bisacodyl is typically administered at bedtime because its time of onset is about 6 h later, in the morning; on the contrary, the suppository bisacodyl acts within 30–60 min [83]. Phenolphthalein, no longer marketed in the United States, has been associated with fixed-drug eruption, protein-losing enteropathy, Stevens–Johnson syndrome, lupus reactions, and possible carcinogenicity [131, 132].

Osmotic Laxatives

High-molecular-weight PEG is a large polymer with substantial osmotic activity that obligates intraluminal water [133]. There are several types of PEG, including polyethylene glycol electrolyte lavage solution (PEG-ELS), sulfate-free electrolyte lavage solution (SF-ELS), and PEG 3350 (MiraLax, Braintree Laboratories, Braintree, MA) [118]. PEG-ELS and SF-ELS, commonly used for preparation prior to colonoscopy, reach a steady-state equilibrium when given in large volumes at high infusion rates (1.5 L/h) and pass through the GI tract with no net water or electrolyte absorption or secretion [134]. This may not necessarily be the case when they are given in small amounts or ingested at slow rates [118]. PEG-ELS is also effective for fecal impaction at a dose of 100 g in 1 L of water/day for up to 3 days [135]; however, manual fragmentation and extraction of impacted stool is required prior to use of oral laxatives [136]. PEG 3350 laxative is a chemically inert polymer that does not contain absorbable salts. For overnight treatment of constipation, 68 g of PEG 3350 provided reliable and safe relief within 24 h [137], without incontinence, cramps, diarrhea, or changes in electrolytes or serum osmolality. Lactulose, sorbitol, manitol and glycerin are poorly absorbed sugars with osmotic action. Recent meta-analysis revealed PEG to be better than lactulose in outcomes of stool frequency per week, form of stool, relief of abdominal pain, and the need for additional products [138]. Glycerin is significantly absorbed in the small bowel to prevent its regular use to treat chronic constipation [118]. Those who are lactose intolerant may simply adjust their consumption of lactose-containing foods to regulate their bowel habits [118].

Enemas

Enemas play an important role in the management and prevention of fecal impaction in those at risk [136]. Lubricant suppositories (glycerin) can help to initiate defecation in fecal impaction. In a study, administration of daily lactulose with a glycerin suppository and a once-weekly tap water enema achieved complete rectal emptying and prevented incontinence related to impaction in institutionalized older patients [139]. Phosphate enemas should be used with caution in patients with impaired renal dysfunction and pre-existing electrolyte imbalance [122, 140, 141]. Soap sud enemas are best avoided as they cause irritation and possible severe colitis [122, 142].

Prokinetic Agents

Tegaserod has been removed from the market because of its association with risk of cardiovascular events [143]. High-quality data are lacking for support of the use of misoprostol in constipation [2].

Newer Agents

Lubiprostone, compared to placebo, has consistently increased complete and spontaneous bowel movements per week, as well as improved stool consistency, straining, constipation severity, and patient-reported treatment effectiveness [144].

Prucalopride, unlike other drugs in its class, such as tegaserod, mosapride, and renzapride, has a lower affinity for the human Ether-a-go-go Related Gene (hERG) protein [145]. It is believed that the effects on the hERG channel may have led to the unfavorable cardiovascular profile seen with tegaserod. In a RCT involving 84 elderly nursing home residents with chronic constipation, 2 mg prucalopride once daily for 4 weeks was safe and well tolerated [146].

Linaclotide, another new agent, increases spontaneous bowel movements and is effective in improving secondary endpoints, such as stool consistency, straining, abdominal discomfort, bloating, global assessments, and quality of life [147].

Colchicine, a medication used for treatment of gout, is known to induce diarrhea in higher doses. In slow-transit constipation, colchicine in a dose of 1 mg daily effectively reduces symptoms of constipation [45].

Prolonged release formulations containing naloxone (less specific than the opiate antagonist widely distributed), and a newer class of peripherally restricted mu-opiate receptor antagonist (alvimopan and methylnaltrexone) are under development [4] for use in opioid constipation; laxation occurs within 1.26 h (methylnaltrexone) or 8 h (alvimopan) [148, 149]. The class of agents also has potential use for other narcotic induced side effects, such as opioid-related nausea and vomiting, urinary retention, pruritus, or postoperative ileus.

Prebiotics and probiotics are being evaluated as potential treatments for constipation [5].

Laxative Abuse or Misuse

Laxatives have been in use for centuries and have been abused or misused in 10–60% of situations [150]. Some users suffer from eating disorders, while others use laxatives for weight loss or to cause factitious diarrhea. Another group although constipated, believe that frequent bowel movements are required for good health. Use among older groups in care homes varies and often not based on rational criteria (A11) [15]. The most misused group is the stimulant class, perhaps because of their onset of action; electrolyte imbalance often results. Addressing the problem involves a certain degree of suspicion, education, stopping the laxative and replacing with fiber supplements, nursing, and psychiatrist involvement where appropriate [15, 150].

Miscellaneous Modalities

Manual Fragmentation

Manual fragmentation and extraction of the fecal mass are almost always initially indicated for fecal impaction [136]. The procedure usually requires local anesthesia and lubrication with lidocaine jelly, followed by gentle, progressive anal dilation with first one and then two fingers [151]. A scissoring action is used to fragment the impaction. In women, applying transvaginal pressure with the other hand may aid fragmentation and expulsion [152]. A pudendal block or spinal or general anesthesia is rarely required [151].

Endoscopy Intervention

When stool impaction is beyond the reach of the fingers, a lavage directed by sigmoidoscopic visualization can be effective to relieve transient bowel obstruction, abdominal pain, and distention [136].

Surgical Therapy

In selected patients with slow colonic transit, subtotal colectomy with ileorectal anastomoses are options when other measures have failed to relieve constipation, provided that defecation dysfunction disorder has been excluded [153, 154]. Segmental colonic resection in constipation is disappointing [3, 155]. Reported side effects of surgery include diarrhea, incontinence, infection, and bowel obstruction. Furthermore, the elderly might be unfit for surgery due to advanced age and comorbidities [14].

Biofeedback Therapy

Biofeedback is an effective treatment for pelvic floor dyssynergia but not slow-transit constipation [156]. Biofeedback involves the use of pressure measurements or averaged electromyographic activity within the anal canal to teach patients to relax pelvic floor muscles when straining to defecate [157]. This is combined with use of appropriate techniques for straining (increasing intra-abdominal pressure) and having the patient practice defecation of a water filled balloon [157]. Audio-visual feedback is provided to the patients as they attempt defecation [14]; sensory defects in older adults must be initially corrected.

Indications for Referral

Physicians should not hesitate to seek consultation to address the presence of alarm signs such as weight loss, melena, recent change in bowel habits, and refractory constipation [5]; consultants in the category include gastroenterologist, geriatrician, psychiatrist, surgeon, pharmacist, nutritionist, or others to meet individual needs (Table 34.7). A collaborative

Table 34.7 Indications for consultation in refractory constipation [6, 69, 83, 90, 122, 171]

Gastroenterologist
Constipation with alarm signs, e.g., recent onset, weight loss, anemia, pain, constipation alternating with diarrhea, gastrointestinal bleeding
Chronic constipation requiring excessive use of laxatives or stool softeners
Fecal incontinence of recent onset
High stool impaction which is beyond the reach of finger
To identify colonic neuropathy, myopathy, or normal colonic motor function before consideration of colectomy in patients with severe constipation
To assess colonic involvement in patients with colonic pseudoobstruction and/or megacolon syndromes and to assess tone/compliance changes
Clinical suggestion of pelvic floor dysfunction
Geriatrician
Chronic constipation not alleviated despite compliance with high-fiber diet, exercise regimen and bowel training program
Coexisting cognitive impairment: e.g., dementia, Parkinson's disease
For the diagnosis of one or more coexisting conditions, requiring expertise in management, e.g., hypothyroidism, diabetes, and heart disease
Where coexisting pain and its management are contributory
Polypharmacy, requiring revision of drug regimen, where constipation may result from drug–drug, drug–nutrient or drug–disease interaction
Surgeon
Constipation associated with vomiting and/or abdominal distension, where volvulus, obstruction, or ischemia are consideration
Complications of constipation, e.g., hemorrhoids, fissures, peri-rectal abscess
Refractory constipation, including the presence of rectocele and rectal prolapse
Severe intractable constipation not due to anorectal dysfunction, suggesting slow colonic transit constipation
Psychiatrist/psychologist
Patients with depression and psychological distress
Following medical evaluation and maximal attempts at therapy, when investigations including bowel transit studies are futile
In those who fail to cooperate with conventional approaches
Patients with irritable bowel syndrome and laxative abuse
Nutritionist, nurse, pharmacist
As indicated, to counsel regarding diet, habits, and medication intake

effort between the primary provider and the consultant offers the best chance for success [83].

Key Points

- Constipation is common in the geriatric population and often a management problem.
- Age-related physiological changes may contribute to development of chronic constipation, but it usually results from a variable combination of improper personal habits involving lifestyle, comorbidity, and adverse drug effect or drug interaction.
- Evaluation of constipation should address the aforementioned areas.
- Treatment of chronic constipation is tailored primarily to nonpharmacological approaches including diet, fluids, and activity.
- Revision of medication regimen should be addressed prior to resorting to the use of stool softeners and laxatives.
- Opioid-induced constipation is a common entity in older adults.
- Laxative use becomes a consideration only after dietary and other non-pharmacologic measures are ineffective.
- Laxative misuse and adverse effects should be recognized and addressed.

References

1. World Gastroenterology Organisation global guideline: constipation—a global perspective. J Clin Gastroenterol. 2011;45:483–7.
2. American College of Gastroenterology Chronic Constipation Task Force. An evidence-based approach to the management of chronic constipation in North America. Am J Gastroenterol. 2005;100 Suppl 1:S1–4.
3. Bouras EP, Tangalos EG. Chronic constipation in the elderly. Gastroenterol Clin North Am. 2009;38:463–80.
4. Camilleri M. Opioid-induced constipation: challenges and therapeutic opportunities. Am J Gastroenterol. 2011;106:835–42; quiz 843.
5. Foxx-Orenstein AE, McNally MA, Odunsi ST. Update on constipation: one treatment does not fit all. Cleve Clin J Med. 2008;75:813–24.
6. Locke III GR, Pemberton JH, Phillips SF. American Gastroenterological Association medical position statement: guidelines on constipation. Gastroenterology. 2000;119:1761–6.
7. Tariq S. Constipation in long-term care. Ann Longterm Care. 2008;16:1–45.
8. Pare P, Ferrazzi S, Thompson WG, et al. An epidemiological survey of constipation in Canada: definitions, rates, demographics, and predictors of health care seeking. Am J Gastroenterol. 2001;96:3130–7.
9. Sandler RS, Jordan MC, Shelton BJ. Demographic and dietary determinants of constipation in the US population. Am J Public Health. 1990;80:185–9.
10. Harari D, Gurwitz JH, Avorn J, et al. Bowel habit in relation to age and gender. Findings from the National Health Interview Survey and clinical implications. Arch Intern Med. 1996;156:315–20.
11. Talley NJ, Weaver AL, Zinsmeister AR, et al. Functional constipation and outlet delay: a population-based study. Gastroenterology. 1993;105:781–90.
12. Drossman DA, Li Z, Andruzzi E, et al. U.S. householder survey of functional gastrointestinal disorders. Prevalence, sociodemography, and health impact. Dig Dis Sci. 1993;38:1569–80.
13. Talley NJ, Fleming KC, Evans JM, et al. Constipation in an elderly community: a study of prevalence and potential risk factors. Am J Gastroenterol. 1996;91:19–25.
14. Rao SS, Go JT. Update on the management of constipation in the elderly: new treatment options. Clin Interv Aging. 2010;5:163–71.
15. Gage H, Goodman C, Davies SL, et al. Laxative use in care homes. J Adv Nurs. 2010;66:1266–72.
16. van Dijk KN, de Vries CS, van den Berg PB, et al. Constipation as an adverse effect of drug use in nursing home patients: an overestimated risk. Br J Clin Pharmacol. 1998;46:255–61.
17. Fosnes GS, Lydersen S, Farup PG. Constipation and diarrhoea—common adverse drug reactions? A cross sectional study in the general population. BMC Clin Pharmacol. 2010;11:2.
18. Martin BC, Barghout V, Cerulli A. Direct medical costs of constipation in the United States. Manag Care Interface. 2006;19:43–9.
19. Tuteja AK, Biskupiak JE. Chronic constipation: overview and treatment options. P&T. 2007;32:91–105.
20. Longstreth GF, Thompson WG, Chey WD, et al. Functional bowel disorders. Gastroenterology. 2006;130:1480–91.
21. McCrea GL, Miaskowski C, Stotts NA, et al. Pathophysiology of constipation in the older adult. World J Gastroenterol. 2008;14:2631–8.
22. Ashraf W, Park F, Lof J, et al. An examination of the reliability of reported stool frequency in the diagnosis of idiopathic constipation. Am J Gastroenterol. 1996;91:26–32.
23. Walter SA, Kjellstrom L, Nyhlin H, et al. Assessment of normal bowel habits in the general adult population: the Popcol study. Scand J Gastroenterol. 2010;45:556–66.
24. Abyad A, Mourad F. Constipation: common-sense care of the older patient. Geriatrics. 1996;51:28–34, 36.
25. Koch A, Voderholzer WA, Klauser AG, et al. Symptoms in chronic constipation. Dis Colon Rectum. 1997;40:902–6.
26. Pandol SJ, Raybould HE, Yee HF. Integrative response of the gastrointestinal tract and liver to a meal. In: Yamada T, Alpers DH, Kalloo AN, Kaplowitz N, Owyang C, Powell DW, editors. Textbook of gastroenterology, vol. 1. 5th ed. Oxford: Blackwell; 2009. p. 3–14.
27. Danjo K, Sakamoto J, Iwane S, et al. Effects of cellulose supplementation on fecal consistency and fecal weight. Dig Dis Sci. 2008;53:712–8.
28. Bhutto A, Morley JE. The clinical significance of gastrointestinal changes with aging. Curr Opin Clin Nutr Metab Care. 2008;11:651–60.
29. Laugier R, Bernard JP, Berthezene P, et al. Changes in pancreatic exocrine secretion with age: pancreatic exocrine secretion does decrease in the elderly. Digestion. 1991;50:202–11.
30. Sprenger N, Julita M, Donnicola D, et al. Sialic acid feeding aged rats rejuvenates stimulated salivation and colon enteric neuron chemotypes. Glycobiology. 2009;19:1492–502.
31. Peck CJ, Samsuria SD, Harrington AM, et al. Fall in density, but not number of myenteric neurons and circular muscle nerve fibres in guinea-pig colon with ageing. Neurogastroenterol Motil. 2009;21:1075–e90.
32. Bernard CE, Gibbons SJ, Gomez-Pinilla PJ, et al. Effect of age on the enteric nervous system of the human colon. Neurogastroenterol Motil. 2009;21:746–e46.
33. Phillips RJ, Powley TL. Innervation of the gastrointestinal tract: patterns of aging. Auton Neurosci. 2007;136:1–19.

34. Phillips RJ, Pairitz JC, Powley TL. Age-related neuronal loss in the submucosal plexus of the colon of Fischer 344 rats. Neurobiol Aging. 2007;28:1124–37.
35. Wiskur B, Greenwood-Van Meerveld B. The aging colon: the role of enteric neurodegeneration in constipation. Curr Gastroenterol Rep. 2010;12:507–12.
36. Phillips RJ, Rhodes BS, Powley TL. Effects of age on sympathetic innervation of the myenteric plexus and gastrointestinal smooth muscle of Fischer 344 rats. Anat Embryol (Berl). 2006;211: 673–83.
37. Holzer P. Treatment of opioid-induced gut dysfunction. Expert Opin Investig Drugs. 2007;16:181–94.
38. Mehendale SR, Yuan CS. Opioid-induced gastrointestinal dysfunction. Dig Dis. 2006;24:105–12.
39. De Schepper HU, Cremonini F, Park MI, et al. Opioids and the gut: pharmacology and current clinical experience. Neurogastroenterol Motil. 2004;16:383–94.
40. Holzer P. Opioids and opioid receptors in the enteric nervous system: from a problem in opioid analgesia to a possible new prokinetic therapy in humans. Neurosci Lett. 2004;361:192–5.
41. Wood JD, Galligan JJ. Function of opioids in the enteric nervous system. Neurogastroenterol Motil. 2004;16 Suppl 2:17–28.
42. Fox JC, Fletcher JG, Zinsmeister AR, et al. Effect of aging on anorectal and pelvic floor functions in females. Dis Colon Rectum. 2006;49:1726–35.
43. Wilson JA. Constipation in the elderly. Clin Geriatr Med. 1999;15:499–510.
44. Glass D, Roubenoff R. Recent advances in the biology and therapy of muscle wasting. Ann N Y Acad Sci. 2010;1211:25–36.
45. Abbott RD, Petrovitch H, White LR, et al. Frequency of bowel movements and the future risk of Parkinson's disease. Neurology. 2001;57:456–62.
46. Braak H, Rub U, Gai WP, et al. Idiopathic Parkinson's disease: possible routes by which vulnerable neuronal types may be subject to neuroinvasion by an unknown pathogen. J Neural Transm. 2003;110:517–36.
47. Clemens KE, Klaschik E. Management of constipation in palliative care patients. Curr Opin Support Palliat Care. 2008;2:22–7.
48. Thomas JR, Cooney GA, Slatkin NE. Palliative care and pain: new strategies for managing opioid bowel dysfunction. J Palliat Med. 2008;11 Suppl 1:S1–19; quiz S21–2.
49. Lat I, Foster DR, Erstad B. Drug-induced acute liver failure and gastrointestinal complications. Crit Care Med. 2010;38:S175–87.
50. Gartlehner G, Jonas DE, Morgan LC, et al. Drug class review on constipation drug: final report [internet]. 2010/05/25th ed. Portland: Oregon Health & Science University; 2007.
51. Chang JY, Locke GR, Schleck CD, et al. Risk factors for chronic constipation and a possible role of analgesics. Neurogastroenterol Motil. 2007;19:905–11.
52. Gibson RJ, Keefe DM. Cancer chemotherapy-induced diarrhoea and constipation: mechanisms of damage and prevention strategies. Support Care Cancer. 2006;14:890–900.
53. Bharucha AE, Phillips SF. Slow transit constipation. Gastroenterol Clin North Am. 2001;30:77–95.
54. O'Brien MD, Camilleri M, von der Ohe MR, et al. Motility and tone of the left colon in constipation: a role in clinical practice? Am J Gastroenterol. 1996;91:2532–8.
55. Mertz H, Naliboff B, Mayer E. Physiology of refractory chronic constipation. Am J Gastroenterol. 1999;94:609–15.
56. Pezim ME, Pemberton JH, Levin KE, et al. Parameters of anorectal and colonic motility in health and in severe constipation. Dis Colon Rectum. 1993;36:484–91.
57. Thompson WG, Irvine EJ, Pare P, et al. Functional gastrointestinal disorders in Canada: first population-based survey using Rome II criteria with suggestions for improving the questionnaire. Dig Dis Sci. 2002;47:225–35.
58. Remes-Troche JM, Rao SS. Neurophysiological testing in anorectal disorders. Expert Rev Gastroenterol Hepatol. 2008;2: 323–35.
59. Rao SS. Dyssynergic defecation and biofeedback therapy. Gastroenterol Clin North Am. 2008;37:569–86, viii.
60. Rao SS, Welcher KD, Leistikow JS. Obstructive defecation: a failure of rectoanal coordination. Am J Gastroenterol. 1998;93:1042–50.
61. Bharucha AE, Croak AJ, Gebhart JB, et al. Comparison of rectoanal axial forces in health and functional defecatory disorders. Am J Physiol Gastrointest Liver Physiol. 2006;290:G1164–9.
62. Scott SM, Gladman MA. Manometric, sensorimotor, and neurophysiologic evaluation of anorectal function. Gastroenterol Clin North Am. 2008;37:511–38, vii.
63. Schubert MC, Sridhar S, Schade RR, et al. What every gastroenterologist needs to know about common anorectal disorders. World J Gastroenterol. 2009;15:3201–9.
64. Talley NJ. How to do and interpret a rectal examination in gastroenterology. Am J Gastroenterol. 2008;103:820–2.
65. McCallum IJ, Ong S, Mercer-Jones M. Chronic constipation in adults. BMJ. 2009;338:b831.
66. Cruz JV, Regadas FS, Murad-Regadas SM, et al. TRREMS procedure (transanal repair of rectocele and rectal mucosectomy with one circular stapler): a prospective multicenter trial. Arq Gastroenterol. 2011;48:3–7.
67. Scarlett Y. Medical management of fecal incontinence. Gastroenterology. 2004;126:S55–63.
68. Kaufman Z, Eiltch E, Dinbar A. Completely obstructive colorectal cancer. J Surg Oncol. 1989;41:230–5.
69. Gallagher P, O'Mahony D. Constipation in old age. Best Pract Res Clin Gastroenterol. 2009;23:875–87.
70. Rao SS, Meduri K. What is necessary to diagnose constipation? Best Pract Res Clin Gastroenterol. 2010;25:127–40.
71. Rao SS, Tuteja AK, Vellema T, et al. Dyssynergic defecation: demographics, symptoms, stool patterns, and quality of life. J Clin Gastroenterol. 2004;38:680–5.
72. Wong RK, Palsson OS, Turner MJ, et al. Inability of the Rome III criteria to distinguish functional constipation from constipation-subtype irritable bowel syndrome. Am J Gastroenterol. 2010;105:2228–34.
73. Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. Scand J Gastroenterol. 1997;32:920–4.
74. Heaton KW, O'Donnell LJ. An office guide to whole-gut transit time. Patients' recollection of their stool form. J Clin Gastroenterol. 1994;19:28–30.
75. Saad RJ, Rao SS, Koch KL, et al. Do stool form and frequency correlate with whole-gut and colonic transit? Results from a multicenter study in constipated individuals and healthy controls. Am J Gastroenterol. 2010;105:403–11.
76. Leung FW, Rao SS. Fecal incontinence in the elderly. Gastroenterol Clin North Am. 2009;38:503–11.
77. Reid MC, Henderson Jr CR, Papaleontiou M, et al. Characteristics of older adults receiving opioids in primary care: treatment duration and outcomes. Pain Med. 2010;11:1063–71.
78. Papaleontiou M, Henderson Jr CR, Turner BJ, et al. Outcomes associated with opioid use in the treatment of chronic noncancer pain in older adults: a systematic review and meta-analysis. J Am Geriatr Soc. 2010;58:1353–69.
79. Williams ME. Geriatric physical diagnosis: a guide to observation and assessment. Jefferson: McFarland; 2008.
80. Tantiphlachiva K, Rao P, Attaluri A, et al. Digital rectal examination is a useful tool for identifying patients with dyssynergia. Clin Gastroenterol Hepatol. 2010;8:955–60.
81. Qureshi W, Adler DG, Davila RE, et al. ASGE guideline: guideline on the use of endoscopy in the management of constipation. Gastrointest Endosc. 2005;62:199–201.

82. Moylan S, Armstrong J, Diaz-Saldano D, et al. Are abdominal X-rays a reliable way to assess for constipation? J Urol. 2010;184: 1692–8.
83. Dharmarajan TS, Rao VSR, Pitchumoni CS. Constipation in older adults: an ancient malady, remains a management enigma. Pract Gastroenterol. 2004;28:40–65.
84. Sadik R, Abrahamsson H, Stotzer PO. Gender differences in gut transit shown with a newly developed radiological procedure. Scand J Gastroenterol. 2003;38:36–42.
85. Rao SS, Ozturk R, Laine L. Clinical utility of diagnostic tests for constipation in adults: a systematic review. Am J Gastroenterol. 2005;100:1605–15.
86. Rao SS. Dyssynergic defecation. Gastroenterol Clin North Am. 2001;30:97–114.
87. Sun WM, Rao SS. Manometric assessment of anorectal function. Gastroenterol Clin North Am. 2001;30:15–32.
88. Karlbom U, Lundin E, Graf W, et al. Anorectal physiology in relation to clinical subgroups of patients with severe constipation. Colorectal Dis. 2004;6:343–9.
89. Diamant NE, Kamm MA, Wald A, et al. AGA technical review on anorectal testing techniques. Gastroenterology. 1999;116: 735–60.
90. Rao SS, Singh S. Clinical utility of colonic and anorectal manometry in chronic constipation. J Clin Gastroenterol. 2011;44: 597–609.
91. Minguez M, Herreros B, Sanchiz V, et al. Predictive value of the balloon expulsion test for excluding the diagnosis of pelvic floor dyssynergia in constipation. Gastroenterology. 2004;126: 57–62.
92. Fletcher JG, Busse RF, Riederer SJ, et al. Magnetic resonance imaging of anatomic and dynamic defects of the pelvic floor in defecatory disorders. Am J Gastroenterol. 2003;98:399–411.
93. Savoye-Collet C, Koning E, Dacher JN. Radiologic evaluation of pelvic floor disorders. Gastroenterol Clin North Am. 2008;37: 553–67, viii.
94. Reiner CS, Tutuian R, Solopova AE, et al. MR defecography in patients with dyssynergic defecation: spectrum of imaging findings and diagnostic value. Br J Radiol. 2011;84:136–44.
95. Rentsch M, Paetzel C, Lenhart M, et al. Dynamic magnetic resonance imaging defecography: a diagnostic alternative in the assessment of pelvic floor disorders in proctology. Dis Colon Rectum. 2001;44:999–1007.
96. Rao SS. Advances in diagnostic assessment of fecal incontinence and dyssynergic defecation. Clin Gastroenterol Hepatol. 2010;8: 910–9.
97. Romero Y, Evans JM, Fleming KC, et al. Constipation and fecal incontinence in the elderly population. Mayo Clin Proc. 1996;71:81–92.
98. Ostaszkiewicz J, Hornby L, Millar L, et al. The effects of conservative treatment for constipation on symptom severity and quality of life in community-dwelling adults. J Wound Ostomy Continence Nurs. 2010;37:193–8.
99. Sikirov D. Comparison of straining during defecation in three positions: results and implications for human health. Dig Dis Sci. 2003;48:1201–5.
100. Rao SS, Kavlock R, Rao S. Influence of body position and stool characteristics on defecation in humans. Am J Gastroenterol. 2006;101:2790–6.
101. Goldstein O, Shaham Y, Naftali T, et al. Toilet reading habits in Israeli adults. Neurogastroenterol Motil. 2009;21:291–5.
102. Everhart JE, Go VL, Johannes RS, et al. A longitudinal survey of self-reported bowel habits in the United States. Dig Dis Sci. 1989;34:1153–62.
103. Schnelle JF, Leung FW, Rao SS, et al. A controlled trial of an intervention to improve urinary and fecal incontinence and constipation. J Am Geriatr Soc. 2010;58:1504–11.
104. Oettle GJ. Effect of moderate exercise on bowel habit. Gut. 1991;32:941–4.
105. Anti M, Pignataro G, Armuzzi A, et al. Water supplementation enhances the effect of high-fiber diet on stool frequency and laxative consumption in adult patients with functional constipation. Hepatogastroenterology. 1998;45:727–32.
106. Morley J. Water, water everywhere and not a drop to drink. J Gerontol A Biol Sci Med Sci. 2000;55:M359–60.
107. Lindeman RD, Romero LJ, Liang HC, et al. Do elderly persons need to be encouraged to drink more fluids? J Gerontol A Biol Sci Med Sci. 2000;55:M361–5.
108. Annells M, Koch T. Constipation and the preached trio: diet, fluid intake, exercise. Int J Nurs Stud. 2003;40:843–52.
109. Wrick KL, Robertson JB, Van Soest PJ, et al. The influence of dietary fiber source on human intestinal transit and stool output. J Nutr. 1983;113:1464–79.
110. Tucker DM, Sandstead HH, Logan Jr GM, et al. Dietary fiber and personality factors as determinants of stool output. Gastroenterology. 1981;81:879–83.
111. Tramonte SM, Brand MB, Mulrow CD, et al. The treatment of chronic constipation in adults. A systematic review. J Gen Intern Med. 1997;12:15–24.
112. Voderholzer WA, Schatke W, Muhldorfer BE, et al. Clinical response to dietary fiber treatment of chronic constipation. Am J Gastroenterol. 1997;92:95–8.
113. Suares NC, Ford AC. Systematic review: the effects of fibre in the management of chronic idiopathic constipation. Aliment Pharmacol Ther. 2011;33:895–901.
114. Slavin JL. Position of the American Dietetic Association: health implications of dietary fiber. J Am Diet Assoc. 2008;108: 1716–31.
115. Attaluri A, Donahoe R, Valestin J, et al. Randomised clinical trial: dried plums (prunes) vs. psyllium for constipation. Aliment Pharmacol Ther. 2011;33:822–8.
116. Gattuso JM, Kamm MA. Clinical features of idiopathic megarectum and idiopathic megacolon. Gut. 1997;41:93–9.
117. Trinkley KE, Porter K, Nahata MC. Prescribing patterns for the outpatient treatment of constipation in the United States. Dig Dis Sci. 2010;55:3514–20.
118. Siegel JD, Di Palma JA. Medical treatment of constipation. Clin Colon Rectal Surg. 2005;18:76–80.
119. Ford AC, Suares NC. Effect of laxatives and pharmacological therapies in chronic idiopathic constipation: systematic review and meta-analysis. Gut. 2011;60:209–18.
120. Fleming V, Wade WE. A review of laxative therapies for treatment of chronic constipation in older adults. Am J Geriatr Pharmacother. 2010;8:514–50.
121. McRorie JW, Daggy BP, Morel JG, et al. Psyllium is superior to docusate sodium for treatment of chronic constipation. Aliment Pharmacol Ther. 1998;12:491–7.
122. Pare P, Bridges R, Champion MC, et al. Recommendations on chronic constipation (including constipation associated with irritable bowel syndrome) treatment. Can J Gastroenterol. 2007;21(Suppl B):3B–22.
123. Xing JH, Soffer EE. Adverse effects of laxatives. Dis Colon Rectum. 2001;44:1201–9.
124. Ramkumar D, Rao SS. Efficacy and safety of traditional medical therapies for chronic constipation: systematic review. Am J Gastroenterol. 2005;100:936–71.
125. Pampati V, Fogel R. Treatment options for primary constipation. Curr Treat Options Gastroenterol. 2004;7:225–33.
126. Lembo A, Camilleri M. Chronic constipation. N Engl J Med. 2003;349:1360–8.
127. Kienzle-Horn S, Vix JM, Schuijt C, et al. Comparison of bisacodyl and sodium picosulphate in the treatment of chronic constipation. Curr Med Res Opin. 2007;23:691–9.

128. Muller-Lissner SA, Kamm MA, Scarpignato C, et al. Myths and misconceptions about chronic constipation. Am J Gastroenterol. 2005;100:232–42.
129. Wald A. Pathophysiology, diagnosis and current management of chronic constipation. Nat Clin Pract Gastroenterol Hepatol. 2006;3:90–100.
130. Arslan GG, Eser I. An examination of the effect of castor oil packs on constipation in the elderly. Complement Ther Clin Pract. 2011;17:58–62.
131. Corazziari E, Badiali D, Bazzocchi G, et al. Long term efficacy, safety, and tolerabilitity of low daily doses of isosmotic polyethylene glycol electrolyte balanced solution (PMF-100) in the treatment of functional chronic constipation. Gut. 2000;46:522–6.
132. Murphy J. Movement away from phenolphthalein in laxatives. JAMA. 2009;301:1770; author reply 1770.
133. Schiller LR, Emmett M, Santa Ana CA, et al. Osmotic effects of polyethylene glycol. Gastroenterology. 1988;94:933–41.
134. DiPalma JA. Current treatment options for chronic constipation. Rev Gastroenterol Disord. 2004;4 Suppl 2:S34–42.
135. Culbert P, Gillett H, Ferguson A. Highly effective new oral therapy for faecal impaction. Br J Gen Pract. 1998;48:1599–600.
136. Wrenn K. Fecal impaction. N Engl J Med. 1989;321:658–62.
137. DiPalma JA, DeRidder PH, Orlando RC, et al. A randomized, placebo-controlled, multicenter study of the safety and efficacy of a new polyethylene glycol laxative. Am J Gastroenterol. 2000;95:446–50.
138. Lee-Robichaud H, Thomas K, Morgan J, et al. Lactulose versus polyethylene glycol for chronic constipation. Cochrane Database Syst Rev. 2010;(7):CD007570.
139. Chassagne P, Jego A, Gloc P, et al. Does treatment of constipation improve faecal incontinence in institutionalized elderly patients? Age Ageing. 2000;29:159–64.
140. Hsu HJ, Wu MS. Extreme hyperphosphatemia and hypocalcemic coma associated with phosphate enema. Intern Med. 2008;47:643–6.
141. Farah R. Fatal acute sodium phosphate enemas intoxication. Acta Gastroenterol Belg. 2005;68:392–3.
142. Harish K, Tony J, Sunilkumar R, et al. Severe colitis induced by soap enemas. Indian J Gastroenterol. 2006;25:99–100.
143. Al-Judaibi B, Chande N, Gregor J. Safety and efficacy of tegaserod therapy in patients with irritable bowel syndrome or chronic constipation. Can J Clin Pharmacol. 2010;17:e194–200.
144. Johanson JF, Morton D, Geenen J, et al. Multicenter, 4-week, double-blind, randomized, placebo-controlled trial of lubiprostone, a locally-acting type-2 chloride channel activator, in patients with chronic constipation. Am J Gastroenterol. 2008;103:170–7.
145. Camilleri M, Kerstens R, Rykx A, et al. A placebo-controlled trial of prucalopride for severe chronic constipation. N Engl J Med. 2008;358:2344–54.
146. Camilleri M, Beyens G, Kerstens R, et al. Safety assessment of prucalopride in elderly patients with constipation: a double-blind, placebo-controlled study. Neurogastroenterol Motil. 2009;21:1256–e117.
147. Lembo AJ, Kurtz CB, Macdougall JE, et al. Efficacy of linaclotide for patients with chronic constipation. Gastroenterology. 2010;138:886–895.e1.
148. Paulson DM, Kennedy DT, Donovick RA, et al. Alvimopan: an oral, peripherally acting, mu-opioid receptor antagonist for the treatment of opioid-induced bowel dysfunction—a 21-day treatment-randomized clinical trial. J Pain. 2005;6:184–92.
149. Portenoy RK, Thomas J, Moehl Boatwright ML, et al. Subcutaneous methylnaltrexone for the treatment of opioid-induced constipation in patients with advanced illness: a double-blind, randomized, parallel group, dose-ranging study. J Pain Symptom Manage. 2008;35:458–68.
150. Roerig JL, Steffen KJ, Mitchell JE, et al. Laxative abuse: epidemiology, diagnosis and management. Drugs. 2010;70:1487–503.
151. Klein H. Constipation and fecal impaction. Med Clin North Am. 1982;66:1135–41.
152. Erdman LH. Fecal impaction. J S C Med Assoc. 1985;81:404–5.
153. Hassan I, Pemberton JH, Young-Fadok TM, et al. Ileorectal anastomosis for slow transit constipation: long-term functional and quality of life results. J Gastrointest Surg. 2006;10:1330–6; discussion 1336–7.
154. Nyam DC, Pemberton JH, Ilstrup DM, et al. Long-term results of surgery for chronic constipation. Dis Colon Rectum. 1997;40:273–9.
155. Rotholtz NA, Wexner SD. Surgical treatment of constipation and fecal incontinence. Gastroenterol Clin North Am. 2001;30:131–66.
156. Chiarioni G, Salandini L, Whitehead WE. Biofeedback benefits only patients with outlet dysfunction, not patients with isolated slow transit constipation. Gastroenterology. 2005;129:86–97.
157. Chiarioni G, Heymen S, Whitehead WE. Biofeedback therapy for dyssynergic defecation. World J Gastroenterol. 2006;12:7069–74.
158. Drukker CA, Heij HA, Wijnaendts LC, et al. Paraneoplastic gastro-intestinal anti-Hu syndrome in neuroblastoma. Pediatr Blood Cancer. 2009;52:396–8.
159. Condom E, Vidal A, Rota R, et al. Paraneoplastic intestinal pseudo-obstruction associated with high titres of Hu autoantibodies. Virchows Arch A Pathol Anat Histopathol. 1993;423:507–11.
160. Viallard JF, Vincent A, Moreau JF, et al. Thymoma-associated neuromyotonia with antibodies against voltage-gated potassium channels presenting as chronic intestinal pseudo-obstruction. Eur Neurol. 2005;53:60–3.
161. Chinn JS, Schuffler MD. Paraneoplastic visceral neuropathy as a cause of severe gastrointestinal motor dysfunction. Gastroenterology. 1988;95:1279–86.
162. Talley NJ, Jones M, Nuyts G, et al. Risk factors for chronic constipation based on a general practice sample. Am J Gastroenterol. 2003;98:1107–11.
163. Ness J, Hoth A, Barnett MJ, et al. Anticholinergic medications in community-dwelling older veterans: prevalence of anticholinergic symptoms, symptom burden, and adverse drug events. Am J Geriatr Pharmacother. 2006;4:42–51.
164. Opie LH. Calcium channel antagonists. Part IV: side effects and contraindications drug interactions and combinations. Cardiovasc Drugs Ther. 1988;2:177–89.
165. Hallberg L, Ryttinger L, Solvell L. Side-effects of oral iron therapy. A double-blind study of different iron compounds in tablet form. Acta Med Scand Suppl. 1966;459:3–10.
166. Trindade E, Menon D, Topfer LA, et al. Adverse effects associated with selective serotonin reuptake inhibitors and tricyclic antidepressants: a meta-analysis. CMAJ. 1998;159:1245–52.
167. Panchal SJ, Muller-Schwefe P, Wurzelmann JI. Opioid-induced bowel dysfunction: prevalence, pathophysiology and burden. Int J Clin Pract. 2007;61:1181–7.
168. Dobben AC, Terra MP, Deutekom M, et al. Anal inspection and digital rectal examination compared to anorectal physiology tests and endoanal ultrasonography in evaluating fecal incontinence. Int J Colorectal Dis. 2007;22:783–90.
169. Tack J. Current and future therapies for chronic constipation. Best Pract Res Clin Gastroenterol. 2011;25:151–8.
170. Castle SC, Cantrell M, Israel DS, et al. Constipation prevention: empiric use of stool softeners questioned. Geriatrics. 1991;46:84–6.
171. Lacy BE, Brunton SA. Partnering with gastroenterologists to evaluate patients with chronic constipation. MedGenMed. 2005;7:19.

Diarrhea

35

Sita Chokhavatia and Arvind J. Trindade

Introduction

Diarrhea is common in the older population. Older patients may be less likely to discuss changes in bowel movement and are often embarrassed to mention their inability to maintain continence of the diarrheal stool. Diarrhea in the older adult may be life-threatening, and due to the covert presentation, is often overlooked. Several factors predispose the older adults to complications from diarrhea (Table 35.1), resulting in significant morbidity. The geriatric patient is at risk for volume depletion, electrolyte abnormalities, falls due to orthostatic hypotension, delirium, social isolation, malnutrition, sacral ulcers (when bed bound), and hospitalization, including institutionalization and death. The frail older patient is particularly vulnerable to complications when the diarrhea is persistent or chronic. Early recognition of symptoms, expedited evaluation for diagnosis, and prompt management are therefore of prime importance.

Epidemiology

Diarrhea is a significant cause of mortality and the second leading cause of death worldwide after cardiovascular fatalities for all age groups [1]. Mortality from diarrhea has been declining worldwide, but more than 1.3 million deaths still occur each year; the majority in children in developing countries but this pattern is reversed in industrialized countries [2]. In the United States, there is a substantial healthcare burden from acute diarrheal diseases, and despite the lower rates, the morbidity and mortality is disproportionately higher in the elderly. Diarrhea-associated deaths are five times more likely in the old than in children. Hospitalizations for diarrhea in the elderly are increasing, unexplained by *Clostridium difficile* infection [3]. Known risk factors for death from diarrheal illnesses include older age, White race, female gender, and residence in a long-term care facility. The majority of diarrhea-related deaths occur in the geriatric population [4].

Definitions

The World Health organization defines diarrhea as three or more loose stools per day, or the passage of more stools than is normal for that individual. Stool weight in excess of 200 g/day has been used to define diarrhea for research studies. Based on duration of symptoms, *acute* diarrhea is defined as an increased frequency with more than three bowel movements per day, with stools of decreased consistency for less than 14 days. If diarrhea persists over 14 days, it is termed *persistent*, and beyond 1 month considered *chronic*. Fecal incontinence is defined as the involuntary loss of solid or liquid feces or gas, often precipitated by loose stools. Overflow diarrhea refers to the voluntary passage or incontinence of loose stools that pass around the obstruction caused by fecal impaction in constipated patients [5, 6].

The intestinal intraluminal fluid content is a balance between mucosal secretion and absorption. In addition to the variable ingestion of foods and liquids, substantial amounts of secreted endogenous fluids are presented daily for mucosal absorption, with only 1–2% excreted in stool [7]. Excessive secretion or decreased absorption results in diarrhea; a classification based on this mechanism of action is termed osmotic, secretory, exudative and inflammatory, or intestinal dysmotility diarrhea. Osmotic diarrhea results from an osmotic load in the intestine from poorly absorbed ingested substances that cause intraluminal retention of water; it typically resolves when fasting or upon removal of the malabsorbed substance from the diet. Secretory diarrhea results from secretion of electrolytes and water into the intestinal lumen or its reduced absorption. Exudative and inflammatory

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Table 35.1 Factors predisposing older adults to complications of diarrhea [4]

Physiologic factors associated with aging
Decreased total body water
Reduced response to thirst sensation
Impaired renal concentrating and diluting ability
Elevated basal and stimulated ANP levels
Lower renin and aldosterone levels
Limited access to fluids due to comorbidity associated with aging:
Impaired mobility
Impaired manual dexterity
Impaired swallowing mechanisms
Impaired communication ability
Impaired cognition
Additional factors
Polypharmacy (diuretics, cholinergics, PPIs, antimicrobials, oral iron, etc.)
Immune suppression from steroids or chemotherapy
Poor nutrition and frailty
Poor hygiene due to disability or dementia
Residency in long-term care
Delay in diagnosis and resuscitation
Fecal incontinence

ANP atrial naturetic peptide; *PPI* proton pump inhibitor

diarrhea results when protein and fluid exude from inflamed ulcerated mucosa and can present as bloody stool. Motility disorders cause diarrhea from rapid transit or a dysmotility causing slow transit and malabsorption [8]. The causes of acute and chronic diarrhea based on mechanisms are listed in Tables 35.2, 35.3, and 35.4.

Predisposing Factors

Achlorhydria and atrophic gastritis are common in older adults and lower protection against enteric organisms, predisposing to diarrheal diseases. Changes in the immune system include a decline in B and T cells, decreased antibody and cytokine production, and decline in mucosal immunity due to decreased IgA secretion. Aging is also associated with alteration in microflora in the intestine; anaerobic and bifidobacterial colonies decrease with concurrent increase in colonization by enterobacteria; any or several of these increase susceptibility to enteric infections [9]. Medication-induced diarrhea is dealt with elsewhere.

Environmental factors are a source for enteric infections. Outbreaks of infectious diarrhea occur frequently in long-term care facilities exposing the predisposed residents to intestinal infections. Increased incidence of *Salmonella*, *Campylobacter*, and *Escherichia coli infections* has been reported in long-term care residents [6]. Hospitalized patients and nursing home residents may develop recurrent or refractory *C. difficile*-associated colitis [6]. Institutionalized patients are exposed to outbreaks of viral gastroenteritis as

Table 35.2 Causes of acute diarrhea in the older adult

Infection
Bacteria
Escherichia coli—ETEC, EIEC, EPEC, EaggEC, EHEC, STEC
Vibrio cholera, *parahaemolyticus*, non-01 vibrio
Salmonella
Shigella
Campylobacter
Yersinia
Clostridium difficile, *perfringens*
Bacillus cereus
Staphylococcus aureus
Aeromonas
Listeria
Viruses
Rotavirus
Calcivirus—Norovirus, *sapporovirus*
Astrovirus
Enteric adenovirus
Cytomegalovirus
Parasites
Giardia
Entamoeba histolytica
Blastocystis hominis
Cryptosporidium
Microsporidium
Cyclospora
Schistosoma
Strongyloides
Inflammation: Ulcerative colitis, Crohn's colitis, segmental colitis associated with diverticulitis (SCAD), ischemic colitis, ischemic enteritis
Medications: Alteration in dose or regimen
Osmotic: Change in diet including tube feeds, enteral nutritional supplements, sorbitol in elixirs, lactose-containing products
Factitious: Laxative use, incontinence

Table 35.3 Causes of acute diarrhea in the older patient based on residence [13, 14, 25]

Sporadic or institutional outbreak of gastroenteritis
Preformed toxin (6–24 h): *S. aureus*, *B. cereus*, *C. perfringens*
(>3 days): ETEC, STEC, *Vibrio*, *Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, *Giardia*, *Cyclospora*, *Cryptosporidia*
Traveler's diarrhea
Cruise ships: Norovirus, ETEC
Africa: ETEC, *Shigella*, *Salmonella*, *Campylobacter*, Norovirus
Latin America: ETEC, EAEC, *Shigella*, *Salmonella*, Norovirus
South Asia: ETEC, EAEC, *Shigella*, *Salmonella*, *Campylobacter*, *Plesiomonas*, *Entamoeba*, *Giardia*, *Cryptosporidia*, *Cyclospora*
Nosocomial diarrhea
C. difficile
Drug-induced
Food contamination
Enteral hyperalimentation
Rehabilitation and long-term care facilities
Constipation and fecal impaction lead to "overflow" diarrhea

Table 35.4 Causes of chronic diarrhea in the older adult [8, 15]

Osmotic	Celiac disease Whipple's disease Small intestinal bacterial overgrowth Bile salt malabsorption—ileal disease, ileal resection Lactose intolerance Chronic pancreatitis Drugs—osmotic laxatives, sorbitol, antacids, enteral hyper alimentation
Secretory	Microscopic colitis—collagenous, lymphocytic Endocrine/neoplasm—carcinoid, gastrinoma, VIPoma, mastocytosis, pheochromocytoma, somatostatinoma, hyperthyroidism, medullary thyroid cancer, Addison's disease, villous adenoma, lymphoma Vasculitis Drugs—stimulant laxatives Epidemic—Brainerd
Dysmotility	Irritable bowel syndrome Diabetic diarrhea Scleroderma Vagotomy
Inflammatory	Ulcerative colitis Crohn's disease Ischemic colitis Radiation enteritis, proctitis Diverticulitis Infections Bacteria (Mycobacteria, *Yersinia*) Protozoa (*Giardia*, *Entamoeba*) Helminth (*Strongyloides*) Virus (cytomegalovirus, herpes simplex, HIV)
Miscellaneous	Colonic tumors

Multiple mechanisms of diarrhea may be involved in causes listed above

are travelers on cruise ships, a travel option favored by the older adult.

Pancreatic exocrine function insignificantly decreases with aging and does not account for diarrhea in the geriatric population [9, 10]. Dietary carbohydrate and fat absorption are not significantly affected with age [11, 12]. Fecal fat tests are similar in the young and old.

Differentiating Acute from Chronic Diarrhea

Acute diarrhea is usually self-limited and symptoms resolve within a week, seldom lasting beyond 2 weeks [13, 14]. Most acute diarrheal etiologies are infectious and exposure to a specific agent varies with the residential status (Tables 35.2 and 35.3). The increased incidence of *C. difficile*-associated diarrhea and attendant morbidity and mortality is dealt with another chapter. Acute diarrhea can result from introduction of a new drug, alteration in the dosage of current medications, altered enteral nutritional formulae or volume, and dietary alterations in any setting. Other noninfectious causes of acute and chronic diarrhea include diabetic diarrhea, celiac disease, small intestinal bacterial overgrowth, lactose intolerance, microscopic colitis, ischemic colitis, radiation proctitis, inflammatory bowel disease (IBD), and hypersecretory tumors. Diarrhea is termed chronic when passage of loose or watery stools with increased daily frequency, more than 3 per day, last beyond 4 weeks [15]. Diagnosis of etiology of chronic diarrhea can be challenging and necessitates obtaining a detailed history and conducting individualized investigations.

Etiologies

Infectious Diarrhea/Gastroenteritis

Gastroenteritis results from either the direct invasion of mucosal epithelium, adhesion to intestinal epithelium, production of enterotoxins, or a combination of these mechanisms.

Acute viral gastroenteritis is usually self-limited, lasts 24–48 h; variable manifestations including nausea, vomiting, diarrhea, abdominal cramps, fever, chills, or headaches. The morbidity and mortality is significant; with the 1979–1987 death rates in the United States over 50% in the 75+ age group [16]. Viral gastroenteritis peaks in the winter months; the agents include calicivruses (genus Norovirus, type Norwalk virus, genus Sapovirus, type Sapporo virus), rotaviruses, adenoviruses, and astroviruses. The viruses, especially Norovirus, are linked to nursing homes outbreaks. The incidence of Norovirus gastroenteritis has increased in long-term care facilities, hospital wards, and cruise ships, accounting for 60% of all gastroenteritis with a known pathogen in the United States, as also most deaths from viral gastroenteritis [17].

Bacterial agents that cause gastroenteritis are *Campylobacter jejuni*, *Shigella*, *Salmonella*, and less frequently *E. coli* O157:H7. Older adults are vulnerable to intestinal bacterial infections, especially *Campylobacter*, with hospitalization 2.6–3.4 times more likely in the over 65 age group [18]. *Salmonella* gastroenteritis in the elderly is associated with septicemia and high mortality rate. Old age is a risk factor for *Shigella* bacteremia and increased mortality [19]. Mode of transmission for delivery of these pathogens are fecal-oral, person to person, and via food and water. Long-term care institutions, hospitals, and daycare facilities are at risk for outbreaks due to the crowded living conditions, common delivery of food and medications, and transmission by healthcare personnel. Prolonged use of proton pump inhibitors and overuse or misuse of antibiotics has increased the risk of acquiring enteric infections in the elderly. Nosocomial spread of *C. difficile* occurs frequently in hospitalized and institutionalized older patients, with higher severity of disease [20].

Protozoal infections such as *Giardia*, *Cryptosporidium*, and *Entamoeba histolytica* can occur in the immune-suppressed older adults. Cryptosporidiosis has been described in the immunocompetent older adult [21]. The risk of severe disease was high in the 1993 waterborne *Cryptosporidium* infection outbreak in Milwaukee. Nursing home residents risk secondary person to person transmission [22]. Older adults also acquire parasitic infestations during overseas travel for work or pleasure and migration at retirement to endemic areas.

Travelers' Diarrhea

The otherwise healthy elderly spend time in recreation-related travel. Table 35.3 lists the common infectious agents causing Travelers' diarrhea (TD) at different destinations. Outbreaks of bacterial and viral infectious diarrhea occur on cruise ships, usually when traveling from a developed to an undeveloped country [23], caused by bacterial, viral, and protozoal organisms. Bacterial organisms such as Enterotoxigenic *E. coli* and Enteroaggregative *E. coli*, *Shigella*, *Campylobacter*, *Salmonella* and noncholera Vibrios more commonly cause diarrhea [24]. The risk is dependent on the viable causative organism count that reaches the intestine. The predisposed include those on acid-suppressing medications, those with altered GI anatomy, rapid gastric emptying, increased intestinal motility, atrophic gastritis with lower gastric acidity, and an immune-suppressed system. Most episodes of TD begin 4–14 days after arrival at the destination, but can occur earlier. The diarrheal illness is usually self-limited, but supportive treatment is necessary for the old, including monitoring hydration status and the need for prompt fluid replacement. The need for prophylactic antibiotics and treatment of infectious diarrhea is determined by the severity of disease, duration of illness, and the presence of bloody diarrhea and other comorbid diseases [25].

Tube Feeding-Associated Diarrhea

A common but often overlooked iatrogenic cause of diarrhea in the elderly is enteral nutrition. Tube feeding-associated diarrhea may occur due to hyperosmolar feeds, stimulation of gastrointestinal peptide release, associated bacterial overgrowth, increased intraluminal volume, and accelerated intestinal motility [26, 27]. Addition of fiber to enteral formulae may influence the occurrence of loose stool based on whether it is semidigested or soluble [28, 29]. High osmolality jejunal feeds cause diarrhea when infused directly into the small bowel. Rarely a gastrocolic fistula may cause persistent diarrhea, requiring consideration in the differential diagnosis for diarrhea in a patient with gastrostomy [30].

Ischemic Colitis

Ischemic colitis is the most common type of mesenteric ischemia and typically seen in the elderly [31–33]. Ischemia results from the sudden, usually temporary, reduction in blood flow to areas of the colon with poor collateral blood flow such as the recto-sigmoid junction, the splenic flexure, and the cecum. The metabolic needs of the colon are not met by the inadequate blood flow in several states.

Inflammatory Bowel Diseases

Diagnosis of IBDs in the elderly is difficult, with a delay in diagnosis and worse hospital outcomes in the older IBD patients [34]. Crohn's disease is increasingly diagnosed in patients >60 years and may be initially misdiagnosed [35]. A bimodal distribution may exist for both Crohn's disease (CD) and ulcerative colitis (UC) with a second peak between 50 and 80 years of age. Twelve percent of patients with UC and 9% with CD have disease onset after the age of 65 years. Colonic Crohn's disease and distal ulcerative colitis may be more common presentations.

Microscopic Colitis

Microscopic colitis is a cause of chronic watery diarrhea in older women over 65 years of age [36]. Microscopic colitis is comprised of two entities based on histology, namely, collagenous colitis and lymphocytic colitis. Intraepithelial lymphocytes and mixed inflammatory infiltration of the lamina propria are seen even in normal appearing colon in lymphocytic colitis. Additionally, a subepithelial collagen band is also seen in collagenous colitis, with the width of the collagen band 7–100 μm. About 10–30% of older adults who have chronic diarrhea and an endoscopically normal appearing colon will have microscopic colitis [37, 38]. The severity of the diarrhea is not related to the thickness of the collagen band but rather to the degree of inflammatory infiltration. Microscopic colitis is associated with celiac disease, hypothyroidism, history of malignancy, autoimmune disorders and use of medications such as proton pump inhibitors, ranitidine, acarbose, selective serotonin reuptake inhibitors, statins, aspirin, nonsteroidal anti-inflammatory drugs, and ticlopidine [39, 40]. Bile acids and toxins are luminal factors implicated in the pathogenesis.

Diverticular Disease

The incidence of diverticular disease increases with age, reaching 60% in persons over 85 years of age. Diverticular

bleed may cause painless, self-limited, lower gastrointestinal bleeding. The presence of segmental colitis in diverticular disease may mimic other causes of diarrhea [41]. Obstruction due to diverticular strictures may be associated with "overflow" diarrhea from liquid feces around the obstructed segment.

Celiac Disease

The prevalence of celiac has increased nearly twofold in the past 20 years, with a bimodal distribution; 20–34% of newly diagnosed celiac disease is in the 60+ age group. The patients may present with altered bowel habits (diarrhea or constipation, and if diarrhea, symptoms may be mild), abdominal pain, anemia, weight loss, and signs of malabsorption [42–44]. Adherence to a gluten-free diet may be difficult in the geriatric patient already on restricted meals.

Small Intestinal Bacterial Overgrowth

Small intestinal bacterial overgrowth (SIBO) is often under-recognized and results from a reduction in gastric acidity, motility disorders such as diabetes, scleroderma and Parkinson's disease, postsurgical blind loops, intestinal diverticulae and strictures predispose the older patient to SIBO. Bacterial overgrowth impairs nutrient absorption, resulting in malabsorption, chronic diarrhea, dyspepsia, nausea, abdominal pain, bloating, anorexia, malnutrition, and weight loss [11, 12]. Asymptomatic older adults may be lactose intolerant due to bacterial overgrowth rather than mucosal lactase deficiency [11]. The diagnosis is made by hydrogen breath tests or duodenal aspirate cultures [45].

Irritable Bowel Syndrome

Irritable bowel syndrome (IBS) is common in the older population although the prevalence of IBS declines with increasing age. The reduced pain perception with aging may partially explain this lower IBS prevalence in the elderly [46]. The Rome III criteria define the requisite symptom characteristics and duration for the diagnosis of IBS [47]; an exhaustive evaluation helps exclude more prevalent structural diseases in this age group, including malignancy, microscopic colitis, bile acids malabsorption, and celiac disease prior to making the diagnosis of functional diarrhea. Evaluation in presumed functional chronic watery diarrhea may reveal organic disease in the majority [48]. The use of alosetron in IBS which is diarrhea-predominant is restricted in the older adult due to adverse effects (risk of ischemic colitis).

Lactose Maldigestion

Lactose is hydrolyzed to galactose and glucose in the small intestinal lumen by lactase, a brush border enzyme. The highest levels of lactase are during infancy and decline after weaning foods are introduced. Lower intestinal lactase levels can result from mucosal injury as occurs in celiac disease and Crohn's disease, or a genetic predisposition termed primary lactase deficiency. Clinically apparent lactose maldigestion is termed lactose intolerance and presents as diarrhea, abdominal pain, gaseousness, and flatulence after ingesting dairy or lactose-containing food products. Lactose intolerance manifests during adolescence and increases in prevalence as age advances [49] Lactose intolerance can present in the elderly who never had a prior history of intolerance to dairy products; lactose malabsorption may be more frequent in individuals aged 74 years or older compared to the below 65 year group [50]. Asymptomatic older adults may have SIBO which can cause lactose malabsorption [11].

Pancreatic Causes of Malabsorption

Chronic pancreatitis with pancreatic insufficiency may lead to steatorrhea, abdominal pain, weight loss, or diabetes. Idiopathic chronic pancreatitis in older patients with no other known cause may represent a form of a genetic disorder [51]. Pancreatic cancer may present with pancreatitis and malabsorption syndrome.

Diabetic Diarrhea

Diabetic autonomic neuropathy may manifest with constipation, diarrhea, and fecal incontinence [52]. The etiology of diabetic diarrhea is multifactorial and in part secondary to autonomic dysfunction. The diarrhea may be severe and tends to be worse at night. Patients may have reduced resting sphincter pressures and reduced threshold of rectal sensation predisposing them to fecal incontinence. Diabetics often have chronic constipation, leading to fecal impaction and subsequent overflow diarrhea. Dietetic foods contain sorbitol and other nonabsorbed disaccharides that cause osmotic diarrhea; patients may relate a history of diarrhea being exacerbated by meals.

Fecal Incontinence and Diarrhea

Diarrhea in the elderly may precipitate fecal incontinence (FI) when the rectal capacity or weakened sphincter is overcome by the watery voluminous stool [6, 53–56]. The presence of loose stools and impaired mobility and mental

capacity predispose the older adult to FI [57]. Incontinent patients may be embarrassed and may report diarrhea instead of FI. The prevalence of FI in the elderly is 20–32% in geriatric hospital wards, up to 50% patients in long-term care facilities, and 80% of hospitalized older adults with dementia [58]. Community Medicare beneficiaries aged over 65 years had a 17% incidence rate of new onset FI in a period of over 4 years and FI was found to have common pathophysiologic mechanisms as for urinary incontinence [59]. FI can be due to overflow incontinence, reservoir dysfunction, and rectosphincteric dysfunction and has been classified as passive FI, urge FI, and fecal seepage. In nursing homes, fecal impaction can occur due to chronic constipation in the cognitively impaired or bedridden individuals and in patients with psychiatric disorders. Fecal impaction is seen in up to 42% of elderly adults [60, 61]. Constipation and stool retention are associated with FI [62]. Besides incontinence, manifestations of impaction include abdominal distension, pain, anorexia, weight loss, intestinal obstruction, and stercoral ulceration with bleeding or perforation [61]. Causes of fecal impaction include metabolic abnormalities such as hypothyroidism, hypercalcemia, hypokalemia, inadequate fiber and water intake, immobility, and delirium. Reservoir dysfunction occurs with diminished colonic or rectal capacity and causes urge incontinence which resembles diarrhea. The liquid stool is the putrefied stool seeping around the impacted feces and oozes out of the rectum, often mistaken for diarrhea. The management of fecal impaction includes disimpaction, colon evacuation, and a maintenance bowel program to prevent recurrence [61]. Despite appropriate treatment, nursing home residents may remain incontinent because of dementia and restraint-related immobility [62].

FI results in embarrassment, isolation, and depression and increases the probability that geriatricians will refer the patient to a nursing home; it is one of the leading causes for institutionalization [63]. The predictive risk factors for FI in a 10-year follow-up study of community living older adults were self-reported onset of diarrhea, incomplete evacuation, pelvic radiation, and development of fecal urgency [64]. Aggressive outpatient treatment of factors predisposing to FI may delay nursing home referral [65].

Diarrhea in Long-Term Care Facilities

Long-term care facility residents have been estimated to have highest incidence of adult diarrheal illness in the developed world and the problem may yet be underdiagnosed [66]. Diarrhea in this setting is a major cause of morbidity (weight loss, dehydration, and delirium) and mortality and increases healthcare costs [67]. Residents of long-term care are much more likely to suffer fatality from gastroenteritis compared to community dwellers. On the other hand, in institutionalized patients, fecal impaction can occur in the cognitively impaired and the bedridden individuals [56, 61].

A recent Australian study revealed that 52% of 6,295 outbreaks of gastroenteritis and food-borne disease were reported from long-term care facilities [68]. The outbreaks between 2002 and 2008 affected nearly 85,000 people with 1,577 hospitalizations and 209 deaths. Norovirus outbreaks were common and most outbreaks were transmitted from person to person, emphasizing the need for effective infection control measures [68]. Norovirus has no natural reservoir other than humans and is transmitted easily between humans; even a small dose is adequate to cause infection, with easy spread in nursing home setting [69]. In long-term care sites, often plagued by staffing problems and financial issues, definitive diagnosis may not be established due to the suboptimal collection of stool specimens; the causative agent for diarrhea remains unidentified in many diarrhea outbreaks.

Diarrhea of Obscure Origin

Obscure causes of diarrhea in the old include radiation enteropathy and proctitis, and rarely hyperthyroidism. The elderly are at risk of waterborne outbreaks of watery diarrhea that can last from 2 to 36 months (Brainerd diarrhea). Malabsorption occurs in Whipple's disease and tropical sprue. Neoplastic diseases presenting with diarrhea include lymphoma, carcinoid syndrome, gastrinoma, glucagonoma, vipomas, villous adenoma, and carcinoma. Drug-induced diarrhea evades diagnosis; the prevalence increases with age, severity of disability, and the number of drugs taken. Up to 9% of adults over age 75 years report diarrhea (related to drugs) in the prior week [70].

Evaluation of Diarrhea in the Elderly

The approach to diagnosis of acute and chronic diarrhea in the elderly does not differ considerably from that in the young, but prompt resuscitation and management is required to prevent the morbidity and mortality in this population, especially crucial in the frail old. A complete history from the patient and caregiver help direct evaluation and dictate order of diagnostic tests [71, 72]. No cost-effective strategy or test is deemed to be of superior diagnostic accuracy [73]. Evaluation includes obtaining a comprehensive history (Table 35.5), focused physical examination and laboratory tests to initially establish the severity of illness, and the timing and necessity of subsequent specific laboratory, radiologic, and endoscopic investigation.

A detailed history addresses diarrhea duration and stool characteristics, presence of systemic symptoms of fever,

Table 35.5 Suggested questionnaire for the patient or caregiver

1. Is the diarrhea recent or longstanding?
2. Is diarrhea related to timing of meal?
3. Related to alterations in diet, ingestion of milk-based products, dietetic foods and fruit juices?
4. Recent addition or alteration in medication regimen, including over-the-counter medications and nutritional supplements?
5. History of recent antibiotic use?
6. Is the diarrhea dark, maroon, black, bloody or nonbloody?
7. Exposure to persons with diarrheal illness?
8. History of recent travel or consumption of food from street vendors?
9. Is there tenesmus (large intestinal) or is it voluminous, watery, or foul smelling (small intestinal or steatorrhea)?
10. Associated symptoms: fever, nausea, vomiting, abdominal pain, rash, arthralgias, and weight loss, and if so over what period?
11. Past medical history of pancreatic disease, diabetes mellitus, alcoholism, and radiation?
12. Prior surgery including gastrectomy, small intestine or colon resections, and cholecystectomy?
Additional considerations for the physician
1. Is it true diarrhea or factitious diarrhea?
2. Is it fecal impaction with "overflow" diarrhea?
3. Is it fecal incontinence?
4. Is it functional (no alarm symptoms) or organic (alarm symptoms present)?

abdominal pain, nausea, vomiting, medication history, comorbidity, sick contacts, diet, travel history, and changes in weight. The etiology may be localized to the small intestine or colon based on some of the stool characteristics. Watery and voluminous stool is more characteristic of small bowel disease; frequent small volume stool associated with urgency is indicative of distal colon or rectal disease and steatorrhea of pancreatic insufficiency. The volume status of the patient is indicated by vital signs and general appearance, and together with abdominal tenderness or distension and digital rectal examination (blood), severity of illness can be assessed. Fecal impaction must be excluded as the cause of pseudodiarrhea. Extended examination should include the thyroid, skin, and joints.

The approach to acute diarrhea is outlined in Fig. 35.1. Acute diarrhea is most commonly caused by viral or bacterial infections. The initial assessment should focus on estimating the hemodynamic status of the patient and presence of blood in the stools. Laboratory evaluation must include a complete blood count to assess hemoconcentration and leucocytosis, as well as laboratory tests (serum sodium, potassium, chloride, bicarbonate and creatinine, and urea nitrogen), stool tests including Wright's stain for leucocytes, *C. difficile*

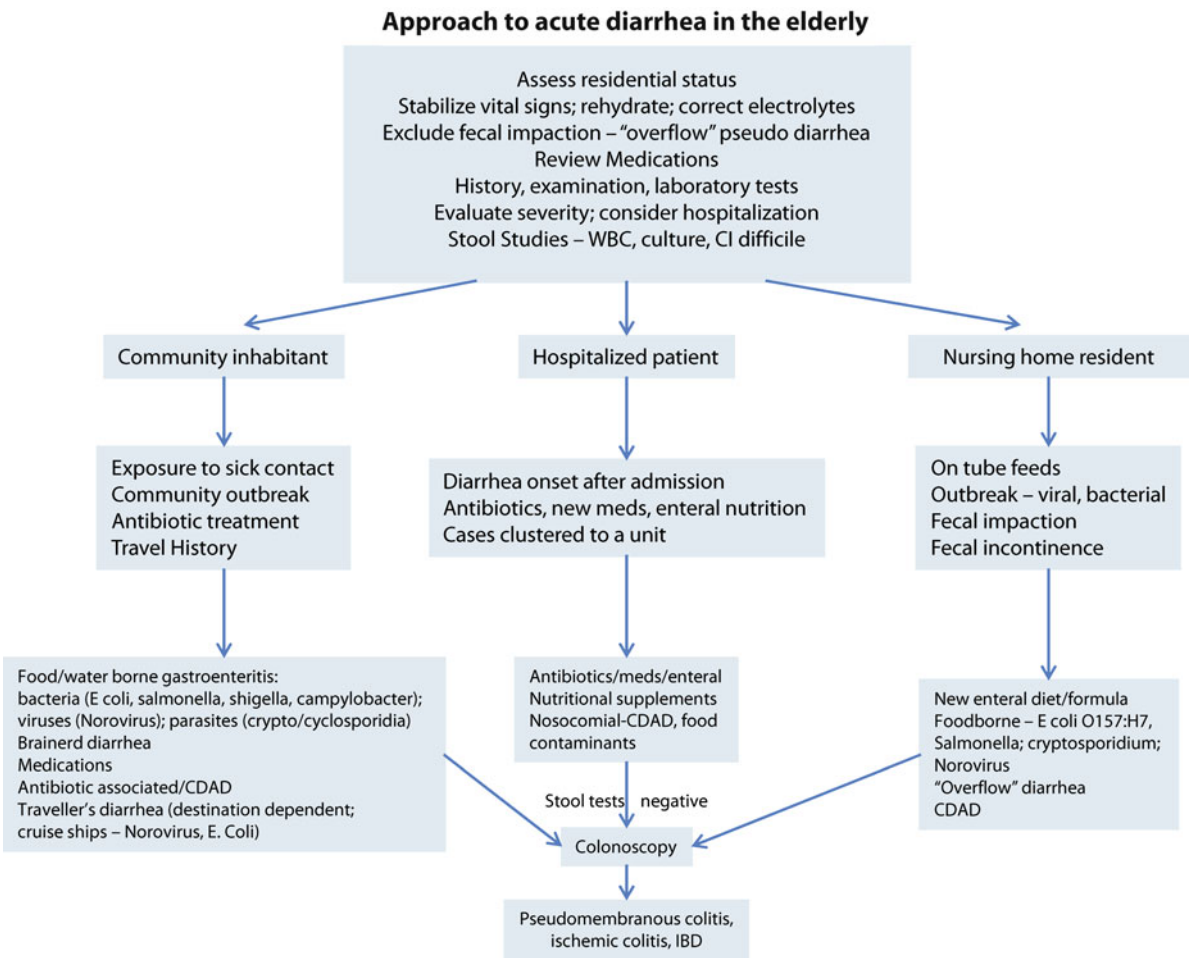

Fig. 35.1 After initial evaluation and management, further diagnostic tests are directed based on the patient's residential status. *CDAD Clostridium difficile*-associated diarrhea; *IBD* inflammatory bowel disease

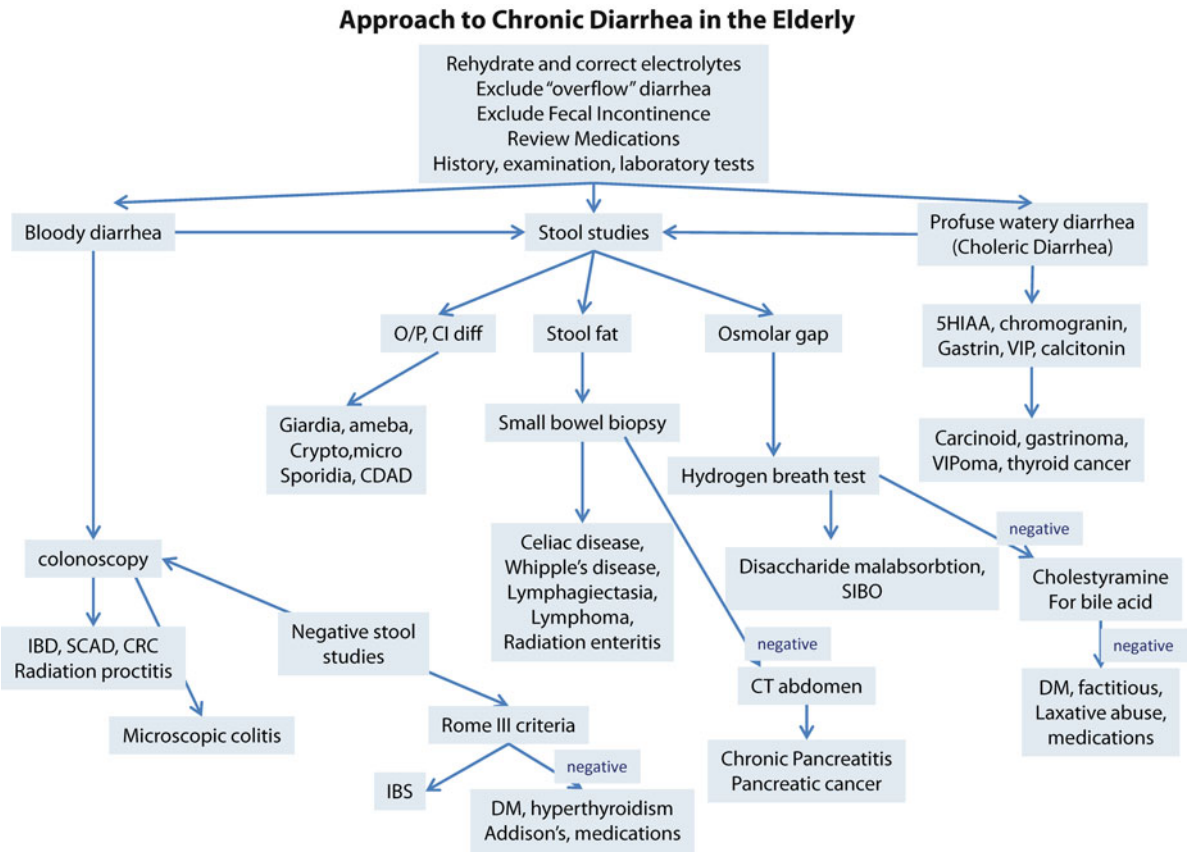

Fig. 35.2 Evaluation of Chronic diarrhea can be exhaustive and is initiated based on stool character. *CDAD C. difficile*-associated diarrhea; *CRC* colorectal cancer; *DM* diabetes mellitus; *IBD* inflammatory bowel disease; *IBS* irritable bowel syndrome; *O/P* ova and parasite; SIBO small intestinal bacterial overgrowth; *SCAD* segmental colitis associated with diverticulosis; *VIP* vasoactive intestinal peptide

toxin, ova, and parasite and bacterial cultures. Endoscopic evaluation with sigmoidoscopy or colonoscopy with biopsy is indicated in patients suspected to have *C. difficile* colitis or ischemic colitis [74].

The approach to evaluation of chronic diarrhea is exhaustive since the differential diagnosis is extensive (Table 35.4). Fecal impaction and pseudodiarrhea and fecal incontinence misreported by patients should be excluded. Attention to drug history and diarrhea as an adverse drug event is important. Likewise, the entire process of tube feeding requires a careful review of the feeding prescription. If the diagnosis is not obvious after the history and physical examination, it is worthwhile to characterize the diarrhea as bloody or nonbloody, and if the latter, whether it is secretory, inflammatory, osmotic or steatorrhea. Figure 35.2 outlines the evaluation of chronic diarrhea. Osmotic diarrhea usually ceases upon fasting, although some decrease in stool output may be seen in all patients irrespective of the etiology of diarrhea. In osmotic diarrhea, the fecal osmotic gap is greater than 50 mOsm/kg [75]. A low stool pH is indicative of carbohydrate malabsorption and should prompt a diet review. Hydrogen breath test may confirm lactose malabsorption and small intestinal bacterial overgrowth. A high blood magnesium level suggests inadvertent or prescribed use of magnesium-containing laxatives as possible basis for diarrhea.

Steatorrhea occurs due to maldigestion resulting from pancreaticobiliary disease or malabsorption resulting from small intestinal mucosal disease. The secretin test evaluates pancreatic exocrine function as does the stool chymotrypsin activity and an empiric trial of pancreatic enzymes.

Secretory or inflammatory diarrhea is usually due to infectious or neoplastic causes. Infectious agents causing chronic diarrhea include bacteria and parasites and can be diagnosed by serologies and stool tests. Structural disease can be evaluated by small bowel radiographs, endoscopy with or without mucosal biopsy, colonoscopy, and abdominal computed tomography scan as dictated by the results of initial workup. Once structural causes are ruled out, selective testing of plasma peptides (gastrin, calcitonin, VIP, and somatostatin), urine (5-HIAA, metanephrines, and histamines), and other tests (TSH, ACTH stimulation, serum protein electrophoresis, and immunoglobulin) should be considered. Therapeutic cholestyramine trial can diagnose bile acid diarrhea.

Treatment

Acute uncomplicated diarrhea is often self-limited and requires no treatment other than self or caregiver-administered oral fluids and, occasionally, with antidiarrheal medications. Self-medication for uncomplicated diarrhea does not cause harm to the patient. Self-treatments include oral rehydration solutions, dietary restrictions, antidiarrheals, probiotics, and antimicrobials by the traveler. The frail elderly and the older adult with multiple comorbidities should be advised to seek medical attention if diarrhea is severe or persistent [76].

Rehydration is essential in the treatment of diarrhea and critical in the elderly patients who have decreased total body water and a reduced response to thirst. Due to decreased mobility, limited dexterity, impaired communication abilities, and at times impaired cognitive function, access to fluids is limited. Dysphagia may compound the problem by limiting oral fluid intake in large amounts. Volume status should be assessed carefully as comorbidities such as congestive heart failure or chronic kidney disease limit the speed of fluid replacement. Volume deficits are manifested as thirst, fatigue, tachycardia, and hypotension and should be addressed promptly by electrolytes and nutrient replacement (addressed in other chapters).

Nonspecific therapy includes antidiarrheal medications such as opiates, adrenergic agents, somatostatin analogs, bile acid-binding resins, and fiber supplements. Opiates should be avoided when an infectious etiology for diarrhea is suspected.

Empiric therapies include specific treatments for suspected disease entities. Pancreatic enzymes are prescribed for pancreatic insufficiency; lactose intolerance is best treated by a lactose-free diet, while celiac disease is addressed by a gluten-free diet; antibiotics and rifaximin are useful in small intestinal bacterial overgrowth, and cholestyramine in bile salts malabsorption.

Definitive therapy in general is tailored to the etiology, and hence the importance of an accurate diagnosis. Antibiotic treatment is limited to patients with invasive infections, severe disease, and outbreaks within a confined environment, guided by clinical suspicion for specific organisms and diagnostic tests. Judicious use of antibiotics is recommended to decrease the incidence and recurrence of disease and prevent emergence of antibiotic resistance [14].

Dietary modifications are important therapies in celiac disease, lactose intolerance, small intestinal bacterial overgrowth, pancreatic insufficiency, and even enteral feeding-associated diarrhea.

Specific pharmacologic agents are needed for IBD, microscopic colitis, neuroendocrine tumors, and metabolic disturbances.

In nursing homes, rehabilitation, and long-term care facilities, an attentive staff is essential to the timely diagnosis and treatment of diarrheal disease and to lower diarrhea-related morbidity and mortality. Close follow-up care to ensure adequate hydration and electrolyte repletion is imperative. Infection control measures to contain infectious outbreaks should be emphasized through staff education [6]. Prompt resuscitation should address fluid and electrolyte repletion. Oral rehydration may not be the optimal approach for older patients with dementia or dysphagia where intravenous fluid resuscitation is often necessary.

Key Points

- Acute and chronic diarrhea occur commonly in the geriatric age group, but are often overlooked and inadequately addressed or treated.
- Several factors increase the risk for diarrheal disease and its complications in the elderly, including polypharmacy.
- Diarrhea may precipitate fecal incontinence, which leads to embarrassment, social isolation, and often to institutionalization.
- Residents of long-term care facilities are especially vulnerable to the outbreaks of diarrhea with increased morbidity and mortality.
- A high degree of suspicion should be maintained for *Clostridium difficile* colitis.
- Corrective approach to diarrhea entails obtaining a detailed history, including diet, drugs, disease status, and residential status, in addition to addressing the clinical status and choosing a select battery of tests.
- Prompt diagnosis and early resuscitation is necessary to prevent complications of diarrhea in the older adult especially if multiple comorbidities, frailty, and poor nutritional status are present.

References

1. Steingart CR, Megran DW. Infectious diarrhea. Curr Treat Opt Infect Dis. 2000;2(4):316–22.
2. Jones TF, McMillian MB, Scallan E, et al. A population-based estimate of the substantial burden of diarrheal disease in the United States; FoodNet, 1996–2003. Epidemiol Infect. 2007;135:293–301.
3. Lopman BA, Hall AJ, Curns AT, et al. Increasing rates of gastroenteritis hospital discharges in US adults and the contribution of norovirus, 1996–2007. Clin Infect Dis. 2011;4:466–74.
4. Adiga GU, Dharmarajan TS, Pitchumoni CS. Diarrhea in older adults. Pract Gastroenterol. 2005;29(4):63–82.
5. Fine KD, Schiller LR. AGA technical review on the evaluation and management of chronic diarrhea. Gastroenterology. 1999;116:1464–86.
6. Trinh C, Prabhakar K. Diarrheal diseases in the elderly. Clin Geriatr Med. 2007;23:833–56.
7. Montrose MH, Keely SJ, Barrett KE. Electrolyte secretion and absorption: small intestine and colon. In: Yamada T, Alpers DH, Laine L, et al., editors. Textbook of gastroenterology, vol. 1. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 1999. p. 320–55.

8. Schiller LR. Diarrhea and malabsorption in the elderly. Gastroenterol Clin North Am. 2009;38:481–502.
9. Holt PR. Diarrhea and malabsorption in the elderly. Gastroenterol Clin North Am. 2001;30(2):427–44.
10. Shah BB, Farah KF, Goldwasser B, et al. Pancreatic diseases in the elderly. Pract Gastroenterol. 2008;32(10):21–32.
11. Almeida JA, Kim R, Stoita A, et al. Lactose malabsorption in the elderly: role of small intestinal bacterial overgrowth. Scand J Gastroenterol. 2008;43:146–54.
12. Riordan SM, McIver CJ, Wakefield D, et al. Small intestinal bacterial overgrowth in the symptomatic elderly. Am J Gastroenterol. 1997;92(1):47–51.
13. Manatsathit S, DuPont HL, Farthing M, et al. Guideline for the management of acute diarrhea in adults. J Gastroenterol Hepatol. 2002;17(Suppl):s54–71.
14. Thielman NM, Guerrant RL. Acute infectious diarrhea. N Engl J Med. 2004;350(1):38–47.
15. Thomas PD, Forbes A, Green J, et al. Guidelines for the investigation of chronic diarrhea, 2nd edition. Gut. 2003;52(Suppl v): v1–15.
16. Lew JF. Diarrheal deaths in the United States, 1979 through 1987. A special problem for the elderly. JAMA. 1991;256(24):3280–4.
17. Meads PS, Slutsker L, Dietz V, et al. Food-related illness and death in the United States. Emerg Infect Dis. 1999;5:607–25.
18. Winquist AG, Roome A, Mshar R, et al. Outbreak of campylobacteriosis at a senior center. J Am Geriatr Soc. 2001;49:304–7.
19. Slotwiner-Nie PK, Brandt LJ. Infectious diarrhea in the elderly. Gastroenterol Clin North Am. 2001;30(3):625–35.
20. Leffler DA, Lamont JT. A 69-year-old woman presenting to the hospital with 48 hours of abdominal pain and diarrhea. Clin Gastroenterol Hepatol. 2009;7:1046–8.
21. Pawlowski SW, Allen CA, Sevilleja EJ, et al. Persistent nausea, vomiting and diarrhea in an immunocompetent elderly gentleman. Clin Infect Dis. 2011;52(4):551–2.
22. Naumova EN, Egorov AI, Morris RD, et al. The elderly and waterborne *Cryptosporidium* infection: gastroenteritis hospitalizations before and during the 1993 Milwaukee outbreak. Emerg Infect Dis. 2003;9(4):418–25.
23. Hill DR, Ericsson CD, Pearson RD, et al. The practice of travel medicine: guidelines by the infectious disease society of America. Clin Infect Dis. 2006;43:1499–539.
24. Adachi JA, Jiang ZD, Mathewson JJ, et al. Enteroaggregative *Escherichia coli* as a major etiologic agent in traveler's diarrhea in 3 regions of the world. Clin Infect Dis. 2001;32(12):1706–9.
25. de la Cabada Bauche J, DuPont HL. New developments in traveler's diarrhea. Gastroenterol Hepatol. 2011;7(2):88–95.
26. Luft VC, Beghetto MG, de Mello ED, et al. Role of enteral nutrition in the incidence of diarrhea among hospitalized adult patients. Nutrition. 2008;24:528–35.
27. Shimoni Z, Averbach Y, Shir E, et al. The addition of fiber and the use of continuous infusion decrease the incidence of diarrhea in elderly tube fed patients. J Clin Gastroenterol. 2007;41:901–5.
28. Scheppach W, Burghardt W, Bartram P, et al. Addition of dietary fiber to liquid formula diets: the pros and cons. J Parenter Enteral Nutr. 1990;14:204–9.
29. Nakao M, Ogura Y, Satake S, et al. Usefulness of soluble fiber for the treatment of diarrhea during enteral nutrition in elderly patients. Nutrition. 2002;18:35–9.
30. Joo YJ, Koo JH, Song SH. Gastrocolic fistula as a cause of persistent diarrhea in a patient with a gastrostomy tube. Arch Phys Med Rehabil. 2010;91(11):1790–2.
31. Higgins PDR, Davis KJ, Laine L. Systematic review: the epidemiology of ischemic colitis. Aliment Pharmacol Ther. 2004;19:729–38.
32. Cangemi JR, Picco MF. Intestinal ischemia in the elderly. Gastroenterol Clin North Am. 2009;38:527–40.
33. Ozden N, Gurses B. Mesenteric ischemia in the elderly. Clin Geriatr Med. 2007;23:871–87.
34. Ananthakrishnan AN, Binion DG. Treatment of ulcerative colitis in the elderly. Dig Dis. 2009;27:327–34.
35. Katz S, Feldstein R. Inflammatory bowel disease of the elderly: a wake up call. Gastroenterol Hepatol. 2008;4(5):337–47.
36. Nyhlin N, Bohr J, Eriksson S, et al. Systematic review: microscopic colitis. Aliment Pharmacol Ther. 2006;23:1525–34.
37. Williams JJ, Beck PL, Andrews CN, et al. Microscopic colitis—a common cause of diarrhea in older adults. Age Ageing. 2010;39(2):162–8.
38. Williams JJ, Kaplan GG, Makhija S, et al. Microscopic colitis-defining incidence rates and risk factors: a population-based study. Clin Gastroenterol Hepatol. 2008;6:35–40.
39. Pardi DS, Kelly CP. Microscopic colitis. Gastroenterology. 2011;140:1155–65.
40. Pardi DS. Microscopic colitis. Gastroenterol Hepatol. 2009;5(4):283–8.
41. Touzios JG, Dozois EJ. Diverticulosis and acute diverticulitis. Gastroenterol Clin North Am. 2009;38:513–25.
42. Johnson MW, Ellis HJ, Asante MA, et al. Celiac disease in the elderly. Nat Clin Pract Gastroenterol Hepatol. 2008;5:697–706.
43. Rashtak S, Murray JA. Celiac disease in the elderly. Gastroenterol Clin North Am. 2009;38:433–46.
44. Vilpulla A, Kaukinen K, Luostarinen L, et al. Increasing prevalence and high incidence of celiac disease in elderly people: a population-based study. BMC Gastroenterol. 2009;9:49, 1–5.
45. Elphick HL, Elphick DA, Sanders DS. Small bowel bacterial overgrowth. Geriatrics. 2006;61:21–6.
46. Bennet G, Talley NJ. Irritable bowel syndrome in the elderly. Best Pract Res Clin Gastroenterol. 2002;16(1):63–76.
47. Spiller RC, Thompson WG. Bowel disorders, Rome foundation diagnostic algorithms. Am J Gastroenterol. 2010;105:775–85.
48. Fernandez-Banaras F, Estave M, Salas A, et al. Systematic evaluation of the causes of chronic watery diarrhea with functional characteristics. Am J Gastroenterol. 2007;102:2520–8.
49. Wilt TJ, Shaukat A, Shamliyan T, et al. Lactose intolerance and health. Evid Rep Technol Assess (Full Rep). 2010;192:1–410.
50. Di Stefano M, Veneto G, Malservisi S, et al. Lactose malabsorption and intolerance in the elderly. Scand J Gastroenterol. 2001;36(12): 1274–8.
51. Laugier R, Sarles H. The pancreas. Clin Gastroenterol. 1985;14:749–56.
52. http://wonder.cdc.gov/wonder/prevguid/p0000063/p0000063.asp. Complications of diabetes mellitus. Accessed 15 Apr 2011.
53. Soffer EE, Hull T. Fecal incontinence: a practical approach to evaluation and treatment. Am J Gastroenterol. 2000;95(8):1873–80.
54. Whitehead WE, Borrud L, Goode PS, et al. Fecal incontinence in US adults: epidemiology and risk factors. Gastroenterology. 2009;137:512–7.
55. Crane SJ, Talley NJ. Chronic gastrointestinal symptoms in the elderly. Clin Geriatr Med. 2007;23:721–34.
56. Karling P, Abrahamsson H, Dolk A, et al. Function and dysfunction of the colon and anorectum in adults: working team report of the Swedish Motility Group (SMoG). Scand J Gastroenterol. 2009;44:646–60.
57. Leung FW, Schnelle JF. Urinary and fecal incontinence in nursing home residents. Gastroenterol Clin North Am. 2008;37:607–707.
58. Chassagne P, Landrin I, Neveu C, et al. Fecal incontinence in the institutionalized elderly. Am J Med. 1999;106:185–90.
59. Markland AD, Good PS, Burgio KL, et al. Incidence and risk factors for fecal incontinence in black and white older adults: a population-based study. J Am Geriatr Soc. 2010;58(7):1341–6.
60. Read NW, Abouzekry L. Why do patients with fecal impaction have fecal incontinence. Gut. 1986;27:283–7.
61. Wald A. Management and prevention of fecal impaction. Curr Gastroenterol Rep. 2008;10(5):499–501.
62. Leung FW, Rao SS. Fecal incontinence in the elderly. Gastroenterol Clin North Am. 2009;38(3):503–11.

63. Al Ameel T, Andrew M, MacKnight C. The association of fecal incontinence with institutionalization and mortality in older adults. Am J Gastroenterol. 2010;105:1830–4.
64. Rey E, Choung RS, Schleck CD, et al. Onset and risk factors for fecal incontinence in a US community. Am J Gastroenterol. 2010;105(2):412–9.
65. Grover M, Busby-Whitehead J, Palmer MH, et al. Survey of geriatricians on the effect of fecal incontinence on nursing home referral. J Am Geriatr Soc. 2010;58(6):1058–62.
66. Archbald-Pannone L, Sevilleja EJ, Guerrant R. Diarrhea, *Clostridium difficile*, and intestinal inflammation in residents of a long-term care facility. J Am Med Dir Assoc. 2010;11(4): 263–7.
67. Morley JE, Steinberg KE. Diarrhea in long-term care: a messy problem. J Am Med Dir Assoc. 2009;10(4):213–7.
68. Kirk MD, Fullerton KE, Hall GV, et al. Surveillance for outbreaks of gastroenteritis in long-term care facilities, Australia, 2002–2008. Clin Infect Dis. 2010;51(8):907–14.
69. Jones TF. When diarrhea gets deadly: a look at gastroenteritis outbreaks in nursing homes. Clin Infect Dis. 2010;51(8):915–6.
70. Pilotto A, Franceschi M, Vitale D, et al. The prevalence of diarrhea and its association with drug use in elderly outpatients: a multicenter study. Am J Gastroenterol. 2008;103(11):2816–23.
71. Schiller LR. A Practical approach to testing patients with chronic diarrhea. Rev Gastroenterol Disord. 2007;7 Suppl 3:S19–26.
72. Schiller LR. Management of diarrhea in clinical practice: strategies for the primary care physician. Rev Gastroenterol Disord. 2008;7 Suppl 3:S27–38.
73. Headstrom PD, Surawicz CM. Chronic diarrhea. Clin Gastroenterol Hepatol. 2005;3:734–7.
74. Schiller LR. Diarrhea. Med Clin North Am. 2000;84:1259–74.
75. Eherer AJ, Fordtran JS. Fecal osmotic gap and pH in experimental diarrhea of various causes. Gastroenterology. 1992;103:545–51.
76. Wingate D, Phillips SF, Lewis SJ, et al. Guidelines for adults on self-medication for the treatment of acute diarrhea. Aliment Pharmacol Ther. 2001;15:773–82.

Upper and Lower Gastrointestinal Bleeding

36

C.S. Pitchumoni and Alexander Brun

Introduction

Acute gastrointestinal (GI) hemorrhage is a common cause of hospitalization in the elderly. Currently, causes of GI bleeding are divided into three categories: upper (proximal to ligament of Treitz), middle (small bowel), and lower (colonic). The section on wireless capsule endoscopy discusses the topic of small bowel (midgut) bleeding. The terms used in the description of gastrointestinal bleeding are tabulated in Table 36.1. While hematochezia points to lower gastrointestinal bleeding (LGIB) as the source, melena and hematemesis indicate upper gastrointestinal bleeding (UGIB).

The incidence of UGIB is approximately 170 cases per 100,000 annually, increasing with age [1]. LGIB is much less common, with only 20 per 100,000 [2]. Given that older age is associated with higher rates of incidence, morbidity, and mortality [3], GI bleeding must be taken seriously and managed promptly.

Upper Gastrointestinal Bleeding

The main causes of UGIB are peptic ulcers, esophagitis, esophageal or gastric varices, gastric tumors, and portal hypertensive gastropathy (see Table 36.2). In January 2010, a group of 34 experts from 15 countries revised the 2003 guidelines for the management of patients with nonvariceal UGIB [4, 5]. Management of UGIB is dictated by the type of lesion and risk of re-bleeding.

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General Management Strategy (See Fig. 36.1)

Initial Evaluation and Resuscitation

The principles guiding evaluation of a patient with UGIB and LGIB are the same.

(a) Initial History
History taking should be focused while simultaneous general resuscitation measures are taken. As in any patient with gastrointestinal bleeding, the initial history should include use of nonsteroidal anti-inflammatory drugs (NSAIDs), dual antiplatelet therapy with aspirin (ASA) and clopidogrel [6], selective serotonin reuptake inhibitors [7], anticoagulants, previous history of peptic ulcer, immunosuppression, vascular disease, past bleeding episodes, radiation therapy for prostatic or pelvic cancer, recent colonoscopy or polypectomy, cirrhosis of liver, anemia, inflammatory bowel disease (IBD), and coagulopathy [8].

(b) Rectal Examination and Nasogastric Tube Aspiration
A proper digital rectal examination helps diagnose rectal neoplasms and confirm the patient's description of stool color [8]. Massive UGIB and a distal source in the colon may manifest as hematochezia, which can be differentiated by the presence or absence of fresh blood in the nasogastric tube aspiration.

(c) Initial Laboratory Studies
Initial laboratory testing should include a complete blood count, coagulation profile, serum chemistry for electrolytes, liver tests, typing, and cross matching of blood. An electrocardiogram should be performed in all cases because it provides critical information about preexisting coronary artery disease, as well as evidence of active ischemia.

(d) Evaluation of Severity
Prognostic scales, such as the pre-endoscopy Glasgow–Blachford and Rockall bleeding score for nonvariceal

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Table 36.1 Terms and their significance [4, 5]

Hematemesis: Vomiting of blood. It indicates an upper GI source of bleeding proximal to the ligament of Treitz. It may consist of bright red blood indicative of active bleeding or coffee ground material
Melena: Passage of black, tarry, foul smelling stool as a result of degradation of hemoglobin to hematin. At least 50 cc of blood in the upper GI tract is required to cause melena. The source of bleeding is almost always in the upper GI tract, but may be in the distal small bowel or right colon (early and slow bleeding)
Hematochezia: Passage of bright red blood through the rectum with or without stool. The source is often the lower GI tract, but brisk UGIB can cause hematochezia
Obscure bleeding: Can have two forms Obscure—occult bleeding which is not visible to the patient and is manifested by recurrent iron deficiency anemia and/or repeated positive fecal occult blood test results Obscure—overt bleeding as manifested by recurrent passage of visible blood
Upper gastrointestinal bleeding: Bleeding site proximal to the ligament of Treitz
Middle gastrointestinal bleeding: Bleeding from the small bowel not visible by EGD or colonoscopy
Lower gastrointestinal bleeding: Bleeding site is usually in the colon *Acute lower gastrointestinal bleeding*: Bleeding of recent duration (arbitrarily defined as <3 days) and may result in the need for blood transfusion, instability of vital signs, and/or anemia *Chronic lower gastrointestinal bleeding*: Bleeding associated with intermittent or slow blood loss over a period of several days or longer

Table 36.2 Causes of acute upper gastrointestinal bleeding (UGIB) [4, 5]

Peptic ulcer disease	Commonly caused by aspirin (ASA) or other NSAIDs, *Helicobacter pylori* infection or both. Patients present with abdominal pain, hematemesis, or melena
Varices	Esophageal varices related to portal hypertension are the second most common cause of severe UGIB
Tumor	Is responsible for a small fraction of UGIB. The tumor is usually ulcerated and large
Mallory–Weiss tear	Mallory–Weiss tear of the lower end of esophagus commonly occur in patients with recurrent emesis. The patient presents with hematemesis
Gastric antral vascular ectasia	Also known as watermelon stomach. Presents with melena and iron deficiency anemia. Stripes of ectatic mucosal blood vessels originating from the pylorus and extending proximally is the classic pattern seen on endoscopy
Dieulafoy's lesion	Is a large submucosal artery that protrudes through the mucosa and can cause severe bleeding

Clinical presentations indicating a higher risk of re-bleeding or mortality include hemodynamic instability, rectal passage of blood, elevated levels of urea, creatinine or serum aminotransferase, melena, and sepsis [4] (see Table 36.3). Age>65, chronic alcoholism, cancer, and comorbid illnesses are other predictive factors of poor prognosis.

(e) Resuscitation

In all cases of GI bleeding, resuscitative measures include fluid administration via large bore intravenous catheters and blood transfusion. The ideal hemoglobin concentration depends on age, bleeding rate, and existence of comorbid conditions. Red blood cell transfusion is recommended in patients with a hemoglobin level of ≤7.0 g/dL [5]. Hemoglobin level is to be maintained at about 10 g/dL (hematocrit 30%) in the elderly with coronary heart disease [8].

Resuscitative measures should aim at lowering the international ratio (INR) to less than 1.8, which is associated with lower mortality and fewer myocardial infarctions [12, 13]. Vitamin K administration may be needed in addition to discontinuance of anticoagulants to achieve optimal results.

Proton pump inhibitor (PPI) therapy is useful in patients with UGIB because it prevents or reduces clot lysis by acid [14]. Pre-endoscopic erythromycin as a prokinetic drug may be helpful in patients who are suspected of having blood clots in the gastrointestinal tract and those who have recently eaten to improve endoscopic which helps identify the source of bleeding and reduces the need for repeat endoscopies [5, 15].

(f) Intensive Care

Admission to the intensive care unit is appropriate when patient-related and endoscopic factors of severity and recurrence warrant it (see Table 36.3).

Endoscopic Management

Esophagogastroduodenoscopy (EGD) should be performed within the first 24 h of presentation (early endoscopy) because it is associated with a reduction in mortality rates (in contrast to older thoughts), the risk of re-bleeding, duration of hospitalization, and the need for surgical intervention [16]. Early endoscopy may have to be delayed in some high-risk patients with active coronary syndrome or when perforation is suspected.

Endoscopic predictors of increased risk for re-bleeding include type of lesion, high risk stigmata of ulcer hemorrhage (active bleeding, nonbleeding visible vessel and adherent clot), ulcer size >2 cm and its location [5, 17–20] (see Table 36.3).

Thermal devices, injection therapy, and hemoclipping are effective hemostatic treatments in patients with high-risk lesions, alone or in combination with epinephrine injection [21, 22]. Monotherapy with epinephrine injection provides suboptimal results [23] (see Table 36.4).

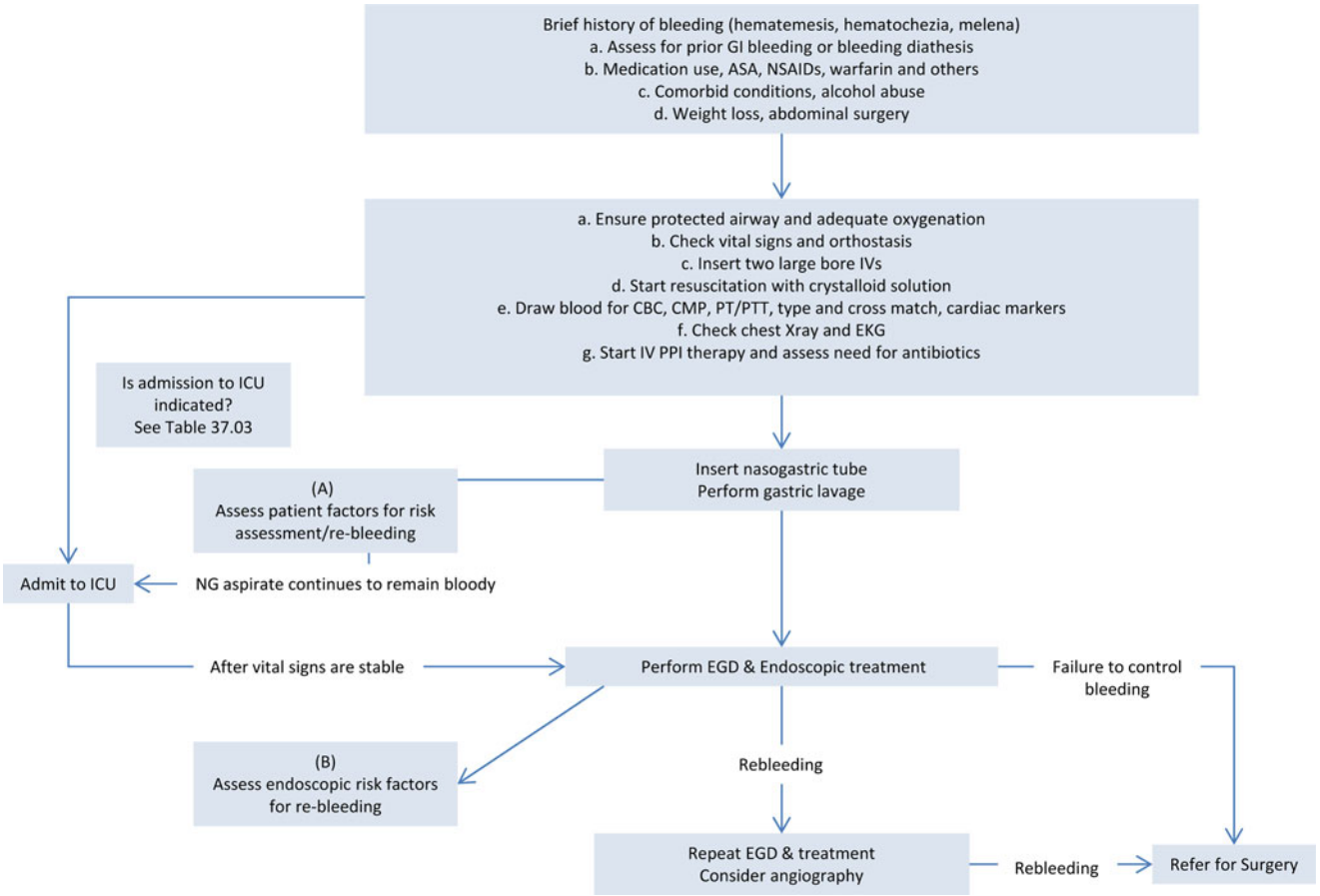

Fig. 36.1 An algorithmic approach to upper gastrointestinal bleeding (UGIB) [8–20]

Table 36.3 Factors predicting mortality and re-bleeding in elderly patient with UGIB

Early predictive factors		
Hemodynamic instability (systolic blood pressure <100 mmHg, hemoglobin <10 mg/dL, and tachycardia with or without orthostasis)		
Presentation as hematemesis or hematochezia		
Bloody NG aspirate that does not clear following lavage		
Concomitant liver, renal, cardiac, or pulmonary failure (acute or chronic)		
Coagulopathy		
In-hospital onset of UGIB		
(The above are some of the indications for ICU admission)		
Endoscopic factors[a]		
Ulcer base >2 cm in diameter		
Posterior duodenal bulb ulcer		
Endoscopic finding	Risk of re-bleeding (%)	Predicted mortality (%)
A. Arterial bleed	55	11
B. Non-bleeding visible vessel	43	11
C. Adherent clot	22	7
D. Flat spot	10	3
E. Clean base	5	2

[a]Endoscopic factors of adverse outcome A, B, C also help in triaging patient to ICU. Data from refs. [17–20]

Non-endoscopic Management Options

In severe UGIB, cases of high-risk bleeding and when endoscopic therapy fails, surgical consultation should be considered. For patients who are high-risk candidates for surgery, arteriographic study with embolization is particularly useful.

Even when endoscopy is successfully performed, high-risk patients should be hospitalized for 72 h to monitor for the risk of re-bleeding [20, 24]. Continuous-infusion of PPI therapy is recommended in patients with high-risk stigmata to decrease re-bleeding after endoscopic therapy. Routine second endoscopy is not necessary; it provides no additional benefits over PPI therapy [25, 26]. A second endoscopy is needed if there is evidence of re-bleeding after initial successful endoscopic therapy.

Peptic Ulcer Disease

Peptic ulcer disease is the most common cause of UGIB in the elderly, accounting for 28–70% of cases [27–29]. It is more often attributed to the mucosal damage caused by use of NSAIDs than due to infection with *Helicobacter pylori* (*H. pylori*) [30, 31]. Patients, however, should be tested for the presence of *H. pylori* even when there is history of NSAID use [32].

Table 36.4 Available options for endoscopic control of GI bleeding [2–23]

Procedure[a]	Comments
Injection of epinephrine/sclerosing agents	Sclerosant agents such as polidocanol or ethanol are popularly used in the USA
Argon plasma coagulation	For non-contact coagulation. Ideal for lesions with large surface areas, i.e., watermelon stomach and portal hypertensive gastropathy
Clips	Provide mechanical hemostasis. Better than epinephrine injection or heater probe. Desirable in patients with coagulopathy, cirrhosis, and multi-system disease. Useful for ulcers, Dieulafoy's lesions and post-polypectomy bleeds
Thermal coagulation Bipolar/heater probe	Applied directly to bleeding point
Band ligation	Effective in varices
Histoacryl glue injection	For acute bleeding and fundal varices; is available in certain countries outside USA

[a]Option is chosen based on the lesion and *expertise of the endoscopist*. Procedures may be combined for better hemostasis

Table 36.5 Causes of acute lower gastrointestinal bleeding (LGIB) [42–50]

Diverticulosis	Acute, painless, and bright red bleeding (may be maroon or melenic depending on the site and rapidity of bleeding). Could be hemodynamically significant in the elderly with comorbid conditions. Bleeding stops spontaneously in most cases
Vascular ectasias	Painless hematochezia. Could be melenic based on the site and rapidity of bleeding. Rarely hemodynamically significant
Neoplasms	Painless, intermittent, small volume bleeding usually in occult fashion
Ischemic colitis	Altered blood mixed with loose stool. History of hypotensive event preceding the bleeding episode supports the diagnosis
Hemorrhoids	Intermittent, low volume bleeding coating the stool
Rectal ulcers	Common cause of severe hematochezia. Multiple painless rectal ulcers occur in bedridden patients, ICU patients or patients with severe constipation
Rectal varices	The frequency increases with degree of portal hypertension. They develop in the rectal mucosa between the superior hemorrhoidal veins (portal) and middle and inferior hemorrhoidal veins (systemic)
Post-polypectomy	Incidence is approximately 3%, commonly following polyp removal. Presents with painless hematochezia soon after polypectomy. It may be delayed up to 3 weeks post procedure

It is estimated that more than 50% of older adults are using either NSAIDs or ASA when they present with a bleeding episode [33]. The risk of bleeding doubles when NSAIDs are taken together with ASA, as opposed to either alone [34]. When ASA is used, even in small doses, the benefit of selective cyclooxygenase-2 (COX-2) inhibitors is hindered [35, 36]. Age >65 [37], past history of ulcer complications, comorbid conditions, alcohol consumption [38], smoking [39], corticosteroid use, antiplatelet, or anticoagulant therapy [37] while on NSAIDs increases the risk of UGIB. Mortality secondary to NSAID-related gastrointestinal bleeding has an annual relative risk of 4.1 compared to nonusers [40].

Continued PPI therapy is necessary to reduce the risk of recurrent bleeding in patients taking NSAIDs or those on cardiovascular prophylaxis with a history of ulcer bleeding [41]. If cardiovascular risks outweigh gastrointestinal ones, ASA therapy should be restarted after bleeding has stopped [42, 43].

Esophageal Varices

Esophageal and gastric varices constitute the second most common cause of serious UGIB, accounting for approximately 11% [28]. Variceal hemorrhage is a major complication of portal hypertension from cirrhosis. Large varices, the presence of red "wale" marks on varices, and hepatic pressure gradient >12 mmHg increase the risk of bleeding [44].

As with peptic ulcers, vasopressin or somatostatin is used as pharmacologic treatments. Endoscopic variceal band ligation has become the treatment of choice [45] and surgical therapy should be considered only as a measure of last resort. Model for End-Stage Liver Disease (MELD) score can be used as a predictor of mortality in patients who experience rebleeding within 6 weeks of endoscopic variceal band ligation [46].

Less Common Causes

On rare occasions, UGIB in the elderly can be caused by Mallory–Weiss tear, gastric antral vascular ectasia, aortoenteric fistula, Dieulafoy's lesion, and/or neoplasm.

Lower Gastrointestinal Bleeding

Diverticular disease, internal hemorrhoids, colitis (IBD, ischemic colitis, infectious colitis and drug-induced colitis), neoplasms, and angiodysplasias are responsible for the majority of LGIB cases [47, 48] (see Table 36.5). The in-hospital mortality rate of LGIB ranges from 2 to 4% [49]. Predictors of mortality include age >70, male gender, intestinal ischemia, two or more comorbidities, unrelated hemorrhage, coagulopathy, and hypovolemia [50].

General Management Strategy (See Fig. 36.2)

Initial Evaluation and Resuscitation

The same initial evaluation and resuscitation measures discussed above for UGIB should be employed for LGIB, with several exceptions noted in that section.

Severe LGIB is defined by transfusion requirements of ≥2 units of blood and/or hematocrit decrease of ≥20%. A syncopal episode, heart rate ≥100 beats/min, and ≤115 mmHg systolic blood pressure are early predictors of severity [51].

Endoscopic Management

Flexible sigmoidoscopy is inexpensive and can be performed even without a standard bowel preparation. However, as a preferred choice, colonoscopy is capable of detecting a definite cause in up to 90% of LGIB cases [52] and can guide therapeutic intervention.

There are many endoscopic treatment options, including BICAP, clips, heater probe, laser, argon plasma coagulation, and epinephrine or sclerosant injection (see Table 36.4). Rarely, acryl glue injection (rectal varices), rubber band (hemorrhoids and rectal varices), cryotherapy (hemorrhoids), infrared coagulation (hemorrhoids), and low voltage current (hemorrhoids) may also be used. The choice depends on the availability of the equipment, experience of local endoscopist, and the type of lesion.

Thorough cleansing of the colon is necessary to achieve optimum results during endoscopic evaluation. Sodium phosphate, magnesium citrate, and polyethylene glycol/electrolyte lavage solutions are the three main groups of osmotically

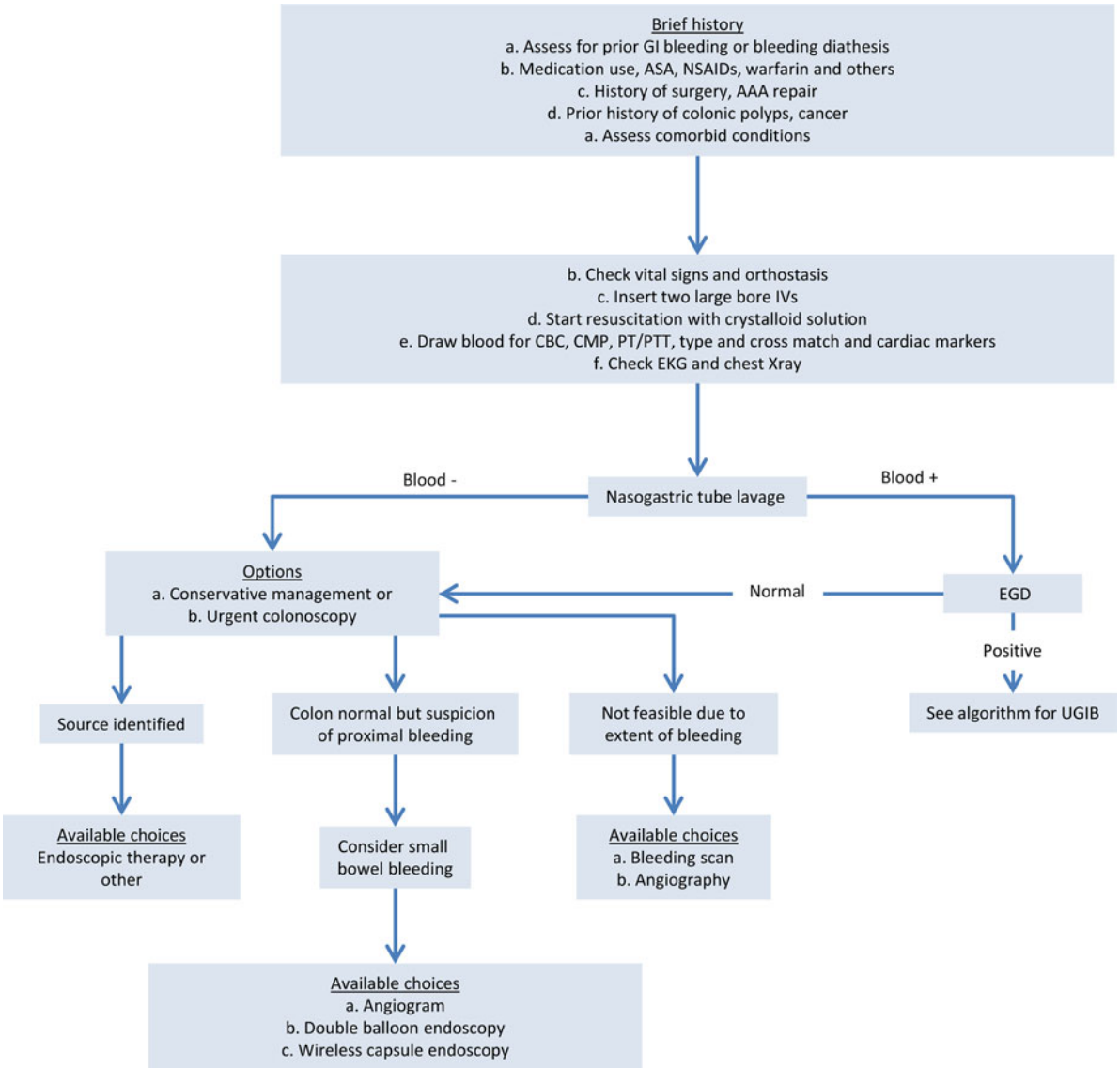

Fig. 36.2 An algorithmic approach to lower gastrointestinal bleeding (LGIB) [47–52]

Table 36.6 Adverse effects of osmotically acting cathartics

	Sodium phosphate	Magnesium citrate	Polyethylene glycol lavage
Hyponatremia	+	+	+
Hypokalemia	+		+
Hypocalcemia	+		
Hypernatremia	+		+
Hyperphosphatemia	+		
Hypermagnesemia		+	+
Other	Acute phosphate nephropathy Aphthous ulcers (rectosigmoidal)		Allergic reactions Aspiration

Table 36.7 Acute phosphate nephropathy risk factors

Age >60
Woman
Medications
Angiotensin converting enzyme inhibitors
Angiotensin receptor blockers
Diuretics
NSAIDs
Comorbidities
Congestive heart failure
Chronic kidney disease
Diabetes mellitus
Hypertension
Low body weight

acting cathartics that are used as bowel-cleansing agents. Although effective, magnesium and sodium-based products raise safety concerns, particularly in the elderly because of their hypertonic nature, which causes shifting in fluid and electrolyte balance in an age-group already prone to such disturbances [53, 54] (see Table 36.6). Absorption of large quantities of phosphorus and magnesium often results in different degrees of hyperphosphatemia and hypermagnesemia, respectively. Sodium-phosphate based products have been reported to cause acute phosphate nephropathy. Comorbidities and medications that affect the glomerular filtration rate, intestinal phosphate absorption, as well as water and electrolyte balance, predispose patients to the development of acute phosphate nephropathy by aggravating hyperphosphatemia [55] (see Table 36.7). By contrast, products containing polyethylene glycol/electrolyte lavage solutions do not lead to significant shifting of fluids and electrolytes since they do not induce absorption or excretion of ions across the intestinal mucosa [53, 56, 57]. Sufficient hydration in the elderly is nonetheless essential.

Non-Endoscopic Management Options

Angiography localizes a bleeding site when the rate of arterial bleeding is at least 0.5 mL/min and may help determine the cause of the bleeding [58]. Immediate cessation of bleeding is one advantage of embolotherapy. Microcatheter embolization using microcoils, polyvinal alcohol particles, and gelfoam is an effective method of controlling hemorrhage with a re-bleeding rate of <15% [59] and clinical success ranging from 70 to 90% [49]. Major adverse events, including vascular injuries, contrast reactions, and transient ischemic attacks may occur rarely [60].

Red blood cell scintigraphy, involving injection of technetium into the patient's bloodstream, detects bleeding in amounts as small as 0.04 mL/min [61]. In pooled data from 16 different studies, bleeding scan was accurate in localizing the bleeding site in 78% of cases [62]. The specificity and sensitivity of this procedure is 93% and 95%, respectively [61].

Surgical intervention is a measure of last resort and, as a rule of thumb, is indicated when the blood transfusion requirement is greater than 4 units in 24 h, or when nonsurgical methods have failed to locate the bleeding source and/or control hemorrhage [47, 63].

Diverticulosis

Diverticular disease is discussed in a separate chapter.

Diverticulosis is the single most common cause of LGIB, accounting for approximately 33% [50]. Regular use of NSAIDs and ASA is a significant risk factor for colonic diverticular hemorrhage [64, 65]. Most diverticula bleed in bursts and cease spontaneously [66, 67]. The risk of re-bleeding ranges from 18 to 38% after spontaneous cessation [63, 68], in comparison to a recurrence rate of 0–38% upon completion of endoscopic therapy [59, 69]. The overall mortality rate in the elderly is approximately 4% [70].

Urgent colonoscopy following a rapid purge with polyethylene glycol-based solution can achieve hemostasis using bipolar probe coagulation, epinephrine injection, metallic clips, fibrous glue, and band ligation [69, 71] (see Table 36.4). Angiographic treatment with vasopressin infusion or embolization of the bleeding vessel is successful in managing persistent bleeding in most cases [72–74]; however, re-bleeding on cessation of vasopressin and intestinal infarction following embolization can occur [75]. Surgery may be necessary in up to a quarter of patients with hemodynamically significant diverticular bleeding [66].

Vascular Ectasias

Approximately 3–12% of acute LGIB cases are due to vascular ectasias [76], which have exclusive occurrence in the right colon. There is an association between severe aortic stenosis and bleeding from intestinal angiodysplasia [77]. On histopathologic examination they are noted to be ectatic, distorted veins, venules, and capillaries mostly lined only by endothelium and, occasionally, by a small amount of smooth muscle [78, 79]. Coagulopathy, platelet dysfunction, and NSAID or ASA use trigger bleeding [80].

Bleeding from vascular ectasias is usually subacute, recurrent, and manifested as iron deficiency anemia and occult blood positivity. A small number of patients may have massive hemorrhage [81]. Definitive treatment for bleeding vascular ectasias is with heater probe or bipolar methods during endoscopy. Intra-arterial trans-catheter embolization may also stop bleeding. When bleeding is recurrent and massive, right hemi-colectomy is recommended.

Colitis (Ischemic, Infectious, and Inflammatory)

Colitis may present with abdominal pain, diarrhea, hematochezia, fever, and/or dehydration. Ischemic and infectious colitis are far more common than IBD in older adults. Severe hemorrhage is rarely secondary to ischemic colitis.

Patients with ischemic colitis often experience crampy abdominal pain followed by bloody diarrhea. The blood may be bright red or maroon, and is commonly mixed with the stool. Ischemic colitis most often involves the watershed areas, i.e., the splenic flexure, right colon or recto-sigmoid junction. It can result from changes in the mesenteric vasculature (anatomic or functional), hypotension or embolic events. Initial KUB or barium enema (no longer commonly performed) may show "thumb impressions" on the wall of the air-filled colon. Sigmoidoscopy can reveal colonic ulcerations, often with rectal sparing. Histologically, mucosal necrosis with a paucity of acute or chronic inflammation is evident.

Most cases resolve with supportive treatment. About 20% of patients may develop chronic colitis, which resembles ulcerative colitis, but differs both in being segmental with rectal sparing, and in being unresponsive to standard ulcerative colitis treatment [82]. Rarely, ischemic colitis can be complicated by perforation or stricture formation and may necessitate surgical intervention [82, 83].

Older adults are at increased risk for infectious colitis and its complications [69], which is associated with higher mortality in this age group [84]. Common causes of enteric infections in elderly patients are *Clostridium difficile, Campylobacter, Salmonella, Shigella,* and *Escherichia coli O157:H7* [85]. Most common organisms can be identified on stool culture. *C. difficile* colitis seldom causes clinically significant LGIB [84].

There is a bimodality in age-specific incidence rate for IBD, with a second peak occurring between the ages of 60–70 [86]. Although gastrointestinal bleeding is common with IBD, severe hematochezia is infrequent. Neither therapy for acute exacerbations nor for quiescent disease has been specifically studied in the older population; however, general principles of management apply to this age group.

Neoplasms

Acute LGIB from colon carcinoma or colonic polyps is unusual, accounting for 5–11% [76] and 2–8% [49] of cases, respectively. Most often bleeding is occult. Bleeding occurs secondary to an overlying erosion or ulceration of the neoplasm and may be exacerbated by initiation of anti-thrombotic medications such as ASA, clopidogrel, or warfarin. Post-polypectomy bleeding can occur within hours of the procedure (in < 3% of cases), in particular after removal of sessile or large polyps [76]. Delayed post-polypectomy bleeding on average occurs after 6 days and is strongly associated with resumption of anticoagulation and with polyp diameter [87]. Prior ASA use has not been shown to be statistically significant in increasing risk of post-polypectomy bleeding [88]. Current guidelines for the management of anticoagulation prior to colonoscopic polypectomy recommend normalization of the INR for the procedure [89, 90].

Internal Hemorrhoids

Hemorrhoids are the second most common cause of hematochezia [68]. They account for 10–20% of LGIB [50]. LGIB often presents with intermittent low-volume bleeding that coats the stool. Hemorrhoids are usually treated with stool softeners, fiber supplements, sitz baths, and steroid-containing suppositories. Direct current electrocoagulation, surgical treatment, or endoscopic therapy may be necessary to treat severe bleeding.

Less Common Causes

LGIB from radiation proctitis and anal fissures is rare. Symptoms of radiation proctitis range from rectal bleeding to tenesmus and diarrhea, and thermal therapy has been described as effective. When anal fissures are the cause, patients usually experience severe pain upon bowel movement. Anal fissures can be treated with a combination of topical calcium channel blockers, fiber supplements, stool softeners, and sitz baths.

Key Points

- In the elderly there is a higher incidence, morbidity, and mortality rate associated with gastrointestinal bleeding episodes.
- The main causes of UGIB are peptic ulcers, esophagitis, esophageal or gastric varices, gastric tumors, and portal hypertensive gastropathy, with peptic ulcers being the most common.
- Initial evaluation including history taking, rectal examination, laboratory testing, and nasogastric tube aspiration ought to be undertaken simultaneously with resuscitative measures.
- Endoscopic treatment options include thermal contact probes, clipping, injections, and band ligation. Combination therapy may reduce the risk of re-bleeding better than monotherapy alone.
- Expertise of the endoscopist or interventional radiologist, the type and location of lesion and its risk of re-bleeding dictate the best management route.
- Surgical intervention is generally resorted to in cases of severe GI bleeding, when endoscopic therapy fails or in recurrent bleeding episodes.
- The risk of UGIB from peptic ulcer disease is increased in elderly patients with a history of smoking, alcohol use, corticosteroid use or on anticoagulant/antiplatelet therapy while using NSAIDs.
- Continued PPI therapy is necessary in patients who have a history of ulcer bleeding and require NSAIDs or cardiovascular prophylaxis.
- Lower gastrointestinal bleeding is most commonly caused by diverticular disease, internal hemorrhoids, colitis, neoplasms, and angiodysplasias.
- Efficient cleansing of the colon, which is accomplished by using osmotically acting cathartics such as sodium phosphate, magnesium citrate, and polyethylene glycol/electrolyte lavage solutions, is essential for optimal endoscopic evaluation. Adverse effects may result from use of magnesium and sodium-based products and should, therefore, be administered with caution in the elderly.

References

1. Sung J. Gastrointestinal bleeding: presentation, differential diagnosis and epidemiology. In: Sung JY, Kuipers EJ, Barkun AN, editors. Gastrointestinal bleeding, 2nd ed. Hoboken: New Jersey, Wiley-Blackwell;2012. p. 1–14.
2. Longstreth GF. Epidemiology and outcome of patients hospitalized with acute lower gastrointestinal hemorrhage: a population-based study. Am J Gastroenterol. 1997;92(3):419–24.
3. Palmer K. Management of haematemesis and melaena. Postgrad Med J. 2004;80(945):399–404.
4. Barkun A, Bardou M, Marshall JK. Consensus recommendations for managing patients with nonvariceal upper gastrointestinal bleeding. Ann Intern Med. 2003;139(10):843–57.
5. Barkun AN, Bardou M, Kuipers EJ, Sung J, Hunt RH, Martel M, et al. International consensus recommendations on the management of patients with nonvariceal upper gastrointestinal bleeding. Ann Intern Med. 2010;152(2):101–13.
6. Alli O, Smith C, Hoffman M, Amanullah S, Katz P, Amanullah AM. Incidence, predictors, and outcomes of gastrointestinal bleeding in patients on dual antiplatelet therapy with aspirin and clopidogrel. J Clin Gastroenterol. 2011;45(5):410–4.
7. de Abajo FJ. Effects of selective serotonin reuptake inhibitors on platelet function: mechanisms, clinical outcomes and implications for use in elderly patients. Drugs Aging. 2011;28(5):345–67.
8. Barnert J, Messmann H. Diagnosis and management of lower gastrointestinal bleeding. Nat Rev Gastroenterol Hepatol. 2009;6(11):637–46.
9. Blatchford O, Murray WR, Blatchford M. A risk score to predict need for treatment for upper-gastrointestinal haemorrhage. Lancet. 2000;356(9238):1318–21.
10. Stanley AJ, Ashley D, Dalton HR, Mowat C, Gaya DR, Thompson E, et al. Outpatient management of patients with low-risk upper-gastrointestinal haemorrhage: multicentre validation and prospective evaluation. Lancet. 2009;373(9657):42–7.
11. Rockall TA, Logan RF, Devlin HB, Northfield TC. Risk assessment after acute upper gastrointestinal haemorrhage. Gut. 1996;38(3):316–21.
12. Baradarian R, Ramdhaney S, Chapalamadugu R, Skoczylas L, Wang K, Rivilis S, et al. Early intensive resuscitation of patients with upper gastrointestinal bleeding decreases mortality. Am J Gastroenterol. 2004;99(4):619–22.
13. Barkun A, Sabbah S, Enns R, Armstrong D, Gregor J, Fedorak RN, et al. The Canadian Registry on Nonvariceal Upper Gastrointestinal Bleeding and Endoscopy (RUGBE): Endoscopic hemostasis and proton pump inhibition are associated with improved outcomes in a real-life setting. Am J Gastroenterol. 2004;99(7):1238–46.
14. Peter S, Wilcox CM. Endoscopic therapy for peptic ulcer bleeding. In: Monkemuller K, Wilcox CM, Munoz-Navas M, editors. Interventional and therapeutic gastrointestinal endoscopy, vol. 27. Basel: Krager; 2010. p. 37–54.
15. Winstead NS, Wilcox CM. Erythromycin prior to endoscopy for acute upper gastrointestinal haemorrhage: a cost-effectiveness analysis. Aliment Pharmacol Ther. 2007;26(10):1371–7.
16. Hearnshaw SA, Logan RF, Lowe D, Travis SP, Murphy MF, Palmer KR. Use of endoscopy for management of acute upper gastrointestinal bleeding in the UK: results of a nationwide audit. Gut. 2010;59(8):1022–9.
17. Laine L, Peterson WL. Bleeding peptic ulcer. N Engl J Med. 1994;331(11):717–27.
18. Segal F, Prolla JC, Maguilnik I, Wolff FH. Clinical and endoscopic aspects in the evolution of patients with bleeding peptic ulcer–a cohort study. Arq Gastroenterol. 2000;37(3):162–7.
19. Mueller X, Rothenbuehler JM, Amery A, Harder F. Factors predisposing to further hemorrhage and mortality after peptic ulcer bleeding. J Am Coll Surg. 1994;179(4):457–61.
20. Hsu PI, Lin XZ, Chan SH, Lin CY, Chang TT, Shin JS, et al. Bleeding peptic ulcer–risk factors for rebleeding and sequential changes in endoscopic findings. Gut. 1994;35(6):746–9.
21. Barkun AN, Martel M, Toubouti Y, Rahme E, Bardou M. Endoscopic hemostasis in peptic ulcer bleeding for patients with high-risk lesions: a series of meta-analyses. Gastrointest Endosc. 2009;69(4):786–99.
22. Marmo R, Rotondano G, Piscopo R, Bianco MA, D'Angella R, Cipolletta L. Dual therapy versus monotherapy in the endoscopic treatment of high-risk bleeding ulcers: a meta-analysis of controlled trials. Am J Gastroenterol. 2007;102(2):279–89; quiz 469.
23. Laine L, McQuaid KR. Endoscopic therapy for bleeding ulcers: an evidence-based approach based on meta-analyses of randomized

controlled trials. Clin Gastroenterol Hepatol. 2009;7(1):33–47; quiz 1–2.
24. Lau JY, Chung SC, Leung JW, Lo KK, Yung MY, Li AK. The evolution of stigmata of hemorrhage in bleeding peptic ulcers: a sequential endoscopic study. Endoscopy. 1998;30(6):513–8.
25. Chiu PW, Lam CY, Lee SW, Kwong KH, Lam SH, Lee DT, et al. Effect of scheduled second therapeutic endoscopy on peptic ulcer rebleeding: a prospective randomised trial. Gut. 2003;52(10):1403–7.
26. Spiegel BM, Ofman JJ, Woods K, Vakil NB. Minimizing recurrent peptic ulcer hemorrhage after endoscopic hemostasis: the cost-effectiveness of competing strategies. Am J Gastroenterol. 2003;98(1):86–97.
27. Jensen D, Mawas I, Lousuebsakul V. Changes in the prevalence of different diagnoses for UGI hemorrhage in the last two decades. Gastrointest Endosc. 2003;57:AB:147.
28. Segal WN, Cello JP. Hemorrhage in the upper gastrointestinal tract in the older patient. Am J Gastroenterol. 1997;92(1):42–6.
29. Blatchford O, Davidson LA, Murray WR, Blatchford M, Pell J. Acute upper gastrointestinal haemorrhage in west of Scotland: case ascertainment study. BMJ. 1997;315(7107):510–4.
30. Huang JQ, Sridhar S, Hunt RH. Role of Helicobacter pylori infection and non-steroidal anti-inflammatory drugs in peptic-ulcer disease: a meta-analysis. Lancet. 2002;359(9300):14–22.
31. Ohmann C, Imhof M, Ruppert C, Janzik U, Vogt C, Frieling T, et al. Time-trends in the epidemiology of peptic ulcer bleeding. Scand J Gastroenterol. 2005;40(8):914–20.
32. Greenspoon J, Barkun A, Bardou M et al. Management of patients with non-variceal upper gastrointestinal bleeding. Clin Gastroenterol Hepatol. 2012;10:234–9.
33. Thomopoulos KC, Vagenas KA, Vagianos CE, Margaritis VG, Blikas AP, Katsakoulis EC, et al. Changes in aetiology and clinical outcome of acute upper gastrointestinal bleeding during the last 15 years. Eur J Gastroenterol Hepatol. 2004;16(2):177–82.
34. Weil J, Colin-Jones D, Langman M, Lawson D, Logan R, Murphy M, et al. Prophylactic aspirin and risk of peptic ulcer bleeding. BMJ. 1995;310(6983):827–30.
35. Chang SY, Howden CW. Is no NSAID a good NSAID? Approaches to NSAID-associated upper gastrointestinal disease. Curr Gastroenterol Rep. 2004;6(6):447–53.
36. Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. JAMA. 2000;284(10):1247–55.
37. Hansen JM, Hallas J, Lauritsen JM, Bytzer P. Non-steroidal anti-inflammatory drugs and ulcer complications: a risk factor analysis for clinical decision-making. Scand J Gastroenterol. 1996;31(2):126–30.
38. Kaufman DW, Kelly JP, Wiholm BE, Laszlo A, Sheehan JE, Koff RS, et al. The risk of acute major upper gastrointestinal bleeding among users of aspirin and ibuprofen at various levels of alcohol consumption. Am J Gastroenterol. 1999;94(11):3189–96.
39. Lanas A, Garcia-Rodriguez LA, Arroyo MT, Gomollon F, Feu F, Gonzalez-Perez A, et al. Risk of upper gastrointestinal ulcer bleeding associated with selective cyclo-oxygenase-2 inhibitors, traditional non-aspirin non-steroidal anti-inflammatory drugs, aspirin and combinations. Gut. 2006;55(12):1731–8.
40. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. N Engl J Med. 1999;340(24):1888–99.
41. Rostom A, Moayyedi P, Hunt R. Canadian consensus guidelines on long-term nonsteroidal anti-inflammatory drug therapy and the need for gastroprotection: benefits versus risks. Aliment Pharmacol Ther. 2009;29(5):481–96.
42. Aguejouf O, Eizayaga F, Desplat V, Belon P, Doutremepuich C. Prothrombotic and hemorrhagic effects of aspirin. Clin Appl Thromb Hemost. 2009;15(5):523–8.
43. Biondi-Zoccai GG, Lotrionte M, Agostoni P, Abbate A, Fusaro M, Burzotta F, et al. A systematic review and meta-analysis on the hazards of discontinuing or not adhering to aspirin among 50,279 patients at risk for coronary artery disease. Eur Heart J. 2006;27(22):2667–74.
44. Merkel C, Zoli M, Siringo S, van Buuren H, Magalotti D, Angeli P, et al. Prognostic indicators of risk for first variceal bleeding in cirrhosis: a multicenter study in 711 patients to validate and improve the North Italian Endoscopic Club (NIEC) index. Am J Gastroenterol. 2000;95(10):2915–20.
45. Villanueva C, Piqueras M, Aracil C, Gomez C, Lopez-Balaguer JM, Gonzalez B, et al. A randomized controlled trial comparing ligation and sclerotherapy as emergency endoscopic treatment added to somatostatin in acute variceal bleeding. J Hepatol. 2006; 45(4):560–7.
46. Chen WT, Lin CY, Sheen IS, Huang CW, Lin TN, Lin CJ, et al. MELD score can predict early mortality in patients with rebleeding after band ligation for variceal bleeding. World J Gastroenterol. 2011;17(16):2120–5.
47. Vernava III AM, Moore BA, Longo WE, Johnson FE. Lower gastrointestinal bleeding. Dis Colon Rectum. 1997;40(7):846–58.
48. Jensen DM, Machicado GA. Colonoscopy for diagnosis and treatment of severe lower gastrointestinal bleeding. Routine outcomes and cost analysis. Gastrointest Endosc Clin N Am. 1997;7(3):477–98.
49. Farrell JJ, Friedman LS. Review article: the management of lower gastrointestinal bleeding. Aliment Pharmacol Ther. 2005;21(11):1281–98.
50. Strate LL, Ayanian JZ, Kotler G, Syngal S. Risk factors for mortality in lower intestinal bleeding. Clin Gastroenterol Hepatol. 2008;6(9):1004–10; quiz 955-.
51. Strate LL, Orav EJ, Syngal S. Early predictors of severity in acute lower intestinal tract bleeding. Arch Intern Med. 2003;163(7):838–43.
52. Richter JM, Christensen MR, Kaplan LM, Nishioka NS. Effectiveness of current technology in the diagnosis and management of lower gastrointestinal hemorrhage. Gastrointest Endosc. 1995;41(2):93–8.
53. Mamula P, Adler DG, Conway JD, Diehl DL, Farraye FA, Kantsevoy SV, et al. Colonoscopy preparation. Gastrointest Endosc. 2009;69(7):1201–9.
54. Nyberg C, Hendel J, Nielsen OH. The safety of osmotically acting cathartics in colonic cleansing. Nat Rev Gastroenterol Hepatol. 2010;7(10):557–64.
55. Carl DE, Sica DA. Acute phosphate nephropathy following colonoscopy preparation. Am J Med Sci. 2007;334(3):151–4.
56. Pelham RW, Nix LC, Chavira RE, Cleveland MV, Stetson P. Clinical trial: single- and multiple-dose pharmacokinetics of polyethylene glycol (PEG-3350) in healthy young and elderly subjects. Aliment Pharmacol Ther. 2008;28(2):256–65.
57. Rothfuss KS, Bode JC, Stange EF, Parlesak A. Urinary excretion of polyethylene glycol 3350 during colonoscopy preparation. Z Gastroenterol. 2006;44(2):167–72.
58. Scheffel H, Pfammatter T, Wildi S, Bauerfeind P, Marincek B, Alkadhi H. Acute gastrointestinal bleeding: detection of source and etiology with multi-detector-row CT. Eur Radiol. 2007;17(6):1555–65.
59. Busch OR, van Delden OM, Gouma DJ. Therapeutic options for endoscopic haemostatic failures: the place of the surgeon and radiologist in gastrointestinal tract bleeding. Best Pract Res Clin Gastroenterol. 2008;22(2):341–54.
60. Egglin TK, O'Moore PV, Feinstein AR, Waltman AC. Complications of peripheral arteriography: a new system to identify patients at increased risk. J Vasc Surg. 1995;22(6):787–94.

61. Zuckier LS. Acute gastrointestinal bleeding. Semin Nucl Med. 2003;33(4):297–311.
62. Zuckerman GR, Prakash C. Acute lower intestinal bleeding: part I: clinical presentation and diagnosis. Gastrointest Endosc. 1998;48(6):606–17.
63. Elta GH. Urgent colonoscopy for acute lower-GI bleeding. Gastrointest Endosc. 2004;59(3):402–8.
64. Tsuruoka N, Iwakiri R, Hara M, Shirahama N, Sakata Y, Miyahara K, et al. NSAIDs are a significant risk factor for colonic diverticular hemorrhage in elder patients: Evaluation by a case–control study. J Gastroenterol Hepatol. 2011;26(6):1047–52.
65. Strate LL, Liu YL, Huang ES, Giovannucci EL, Chan AT. Use of Aspirin or Nonsteroidal Anti-inflammatory Drugs Increases Risk for Diverticulitis and Diverticular Bleeding. Gastroenterology. 2011;140(5):1427–33.
66. Bokhari M, Vernava AM, Ure T, Longo WE. Diverticular hemorrhage in the elderly–is it well tolerated? Dis Colon Rectum. 1996;39(2):191–5.
67. Gayer C, Chino A, Lucas C, Tokioka S, Yamasaki T, Edelman DA, et al. Acute lower gastrointestinal bleeding in 1,112 patients admitted to an urban emergency medical center. Surgery. 2009;146(4):600–6; discussion 6–7.
68. Jensen DM. Management of patients with severe hematochezia–with all current evidence available. Am J Gastroenterol. 2005;100(11):2403–6.
69. Jensen DM, Machicado GA, Jutabha R, Kovacs TO. Urgent colonoscopy for the diagnosis and treatment of severe diverticular hemorrhage. N Engl J Med. 2000;342(2):78–82.
70. Alvarez JA, Baldonedo RF, Bear IG, Otero J, Pire G, Alvarez P, et al. Presentation, management and outcome of acute sigmoid diverticulitis requiring hospitalization. Dig Surg. 2007;24(6):471–6.
71. Farrell JJ, Graeme-Cook F, Kelsey PB. Treatment of bleeding colonic diverticula by endoscopic band ligation: an in-vivo and ex-vivo pilot study. Endoscopy. 2003;35(10):823–9.
72. Kuo WT, Lee DE, Saad WE, Patel N, Sahler LG, Waldman DL. Superselective microcoil embolization for the treatment of lower gastrointestinal hemorrhage. J Vasc Interv Radiol. 2003;14(12):1503–9.
73. Funaki B, Kostelic JK, Lorenz J, Ha TV, Yip DL, Rosenblum JD, et al. Superselective microcoil embolization of colonic hemorrhage. AJR Am J Roentgenol. 2001;177(4):829–36.
74. Defreyne L, Vanlangenhove P, De Vos M, Pattyn P, Van Maele G, Decruyenaere J, et al. Embolization as a first approach with endoscopically unmanageable acute nonvariceal gastrointestinal hemorrhage. Radiology. 2001;218(3):739–48.
75. Tan KK, Wong D, Sim R. Superselective embolization for lower gastrointestinal hemorrhage: an institutional review over 7 years. World J Surg. 2008;32(12):2707–15.
76. Zuckerman GR, Prakash C. Acute lower intestinal bleeding. Part II: etiology, therapy, and outcomes. Gastrointest Endosc. 1999;49(2):228–38.
77. Pate GE, Mulligan A. An epidemiological study of Heyde's syndrome: an association between aortic stenosis and gastrointestinal bleeding. J Heart Valve Dis. 2004;13(5):713–6.
78. Boley SJ, Sprayregen S, Sammartano RJ, Adams A, Kleinhaus S. The pathophysiologic basis for the angiographic signs of vascular ectasias of the colon. Radiology. 1977;125(3):615–21.
79. Reinus JF, Brandt LJ. Vascular ectasias and diverticulosis. Common causes of lower intestinal bleeding. Gastroenterol Clin North Am. 1994;23(1):1–20.
80. Kwan V, Bourke MJ, Williams SJ, Gillespie PE, Murray MA, Kaffes AJ, et al. Argon plasma coagulation in the management of symptomatic gastrointestinal vascular lesions: experience in 100 consecutive patients with long-term follow-up. Am J Gastroenterol. 2006;101(1):58–63.
81. Green BT, Rockey DC, Portwood G, Tarnasky PR, Guarisco S, Branch MS, et al. Urgent colonoscopy for evaluation and management of acute lower gastrointestinal hemorrhage: a randomized controlled trial. Am J Gastroenterol. 2005;100(11):2395–402.
82. Cappell MS. Intestinal (mesenteric) vasculopathy. II. Ischemic colitis and chronic mesenteric ischemia. Gastroenterol Clin North Am. 1998;27(4):827–60, vi.
83. Simi M, Pietroletti R, Navarra L, Leardi S. Bowel stricture due to ischemic colitis: report of three cases requiring surgery. Hepatogastroenterology. 1995;42(3):279–81.
84. Slotwiner-Nie PK, Brandt LJ. Infectious diarrhea in the elderly. Gastroenterol Clin North Am. 2001;30(3):625–35.
85. Guerrant RL, Van Gilder T, Steiner TS, Thielman NM, Slutsker L, Tauxe RV, et al. Practice guidelines for the management of infectious diarrhea. Clin Infect Dis. 2001;32(3):331–51.
86. Lindner AE. Inflammatory bowel disease in the elderly. Clin Geriatr Med. 1999;15(3):487–97.
87. Sawhney MS, Salfiti N, Nelson DB, Lederle FA, Bond JH. Risk factors for severe delayed postpolypectomy bleeding. Endoscopy. 2008;40(2):115–9.
88. Yousfi M, Gostout CJ, Baron TH, Hernandez JL, Keate R, Fleischer DE, et al. Postpolypectomy lower gastrointestinal bleeding: potential role of aspirin. Am J Gastroenterol. 2004;99(9):1785–9.
89. Eisen GM, Baron TH, Dominitz JA, Faigel DO, Goldstein JL, Johanson JF, et al. Guideline on the management of anticoagulation and antiplatelet therapy for endoscopic procedures. Gastrointest Endosc. 2002;55(7):775–9.
90. Zuckerman MJ, Hirota WK, Adler DG, Davila RE, Jacobson BC, Leighton JA, et al. ASGE guideline: the management of low-molecular-weight heparin and nonaspirin antiplatelet agents for endoscopic procedures. Gastrointest Endosc. 2005;61(2):189–94.

Part IX

Hepato Biliary System and Pancreas

Liver Function Tests and Interpretation

37

Jacob Alexander and Kris V. Kowdley

Introduction

Liver volume and blood flow have been shown to decrease by 20–40% between the third and the tenth decade of life (Fig. 37.1) [1, 2]. In addition, hepatocyte proliferative response, which has implications in hepatic regeneration after liver disease or partial hepatectomy, appears to decline in the elderly, and has been linked to a reduction in hepatocyte telomere length [3, 4]. Despite these well-documented age-related changes in hepatic function, aging is not associated with significant abnormalities in most of the blood tests commonly performed to assess liver function [1]. However abnormal liver function tests are a common reason for referral to a specialist; investigating the older adult with abnormal liver function tests is hence common [5].

The commonly performed clinical liver function tests are summarized in Table 37.1 and the typical abnormalities in liver function tests in selected liver diseases are shown in Table 37.2. Though age by itself is not associated with specific changes in these tests, abnormal results are increasingly recognized in older adults secondary to the twin epidemics of hepatitis C and nonalcoholic fatty liver disease. In addition to demographic trends in the older population, use of potentially hepatotoxic medications to treat comorbid states, and the widespread availability of automated liver function tests, contributes to the physician encountering abnormal liver function tests routinely [6–9]. It has become common practice to obtain automated liver function tests during periodic health screening, blood banking, insurance physicals, and hospitalizations for unrelated illnesses [6]. The results of these tests need to be interpreted in the context of the patient's risk factors for liver disease, local epidemiology, symptoms, physical findings, and other laboratory or imaging findings [10]. These findings are summarized in Table 37.3.

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Tests of Hepatocellular Injury

Classifying the magnitude of aminotransferase alteration as "mild" (arbitrarily defined as <5 times the upper limit of normal (ULN)), "moderate" (5–15 times the ULN), or "marked" (>15 times the ULN) can be diagnostically useful [6].

Though the ULN for alanine aminotransferase (ALT) has traditionally been set at 40 U/L, this had been calculated from reference populations which likely included persons with nonalcoholic fatty liver disease [11]. Analysis of a large group of individuals with normal body mass index; normal serum cholesterol, triglyceride, and glucose levels; and no concurrent medication use identified the ULN to be 30 U/L in men and 19 U/L in women [11]. A larger population study in Israel evaluating individuals with normal triglycerides, cholesterol, glucose, and HbA1c and receiving no hepatotoxic medications identified 37.5 U/L as the ULN [12].

1. *Conditions with mild aspartate aminotransferase (AST), ALT elevation*
   Mild aminotransferase elevations are found in approximately 5% of the US population above the age of 70, and are often asymptomatic and not associated with other liver function abnormalities [13]. Nonalcoholic fatty liver disease is considered to be the most common etiology for the aminotransferase elevation in patients with mild aminotransferase elevation [13, 14]. High alcohol intake, hepatitis B or C infection, and iron overload, traditionally considered to be the most common causes of mild aminotransferase elevation, account for only a minority of cases of aminotransferase elevation among these patients [13, 14]. However, given the potential for treatment, these conditions should be sought for in all patients with aminotransferase elevation. Five to fifteen percentage of people

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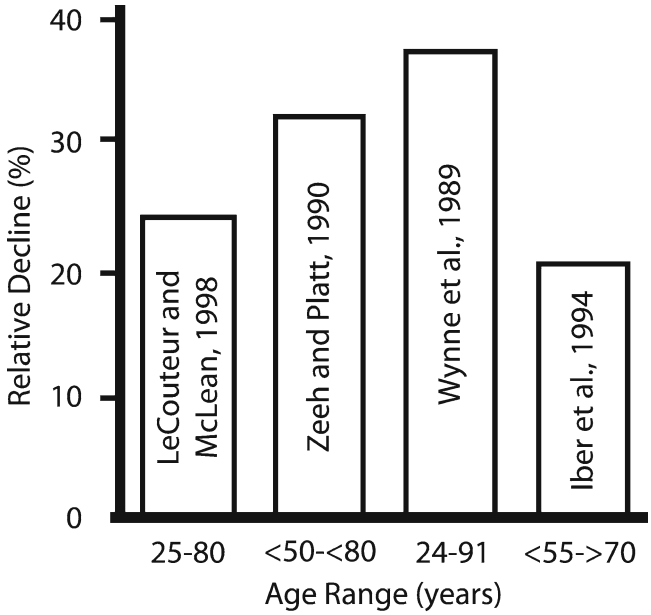

Fig. 37.1 Age-related decline in liver volume in humans (percentage of original volume) measured by ultrasound (from Schmucker [1], reproduced with permission)

Table 37.1 Summary of liver function tests

Test	Liver function tested	Extrahepatic factors affecting the tests
Aspartate aminotransferase (AST)	Hepatocellular injury	Increased Muscle injury Hemolysis
Alanine aminotransferase (ALT)	Hepatocellular injury	Relatively more specific for liver compared to AST; affected less by extrahepatic factors
Alkaline phosphatase (ALP)	Cholestasis	Increased Bone disease Tumors producing ALP
γ-glutamyl-transferase (GGT)	Cholestasis	Increased Heart failure Cytochromal enzyme-inducing drugs Alcohol Smoking
Bilirubin	Hepatic uptake and transport	Increased Hemolysis
Albumin	Hepatic protein synthesis	Decreased Renal or GI losses Malnutrition Systemic inflammation
Prothrombin time	Hepatic protein synthesis	Increased Fat malabsorption Vitamin K antagonists

over the age of 65 are reported to abuse alcohol, with alcohol consumption on the increase in this age group based on recent epidemiological studies [15, 16]. Chronic hepatitis C and hepatocellular carcinoma are two other liver diseases that are particularly more common in older adults [17–19]. The incidence of hepatocellular carcinoma increases with age in patients with cirrhosis [20]. The prevalence of chronic hepatitis B is variable depending on geographic origin and other risk factors [18, 19].

2. *Conditions with moderate to marked AST, ALT elevation*
   Conditions causing moderate to marked increase in aminotransferase levels often follow typical temporal profiles. In ischemic hepatitis, aminotransferase levels reach the peak rapidly, and then decrease rapidly over a few days [5]. This process is relatively slower and typically happens over a period of weeks in the case of acute viral hepatitis [5]. The tempo could be fast or slow in drug-induced hepatitis [5]. Acute biliary obstruction is marked by aminotransferase elevation that precedes elevation of markers of cholestasis [5]. Though relatively less common, autoimmune hepatitis must be considered in the differential diagnosis of older patients presenting "acutely" with tenfold increase in aminotransferases, jaundice, and hyper-gammaglobulinemia to avoid delay in initiation of immunosuppressive therapy [17].
3. *Significance of AST:ALT ratio*
   ALT is comparatively more specific for hepatic injury as its distribution in the body is primarily limited to the liver and kidney, in contrast to AST which is more widely distributed [21]. Therefore, a disproportionate elevation of AST compared to ALT raises the possibility of extrahepatic origin of aminotransferase elevation. An AST:ALT ratio of more than 2 is indicative of alcoholic liver disease, and is postulated to result from the combination of direct toxicity of alcohol on the AST-rich mitochondria in the hepatocytes and the formation of AST–immunoglobulin complexes resulting in more prolonged serum half-life of AST [22]. Additionally, AST:ALT ratio above 1 is predictive of cirrhosis in many forms of chronic liver disease [23–25].
4. *Effect of aging*
   Similar to most liver function tests, there are no age-specific changes in serum aminotransferase levels in older adults [8, 9]. Some studies have noted modest increases in AST levels with age [9, 26] while others do not suggest a change with age [27]. Some studies have noted the levels of serum ALT to remain essentially unchanged with advancing age [9], but others have found lower levels with advanced age [28]. Low ALT has been associated with frailty and reduced survival, but the relationship between ALT and survival disappears once frailty and age are included in the survival analysis, indicating that the effect of low ALT on survival is mediated by its association with frailty and increasing age [28]. A potential confounding factor in these studies is the effect of decline in renal function with advancing age

Table 37.2 Typical abnormalities in liver function tests in selected liver diseases

	Aminotransferases	AST:ALT ratio	ALP	Bilirubin	Albumin
Ischemic hepatitis	Marked elevation	>1	Normal	Normal	Normal
Acute viral hepatitis	Marked elevation	<1	Normal or elevated	Elevated	Normal
Autoimmune hepatitis	Moderate elevation	<1	Normal or elevated	Normal or elevated	Normal or low
Alcoholic hepatitis	Mild to moderate elevation	>2	Normal or elevated	Elevated	Normal or low
Chronic viral hepatitis	Mild to moderate elevation	<1	Normal or elevated	Normal or elevated	Normal or low
Intrahepatic cholestasis	Normal or mild elevation	<1	Elevated	Normal or elevated	Normal or low
Biliary obstruction	Normal or mild elevation	<1	Elevated	Elevated	Normal or low
Infiltrative/granulomatous liver disease	Normal or mild elevation	<1	Normal or elevated	Normal	Normal or low
Cirrhosis	Normal or mild elevation	>1	Normal	Normal or elevated	Low

Table 37.3 Typical features in selected liver diseases

Liver disorder	Suggestive clinical features	Potential confirmatory tests
Alcoholic hepatitis	Hepatomegaly Prominent spider angiomata	Normalization of liver tests after a period of abstinence
Drug-induced liver disease	Temporal association with drug intake	Normalization of liver tests after discontinuation of the drug
Nonalcoholic fatty liver disease	Features of metabolic syndrome	
Viral hepatitis	Risk factors for viral hepatitis Other blood-borne infections	Serological markers of viral hepatitis
Autoimmune hepatitis	Women Hyperglobulinemia	Antinuclear antibody Anti-smooth muscle antibody
Primary biliary cirrhosis	Middle-aged women Long-standing pruritus	Antimitochondrial antibody
Primary sclerosing cholangitis	Young male Inflammatory bowel disease	ERCP, MRCP
Hereditary hemochromatosis	Arthropathy Skin pigmentation Diabetes Erectile dysfunction	Increased transferrin saturation Increased ferritin Positive HFE gene mutation testing

as chronic renal dysfunction has been shown to be associated with decrease in aminotransferase levels [29].

5. *Extrahepatic influences*
   The common extrahepatic causes of elevated aminotransferase levels are hemolysis and muscle injury [21]. As stated, alcohol can increase aminotransferase levels by both hepatotoxic effects and a direct effect on AST, resulting in the disproportionately high elevations of AST compared to ALT, as observed in alcoholic liver disease [21]. Thyroid functional abnormalities may manifest with aminotransferase elevations in the absence of hepatic disease [30].

Tests of Cholestasis

Tests of cholestasis include serum levels of alkaline phosphatase (ALP) and γ-glutamyl-transferase (GGT). Because of the multiple sources for ALP, hepatic origin of ALP often needs to be ascertained through estimation of the levels of either GGT or the isoenzymes of ALP. Of the two, estimation of GGT is preferred as it can be performed with an automated analysis rather than through sophisticated and expensive techniques. A suggested approach to ALP elevation is given in Fig. 37.2. Apart from primary liver disease, malignant hepatic metastasis and lymphoma can also cause elevation of hepatic ALP. Common extrahepatic causes of elevated ALP levels are bone disease and tumors producing ALP [21].

The primary clinical utility of GGT is to confirm the hepatic origin of ALP [5]. Elevation of GGT disproportionate to the elevation of ALP (GGT:ALP ratio >2.5) indicates either extrahepatic origin of GGT as can happen in acute myocardial infarction, chronic obstructive pulmonary disease, and renal failure, or induction of hepatic GGT by alcohol or drugs [5].

In addition to being a marker of cholestasis, ALP is influenced by changes in bone turnover; serum levels progressively increase with age, with the rate of increase greater in women [26, 31]. In a study on laboratory values in healthy older individuals aged 60–90 years, ALP levels were in the 46–122 range in males and 50–162 range in females [9]. The corresponding figures in those older than 90 were 56–155 in

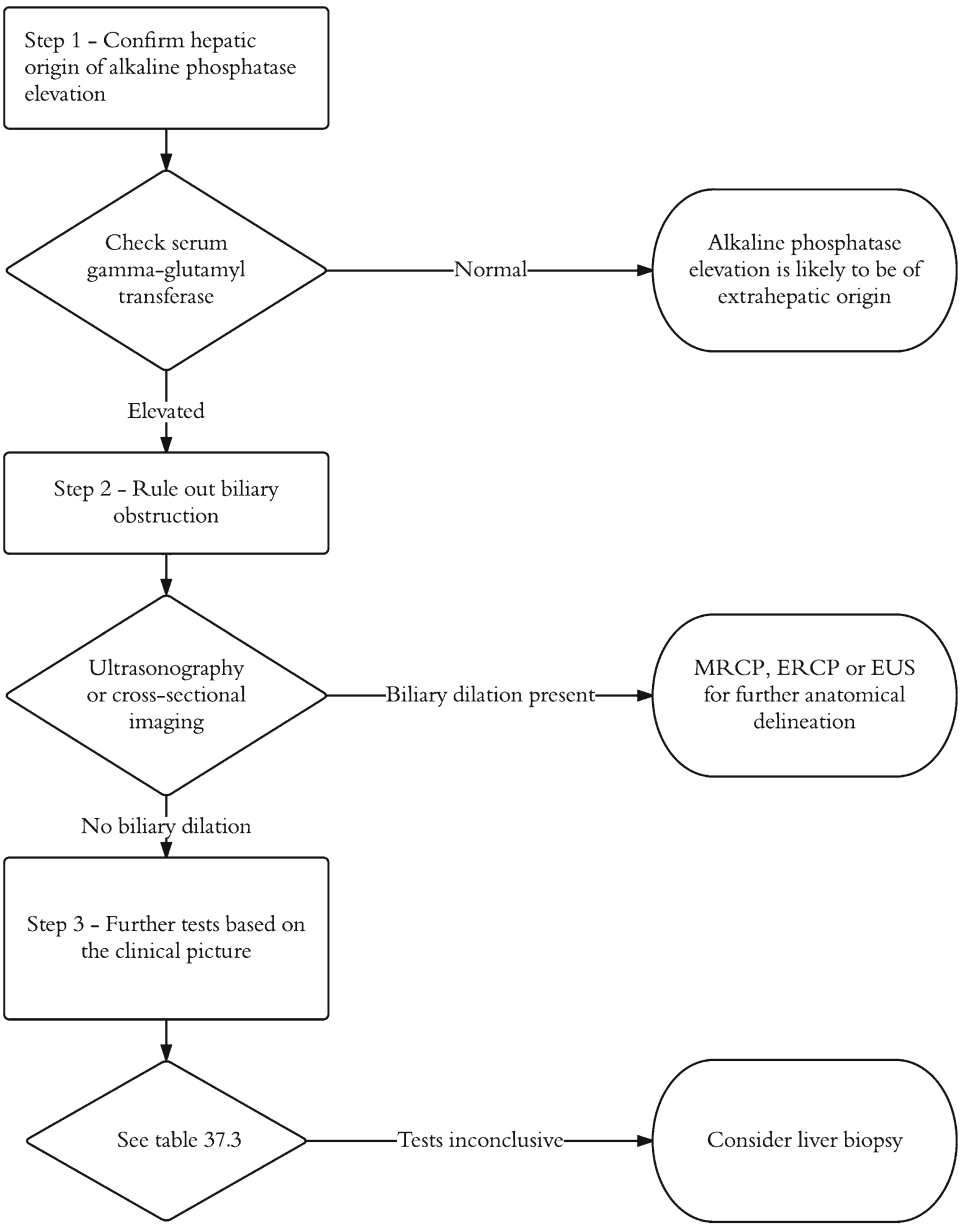

Fig. 37.2 Approach to elevated serum alkaline phosphatase

males, and 43–160 in females [9]. An age-related increase in the GGT levels was also noted in the same study [9]. A study comparing GGT levels in women aged 21–34 years with women in the age range 75–91 years also found higher GGT levels in older women [32]. However, another study found no age-related changes in men or women [27]; no age-adjusted reference limits are currently available for clinical use [8].

Elevated levels of serum bilirubin can result from increased catabolism of hemoglobin, or decreased hepatic uptake, conjugation, or biliary secretion of bilirubin. Conditions causing increased catabolism of hemoglobin result in hyperbilirubinemia with bilirubin predominantly in the unconjugated form, as opposed to conditions causing decreased hepatic uptake, conjugation, or biliary secretion where the hyperbilirubinemia is predominantly in the conjugated form. A suggested approach to evaluation of hyperbilirubinemia is summarized in Fig. 37.3 [5]. Overall, there is very little change in serum bilirubin levels with aging [8], though data does suggest a slight decrease with older age [9, 33].

Tests of Hepatic Synthetic Function

Albumin level and prothrombin time are the two commonly used parameters for hepatic synthetic function [34]. Serum albumin, with its relatively long plasma half-life (20 days), is

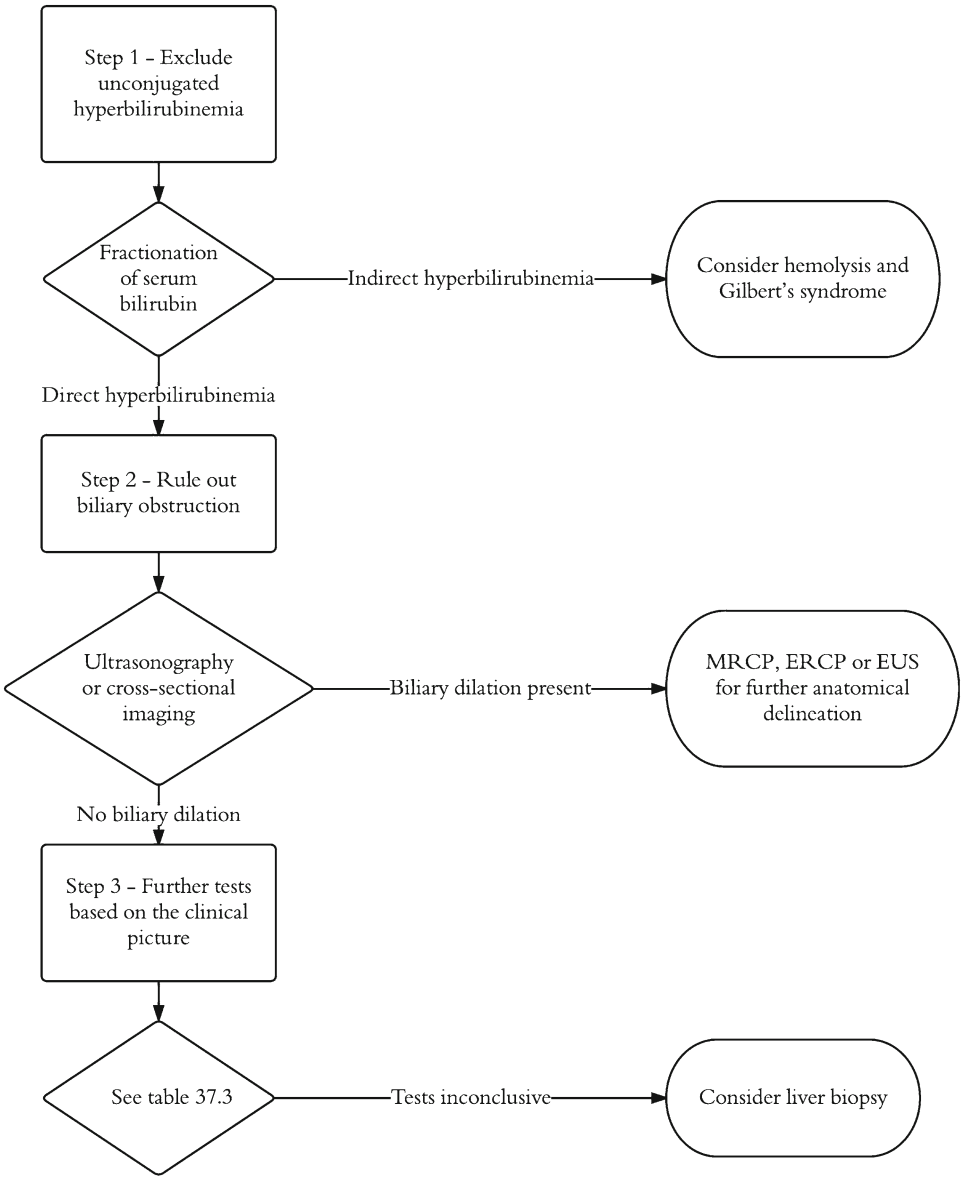

Fig. 37.3 Approach to elevated serum bilirubin

a useful indicator of hepatic synthetic function in cirrhosis, but not in acute liver failure. Albumin may however be low in several conditions other than liver disease. These include nephrotic syndrome, malabsorption or protein-losing enteropathy, malnutrition, cancer, sepsis, extensive burns, pregnancy, and various inflammatory states [5, 35].

Low albumin levels have been found to be a predictor of mortality in healthy older subjects after adjusting for age, sex, and lifestyle factors such as smoking, exercise, and alcohol consumption [36]. However, it has been shown that low serum albumin level is predictive of mortality only in the absence of significant inflammation as estimated by serum interleukin-6 levels [37].

Aging per se appears to have minimal effect on serum albumin levels, with only minimal decline documented with increasing age [9]. Interestingly, the decrease in the lower limit of albumin is more pronounced than the decrease in the upper limit [9]. Another study reported a decline of only 0.54 g/L for each decade of advancing age among healthy adults [38].

Prealbumin, also called transthyretin, is a protein synthesized in liver and with a short half-life of 2 days, whose main clinical use is screening of malnutrition and monitoring of nutritional therapy, including in patients with liver disease [39]. As in the case of albumin, the use of prealbumin as a marker of hepatic synthetic function is limited by

malnutrition and inflammation which cause its levels to be reduced [40].

Prothrombin time, which is determined by the hepatic synthesis of vitamin K-derived coagulation factors II, V, VII, IX, X, and XI, is a useful marker of hepatic synthetic dysfunction in both cirrhosis and acute liver failure [5, 41]. Prothrombin time is incorporated in both Child–Pugh's classification and the model for end-stage liver disease (MELD) for assessing prognosis in cirrhosis [42]. However, it has been shown that both prothrombin time and partial thromboplastin time overestimate the bleeding risk in cirrhosis, as these tests do not take into account the reduction in anticoagulant activity due to reduced hepatic synthesis of vitamin K-derived endogenous anticoagulants [43]. Additionally, prothrombin time can be prolonged in warfarin treatment, deficiency in vitamin K, and consumptive coagulopathy [5].

Liver Function Tests and Mortality

A follow-up of over 500,000 life insurance applicants suggested a consistent progression of increasing risk ratios with increasing severity of liver function tests. With elevations of GGT or both AST and ALT elevations, mortality risk became elevated; this trend was evident with progressively higher levels of AST, ALT, and GGT [44]. Finally, variations in LFT proteins are under significant genetic and environmental control, although sex, alcohol, age, and BMI play roles; the genetic contributions may explain the wide variations in liver function in different individuals [45].

Key Points

- Liver function tests should be interpreted in the context of clinical and epidemiological characteristics of the patient.
- Aging by itself has limited effect on liver tests, but other medical conditions associated with aging often influence the liver function tests.
- Paying attention to the magnitude and temporal profile of aminotransferase elevation is useful in differential diagnosis.
- The first step in the evaluation of elevated cholestatic markers is distinguishing between hepatic and extrahepatic origin.
- Albumin and prealbumin can be useful markers of hepatic synthetic function, but there are multiple other conditions that can affect these parameters.
- Conventional tests of coagulation have limited utility in identifying bleeding risk, but have prognostic implications.

References

1. Schmucker DL. Age-related changes in liver structure and function: implications for disease? Exp Gerontol. 2005;40(8–9):650–9.
2. Wynne HA, Cope LH, Mutch E, et al. The effect of age upon liver volume and apparent liver blood flow in healthy man. Hepatology. 1989;9(2):297–301.
3. Aikata H, Takaishi H, Kawakami Y, et al. Telomere reduction in human liver tissues with age and chronic inflammation. Exp Cell Res. 2000;256(2):578–82.
4. Takubo K, Nakamura K, Izumiyama N, et al. Telomere shortening with aging in human liver. J Gerontol A Biol Sci Med Sci. 2000;55(11):B533–6.
5. Giannini EG, Testa R, Savarino V. Liver enzyme alteration: a guide for clinicians. CMAJ. 2005;172(3):367–79.
6. Green RM, Flamm S. AGA technical review on the evaluation of liver chemistry tests. Gastroenterology. 2002;123(4):1367–84.
7. Premoli A, Paschetta E, Hvalryg M, et al. Characteristics of liver diseases in the elderly: a review. Minerva Gastroenterol Dietol. 2009;55(1):71–8.
8. Anantharaju A, Feller A, Chedid A. Aging Liver. A review. Gerontology. 2002;48(6):343–53.
9. Tietz NW, Shuey DF, Wekstein DR. Laboratory values in fit aging individuals–sexagenarians through centenarians. Clin Chem. 1992;38(6):1167–85.
10. Johnston DE. Special considerations in interpreting liver function tests. Am Fam Physician. 1999;59(8):2223–30.
11. Prati D, Taioli E, Zanella A, et al. Updated definitions of healthy ranges for serum alanine aminotransferase levels. Ann Intern Med. 2002;137(1):1–10.
12. Kariv R, Leshno M, Beth-Or A, et al. Re-evaluation of serum alanine aminotransferase upper normal limit and its modulating factors in a large-scale population study. Liver Int. 2006;26(4):445–50.
13. Clark JM, Brancati FL, Diehl AM. The prevalence and etiology of elevated aminotransferase levels in the United States. Am J Gastroenterol. 2003;98(5):960–7.
14. Hultcrantz R, Glaumann H, Lindberg G, et al. Liver investigation in 149 asymptomatic patients with moderately elevated activities of serum aminotransferases. Scand J Gastroenterol. 1986;21(1):109–13.
15. Culberson JW. Alcohol use in the elderly: beyond the CAGE. Part 1 of 2: prevalence and patterns of problem drinking. Geriatrics. 2006;61(10):23–7.
16. Kalapatapu RK, Paris P, Neugroschl JA. Alcohol use disorders in geriatrics. Int J Psychiatry Med. 2010;40(3):321–37.
17. Floreani A. Liver disorders in the elderly. Best Pract Res Clin Gastroenterol. 2009;23(6):909–17.
18. Chien NT, Dundoo G, Horani MH, et al. Seroprevalence of viral hepatitis in an older nursing home population. J Am Geriatr Soc. 1999;47(9):1110–3.
19. Hoshida Y, Ikeda K, Kobayashi M, et al. Chronic liver disease in the extremely elderly of 80 years or more: clinical characteristics, prognosis and patient survival analysis. J Hepatol. 1999;31(5):860–6.
20. Ikeda K, Saitoh S, Suzuki Y, et al. Disease progression and hepatocellular carcinogenesis in patients with chronic viral hepatitis: a prospective observation of 2215 patients. J Hepatol. 1998;28(6):930–8.
21. Dufour DR, Lott JA, Nolte FS, et al. Diagnosis and monitoring of hepatic injury. I. Performance characteristics of laboratory tests. Clin Chem. 2000;46(12):2027–49.
22. Majhi S, Baral N, Lamsal M, et al. De Ritis ratio as diagnostic marker of alcoholic liver disease. Nepal Med Coll J. 2006;8(1):40–2.

23. Park GJ, Lin BP, Ngu MC, et al. Aspartate aminotransferase: alanine aminotransferase ratio in chronic hepatitis C infection: is it a useful predictor of cirrhosis? J Gastroenterol Hepatol. 2000; 15(4):386–90.
24. Nyblom H, Björnsson E, Simrén M, et al. The AST/ALT ratio as an indicator of cirrhosis in patients with PBC. Liver Int. 2006;26(7): 840–5.
25. Nyblom H, Nordlinder H, Olsson R. High aspartate to alanine aminotransferase ratio is an indicator of cirrhosis and poor outcome in patients with primary sclerosing cholangitis. Liver Int. 2007;27(5): 694–9.
26. Dybkaer R, Lauritzen M, Krakauer R. Relative reference values for clinical chemical and haematological quantities in 'healthy' elderly people. Acta Med Scand. 1981;209(1–2):1–9.
27. Garry PJ, Hunt WC, VanderJagt DJ, et al. Clinical chemistry reference intervals for healthy elderly subjects. Am J Clin Nutr. 1989;50 Suppl 5:1219–30; discussion 1231–5.
28. Le Couteur DG, Blyth FM, Creasey HM, et al. The association of alanine transaminase with aging, frailty, and mortality. J Gerontol A Biol Sci Med Sci. 2010;65(7):712–7.
29. Fabrizi F, Lunghi G, Finazzi S, et al. Decreased serum aminotransferase activity in patients with chronic renal failure: impact on the detection of viral hepatitis. Am J Kidney Dis. 2001;38(5): 1009–15.
30. Bayraktar M, Van Thiel DH. Abnormalities in measures of liver function and injury in thyroid disorders. Hepatogastroenterology. 1997;44(18):1614–8.
31. Eastell R, Hannon RA. Biomarkers of bone health and osteoporosis risk. Proc Nutr Soc. 2008;67(2):157–62.
32. Reibnegger G, Huber LA, Jürgens G, et al. Approach to define "normal aging" in man. Immune function, serum lipids, lipoproteins and neopterin levels. Mech Ageing Dev. 1988;46(1–3):67–82.
33. Fülöp Jr T, Wórum I, Varga P, et al. Blood laboratory parameters of carefully selected healthy elderly people. Arch Gerontol Geriatr. 1989;8(2):151–63.
34. Nagao Y, Sata M. Serum albumin and mortality risk in a hyperendemic area of HCV infection in Japan. Virol J. 2010;7(1):375.
35. Prinsen BH, De Sain-van der Velden MG. Albumin turnover: experimental approach and its application in health and renal diseases. Clin Chim Acta. 2004;347(1–2):1–14.
36. Klonoff-Cohen H, Barrett-Connor EL, Edelstein SL. Albumin levels as a predictor of mortality in the healthy elderly. J Clin Epidemiol. 1992;45(3):207–12.
37. Reuben DB, Ferrucci L, Wallace R, et al. The prognostic value of serum albumin in healthy older persons with low and high serum interleukin-6 (IL-6) levels. J Am Geriatr Soc. 2000;48(11): 1404–7.
38. Campion EW, DeLabry LO, Glynn RJ. The effect of age on serum albumin in healthy males: report from the Normative Aging Study. J Gerontol. 1988;43(1):M18–20.
39. Roongpisuthipong C, Sobhonslidsuk A, Nantiruj K, et al. Nutritional assessment in various stages of liver cirrhosis. Nutrition. 2001;17(9):761–5.
40. Dennis RA, Johnson LE, Roberson PK, et al. Changes in prealbumin, nutrient intake, and systemic inflammation in elderly recuperative care patients. J Am Geriatr Soc. 2008;56(7):1270–5.
41. Peck-Radosavljevic M. Review article: coagulation disorders in chronic liver disease. Aliment Pharmacol Ther. 2007;26 Suppl 1:21–8.
42. Kamath PS, Wiesner RH, Malinchoc M, et al. A model to predict survival in patients with end-stage liver disease. Hepatology. 2001;33(2):464–70.
43. Tripodi A, Salerno F, Chantarangkul V, et al. Evidence of normal thrombin generation in cirrhosis despite abnormal conventional coagulation tests. Hepatology. 2005;41(3):553–8.
44. Pinkham CA, Krause KJ. Liver function tests and mortality in a cohort of life insurance applicants. J Insur Med. 2009;41(3): 170–7.
45. Rahmioglu N, Andrew T, Cherkas L, et al. Epidemiology and genetic epidemiology of the liver function test proteins. PLoS One. 2009;4(2):e4435.

Viral Liver Diseases

38

Satheesh Nair and Jihad O. Arteh

Hepatitis A

According to the World Health Organization, approximately 1.5 million clinical cases of hepatitis A occur worldwide annually [1], but seroprevalence data indicate that tens of millions of hepatitis A virus (HAV) infections occur each year. Even though the prevalence of anti-HAV antibody is high among the older population (at 75%) [2, 3], those who are not immune and acquire the infection are at increased risk of complications and higher likelihood for hospitalization.

Clinical Features and Diagnosis

Clinical illness varies from a mild flu-like sickness to fulminant hepatic failure. The average incubation period is 28 days (range, 15–50 days), following which symptoms include nausea, abdominal pain, fatigue, fever, dark urine, and jaundice along with abnormal liver function including high transaminases and bilirubin. The illness is usually self-limited with most symptoms resolving within 2–4 weeks (Fig. 38.1). Rarely, HAV infection can cause a relapsing or cholestatic form of hepatitis lasting several months before eventual recovery. However, unlike hepatitis B and C, hepatitis A does not cause chronic infection and only rarely leads to fulminant hepatic failure. Fulminant hepatitis A is seen more commonly in patients with chronic liver disease, particularly when it is secondary to chronic hepatitis C virus (HCV) infection [4].

The diagnosis of acute HAV infection is established by the detection of IgM antibodies to HAV (IgM anti-HAV). Following resolution, IgM antibody is replaced by immunoglobulin G (IgG) anti-HAV, which remains detectable for life, and affords lifelong immunity (Fig. 38.2). People who have received hepatitis A vaccine will also have detectable total anti-HAV antibodies.

Treatment

HAV infection is usually self-limited and treatment is therefore supportive. The majority recover without sequelae. However, fatalities associated with the infection and the rate of hospitalization are more common with advancing age [1–4]. Thus, special care is indicated for the elderly with acute infection.

Prevention

International travel remains the most commonly identified risk factor for acquiring HAV. Travel to endemic areas is common among older adults who now have increased life expectancy and mobility. Therefore, all older travelers lacking naturally acquired immunity should be vaccinated at least 4 weeks before travel. However, the elderly population may have suboptimal immune response to vaccination and hence HAV antibody status should be verified after vaccination.

Hepatitis E

Hepatitis E resembles HAV in mode of transmission, clinical presentation, and natural history. HEV is rare in the USA, although sporadic cases have been reported. HEV in endemic areas of the world is caused by genotypes 1 and 2. In the industrial world, HEV infection is caused by genotypes 3 and 4, possibly acquired as a zoonotic infection. There are several reports of HEV evolving into a chronic infection in severely immunocompromised patients.

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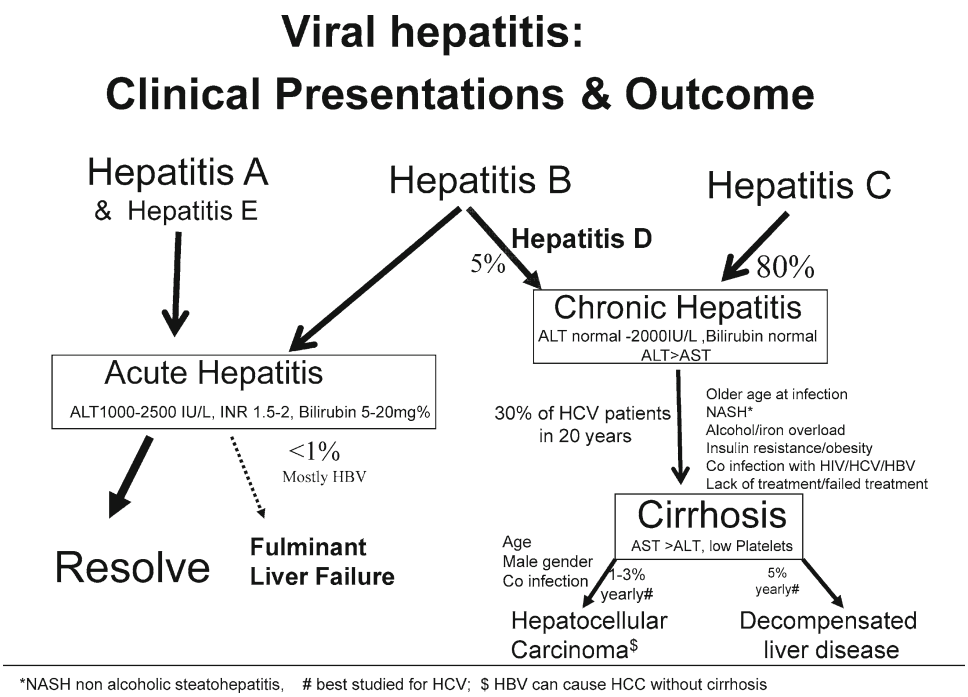

Fig. 38.1 Viral hepatitis: clinical presentations and outcomes

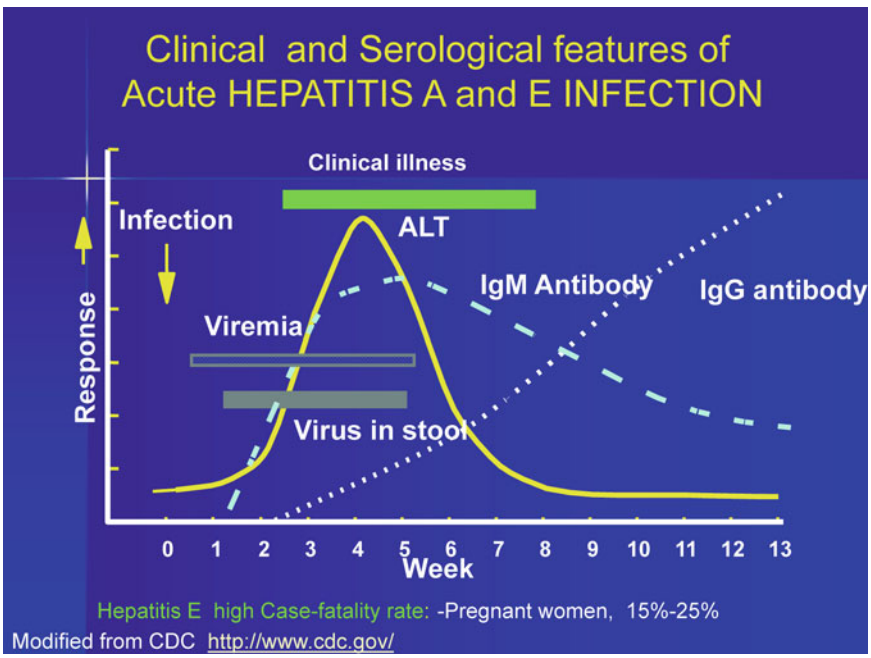

Fig. 38.2 Clinical and serological features of acute viral hepatitis A and E (modified from www.cdc.gov)

Acute hepatitis due to HEV is a self-limited disease, but is known to be more serious in the elderly. There are no FDA-approved tests for diagnosing HEV, but IgM anti-HEV antibody testing is available commercially. Like HAV, detection of IgM anti-HEV indicates acute infection and IgG anti-HEV becomes positive when infection resolves. HEV PCR assays are also available and usually positive during the acute illness. These commercial assays are not well standardized and false positive tests are possible. HEV vaccine is likely to be available soon, having undergone successful phase 3 studies.

Hepatitis C

It is estimated that more than 170 million persons are infected with hepatitis C worldwide with an incidence of three to four million new cases annually. In the USA, 1.6% of the population was positive for HCV antibodies (4.1 million anti-HCV-positive persons) [5]. The prevalence of HCV in the geriatric population is projected to increase in the next 2–3 decades. Because of the longer duration of infection, older adults with

hepatitis C are more likely to have advanced disease. HCV is the leading indication for liver transplant in the USA and Europe. Twenty-five to thirty percent of those chronically infected will progress to cirrhosis in 20–25 years after acquiring the infection. The rate of progression depends on the age at which infection was acquired; when contracted at an older age, the disease progression is more rapid [6]. Once cirrhosis is established, the risk of liver failure is 5% every year and the risk of hepatocellular carcinoma (HCC) is 1–3%/year (Fig. 38.1). Several other factors have been linked with higher rate of disease progression [7, 8]. Figure 38.1 summarizes the natural history of HCV infection.

Mode of Transmission and Risk Factors

HCV is transmitted primarily through exposure to infected blood and blood products. Most patients with HCV in a geriatric practice probably acquired the infection from the use of unsterilized syringes and needles or from blood transfusion prior to 1990 [6].

Clinical Features and Diagnosis

Majority of patients (80%) infected with HCV evolve into chronic hepatitis C, without presenting with an acute phase, with the remaining 20% spontaneously clearing the virus. Hence acute HCV is rarely encountered in clinical practice. Factors including younger age, female gender, certain major histocompatibility complex genes, white race, and interleukin 28 gene polymorphism (IL 28 CC genotype) are associated with spontaneous clearance of HCV infection. Chronic HCV infection is asymptomatic and is routinely diagnosed during evaluation for elevated transaminases. In many instances, however, the initial presentation can be with symptoms and signs of liver failure, especially in geriatric patients, who may have acquired the infection 30–40 years earlier. Serum ALT and AST are typically elevated up to five times the upper limit of normal. Serum ALT is higher than AST in the milder stages of HCV but as the disease evolves into cirrhosis, AST/ALT ratio is reversed (serum AST > ALT). The diagnosis is established by demonstration of HCV RNA in the serum using polymerase-chain-reaction assay. The presence of HCV antibody indicates exposure, but testing for HCV RNA is required to diagnose active infection. Typically the HCV RNA levels are reported as IU/mL. HCV RNA level greater than 400,000 IU/mL is considered a "high" viral load and is indicative of lower response to treatment.

Liver biopsy remains the most accurate test for determining the severity of liver disease in chronic HCV infection. Fibrosis is typically classified from I to IV (METAVIR system, stage IV = cirrhosis). Liver biopsy may reveal the presence of concomitant diseases such as hemochromatosis, alcoholic hepatitis, and hepatic sarcoidosis. Several noninvasive serological tests help assess the fibrosis, with some commercially available. An ultrasound scan, "fibroscan," seems promising, but is not widely available.

Liver biopsy can help in patient selection for treatment. Naturally, patients who have higher stages of fibrosis (stage II or more) are likely to progress to end-stage liver disease sooner and hence are potential candidates for treatment. On the other hand a patient, who is older than 65 years with stage 0 (no fibrosis) or stage I fibrosis, 20–30 year after acquiring HCV, is unlikely to develop cirrhosis in the next 5 years and can await more effective, safer therapy. Mild thrombocytopenia and reversal of AST:ALT ratio (AST > ALT, but AST/ALT ratio is <2) are markers for advanced fibrosis (Stage III or IV) in patients with HCV.

HCV Genotypes

HCV viral genome exhibits substantial genetic variations; six major types of HCV, called genotypes, are identified worldwide. About 75% of patients in the USA have genotype 1 and 25% have genotypes 2 and 3. Within these genotypes there are several subtypes and quasispecies. Genotypes do not influence the natural history of HCV, but are major determinants of response to antiviral therapy.

Extrahepatic Manifestations

HCV infection is well known to be associated with membranous glomerulonephritis and mixed cryoglobulinemia, whereas its association with B cell lymphoma is not proven. There are reports of higher incidence of diabetes and increased insulin resistance in HCV patients, even in the absence of cirrhosis. It is not unreasonable to screen patients with diabetes for HCV and cirrhosis [9]. Insulin resistance is also associated with higher rate of progression of fibrosis and is known to improve with HCV treatment [10, 11]. HCV antibody is frequently seen in patients with rheumatoid arthritis; HCV PCR is required to confirm the diagnosis of active infection. Conversely rheumatoid factor is present in many patients with HCV, but without any other evidence of rheumatoid arthritis. A detailed review of extrahepatic manifestations of HCV was recently published [12].

Treatment

The end point of HCV therapy is defined as sustained virologic response (SVR), meaning undetectable HCV RNA by a sensitive assay, 6 months after stopping the treatment. The rate of SVR for genotype 1 infection is 65–79% [13], whereas for genotypes 2 and 3, SVR rate is 80–90% [14]. Typically genotype 1 patients are treated for 1 year and genotypes 2 and 3

patients are treated for 6 months. Shorter duration of treatment is possible in selected patients with genotypes [15, 16]. Once SVR is achieved, HCV RNA remains undetectable for prolonged periods of time (durability of response) and hence clinicians use the term "cure" in patients who achieve SVR [17]. SVR is also known to decrease adverse outcomes in patients with cirrhosis, although these patients are still at risk for HCC [18]. Moreover, several studies have shown that fibrosis is reversible in those who achieve sustained viral suppression in both HCV and HBV.

The current available treatment for HCV consists of a combination of pegylated interferon alpha ribavirin, and an NS3 protease inhibitor. Two types of pegylated interferons are available: peginterferon α 2a (PEGASYS™, Genentech) and peginterferon α 2b (PEG Intron™ Merck). Both are given as weekly injections. Ribavirin is administered orally every day in two divided doses. There are two types of protease inhibitors available: telaprevir (Incivek™ Vertex) and boceprevir (Victrelis™ Merck) [19, 20]. Protease inhibitors are the first generation of directly acting antiviral agents (DAA) available to treat HCV. They are both given orally every 8 h. Interferon therapy is associated with several complications such as neutropenia, thrombocytopenia, exacerbation of autoimmune disorders, thyroid dysfunction, and retinal changes. In addition, 10–15% of patients in the registration trials developed depression. It is important to know that interferon can worsen liver function in patients with cirrhosis and lead to decompensation. Therefore, eligibility for liver transplantation is an important consideration before treating cirrhotic patients. Ribavirin can cause hemolytic anemia, especially in patients with renal insufficiency. The protease inhibitors can exacerbate the anemia induced by ribavirin. Addition of protease inhibitors to the treatment regimen increases the cost of treatment of HCV substantially. In addition, development of resistance or selection of previously existing resistance mutations can be a major issue with these drugs.

The available data for treatment of hepatitis C in the elderly is scarce due to exclusion of subjects who were 65 years or older in many trials. Therapy-related complications are likely to be higher in older patients. Current American Association on Study of Liver disease guidelines (www.AASLD.org practice guidelines/HCV) do not stipulate an upper age limit for antiviral therapy. Therefore, advanced age alone should not preclude treatment in patients with hepatitis C who are otherwise deemed appropriate candidates [21]. Patients older than 65 years are likely to have advanced disease, and hence the response rate will be lower. Because of age and comorbidity, their ability to tolerate interferon is low, thus decreasing the response rate even further. Therefore, careful risk and benefit analysis is essential before initiating treatment in patients over 65 years. Since HCV is a relatively slow progressing disease, life expectancy of the patient is another important consideration when deciding on treatment.

In addition to genotype, several other factors adversely influence response to interferon-based anti-HCV therapy. These are high pretreatment HCV RNA levels, older age, more advanced disease, coinfection with HIV, African American race, and inability to take 80% of recommended doses of interferon and ribavirin. In a landmark paper published in 2009, Interleukin 28B (IL 28 is synonymous with interferon lambda) gene polymorphism was a major determinant of response to interferon [22, 23]. For example, a Caucasian patient with IL 28B genotype CC has an almost 80% chance for SVR [24]. However, it is likely that many of these host and virological factors will become irrelevant with the advent of more potent directly acting drugs (DAA). Unlike interferon, these agents directly target the HCV replication process by interfering with HCV proteases and RNA-dependent polymerase. At this time, at least 55 small molecules targeting different components of HCV, viral entry, and release of HCV from the hepatocytes are in various stages of development. As therapeutic options expand, HCV treatment will undergo radical changes in the near future. It is anticipated that in the next few years, HCV treatment will comprise a cocktail of different classes of drugs such as protease inhibitors and polymerase inhibitors without the need for interferon. Non-interferon-based regimens will significantly enhance the tolerability of therapy.

Hepatitis B

The incidence of hepatitis B infection in the USA is increasing due to immigration from endemic areas. The Center for Disease Control recommends screening for all individuals from endemic countries (Far East, sub-Saharan Africa). HBV is parenterally transmitted and hence screening is recommended for individuals with high-risk behavior or those with exposure to blood products or contaminated needles.

Clinical Features and Diagnosis

HBV can present as acute HBV, with a clinical presentation very similar to acute HAV (Fig. 38.3). Almost 90–95% patients with acute HBV spontaneously clear the infection and develop immunity. Five percent of patients, however, progress into chronic hepatitis B as evidenced by persistence of HBV surface antigen (HBsAg) beyond 6 months. Once chronic infection is established, HBV infection evolves through different stages based on the interaction with the immune system of the host (Fig. 38.2). Most chronic HBV encountered in adults over 65 years will be "e antigen"-negative chronic HBV and have "pre-core mutant HBV" (HBV lose the ability to produce HBV e antigen) and hence the typical serological pattern will be HBsAg antigen positive, HBV

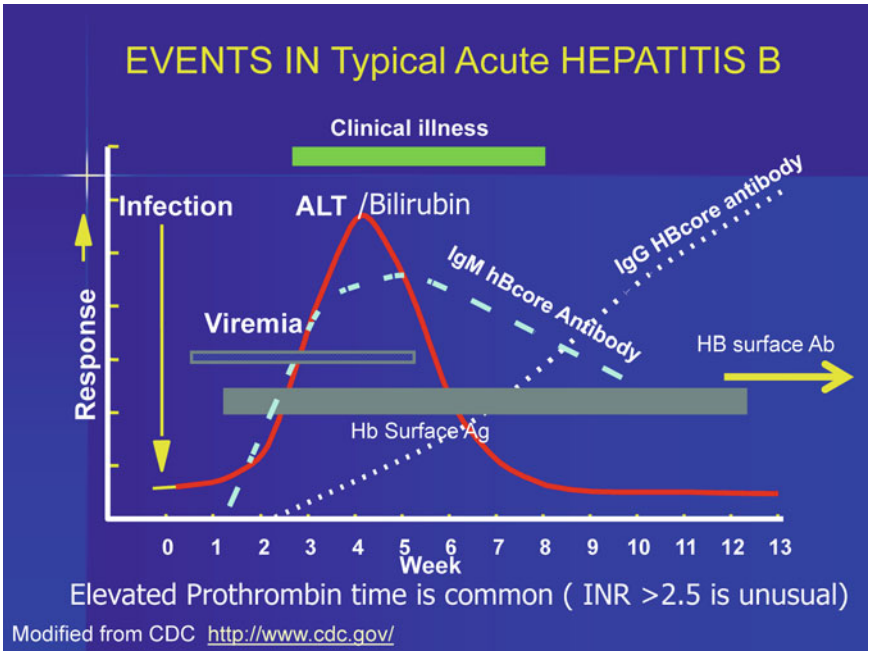

Fig. 38.3 Events in acute viral hepatitis B (modified from www.cdc.gov)

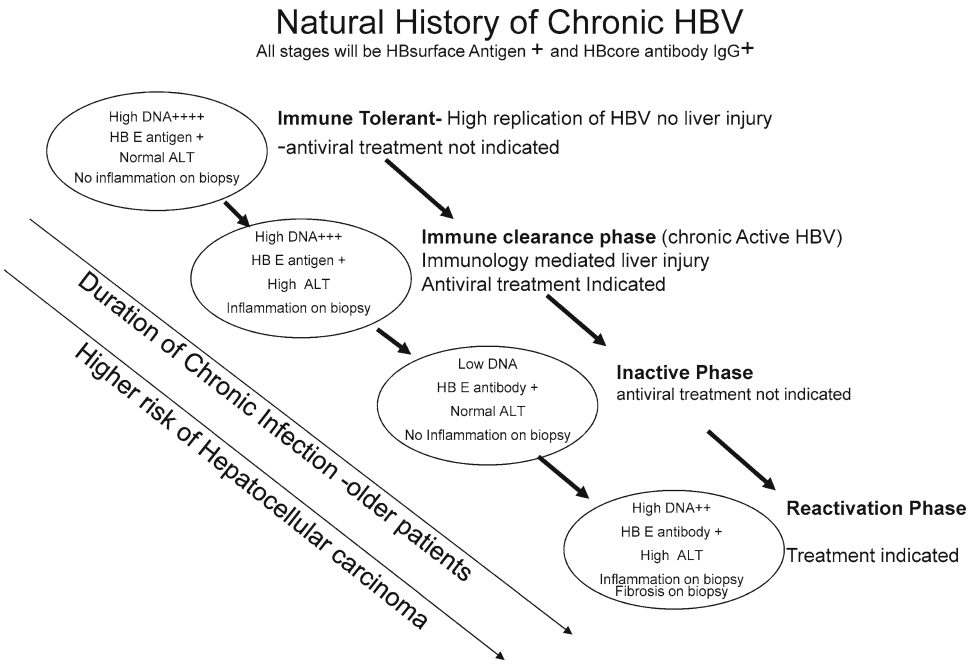

Fig. 38.4 Natural history of chronic hepatitis B infection

e antibody positive (anti-HBe), and HBV e antigen negative (HBeAg). HBV DNA and serum ALT levels will depend on whether the patient is in the inactive phase or the reactivation phase of chronic HBV infection (Fig. 38.4).

It is important to note that unlike Hepatitis C, HBV can lead to HCC even in the absence of cirrhosis. Age is an important risk factor for HCC in hepatitis B and hence older adults need close surveillance for HCC irrespective of the severity of liver disease. Other factors that increase the risk of HCC in patients with chronic HBV include male gender, family history of HCC, presence of cirrhosis, higher level of HBV DNA, and coinfection with HIV, hepatitis delta (HDV).

HBV Genotypes

Several genotypes of HBV are identified named A to F. Some genotypes are responsive to interferon (genotype A), while

Table 38.1 Viral hepatitis serology and interpretation

IgM anti-HAV antibody	Acute hepatitis A
IgG anti-HAV antibody	Previous exposure. Immunity
IgM HEV antibody	Acute hepatitis E infection
IgG HEV	Prior infection
HCV antibody	Chronic hepatitis C or prior infection—no immunity
HCV RNA	Active HCV infection
IgM anti-HB core Ab	Acute HBV (rarely seen in reactivation phase)
IgG HB core Ab	Prior exposure to HBV
HBsAg	Active HBV infection (>6 months indicates chronic HBV infection)
Anti-HBsAb	No active HBV and immunity
Anti-HBsAb(+) and IgG HBcore Ab(+)	Resolved HBV infection
Anti-HBsAb(+) and IgG HBcore Ab(−)	Vaccination
Anti-HBsAb(−) IgG HBcore(+) HBsAg(−)	Prior infection (small % pt could have DNA in serum/liver-occult infection—risk of reactivation with immunosuppression)
HBe antigen	Active replication (immune-tolerant and immune-clearance phase)
Anti-HBe antibody	Inactive or reactivation phase or resolved HBV
HDV antibody	Infection/exposure
HDV PCR	Active infection

others are associated with higher risk of cancer (genotype C) [25]. But unlike HCV there are no definitive treatment guidelines based on the genotype.

Reactivation of HBV

Since hepatitis B can be clinically silent in many, it is relevant to screen for HBV markers (HBsAg) in patients scheduled for immunosuppressive treatments such as prolonged course of steroids, chemotherapy, or anti-TNF alpha agents [26]. If a patient is HBsAg positive, prophylaxis is recommended for the entire period of immunosuppressive therapy and 6 months following completion of immunosuppressive therapy. Any of the oral antiviral agents can be used for prophylaxis but entecavir or tenofovir is preferred. Even in patients with prior infection (negative HBsAg, positive HBcore Ab, Table 38.1) a small amount of HBV DNA could be present in the hepatocytes and reactivation is possible. Prophylaxis may be indicated in these patients also.

Treatment of HBV

Primary goal of HBV treatment is to limit progressive liver injury; hence treatment is reserved for patients with evidence of liver injury on liver biopsy or elevated ALT [27, 28]. Patients in the "inactive stage" of the liver disease should not be treated as the effectiveness of treatment is not clear in this situation. Similarly patients in the immune tolerant phase should not be treated (Fig. 38.2) [27]. HBV treatment has evolved over the last 10 years with the advent of potent antiviral agents. Earlier antiviral agents such as lamivudine (Epivir™) and adefovir (Hepsera™) are no longer used as first-line therapy for HBV because of unacceptably high rate of resistance. As per recent guidelines, the first line of treatment is entecavir (Baraclude™ 0.5 mg/day PO, nulcleoside analogue), tenofovir (Viread™ 300 mg PO/day nucleotide analogue), or pegylated Interferon (PEGASYS 180 μg/week). Unlike HCV, HBV is treated with a single drug. The only instance to use two drugs is following resistance to one of the drugs. Both entecavir and tenofovir are well tolerated and have excellent resistance profiles. Interferon is contraindicated in patients with cirrhosis due to risk of liver failure with treatment-associated flares. On the other hand both entecavir and tenofovir are well tolerated even in decompensated cirrhotic patients [29]. It is worth noting that current HBV treatment will not cure HBV infection (HBsAg loss) in most patients even with prolonged treatment. In HBe Ag-negative individuals, the clearance of HBsAg is only 5%. This is in contrast to HCV, where the majority can be "cured" with a complex regimen of antiviral agents in near future.

Since HBV infection cannot be cured, surrogate goals of treatment are often used. These include the following: conversion of anti-HBe antibody positivity to negativity in HBeAg-positive patients (immune clearance phase) and decrease in HBV DNA to undetectable levels and eventually improve the liver histology in HBeAg-negative patients (reactivation phase). Since the majority of patients over 65 years are HBeAg negative, the treatment is usually lifelong. This is a relevant consideration when instituting treatment for HBV. HIV and HBV coinfection also demands special attention; the choice of agents depends on whether HIV needs treatment. If HIV is to be treated, tenofovir is the agent of choice as it has excellent activity against both HIV and HBV. There is no age limit to treat HBV as the treatment is well tolerated.

Table 38.2 Treatment for viral hepatitis

Hepatitis A	Supportive
Acute HBV	Supportive (entecavir or tenofovir in prolonged acute HBV)
Chronic hepatitis B[a]	Pegylated interferon α (contraindicated in cirrhosis) Nucleoside agents: entecavir Nucleotide agents: tenofovir
HCV[b]	Pegylated interferons (subcutaneous once a week) Ribavirin (PO, 13–15 mg/kg/day—BID) Protease inhibitors (telaprevir and boceprevir) Polymerase inhibitors (in advanced stages of development)
Hepatitis D	Pegylated interferon α (pegylated interferon α 2a 180 μg/week [30])
Fulminant hepatic failure	Liver transplant/supportive
Cirrhosis with no liver failure	Treat with antiviral agents as above
Cirrhosis with liver failure	Liver transplantation (treat HBV to prevent recurrence—HCV treatment contraindicated at present)

[a]Treat immune-clearance/reactivation phase
[b]Rapidly evolving—requires combination of two/three drugs

Hepatitis Delta

Hepatitis D, being an incomplete virus, will only infect patients who have Hepatitis B surface antigen. It can be a coinfection: i.e., infect along with HBV or as superinfection (infection of a patient with already established HBV). HDV increases the severity of HBV infection or can cause acute exacerbation of chronic HBV. HDV is difficult to treat; about 25% response can be achieved with pegylated interferon [30]. HBV viral suppression will not affect HDV disease, unless HBV treatment results in HBsAg loss (Table 38.2).

Key Points

- Hepatitis A presents as acute hepatitis and in most patients resolves without complication.
- Hepatitis E is rare and clinically resembles hepatitis A.
- Hepatitis E infection carries a higher mortality in older adults.
- Most cases of acute HBV resolve but rarely develop fulminant hepatic failure.
- About 5% of HBV infections go on to chronic state; most chronic HBV infections in the older population are either in inactive carrier state or reactivation phase.
- Chronic hepatitis B can be effectively controlled by antiviral agents but HBV infection cannot be eradicated.
- HBV can cause liver cancer even in the absence of cirrhosis; hence surveillance is indicated in select patients.
- HCV is the most common viral hepatitis in the USA and the leading cause of cirrhosis and liver cancer.
- Acute HCV is rarely seen in clinical practice; most cases are chronic HCV.
- Hepatitis C can be cured by combination treatment in up to 70–80% of patients.
- Drugs that target HCV replication process are likely to improve the treatment tolerability and efficacy in the future.

References

1. Daniels D, Grytdal S, Wasley A. Surveillance for acute viral hepatitis—United States, 2007. Centers for Disease Control and Prevention (CDC). MMWR Surveill Summ. 2009;58(3):1–27.
2. Bell BP, Kruszon-Moran D, Shapiro CN, et al. Hepatitis A virus infection in the United States: serologic results from the Third National Health and Nutrition Examination Survey. Vaccine. 2005;23:5798–806.
3. Forbes A, Williams R. Increasing age. An important adverse prognostic factor in hepatitis A virus infection. J R Coll Physicians Lond. 1988;22:237–9.
4. Vento S, Garofano T, Renzini C, et al. Fulminant hepatitis associated with hepatitis A virus superinfection in patients with chronic hepatitis C. N Engl J Med. 1998;338:286.
5. Armstrong GL, Wasley A, Simard EP, et al. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. Ann Intern Med. 2006;144:705.
6. Thabut D, Le Calvez S, Thibault V, et al. Hepatitis C in 6,865 patients 65 years or older: a severe and neglected curable disease? Am J Gastroenterol. 2006;101:1260–7.
7. Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. Lancet. 1997; 349(9055):825–32.
8. Poynard T, Ratziu V, Charlotte F, Goodman Z, McHutchison J, Albrecht J. Charlotte rates and risk factors of liver fibrosis progression in patients with chronic hepatitis C. J Hepatol. 2001;34: 730–9.
9. Eslam M, Khattab MA, Harrison SA. Insulin resistance and hepatitis C: an evolving story. Gut. 2011, Gut Online First, published on 19 Jan 2011 as 10.1136/gut.2010.
10. Patel K, Thompson A, Chuang W, et al. Insulin resistance is independently associated with significant hepatic fibrosis in Asian chronic hepatitis C genotype 2 or 3 patients. J Gastroenterol Hepatol. 2011;26(7):1182–8.
11. Conjeevaram HS, Wahed AS, Afdhal N, et al., Virahep-C Study Group. Changes in insulin sensitivity and body weight during and after PEG interferon and ribavirin therapy for hepatitis C. Gastroenterology. 2011;140:469–77.
12. Jacobson IM, Cacoub P, Dal Maso L, Harrison SA, Younossi ZM. Manifestations of chronic hepatitis C virus infection beyond the liver. Clin Gastroenterol Hepatol. 2010;12:1017–29.
13. Rosen HR. Chronic hepatitis C infection. N Engl J Med. 2011;364:2429–38.
14. Shiffman ML, Suter F, Bacon BR, Nelson D, Harley H, Solá R, et al., ACCELERATE Investigators. Peginterferon alfa-2a and ribavirin for 16 or 24 weeks in HCV genotype 2 or 3. N Engl J Med. 2007;357(2):124–34.
15. Diago M, Shiffman ML, Bronowicki JP, Zeuzem S, Rodriguez-Torres M, Pappas SC, et al. Identifying hepatitis C virus genotype 2/3 patients who can receive a 16-week abbreviated course of

peginterferon alfa-2a (40KD) plus ribavirin. Hepatology. 2010; 51(6):1897–903.
16. Mecenate F, Pellicelli AM, Barbaro G, et al., Club Epatologi Ospedalieri (CLEO) Group. Short versus standard treatment with pegylated interferon alfa-2A plus ribavirin in patients with hepatitis C virus genotype 2 or 3: the CLEO trial. BMC Gastroenterol. 2010;10:21–7.
17. Swain MG, Lai MY, Shiffman ML, et al. A sustained virologic response is durable in patients with chronic hepatitis C treated with peginterferon alfa-2a and ribavirin. Gastroenterology. 2010;139(5): 1593–601.
18. Morgan TR, Ghany MG, Kim HY, HALT-C Trial Group. Outcome of sustained virological responders with histologically advanced chronic hepatitis C. Hepatology. 2010;52(3):833–44.
19. Poordad F, McCone J Jr, Bacon BR, et al., SPRINT-2 Investigators. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med. 2011;364(13):1195–206.
20. Jacobson IM, McHutchison JG, Dusheiko G, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med. 2011;364(25):2405–16.
21. Oze T, Hiramatsu T, Yakushijin T, et al. Indications and limitations for aged patients with chronic hepatitis C in pegylated interferon alfa-2b plus ribavirin combination therapy (original research article). J Hepatol. 2011;54:604–11.
22. Ge D, Fellay J, Thompson AJ, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. Nature. 2009;461(7262):399–401.
23. Thompson AJ, Muir AJ, Sulkowski MS, et al. Interleukin-28B polymorphism improves viral kinetics and is the strongest pretreatment predictor of sustained virologic response in genotype 1 hepatitis C virus. Gastroenterology. 2010;139(1):120–9.
24. Sarrazin C, Susser S, Doehring A, et al. Importance of IL28B gene polymorphisms in hepatitis C virus genotype 2 and 3 infected patients. J Hepatol. 2011;54(3):415–21.
25. Lin CL, Kao JH. The clinical implications of hepatitis B virus genotype: recent advances. J Gastroenterol Hepatol. 2011;26 Suppl 1:123–30.
26. Gisbert JP, Chaparro M, Esteve M. Review article: prevention and management of hepatitis B and C infection in patients with inflammatory bowel disease. Aliment Pharmacol Ther. 2011; 33(6):619–33.
27. Lok ASF, McMahon BJ. AASLD practice guideline hepatitis B 2007. 2009 http://www.aasld.org/practiceguidelines/Pages/NewUpdatedGuidelines.aspx (free download).
28. Yuen MF, Lai CL. Treatment of chronic hepatitis B: evolution over two decades. J Gastroenterol Hepatol. 2011;26 Suppl 1:138–43.
29. Liaw YF, Sheen IS, Lee CM, et al. Tenofovir disoproxil fumarate (TDF), emtricitabine/TDF, and entecavir in patients with decompensated chronic hepatitis B liver disease. Hepatology. 2011;53(1): 62–72.
30. Wedemeyer H, Yurdaydìn C, Dalekos GN, et al., HIDIT Study Group. Peginterferon plus adefovir versus either drug alone for hepatitis delta. N Engl J Med. 2011;364(4):322–31.

Tumors of the Liver

39

Satheesh Nair and Jihad O. Arteh

Widespread availability and use of imaging studies have led to an increase in the number of patients being evaluated for liver tumors. Most of these tumors are benign and require no further follow-up. The challenge is, however, to identify those tumors that are malignant. A combination of clinical history and radiological studies helps diagnosis in most cases (see Fig. 39.1). Patients with underlying liver disease, those presenting with abnormal liver function tests or significantly elevated tumor markers, are likely to have malignant disease. Since the risk of malignant disease increases with age, older patients with a liver mass require closer evaluation. In obese patients or alcoholics, abnormal fat distribution may mimic a tumor, at times followed by unnecessary interventions. With refinement and sophistication of imaging techniques, accurate diagnosis can be reached without the need for tissue sampling [1]. A guided biopsy of the lesion may be required when the diagnosis is uncertain or malignancy cannot be excluded. Figure 39.1 outlines a practical approach to patients presenting with an incidental mass.

Benign Tumors of the Liver

Hemangioma (HA) and focal nodular hyperplasia (FNH) are the most common solid tumors of the liver in the clinical practice. Most benign tumors are easily diagnosed with contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) [2]. Once diagnosis is established, HA and FNH typically do not require follow-up or treatment [2].

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Hepatic Angioma

Hepatic angioma (*Hemangioma*, *HA*) is the most common benign mesenchymal tumor of the liver with prevalence in the range of 3–20%. HAs occur in all ages, but frequently detected in woman aged 30–50 years. They are often asymptomatic and found incidentally on imaging studies. Large HA can present with rupture, bleeding, or compression of adjacent organs. The best imaging diagnostic method is contrast-enhanced MRI. Most HAs have benign course and remain stable over time.

Focal Nodular Hyperplasia

Focal nodular hyperplasia is the second most common benign solid tumor of the liver comprising up to 8% of all hepatic tumors. The prevalence is estimated at 0.9% and occurs in both genders and across all ages, but predominantly in women of child-bearing years (20–40 years). Contrast-enhanced CT scan or MRI aid diagnosis.

FNH is a benign tumor with no risk of malignant transformation, rupture, or hemorrhage. Malignant degeneration can occur in the telangiectatic variant of FNH.

Hepatocellular Adenoma

Hepatocellular adenoma (HCA) occurs predominantly in women (aged 20–40 years) and strongly associated with estrogen use, and in men following use of anabolic steroids. Patients with glycogon storage disease (type 1 and 3) are also at increased risk for developing multiple HCA. HCAs are usually well circumscribed and are typically located in the right hepatic lobe. They tend to be solitary (in 70–80%) and range in size from <1 to 15 cm.

Most patients with small adenomas are asymptomatic. Complications arise only in large adenomas >5 cm in size. HCA can spontaneously rupture or bleed causing acute

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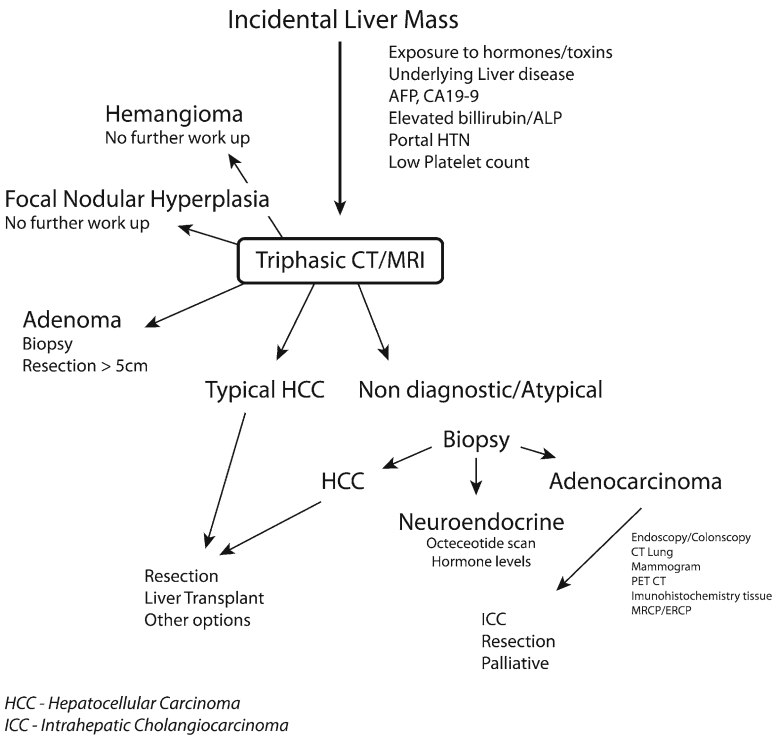


Fig. 39.1 Suggested evaluation of an incidentally detected solid liver mass

abdominal pain or hemorrhagic shock. Malignant transformation has been reported in patients with large tumors. Some gene mutations can identify adenomas at risk for development of malignant degeneration. Beta-catenin mutation is more prone to cytologic atypia and to development of hepatocellular carcinoma (HCC). On the other hand, the TCF-1 gene mutation is rarely associated with cytologic atypia or malignant changes.

Resection is recommended for large lesion, over 5 cm, symptoms attributable to HCA, or when there is suggestion of malignant transformation such as rapid growth, change in radiological appearances, or elevated alpha feto protein (AFP). Most older adults can safely undergo elective liver resection without major complications. Laparoscopic surgical resection has become the standard of care in treatment of benign tumors of the liver [2]. Discontinuation of hormonal therapy may lead to resolution of adenomas.

Nodular Regenerative Hyperplasia

Nodular regenerative hyperplasia (NRH) is a benign proliferative process in which normal hepatic parenchyma is transformed into small regenerative nodules of hepatocytes with minimal or no associated fibrosis. It affects men and women equally and is more common in the elderly. A wide spectrum of systemic diseases and drugs have been associated with NRH including rheumatoid arthritis, connective tissue disorders, myeloproliferative disorders, lymphoproliferative disorders, amyloidosis, polyarteritis nodosa, bone marrow transplantation, and immunosuppressant drugs. These patients present with features of portal hypertension and may be mistakenly diagnosed to have cirrhosis. Liver function tests are normal, with liver biopsy often necessary for diagnosis. Treatment addresses the underlying cause and portal hypertension.

Cystic Tumors

Simple cysts are relatively common and found in about 1% of the population. They are asymptomatic and incidentally found on imaging studies at any age and are more prevalent in women. They do not require additional studies or treatment.

Polycystic liver disease (*PCL*) is arbitrarily defined as presence of more than 20 cysts in the liver. PCL is the phenotypic expression of two distinct inherited disorders. It may occur as a part of autosomal dominant polycystic kidney disease (gene mutations in PKD1 or PKD2) or as isolated PCL (gene mutations in PRKCSH *or* SEC63) [3]. Patients present with abdominal pain due to increasing liver volume caused by the cyst growth. Rare complications include portal hypertension and malignant transformation of the biliary epithelium lining the cysts. In most cases, liver function tests remain normal in all stages of the disease. Mild increase in gamma-glutamyl transferase (GGT) may occur. Carbohydrate antigen (CA 19-9) can be elevated even in the absence of

malignancy. Surgical deroofing of the cyst or CT-guided aspiration may be performed when a large dominant cyst causes symptoms, but recurrence is common [4]. Somatostatin analogues, by inhibiting secretion from the cyst epithelium, show promise in decreasing cyst growth and reducing liver volume [5, 6]. Mammalian target of rapamycin (mTOR) inhibitors such as sirolimus may have a role. Liver transplantation is the definitive treatment of PCL [4].

Malignant Liver Tumors

Intrahepatic Cholangiocarcinoma

Intrahepatic cholangiocarcinoma, sometimes referred to as peripheral cholangiocarcinoma, is a primary adenocarcinoma of the liver arising from the intrahepatic bile duct epithelium. It is the second most common primary hepatic neoplasm in adults, with the incidence increasing worldwide. ICC is more common in women and risk increases with age. Risk factors associated with ICC include primary sclerosing cholangitis, choledochal cysts, intrahepatic cholelithiasis, and fluke infestation (*Clonorchis sinensis* and *Opisthorchis viverrini*). Other risk factors reported include Hepatitis C infection, nonalcoholic liver disease, and obesity [7].

Diagnosis

ICC is often detected as an incidental liver lesion on imaging performed for other purposes. In contrast-enhanced CT, ICC often has a rim-like area of hypervascularity surrounding a central area of low attenuation, followed by diffuse enhancement of the mass with contrast in the delayed phase. On MRI, ICC is either isointense or hypointense on T1-weighted images and hyperintense on T2-weighted images. Liver biopsy is often required for accurate diagnosis. However, with poorly differentiated tumor or tumors where immunohistochemical stains are not confirmatory, further evaluation of an extrahepatic primary tumor is warranted (see Fig. 39.1).

Tumors markers such as CA 19-9 or carcinoembryonic antigen (CEA) levels might be elevated, but these markers lack sensitivity and are not diagnostic of ICC.

Management

Several staging systems have been proposed for ICC [8]. Surgical resection of ICC is the only potentially curative option with reported 5-year survival after resection ranging from 14 to 40% [7]. Vascular invasion and multiple lesions are associated with high recurrence rate and should not be considered for surgical resection [8]. For unresectable ICC, options include chemoembolization and radioembolization [9]. For metastatic or advanced cancer, systemic therapy with gemcitabine and cisplatin, or 5-flurouracil can be considered [10].

Hepatocellular Carcinoma

The incidence of HCC in the United States has been rising, with the rise attributable to an increase in the number of patients infected with hepatitis C for over 20 years [11]. Immigration to US from high endemic areas of Hepatitis B (HBV) is also increasing the incidence of HBV-related HCC.

The most important risk factor for HCC is cirrhosis (Table 39.1). Nonalcoholic fatty liver disease (NAFLD) is the leading underlying etiology of cirrhosis in patients over 65 years. Early stages of cirrhosis due to NAFLD are clinically silent and hence diagnosis of those at risk can be missed. In obese patients or long-standing metabolic syndrome, it is not unreasonable to screen for fatty liver and cirrhosis, especially if they manifest mild thrombocytopenia. HCC is increasingly seen in patients with cirrhosis due to NAFLD [12]. Obesity and diabetes also increase the risk of HCC, but it is not clear whether this is due to higher risk of NAFLD in these patients. Chronic HBV can cause HCC even without cirrhosis and therefore screening is recommended in the subset of patients with HBV who are at high risk for HCC. HCV infection does not cause HCC in the absence of cirrhosis. Age is an important risk factor for HCC; geriatric patients should undergo rigorous screening for HCC if they have risk factors.

Screening of HCC is critical in identifying early stages of HCC, when curative treatment is possible. Evidence suggests

Table 39.1 Indications for screening for hepatocellular carcinoma (HCC) and risk of HCC [11, 12]

Disease	Risk
High risk (*screening recommended*)	
Hepatitis C with cirrhosis	3–5%/year
Hepatitis B with cirrhosis	3–8%/year
Primary biliary cirrhosis stage 4	3–4%/year
Cirrhosis due to NAFLD[a]	Unknown (likely high)
Risk not exactly known but high enough to recommend screening	
Genetic hemochromatosis	Unknown
Alpha 1 antitrypsin	Unknown
Other cirrhosis	Unknown
Asian males with HBV > 40 years	0.5%/year
Asian female with HBV > 50 years	0.5%/year
Chronic HBV carries with family history of HCC	Unknown
North African men with HBV	Unknown
HBV with HIV coinfection	Unknown
Risk is not known but no recommendations to screen[b]	
Hepatitis C with stage 3 fibrosis	
NAFLD with stage 3 fibrosis	
Chronic HBV not belonging to above categories	

[a]Cirrhosis due to NAFLD likely has high risk close to hepatitis C cirrhosis

[b]Many hepatologists opt to screen these patients at least yearly

Table 39.2 Tumor markers and liver [14]

Tumor marker	Clinical correlation and use in clinical practice
1. Alpha feto protein	Should not be used alone for screening for HCC
	High in pregnancy and germ cell tumors
	Mild increase up to 50–100 ng/mL in hepatitis C due to inflammation
	Close follow-up needed to rule out HCC
	Regenerative phase following hepatocyte necrosis
AFP > 200 ng/mL	Highly suspicious for HCC
AFP > 500 ng/mL	Get automatic upgrade on organ allocation system for HCC even without radiological evidence of tumor
AFP > 1,000 ng/mL	Concerning for vascular invasion of HCC, increases the risk of recurrence following resection or transplantation
2. AFP L3 (glycosylated AFP)	Not useful for routine screening
	May be useful when total AFP is elevated in the absence of radiological evidence of HCC
3. DCP (des gamma carboxy protein)	Not useful for routine screening
	May be useful when total AFP is elevated in the absence of radiological evidence of HCC
4. CA 19-9	>100 ng/mL suspicious of cholangiocarcinoma; low specificity correlate with clinical findings
	False elevation seen with high bilirubin (due biliary obstruction)
	High CA 19-9 seen normally in cyst fluid on polycystic liver
5. CA 125	Can be high in Liver dysfunction, does not indicate any tumor
6. CEA	Slightly high in cholangiocarcinoma; clinical use is limited

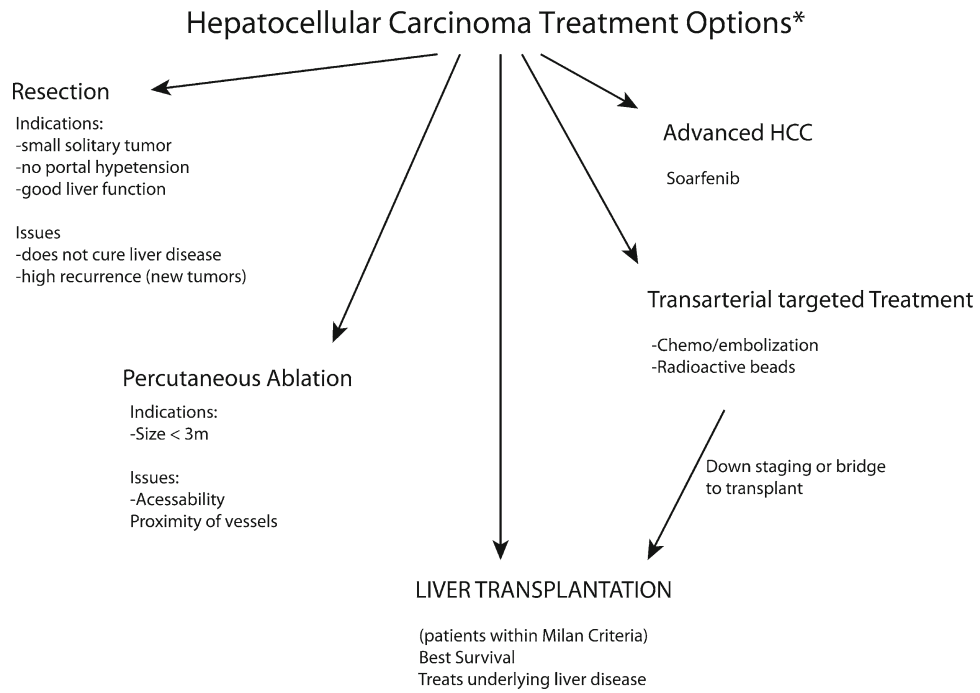
that surveillance decreases mortality in patients with cirrhosis. Current recommendations dictate that all patients with cirrhosis, regardless of the underlying cause, be screened for HCC every 6 months using ultrasound examination. AFP is a widely available test, but can be normal up to 60% of HCC. Hence, AFP measurement alone is not an adequate screening test. A slightly elevated AFP is common in hepatitis C. It is sound clinical judgment to perform triple-phase CT scan or MRI if AFP is elevated beyond 50 ng/mL. AFP L3 and des-γ-carboxy prothrombin (DCP) are other tumor markers for screening, but no specific recommendations exist (Table 39.2). Ultrasound, on the other hand, is operator-dependent and not very sensitive in a small cirrhotic liver. Therefore, most clinicians use a combination of AFP level and ultrasound every 6 months to screen for HCC. Despite established guidelines and availability of screening methods, a large Veteran Administration (VA)-based study showed that very few patients with HCV cirrhosis received appropriate screening [13], highlighting the need for awareness among medical professionals about risk of and importance of screening. Abnormal findings in ultrasound should prompt specific tests such as triple-phase contrast-enhanced CT or MRI.

Diagnosis

HCC should be suspected in any patient with a solid liver tumor. In the presence of underlying liver disease or cirrhosis, a solid tumor should be considered as HCC unless proven otherwise. Recommendations to evaluate a suspected nodule are described in the American Association for the study of Liver Diseases (AASLD) guidelines [14]. Typically, a three-phase CT scan or MRI scan is diagnostic. Three-phase CT/MRI utilizes the fact that HCC is supplied by hepatic artery and enhances with contrast on the arterial phase of CT scan and washes out during the portal venous phase. A biopsy is not needed once typical radiological features are seen on CT or MRI scans in patients with cirrhosis. Liver biopsy may be indicated in patients with atypical radiological characteristics and in those without risk factors for HCC. Liver biopsy can determine the grade of HCC and provide additional prognostic information. In those without a history of cirrhosis, a biopsy of normal appearing (non tumor) liver parenchyma helps rule out cirrhosis, as this will be important when deciding feasibility of surgical resection.

Treatment

Figure 39.2 outlines the overview of the management options for HCC. The first step in the treatment of HCC is to determine the stage of HCC, severity of liver dysfunction, and degree of portal hypertension. Barcelona-Clinic Liver Cancer Group algorithm is the best management guideline and incorporates the stage of HCC, liver function, and the performance status of the patient [14]. Generally, surgical resection is reserved for smaller tumors with well-preserved liver function in the absence of significant portal hypertension. Liver transplantation is the only hope for cure in patients with liver failure and HCC. Liver transplantation also offers the advantage of treating the underlying liver disease and alleviating the symptoms and complications of cirrhosis. Patient survival after liver transplantation is determined by the size and the number of HCC. "MILAN" Criteria are the most widely accepted and used criteria to determine the suitability of patients with HCC for liver transplantation [15]. MILAN



HCC - hepatocellular carcinoma
** Detailed algorithm please refer to Forner A et al, Semin Liver Dis. 2010 Feb 30;(1):61-74.*

Fig. 39.2 Treatment options for hepatocellular carcinoma

Criteria is defined as one tumor less than 5 cm in size or up to three separate tumors all ≤3 cm with no evidence of gross vascular invasion, or no regional or distant metastases. Patients who meet "Milan Criteria" get a high priority on the transplantation waiting list and are automatically granted additional points on the Model for End Stage Liver Disease (MELD) score for organ allocation system in the US (Policy www.UNOS.org). Some patients who do not meet the "Milan Criteria" can qualify for a downstaging protocol where the tumor size and/or number are reduced by chemoembolization or radiofrequency ablation [16]. Large tumors >8 cm or tumors with radiological evidence of vascular invasion are usually not considered for liver transplantation. Markedly elevated AFP levels (>1,000 ng/mL) are often an indication of tumor vascular invasion. Portal vein thrombosis in a patient with cirrhosis should raise suspicion for HCC and tumor thrombus.

Treatment of HCC in the elderly is challenging. Since HCC within the Milan Criteria is curable with liver transplantation, it is important to determine whether the patients qualify for liver transplantation. Many liver transplant programs are generally reluctant to offer a liver to a patient over 70 years of age, but the decision is best individualized and based on overall functional status along with life expectancy in the absence of HCC [17]. Patients over 65 years with HCC who are not surgical or transplant candidates may be considered for alternative treatment strategies. Those with small HCC can benefit from targeted treatment of the tumor using percutaneous radiofrequency ablation, transarterial chemoembolization, or transarterial radiation beads. These procedures, while not as effective as liver transplantation in terms of survival, offer reasonable disease control and life expectancy. Moreover, these treatments are well tolerated and mostly performed as outpatient procedures in experienced centers. It is common to see older patients preferring minimally invasive therapies even if they are suitable candidates for resection, primarily because of less morbidity.

Patients with large tumors can potentially benefit from palliative treatments. Multitargeted tyrosine kinase inhibitors that affect the cellular proliferation and angiogenesis are approved to treat patients with advanced HCC. A large phase 3 randomized controlled study using sorfaenib was prematurely terminated because significant benefit was seen in the treatment arm [18]. Several drugs in this category are under development and presently approved only for advanced HCC [19]. The drugs may serve as a useful bridge to liver transplantation and more definitive treatments.

Some tumors exhibit *mixed HCC and cholangiocarcinoma* features on histology. High rate of recurrence and lower survival were seen in patients with mixed tumors who underwent liver transplantation [20].

Liver Metastases

Metastases are the most common malignant liver tumors and occur 20 times more frequently than primary hepatic neoplasms. Most metastases typically manifest as multiple discrete lesions, but may present as a solitary mass. The radiological appearance of the tumors vary depending on tumor vascularity. Colon, breast, lung, and gastric carcinomas are the most common causes of hypovascular liver metastasis. Hypervascular metastases are usually from neuroendocrine tumors (e.g., carcinoid, pheochromocytoma, and islet cell tumors), renal cell carcinoma, melanoma, thyroid carcinoma, and choriocarcinoma. Breast carcinoma and, rarely, pancreatic adenocarcinoma can also cause hypervascular metastases. Usually liver biopsy is required for diagnosis unless a primary site is already known.

Significant advances have occurred in the management of patients with metastatic colon cancer and neuroendocrine tumors. A multidisciplinary approach has resulted in good outcomes in select patients with colon cancer metastasis. Systemic chemotherapy/local therapy followed by surgical resection have achieved excellent survival in solitary metastatic lesion from colon cancer [21].

Neuroendocrine tumors are typically slow growing and selected patients with liver metastasis can benefit from liver transplantation [22]. Two randomized controlled trials have shown promise with kinase inhibitor and mTor inhibitor in the treatment of metastatic neuroendocrine tumor [23, 24].

Rare Tumors

Rare vascular tumors of the liver include epithelioid hemangioendothelioma (EHE), hepatic angiosarcoma, hepatic Kaposi sarcoma, and spongiotic pericytoma. EHE can be treated with liver transplantation if there is no extrahepatic disease. Primary hepatic lymphoma is rare, but responds to systemic chemotherapy.

Key Points

- Incidence of hepatocellular carcinoma is on the increase.
- A contrast-enhanced CT scan or magnetic resonance imaging (MRI) can be diagnostic for some liver tumors and a biopsy may not be required.
- MILAN Criteria are the most widely accepted and used criteria to determine the suitability of patients with hepatocellular carcinoma (HCC) for liver transplantation.
- Liver transplantation offers the best means for survival in patients with hepatocellular carcinoma.
- Drugs that target angiogenesis and cellular proliferation are likely to improve survival in some patients with hepatocellular carcinoma and neuroendocrine tumors.

References

1. Boutros C. Management of an incidental liver mass. Surg Clin North Am. 2010;90(4):699–718.
2. Buell JF. Management of benign hepatic tumors. Surg Clin North Am. 2010;90(4):719–35.
3. Janssen MJ, Waanders E, Woudenberg J, et al. Congenital disorders of glycosylation in hepatology: the example of polycystic liver disease. J Hepatol. 2010;52(3):432–40.
4. Drenth JP, Chrispijn M, Nagorney DM, et al. Medical and surgical treatment options for polycystic liver disease. Hepatology. 2010; 52(6):2223–30.
5. van Keimpema L, Nevens F, Vanslembrouck R, et al. Lanreotide reduces the volume of polycystic liver: a randomized, double-blind, placebo-controlled trial. Gastroenterology. 2009;137:1661–8.
6. Hogan MC, Masyuk TV, Page LJ, et al. Randomized clinical trial of long-acting somatostatin for autosomal dominant polycystic kidney and liver disease. J Am Soc Nephrol. 2010;21:1052–61.
7. Poultsides GA. Intrahepatic cholangiocarcinoma. Surg Clin North Am. 2010;90(4):817–37.
8. Nathan H, Aloia TA, Vauthey JN, et al. A proposed staging system for intrahepatic cholangiocarcinoma. Ann Surg Oncol. 2009; 16(1):14–22.
9. Ahmadzadehfar H, Biersack HJ, et al. Radioembolization of liver tumors with yttrium-90 microspheres. Semin Nucl Med. 2010; 40:105–21.
10. Valle J, Wasan H, Palmer DH, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med. 2010; 362:1273–81.
11. Kanwal F, Hoang T, Kramer JR, et al. Increasing prevalence of HCC and cirrhosis in patients with chronic hepatitis C virus infection. Gastroenterology. 2011;140(4):1182–8.
12. Yang JD, Harmsen WS, Slettedahl SW, et al. Factors that affect risk for hepatocellular carcinoma and effects of surveillance. Clin Gastroenterol Hepatol. 2011;9(7):617–23.
13. Davila JA, Henderson L, Kramer JR, et al. Utilization of surveillance for hepatocellular carcinoma among hepatitis C virus-infected veterans in the United States. Ann Intern Med. 2011;154(2): 85–93.
14. Bruix J, Sherman M. AASLD practice guidelines update 2011. Hepatoloy. 2011;53;1021–23—full website of AASLD practice guidelines. http://www.aasld.org/practiceguidelines/Pages/NewUpdatedGuidelines.aspx.
15. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med. 1996;334(11):693–9.
16. Yao FY, Kerlan Jr RK, Hirose R, et al. Excellent outcome following down-staging of hepatocellular carcinoma prior to liver transplantation: an intention-to-treat analysis. Hepatology. 2008;48(3):819–27.
17. Nanashima A, Abo T, Nonaka T, et al. Prognosis of patients with hepatocellular carcinoma after hepatic resection: are elderly patients suitable for surgery? J Surg Oncol. 2011;104(3):284–91. doi:10.1002/jso.21932.
18. Llovet JM, Ricci S, Mazzaferro V, et al. SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359(4):378–90.
19. Tanaka S, Arii S. Molecular targeted therapy for hepatocellular carcinoma in the current and potential next strategies. J Gastroenterol. 2011;46(3):289–96.

20. Sapisochin G, Fidelman N, Roberts JP, et al. Mixed hepatocellular-cholangiocarcinoma (HCC-CC) and intra-hepatic cholangiocarcinoma (I-CC) in patients transplanted for hepatocellular carcinoma. Liver Transpl. 2011;17(8):934–42. doi:10.1002/lt.22307.
21. Gallagher DJ, Kemeny N. Metastatic colorectal cancer: from improved survival to potential cure. Oncology. 2010;78(3–4):237–48.
22. Rea DJ, Rosen CB, Nagorney DM, et al. Transplantation for cholangiocarcinoma: when and for whom? Surg Oncol Clin N Am. 2009;18(2):325–37.
23. Yao JC, Shah MH, Ito T, et al. Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med. 2011;364(6):514–23.
24. Raymond E, Dahan L, Raoul JL, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. N Engl J Med. 2011;364(6):501–13.

Nonalcoholic Fatty Liver Disease (NAFLD) and Nonalcoholic Steatohepatitis (NASH)

40

C.S. Pitchumoni

Fatty liver, once considered to be a benign term for accumulation of lipids in the liver in many overweight individuals, is currently considered the most common form of "liver disease" with albeit a small potential for cirrhosis and even hepatoma. "Cryptogenic cirrhosis" was a term once popular in describing cirrhosis of the liver with no identifiable etiological factors; currently, it is clear that "cryptogenic cirrhosis" in older adults is secondary to accumulation of fat in the liver from decades earlier [1–4].

The term "non-alcoholic steatohepatitis," first described as a clinical entity by Ludwig et al. [5], was used to describe liver biopsy findings resembling alcoholic hepatitis in patients who did not have a history of heavy drinking. The umbrella term, nonalcoholic fatty liver disease (NAFLD), is now a part of a spectrum of liver disorders that begins as NAFLD and may progress to steatohepatitis (NASH) and rarely to cirrhosis and even hepatoma. Many causes contribute to the development of fatty liver (Table 40.1), with the presence of fat in the liver considerably abnormal. By itself, however, the presence of fat in the liver should not cause harm or permanent damage.

NAFLD is a common chronic liver disorder in adults worldwide [6, 7]. NAFLD-related cirrhosis is becoming the most common cause of cirrhosis, a cause of primary hepatocellular carcinoma, and rarely intra-hepatic cholangiocarcinoma [8–10].

NAFLD and NASH represent the hepatic manifestation of "metabolic syndrome" [11, 12] (Table 40.2), comprising central fat distribution, obesity, diabetes, dyslipidemia, hypertension, and atherosclerotic cardiovascular disease [13]. It is well established that obesity is growing rapidly in the USA and in other parts of the world [14–17]. The National Health and Nutrition Examination Survey (NHANES) data from 2007 to 2008 indicate the prevalence of obesity in the US to be 32.2% among adult men and 35.5% among adult women [17].

Even developing nations are noticing similar trends [15]. For example, in India where malnutrition is still rampant, NAFLD is present in a third of the urban population [7]. South Asians (from India, Pakistan, Nepal, Malaysia, Bangladesh, Sri Lanka) in particular have a high prevalence of the metabolic syndrome, abdominal obesity, diabetes, and NAFLD, even though they may have normal BMI (body mass index) by Western standards [7]. The additional weight increases the risk of comorbidities, functional decline, impaired health-related quality of life (HRQL), increased use of health resources, and mortality [18, 19].

As the obesity epidemic increases worldwide, the incidence and prevalence of NAFLD is also expected to rise [20]. Diabetes, hypertension, dyslipidemia (components of metabolic syndrome), arthritis, and certain cancers (breast, adenocarcinoma of esophagus, pancreas, and colon) are some comorbidities in the obese adult [21].

Epidemiology and Prevalence of NAFLD and NASH

The exact prevalence of NAFLD or NASH is difficult to determine since only a subset of the population undergo biochemical or early imaging studies and a smaller subset, liver biopsy, the "gold standard." The prevalence of NAFLD in the general population ranges from 20 to 40% and increases with age [22, 23]. The prevalence of NAFLD after age 75 tends to decrease perhaps due to early mortality from comorbid effects of the metabolic syndrome [24, 25]. An Italian population survey based on abdominal ultrasound noted the frequency of steatosis to be 16.4% in the general population, 46.4% in alcoholics, but as high as 75.8% in obese subjects, and 94.5%

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Table 40.1 Causes of fatty liver disease [1–3, 5]

Insulin resistance and hyperinsulinemia
Obesity (central distribution)
Type 2 diabetes mellitus
Drugs
Valproic acid
Aspirin
Acetaminophen
NSAID (naproxen, ibuprofen, ketoprofen)
Nucleoside analogs (ziduvudine, didanosine, zalcitabine, fialuridine)
Corticosteroids
Tamoxifen
Estrogens
Amiodarone
Calcium channel blockers
Chloroquine
Metabolic
Wilson disease
Nutritional
Starvation
Protein deficiency
TPN
Gastrointestinal surgery for obesity
Infections
Chronic hepatitis C
Toxins
Environmental toxins
Ethanol
Toxic shock syndrome
Other
HIV [114]
Inflammatory bowel disease

Table 40.2 Components of the metabolic syndrome [7, 13, 32, 35]

Abdominal obesity (waist circumference in men >40 in. and in women >35 in.)
Triglycerides ≥150 mg/dL
HDL cholesterol <40 mg/dL in men and <50 mg/dL in women
Blood pressure ≥130/85 mmHg
Fasting glucose ≥110 mg/dL

Note: For Asians, the criteria differ: fasting glucose ≥100 mg/dL; abdominal obesity is described as waist circumference in men >35.4 in. and in women >31.5 in. [7]

of obese alcoholics [26]. The overall prevalence of NAFLD among type 2 diabetics ranges from 40 to 70% [27].

NAFLD affects all age groups and races, but men are more at risk for developing the disease. The prevalence of NAFLD is greater among Hispanic Americans and Caucasians than in African Americans [22]. South Asian populations, for reasons mentioned earlier, represent a growing population with NAFLD [6, 28, 29].

Any level of obesity increases the prevalence of NAFLD in the patient with diabetes mellitus [30, 31]. NAFLD, although primarily associated with increased central obesity and visceral fat, is also seen in lean individuals who do not meet the criteria for overweight or obesity categories [32–35]. Most South Asians may have normal BMI and waist circumference and waist:hip ratio, but yet demonstrate metabolic syndrome and NAFLD (Table 40.2). Hence, diagnostic criteria for obesity in South Asians have been recently modified.

Nonalcoholic steatohepatitis (NASH), the second stage of fatty liver disease, is estimated to affect 19% of the obese U.S. population [30, 31]. In the morbidly obese, the prevalence of NAFLD is as high as 95%, while the prevalence of NASH may be close to 25% [36]. NASH is a more aggressive condition that is associated with inflammation, hepatocyte injury and/or hepatic fibrosis, and ultimately cirrhosis. Cirrhosis is irreversible resulting in multiple, systemic sequelae.

Diagnosis of NAFLD and NASH

Clinical Evaluation

Most people with NAFLD are asymptomatic. Fatigue, weight loss, weakness, and right upper quadrant abdominal pain are rare, and signs including jaundice, ascites, gynecomastia, and spider angiomata are noted only in advanced stages of the disease. In 15–50% of cases, liver fibrosis or cirrhosis are seen as the initial presentation [37].

The majority of patients come to the clinician's attention usually because of abnormal serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels noted in routine serologic examination. No specific serologic markers for NAFLD are available. Testing is done to exclude other liver diseases such as hepatitis B, hepatitis C, autoimmune hepatitis, primary biliary cirrhosis, hereditary hemachromatosis, Wilson's disease, or alpha-1 antitrypsin deficiency. Markers of metabolic syndrome, including hemoglobin-A1c, increased total cholesterol, increased low density lipoproteins (LDL), and increased triglycerides, should alert clinicians to the possibility of concomitant NAFLD. Patients with NAFLD usually have mild (two to threefold) elevation of serum AST, ALT or both and rarely more than 3 times the upper limit of normal [38]. Alkaline phosphatase or gamma-glutamyltransferase may also be mildly elevated, but seldom in the absence of AST, ALT abnormalities [39]. Autoantibodies may be positive in patients with NAFLD in the absence of autoimmune hepatitis [40]. The international normalized ratio (INR), serum bilirubin, and serum creatinine may be abnormal in advanced disease.

The goals in the diagnosis are to confirm the etiology of liver disease, to evaluate the specific type of fatty liver, and to establish clinical severity. A diagnosis of NAFLD requires that (a) the patient has no prior history of significant alcohol consumption (typical threshold is <20 g/day for women and

<30 g/day for men) [41] (b) other liver diseases, including hepatitis C, hemochromatosis, alpha-1 antitrypsin deficiency, and Wilson's disease are ruled out, although NAFLD can occur in conjunction with the above-mentioned diseases, and (c) histopathologic features of NAFLD are confirmed in liver biopsy.

Imaging Studies

Imaging studies, including abdominal ultrasound, CT scan of the abdomen/pelvis, magnetic resonance imaging (MRI), and magnetic resonance spectroscopy (MRS), can detect fatty infiltration of the liver. Ultrasonography is a relatively simple, cost-effective, and noninvasive study most commonly employed to detect steatosis, with a sensitivity of 66–100% for a fat content of >33% [32, 42]. The fatty liver is diffusely echogenic and bright and depicted in ultrasound. Cirrhosis can have a similar picture [43].

The diagnostic sensitivity/specificity of ultrasound in thin individuals is high (100% and 91–97%, respectively), but in the mildly obese (category of most patients with fatty liver) the diagnostic accuracy of ultrasound declines [44]. Noncontrast CT scan of the abdomen gains accuracy in predicting steatosis only when the steatosis is greater than 30% [45]. In those with more accumulation of fat, the diagnostic accuracy increases with liver-spleen attenuation ratios [45, 46].

Although MRI is useful in the diagnosis of NAFLD, it is expensive and is not justifiable for the evaluation of an asymptomatic, common problem. MRI cannot be performed in those with implantable devises and is a difficult examination for claustrophobics. Both problems may be encountered in the older adult.

None of the above imaging studies differentiate between steatosis (NAFLD) and steatohepatitis (NASH).

Since liver biopsy, an invasive test, is not appropriate or practical, it may not be prudent to subject an older adult to liver biopsy in the absence of compelling indications. Several studies have looked at transient elastography, an ultrasound-based technology that measures liver stiffness and clinical scores [47, 48]. A stepwise decrease in elasticity is seen in hepatic fibrosis [49]; however, elastography and clinical scores only indicate the degree of fibrosis and do not predict the disease progression. An MR equivalent of the above is being investigated. Early studies demonstrate a 98 and 99% sensitivity and specificity for identifying fibrosis [50].

The NAFLD Fibrosis Score and FIB4 score are examples of validated nonproprietary clinical scores for estimating severity of liver fibrosis; the ELF (Enhanced Liver Fibrosis) test and Fibrotest are proprietary for the noninvasive assessment of liver fibrosis based on clinical biochemical indices and panels of specific serum markers [41].

Pathophysiology

The exact pathogenesis of NASH is largely unclear [51]. The "two-hit" hypothesis, developed in 1998 by Day et al., is the leading theory in the pathogenesis of NASH [52]. The first hit is insulin resistance, which is believed to lead to the accumulation of triglycerides in hepatocytes. This results from increased synthesis of fatty acids and delivery to the liver, decreased degradation of fatty acids, and release of triglycerides from the liver. Numerous studies support the hypothesis as most patients with NAFLD have hyperinsulinemia, insulin resistance, and the metabolic syndrome [53–58].

The second hit of the hypothesis suggests several potential insults to the liver, leading to the development of NAFLD. Oxidative stress occurs when oxidant substrates are produced, exceeding the ability of the liver to scavenge antioxidants. Oxidative stress is caused by the reactive oxidative species that leak from the mitochondria during oxidation of fatty acids, P450 enzymes, tumor-necrosis factor-alpha (TNF-alpha), and hepatic iron load [59–63]. Oxidative stress can cause hepatocyte death contributing to hepatocellular injury and fibrosis. In addition, proinflammatory cytokine production is also increased in NASH. Elevated hepatic-free fatty acids in patients with NAFLD can be directly hepatotoxic.

Genetic predisposition also plays a role in the second hit, contributing to the determination of insulin sensitivity, obesity and its distribution, and oxidative stress generation [64–66].

A possible third hit, involving the protein leptin, has also been hypothesized in the development of NAFLD [67]. Leptin derived primarily from adipocytes promotes insulin resistance and contributes to oxidative stress and increase in the proinflammatory and profibrogenic responses in the liver [67–70].

Excessive adiposity may also contribute to tissue damage that occurs in metabolic syndrome because fat-derived factors regulate the inflammatory response. At least three of these factors including fatty acids, adiponectin, and tumor-necrosis factor-alpha (TNF-alpha) promote NAFLD by modulating the hepatic inflammatory response, plasminogen activator inhibitor (PAI-1) [71, 72].

TNF-alpha is proinflammatory, causing apoptosis, recruiting white blood cells (WBC), and promoting insulin resistance. Adiponectin is anti-inflammatory, inhibiting fatty acid uptake, stimulating fatty acid oxidation, and enhancing insulin sensitivity. Obesity can lead to the overproduction of TNF-alpha leading to reduced adiponectin activity. Interestingly, TNF-alpha and adiponectin inhibit each other's production and activity. In summary, the combination of high TNF-alpha and low adiponectin favors steatosis (NAFLD), cell death, inflammation (NASH), and insulin resistance [73–75].

Gut microbiota have shown increasing relevance to the development of NAFLD. Microbiota can influence several

factors in the pathogenesis including absorption of dietary lipids promoting obesity, diabetes (type 1 and type 2), and generation of free fatty acids [76]. All these factors promote steatosis, leading to NAFLD.

Many drugs used in the older adult such as amiodarone and nifedipine are implicated in the development of fatty liver due to oxidative stress (Table 40.1) [42]. In addition, significant alterations of drug-metabolizing enzymes may affect the clearance of many medications and may be a contributory factor to fatty liver [77].

Pathology

Liver biopsy is the "gold standard" to confirm or exclude NASH [78], although biopsy is performed only selectively in those suspected to have NAFLD. The diagnosis and differentiation between NAFLD and NASH can be determined only by liver histology and cannot be predicted by clinical or laboratory findings [79] (Table 40.3). However, NAFLD being generally a benign disorder does not need an invasive diagnostic procedure such as liver biopsy. Biopsy in patients with NAFLD is usually reserved for those with diabetes, obesity, age over 50 years, and with persistently abnormal AST and ALT levels, despite lifestyle modifications for a minimum of 6 months [78, 80].

Liver biopsy is invasive and associated with risk of hemorrhage; further treatment is not modified by biopsy findings. Biopsy is associated with a 0.06–0.35% risk of morbidity and 0.1–0.01% risk of mortality [81].

The minimum histologic criteria for NAFLD is the presence of fat in >5% of hepatocytes. Steatosis consists of triglycerides and is mostly macrovesicular or as smaller, well-circumscribed droplets admixed with cytoplasmic contents. Severity of steatosis is associated with lobular inflammation.

The histologic criteria for NASH include the following: macrovesicular fatty change, hepatocellular ballooning degeneration and mild diffuse lobular inflammation [11]. When there is sustained injury, the extracellular matrix accumulates along with fibrosis [81]. Fibrosis, when present, is usually within the perisinusoidal/pericellular spaces of zone three.

Other features for NASH include Mallory hyaline bodies, megamitochondria, glycogenated nuclei, and variable degrees of ductular reaction correlating with advances stages of fibrosis [82]. NASH and NAFLD may coexist with other diseases such as Wilson disease, hemochromatosis, alpha-1-anti trypsin deficiency, and chronic hepatitis C infection.

Table 40.3 Types of nonalcoholic fatty liver disease [79]

Type 1: Fat alone
Type 2: Fat plus inflammation
Type 3: Fat plus ballooning degeneration
Type 4: Fat plus fibrosis and/or Mallory bodies

A scoring system has been developed by NIH (NAFLD Activity Score) [83] for the grading and staging of the histopathologic lesions noted in patients with NAFLD. It is based on the presence of steatosis, hepatocellular ballooning, and lobular inflammation. The score is utilized mostly for research, and not for clinical purposes [78].

Complications of NAFLD

Most patients with NAFLD have good prognosis; however, a few with steatohepatitis may progress to fibrosis and to cirrhosis. Several studies demonstrate NASH to be an important cause of cirrhosis and hepatocellular carcinoma [8–10, 84, 85].

NASH is among the most common causes of advanced liver disease after hepatitis C and alcoholism [86]. It is estimated that about 50% of patients with NASH develop liver fibrosis, 15% develop cirrhosis, and 3% progress to terminal liver failure, requiring liver transplantation [87]. Follow-up demonstrates that almost 30% of patients with NASH and fibrosis become cirrhotic within 5–10 years. In contrast, only about 3% of individuals with milder forms of NAFLD develop cirrhosis after over a decade of follow-up [42, 79].

Progression of liver disease from NAFLD to cirrhosis is probably influenced by genetic and environmental factors, with very few recognized [88–90]. Independent risk factors for progression include age >45 years, presence of diabetes (or severity of insulin resistance), obesity (BMI > 30 kg/m^2), and hypertension [89].

Management of NAFLD and NASH

Currently, there are no specific treatments for NAFLD. Lifestyle modifications, weight reduction, avoidance of alcohol, and hepatotoxic medications are early steps in the treatment of NAFLD [91–94].

(a) A major attempt should be made to lower weight to a healthy range. The initial target weight loss should be 10% of the baseline weight and should proceed at a rate of 1–2 lb/week [95]. Morbidly obese patients should be discouraged to reduce weight rapidly as this can worsen the hepatic inflammation and fibrosis [96]. Weight loss only, however, may not reduce liver-related mortality [97].

(b) Treatment should be directed at controlling diabetes, hyperlipidemia, and hypertension. NAFLD may be reversible with general improvement in the metabolic syndrome.

(c) Lipid-lowering agents, specifically statins and fibrates, reduce histologic evidence of hepatocyte damage and

decrease serum animotransferase levels, respectively. Withholding statins because of baseline abnormalities in AST, ALT levels is not justifiable. Statin treatment is safe and effective in patients with NAFLD [98], especially in the older adult with cardiovascular disease [99].

(d) The use of insulin-sensitizing agents, even in individuals without diabetes, has been proposed to treat patients with NASH [100]. Biguanides (metformin) improve insulin sensitivity by suppressing hepatic gluconeogenesis, increasing peripheral glucose uptake, and increasing fatty acid oxidation. In one study, metformin led to the reduction of serum aminotransferases, insulin resistance, and liver volume, but effects of the drug on liver histology were not assessed [101]. In a more recent study, treatment with metformin only showed a transient improvement in liver aminotransferases without a sustained reduction of insulin sensitivity [102].

Thiazolidinediones (TZD) improve insulin resistance in skeletal muscle, adipose tissue and in the liver by increasing adiponectin levels and fatty acid oxidation, and decreasing fatty acid synthesis. In a small study, treatment with rosiglitazone showed significantly greater improvement in steatosis and less ballooning, inflammation, and fibrosis on histologic examination of patients with NASH [103]. Further research is required to assess the long-term improvement of NAFLD and NASH with the use of insulin-sensitizing medications.

(e) Vitamins C and E, ursodeoxycholic acid, and pentoxifylline have been proposed to improve steatosis and reduce liver damage in patients with NAFLD and NASH.

Vitamin E inhibits lipid peroxidation and inflammatory cytokines, thereby reducing oxidative stress to the liver. In a study, vitamins C and E improved fibrosis scores in liver biopsies, but no change was observed in ALT or incidence of hepatic inflammation or fibrosis [104]. A study recently concluded that Vitamin E is superior to placebo for the treatment of NASH in adult diabetics [105].

Urodeoxycholic acid, another experimental agent, in theory, improves liver biochemistry and steatosis, but a multicenter study showed no benefit when compared to placebo in NASH [106]. Another recent study showed similar results [107].

Pentoxifylline was shown to improve transaminitis and liver histology in patients with NASH when compared to baseline, but failed to show a significant improvement of the above-mentioned parameters when compared to placebo [108].

(f) In the morbidly obese, weight loss with diet, exercise, medications, and lifestyle modification may not suffice. Bariatric surgery may be an option for patients with a BMI ≥40 kg/m^2 or ≥35 kg/m^2 in the presence of major comorbidities [109]. Bariatric surgery has proven effective in losing weight and sustaining weight loss even in the morbidly obese population [110] and surgery may improve or completely resolve the metabolic syndrome [111].

It is prudent to consider age, comorbid conditions, and life expectancy before subjecting an elderly patient to bariatric surgery. A select few older adults, who are otherwise healthy and free of comorbidity, may be candidates for bariatric surgery. A recent study evaluating Medicare beneficiaries (aged ≥75 years) showed fivefold greater odds of death within 90 days of bariatric surgery when compared to those 65–74 years of age [112]. For the older adult, laparoscopic-adjustable silicone gastric banding may be more feasible, safe, and effective for the improvement of comorbid conditions [113].

An algorithmic approach to suspected NAFLD/NASH is presented in Fig. 40.1.

Key Points

- Nonalcoholic fatty liver disease (NAFLD) is a spectrum of changes in the liver ranging from benign steatosis, steatohepatitis, cirrhosis to hepatocellular carcinoma.
- The prevalence of NAFLD is estimated to be increasing compared to other forms of liver diseases due to the growing obesity epidemic.
- Insulin resistance is the key feature in the development of NAFLD. The metabolic syndrome (obesity (especially central fat distribution), hyperlipidemia, hypertension, and diabetes) is also closely linked to development of NAFLD.
- The "two-hit" hypothesis is the leading theory in the pathogenesis of nonalcoholic steatohepatitis (NASH). The first hit is insulin resistance, and the second hit suggests several potential insults to the liver resulting in oxidative stress.
- No specific serologic study is diagnostic of NAFLD. Liver enzymes (aspartate aminotransferase/alanine aminotransferase) may be elevated, but rarely more than three times the upper limit of normal. Clinicians should consider NAFLD in patients with metabolic syndrome.
- Liver biopsy is the "gold standard" in diagnosis and must be performed carefully considering biopsy and benefits.
- Treatment of NAFLD is largely based on lifestyle modification, weight reduction, and avoidance of hepatotoxic substances including alcohol and certain medications.
- Vitamin E and insulin sensitizers may be of value in the treatment of NASH. The author thanks Neelam G. Gidwaney MD for technical help received.

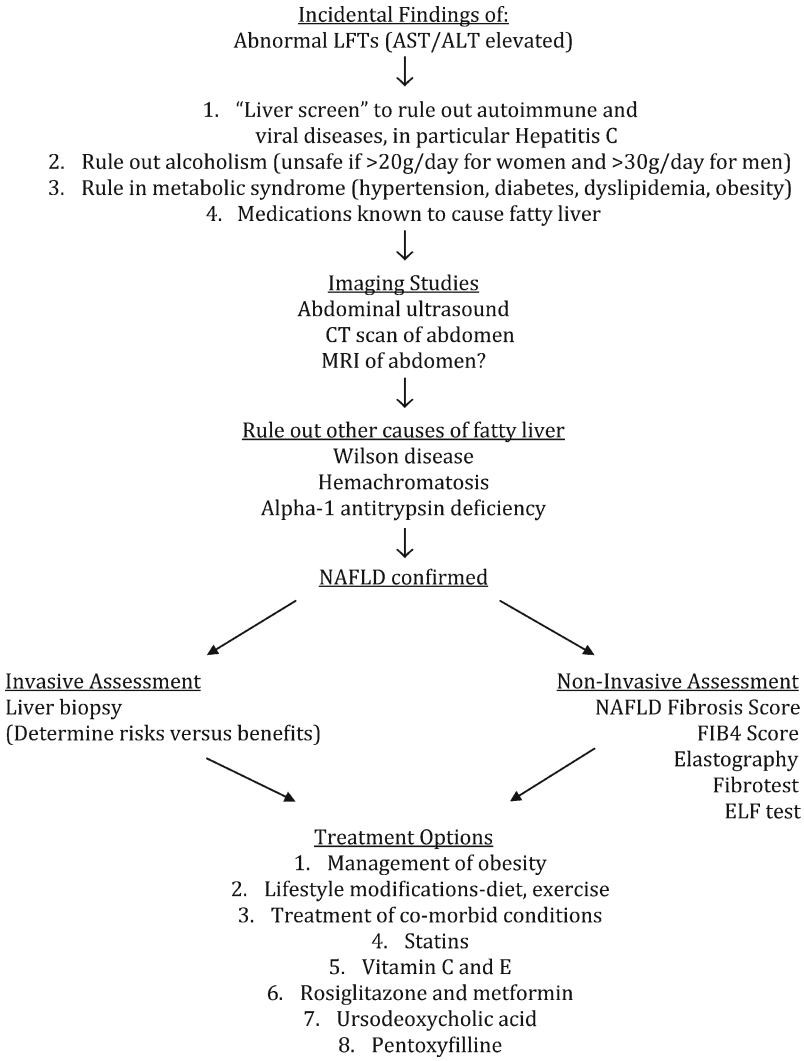

Fig. 40.1 Algorithmic approach to suspected nonalcoholic fatty liver disease and nonalcoholic steatohepatitis [2, 11, 42, 78, 101–106, 115, 116]

References

1. Schaffner F, Thaler H. Nonalcoholic fatty liver disease. Prog Liver Dis. 1986;8:283–98.
2. Angulo P. Nonalcoholic fatty liver disease. N Engl J Med. 2002;346:1221–31.
3. Neuschwander-Tetri BA, Caldwell SH. Nonalcoholic steatohepatitis: summary of an AASLD single topic conference. Hepatology. 2003;37:1202–19.
4. Floreani A. Liver diseases in the elderly: an update. Dig Dis. 2007;25:138–43.
5. Ludwig J, Viggiano TR, McGill DB, Oh BJ. Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease. Mayo Clin Proc. 1980;55:434–8.
6. Chitturi S, Wong VW, Farrell G. Nonalcoholic fatty liver in Asia: firmly entrenched and rapidly gaining ground. J Gastroenterol Hepatol. 2011;26 Suppl 1:163–72.
7. Mohan V, Farooq S, Deepa M, Ravikumar R, Pitchumoni CS. Prevalence of non-alcoholic fatty liver disease in urban south Indians in relation to different grades of glucose intolerance and metabolic syndrome. Diabetes Res Clin Pract. 2009;84:84–91.
8. Ong J, Younossi ZM, Reddy V, et al. Cryptogenic cirrhosis and posttransplantation nonalcoholic fatty liver disease. Liver Transpl. 2001;7:797–801.
9. Cuadrado A, Orive A, Garcia-Suarez C, et al. Non-alcoholic steatohepatitis (NASH) and hepatocellular carcinoma. Obes Surg. 2005;15:442–6.
10. Bugianesi E, Leone N, Vanni E, et al. Expanding the natural history of nonalcoholic steatohepatitis: from cryptogenic cirrhosis to hepatocellular carcinoma. Gastroenterology. 2002;123:134–40.
11. Sanyal AJ. AGA technical review on nonalcoholic fatty liver disease. Gastroenterology. 2002;123:1705–25.
12. de Alwis NM, Day CP. Non-alcoholic fatty liver disease: the mist gradually clears. J Hepatol. 2008;48 Suppl 1:S104–12.
13. Kim CH, Younossi ZM. Nonalcoholic fatty liver disease: a manifestation of the metabolic syndrome. Cleve Clin J Med. 2008;75:721–8.
14. Flegal KM, Carroll MD, Kuczmarski RJ, Johnson CL. Overweight and obesity in the United States: prevalence and trends, 1960–1994. Int J Obes Relat Metab Disord. 1998;22:39–47.
15. Prentice AM. The emerging epidemic of obesity in developing countries. Int J Epidemiol. 2006;35:93–9.

16. Ogden CL, Yanovski SZ, Carroll MD, Flegal KM. The epidemiology of obesity. Gastroenterology. 2007;132:2087–102.
17. Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and trends in obesity among US adults, 1999–2008. JAMA. 2010;303:235–41.
18. Ledikwe JH, Smiciklas-Wright H, Mitchell DC, et al. Nutritional risk assessment and obesity in rural older adults: a sex difference. Am J Clin Nutr. 2003;77:551–8.
19. Villareal DT, Apovian CM, Kushner RF, Klein S. Obesity in older adults: technical review and position statement of the American Society for Nutrition and NAASO, The Obesity Society. Am J Clin Nutr. 2005;82:923–34.
20. Angulo P. Obesity and nonalcoholic fatty liver disease. Nutr Rev. 2007;65:S57–63.
21. Kowdley KV, Caldwell S. Nonalcoholic steatohepatitis: a twenty-first century epidemic? J Clin Gastroenterol. 2006;40 Suppl 1: S2–4.
22. Browning JD, Szczepaniak LS, Dobbins R, et al. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. Hepatology. 2004;40:1387–95.
23. Chitturi S, Farrell GC, George J. Non-alcoholic steatohepatitis in the Asia-Pacific region: future shock? J Gastroenterol Hepatol. 2004;19:368–74.
24. Clark JM. The epidemiology of nonalcoholic fatty liver disease in adults. J Clin Gastroenterol. 2006;40 Suppl 1:S5–10.
25. Floreani A. Liver disorders in the elderly. Best Pract Res Clin Gastroenterol. 2009;23:909–17.
26. Bellentani S, Saccoccio G, Masutti F, et al. Prevalence of and risk factors for hepatic steatosis in Northern Italy. Ann Intern Med. 2000;132:112–7.
27. Argo CK, Caldwell SH. Epidemiology and natural history of non-alcoholic steatohepatitis. Clin Liver Dis. 2009;13:511–31.
28. Tabibian JH, Lazo M, Durazo FA, et al. Nonalcoholic fatty liver disease across ethno-racial groups: do Asian-American adults represent a new at-risk population? J Gastroenterol Hepatol. 2011;26:501–9.
29. Duseja A. Nonalcoholic fatty liver disease in India—a lot done, yet more required! Indian J Gastroenterol. 2010;29:217–25.
30. Wanless IR, Lentz JS. Fatty liver hepatitis (steatohepatitis) and obesity: an autopsy study with analysis of risk factors. Hepatology. 1990;12:1106–10.
31. Silverman JF, O'Brien KF, Long S, et al. Liver pathology in morbidly obese patients with and without diabetes. Am J Gastroenterol. 1990;85:1349–55.
32. Mouralidarane A, Lin C, Suleyman N, Soeda J, Oben J. Practical management of the increasing burden of non-alcoholic fatty liver disease. Frontline Gastroenterol. 2010;1(3):149–55.
33. Speliotes EK, Massaro JM, Hoffmann U, et al. Fatty liver is associated with dyslipidemia and dysglycemia independent of visceral fat: the Framingham Heart Study. Hepatology. 2010;51: 1979–87.
34. Kral JG, Schaffner F, Pierson Jr RN, Wang J. Body fat topography as an independent predictor of fatty liver. Metabolism. 1993;42: 548–51.
35. Eguchi Y, Eguchi T, Mizuta T, et al. Visceral fat accumulation and insulin resistance are important factors in nonalcoholic fatty liver disease. J Gastroenterol. 2006;41:462–9.
36. Dixon JB, Bhathal PS, O'Brien PE. Nonalcoholic fatty liver disease: predictors of nonalcoholic steatohepatitis and liver fibrosis in the severely obese. Gastroenterology. 2001;121: 91–100.
37. Falchuk KR, Fiske SC, Haggitt RC, et al. Pericentral hepatic fibrosis and intracellular hyalin in diabetes mellitus. Gastroenterology. 1980;78:535–41.
38. Harrison SA, Neuschwander-Tetri BA. Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. Clin Liver Dis. 2004;8:861–79, ix.
39. Pantsari MW, Harrison SA. Nonalcoholic fatty liver disease presenting with an isolated elevated alkaline phosphatase. J Clin Gastroenterol. 2006;40:633–5.
40. Vuppalanchi R, Gould RJ, Wilson LA, et al. Clinical significance of serum autoantibodies in patients with NAFLD: results from the nonalcoholic steatohepatitis clinical research network. Hepatol Int. 2011; 6:379–85.
41. Anstee QM, McPherson S, Day CP. How big a problem is non-alcoholic fatty liver disease? BMJ. 2011;343:d3897.
42. McCullough AJ. The clinical features, diagnosis and natural history of nonalcoholic fatty liver disease. Clin Liver Dis. 2004;8:521–33, viii.
43. Brunt EM. Nonalcoholic steatohepatitis: definition and pathology. Semin Liver Dis. 2001;21:3–16.
44. Mottin CC, Moretto M, Padoin AV, et al. The role of ultrasound in the diagnosis of hepatic steatosis in morbidly obese patients. Obes Surg. 2004;14:635–7.
45. Park SH, Kim PN, Kim KW, et al. Macrovesicular hepatic steatosis in living liver donors: use of CT for quantitative and qualitative assessment. Radiology. 2006;239:105–12.
46. Lee SW, Park SH, Kim KW, et al. Unenhanced CT for assessment of macrovesicular hepatic steatosis in living liver donors: comparison of visual grading with liver attenuation index. Radiology. 2007;244:479–85.
47. Angulo P. Noninvasive assessment of fibrosis and steatosis in NASH and ASH. Gastroenterol Clin Biol. 2009;33:940–8.
48. McPherson S, Stewart SF, Henderson E, et al. Simple non-invasive fibrosis scoring systems can reliably exclude advanced fibrosis in patients with non-alcoholic fatty liver disease. Gut. 2010;59:1265–9.
49. Yoneda M, Fujita K, Inamori M, Tamano M, Hiriishi H, Nakajima A. Transient elastography in patients with non-alcoholic fatty liver disease (NAFLD). Gut. 2007;56:1330–1.
50. Yin M, Talwalkar JA, Glaser KJ, et al. Assessment of hepatic fibrosis with magnetic resonance elastography. Clin Gastroenterol Hepatol. 2007;5:1207–13e2.
51. Koek GH, Liedorp PR, Bast A. The role of oxidative stress in non-alcoholic steatohepatitis. Clin Chim Acta. 2011;412:1297–305.
52. Day CP, James OF. Steatohepatitis: a tale of two "hits"? Gastroenterology. 1998;114:842–5.
53. Cortez-Pinto H, Camilo ME, Baptista A, De Oliveira AG, De Moura MC. Non-alcoholic fatty liver: another feature of the metabolic syndrome? Clin Nutr. 1999;18:353–8.
54. DeFronzo RA, Ferrannini E. Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. Diabetes Care. 1991;14:173–94.
55. Chitturi S, Abeygunasekera S, Farrell GC, et al. NASH and insulin resistance: insulin hypersecretion and specific association with the insulin resistance syndrome. Hepatology. 2002;35:373–9.
56. Marchesini G, Brizi M, Bianchi G, et al. Nonalcoholic fatty liver disease: a feature of the metabolic syndrome. Diabetes. 2001;50: 1844–50.
57. Marchesini G, Brizi M, Morselli-Labate AM, et al. Association of nonalcoholic fatty liver disease with insulin resistance. Am J Med. 1999;107:450–5.
58. Pagano G, Pacini G, Musso G, et al. Nonalcoholic steatohepatitis, insulin resistance, and metabolic syndrome: further evidence for an etiologic association. Hepatology. 2002;35:367–72.
59. Nelson JE, Wilson L, Brunt EM, et al. Relationship between the pattern of hepatic iron deposition and histological severity in non-alcoholic fatty liver disease. Hepatology. 2011;53:448–57.
60. Moirand R, Mortaji AM, Loreal O, Paillard F, Brissot P, Deugnier Y. A new syndrome of liver iron overload with normal transferrin saturation. Lancet. 1997;349:95–7.
61. Mendler MH, Turlin B, Moirand R, et al. Insulin resistance-associated hepatic iron overload. Gastroenterology. 1999;117: 1155–63.

62. George DK, Goldwurm S, MacDonald GA, et al. Increased hepatic iron concentration in nonalcoholic steatohepatitis is associated with increased fibrosis. Gastroenterology. 1998;114:311–8.
63. Medina J, Fernandez-Salazar LI, Garcia-Buey L, Moreno-Otero R. Approach to the pathogenesis and treatment of nonalcoholic steatohepatitis. Diabetes Care. 2004;27:2057–66.
64. Shepherd PR, Kahn BB. Glucose transporters and insulin action—implications for insulin resistance and diabetes mellitus. N Engl J Med. 1999;341:248–57.
65. Masuzaki H, Paterson J, Shinyama H, et al. A transgenic model of visceral obesity and the metabolic syndrome. Science. 2001;294:2166–70.
66. Barsh GS, Farooqi IS, O'Rahilly S. Genetics of body-weight regulation. Nature. 2000;404:644–51.
67. Chitturi S, Farrell G, Frost L, et al. Serum leptin in NASH correlates with hepatic steatosis but not fibrosis: a manifestation of lipotoxicity? Hepatology. 2002;36:403–9.
68. Bouloumie A, Marumo T, Lafontan M, Busse R. Leptin induces oxidative stress in human endothelial cells. FASEB J. 1999;13:1231–8.
69. Loffreda S, Yang SQ, Lin HZ, et al. Leptin regulates proinflammatory immune responses. FASEB J. 1998;12:57–65.
70. Ikejima K, Honda H, Yoshikawa M, et al. Leptin augments inflammatory and profibrogenic responses in the murine liver induced by hepatotoxic chemicals. Hepatology. 2001;34:288–97.
71. Garg R, Tripathy D, Dandona P. Insulin resistance as a proinflammatory state: mechanisms, mediators, and therapeutic interventions. Curr Drug Targets. 2003;4:487–92.
72. Chaldakov GN, Stankulov IS, Hristova M, Ghenev PI. Adipobiology of disease: adipokines and adipokine-targeted pharmacology. Curr Pharm Des. 2003;9:1023–31.
73. Stefan N, Stumvoll M. Adiponectin—its role in metabolism and beyond. Horm Metab Res. 2002;34:469–74.
74. Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. Science. 1993;259:87–91.
75. Bruun JM, Lihn AS, Verdich C, et al. Regulation of adiponectin by adipose tissue-derived cytokines: in vivo and in vitro investigations in humans. Am J Physiol Endocrinol Metab. 2003;285:E527–33.
76. Abu-Shanab A, Quigley EM. The role of the gut microbiota in nonalcoholic fatty liver disease. Nat Rev Gastroenterol Hepatol. 2010;7:691–701.
77. Merrell MD, Cherrington NJ. Drug metabolism alterations in nonalcoholic fatty liver disease. Drug Metab Rev. 2011;43:317–34.
78. Tiniakos DG. Nonalcoholic fatty liver disease/nonalcoholic steatohepatitis: histological diagnostic criteria and scoring systems. Eur J Gastroenterol Hepatol. 2010;22:643–50.
79. Matteoni CA, Younossi ZM, Gramlich T, et al. Nonalcoholic fatty liver disease: a spectrum of clinical and pathological severity. Gastroenterology. 1999;116:1413–9.
80. Angulo P, Keach JC, Batts KP, Lindor KD. Independent predictors of liver fibrosis in patients with nonalcoholic steatohepatitis. Hepatology. 1999;30:1356–62.
81. Brunt EM. Pathology of nonalcoholic fatty liver disease. Nat Rev Gastroenterol Hepatol. 2010;7:195–203.
82. Richardson MM, Jonsson JR, Powell EE, et al. Progressive fibrosis in nonalcoholic steatohepatitis: association with altered regeneration and a ductular reaction. Gastroenterology. 2007;133:80–90.
83. Kleiner DE, Brunt EM, Van Natta M, et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology. 2005;41:1313–21.
84. Farrell GC, Larter CZ. Nonalcoholic fatty liver disease: from steatosis to cirrhosis. Hepatology. 2006;43:S99–112.
85. Regimbeau JM, Colombat M, Mognol P, et al. Obesity and diabetes as a risk factor for hepatocellular carcinoma. Liver Transpl. 2004;10:S69–73.
86. Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. Aliment Pharmacol Ther. 2011;34:274–85.
87. Sheth SG, Gordon FD, Chopra S. Nonalcoholic steatohepatitis. Ann Intern Med. 1997;126:137–45.
88. Ekstedt M, Franzen LE, Mathiesen UL, et al. Long-term follow-up of patients with NAFLD and elevated liver enzymes. Hepatology. 2006;44:865–73.
89. Ratziu V, Bellentani S, Cortez-Pinto H, et al. A position statement on NAFLD/NASH based on the EASL 2009 special conference. J Hepatol. 2010;53:372–84.
90. Anstee QM, Daly AK, Day CP. Genetics of alcoholic and nonalcoholic fatty liver disease. Semin Liver Dis. 2011;31:128–46.
91. Clark JM. Weight loss as a treatment for nonalcoholic fatty liver disease. J Clin Gastroenterol. 2006;40 Suppl 1:S39–43.
92. Perlemuter G, Bigorgne A, Cassard-Doulcier AM, Naveau S. Nonalcoholic fatty liver disease: from pathogenesis to patient care. Nat Clin Pract Endocrinol Metab. 2007;3:458–69.
93. Thoma C, Day CP, Trenell MI. Lifestyle interventions for the treatment of non-alcoholic fatty liver disease in adults: a systematic review. J Hepatol. 2012;56(1):255–66.
94. Tsochatzis EA, Papatheodoridis GV. Is there any progress in the treatment of non-alcoholic fatty liver disease? World J Gastrointest Pharmacol Ther. 2011;2:1–5.
95. Expert panel on the identification, evaluation, and treatment of overweight and obesity in adults. Executive summary of the clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults. Arch Intern Med 1998;158:1855–67.
96. Andersen T, Gluud C, Franzmann MB, Christoffersen P. Hepatic effects of dietary weight loss in morbidly obese subjects. J Hepatol. 1991;12:224–9.
97. Valori R. Non-alcoholic fatty liver disease: a non-problem or a public health catastrophe? Frontline Gastroenterol. 2010;1:147–8.
98. Chalasani N. Statins and hepatotoxicity: focus on patients with fatty liver. Hepatology. 2005;41:690–5.
99. Athyros VG, Tziomalos K, Gossios TD, et al. Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and abnormal liver tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) Study: a post-hoc analysis. Lancet. 2010;376:1916–22.
100. Ratziu V, Pienar L. Pharmacological therapy for non-alcoholic steatohepatitis: how efficient are thiazolidinediones? Hepatol Res. 2011;41:687–95.
101. Marchesini G, Brizi M, Bianchi G, Tomassetti S, Zoli M, Melchionda N. Metformin in non-alcoholic steatohepatitis. Lancet. 2001;358:893–4.
102. Nair S, Diehl AM, Wiseman M, et al. Metformin in the treatment of non-alcoholic steatohepatitis: a pilot open label trial. Aliment Pharmacol Ther. 2004;20:23–8.
103. Ratziu V, Charlotte F. A one-year randomized, placebo-controlled, double-blind trial of rosiglitazone in non alcoholic steatohepatitis. Result of the FLIRT pilot trial. J Hepatol. 2006;44:201A.
104. Harrison SA, Torgerson S, Hayashi P, et al. Vitamin E and vitamin C treatment improves fibrosis in patients with nonalcoholic steatohepatitis. Am J Gastroenterol. 2003;98:2485–90.
105. Sanyal AJ, Chalasani N, Kowdley KV, et al. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. N Engl J Med. 2010;362:1675–85.
106. Lindor KD, Kowdley KV, Heathcote EJ, et al. Ursodeoxycholic acid for treatment of nonalcoholic steatohepatitis: results of a randomized trial. Hepatology. 2004;39:770–8.
107. Adams LA, Angulo P. Treatment of non-alcoholic fatty liver disease. Postgrad Med J. 2006;82:315–22.

108. Van Wagner LB, Koppe SW, Brunt EM, et al. Pentoxifylline for the treatment of non-alcoholic steatohepatitis: a randomized controlled trial. Ann Hepatol. 2011;10:277–86.
109. Shaffer EA. Bariatric surgery: a promising solution for nonalcoholic steatohepatitis in the very obese. J Clin Gastroenterol. 2006;40 Suppl 1:S44–50.
110. Buchwald H, Avidor Y, Braunwald E, et al. Bariatric surgery: a systematic review and meta-analysis. JAMA. 2004;292:1724–37.
111. Mummadi RR, Kasturi KS, Chennareddygari S, Sood GK. Effect of bariatric surgery on nonalcoholic fatty liver disease: systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2008;6: 1396–402.
112. Flum DR, Salem L, Elrod JA, et al. Early mortality among Medicare beneficiaries undergoing bariatric surgical procedures. JAMA. 2005;294:1903–8.
113. Abu-Abeid S, Keidar A, Szold A. Resolution of chronic medical conditions after laparoscopic adjustable silicone gastric banding for the treatment of morbid obesity in the elderly. Surg Endosc. 2001;15:132–4.
114. McGovern BH. Hepatic steatosis in HIV/HCV-coinfected patients: time to reevaluate! Gastroenterology. 2011;140:772–5.
115. National Cholesterol Education Program (NCEP). Third report of the National Cholesterol Education Program (NCEP) Expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report. Circulation. 2002;106:3143–421.
116. Ferrell GC, van Rooven D, Gan L et al. NASH is an inflammatory disorder: pathogenetic, prognostic and therapeutic implications. Gut Liver. 2012;6:149–71.

Drug-Induced Liver Injury

41

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Background

Drug-induced liver injury (DILI) results from several prescription and nonprescription medications, nutritional and herbal supplements. Comorbidity and polypharmacy in the geriatric population are major predispositions to DILI. Altered age-related pharmacokinetics and pharmacodynamics influence drug metabolism, contributing to adverse drug reactions (ADRs) often involving the liver. The spectrum of DILI ranges from asymptomatic elevations in liver enzymes without overt clinical disease to acute illness with jaundice resembling viral hepatitis and acute hepatic failure with encephalopathy and fatality.

Epidemiology

Most medications do not cause DILI. The reported incidence is 1 in 10,000–100,000 with several approved drugs [1–3]. The U.S. Acute Liver Failure Study Group suggested that acetaminophen and idiosyncratic drug reactions combined account for approximately 50% of cases of acute liver failure (ALF) [4]. A recent analysis of ALF study showed that antibiotics were the most common cause of idiosyncratic ALF in the US, mostly in women (70.7%), although there was overrepresentation of minorities [5]. While the precise incidence of hepatic ADRs is unknown, a French population-based prospective study mentions the incidence to be 13.9 per 100,000 inhabitants, a frequency 16-fold higher than estimates from spontaneous reporting. In this study, the incident male/female ratio was 0.86 until 49 years of age, increasing to 2.62 beyond age 49 [6]; perhaps over 8,000 cases of DILI occur in France annually, resulting in approximately 500 deaths [6]. With DILI-associated jaundice, the incidence of liver transplantation and death was 11.7% in a Spanish registry [7].

Drug-Induced Liver Injury: Mechanisms

Drug induced liver disease may be dose-dependent or predictable and dose independent or unpredictable (also termed idiosyncratic). Most reactions are idiosyncratic.

The pathological changes associated with DILI may resemble any form of acute and chronic hepatobiliary disease. The pathogenesis remains poorly understood and may relate to complex interactions between genetic and nongenetic host susceptibility factors, coupled with drug–drug interactions [8–11]. The liver which plays important role in the clearance and biotransformation of drugs, suffers most often from their metabolism. Most drugs are lipid-soluble in nature. Hepatic drug-metabolizing enzymes convert them into water-soluble form, thus permitting their entry into the plasma, excretion in the urine, or elimination into the bile. Most drugs are biotransformed by hepatic phase I and phase II metabolic reactions. Oxidation (e.g., hydroxylation and dealkylation) and reduction (e.g., nitroreduction) are phase I reactions, whereas phase II reactions include conjugation (glucoronidation, sulfation, and acetylation) of the parent compound or a metabolite.

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The cytochrome P450 superfamily (CYP) is a diverse group of enzymatic proteins, identified in most forms of life that catalyze the oxidation of organic substances. The CYP located in the mitochondria and endoplasmic reticulum is present not only in the liver, but also expressed in other sites such as the gut, kidney, lungs, pancreas, and brain. CYP system accounts for much of the bioactivation and metabolism of drugs. CYP is abundant in the centrilobular zone compared to the periportal area; centrilobular necrosis is characteristic of DILI, suggesting that drug-metabolizing enzymes play a role in DILI. Most drugs are metabolized by CYP1, CYP2, and CYP3 families. CYP 3A is a prominent subfamily. While sex does not appear to influence CYP3A-mediated clearance of substrates, aging affects hepatic blood flow and CYP3A activity [12]. Hepatic expression of each CYP enzyme is genetically determined, subject to polymorphic inheritance [13]. Factors that alter CYP activity increase toxicity by reducing drug conversion to nontoxic metabolites or by increasing conversion to toxic metabolites [14].

N-acetylation is a phase II reaction, with *N*-acetyltransferase 2 (NAT2), highly polymorphic in expression. Slow rates of acetylation are known to increase isoniazid hepatotoxicity [15–17]. With isoniazid, typically used for months, periodic testing of liver function is prudent in older adults. Glutathione S-transferases (GST) detoxify a variety of drugs through glutathione. Two isoforms, GSTM1 and GSTT1, are absent in some individuals due to gene deletions. Individuals who are homozygous null for both M1 and T1 are at risk for idiosyncratic DILI, predominantly in women [18].

Data demonstrate a relationship between genetic polymorphisms that influence immune function (e.g., HLA class II antigens or cytokines) and risk for DILI. There is evidence for associations between the HLA haplotype and cholestatic reactions to amoxicillin-clavulanic acid [19], with HLA-B5701 genotype determining DILI from flucoxacillin [20]. In future, genomic associations may offer opportunity to better diagnose and predict DILI.

Interleukins (IL), especially IL-10, IL-4, and TNF-alpha polymorphism, influence occurrence of DILI. Variants with low IL-10 and high IL-4 gene transcription are at risk of diclofenac hepatotoxicity [21]; diclofenac-mediated stress signaling suppresses TNF-alpha-induced survival signaling routes and sensitizes cells to apoptosis [22].

Hepatic transport systems maintain hepatic uptake and efflux processes in bile formation and are expressed in liver cells; one role is to determine drug exposure and clearance. Increasing evidence indicates that cholestatic DILI results from drug-mediated inhibition of hepatobiliary transporter systems [23, 24]. Transporter proteins influence drug disposition and interactions, thereby influencing the occurrence of ADRs. A functional disturbance from mutations and polymorphisms of the exporter proteins causes intracellular accumulation of toxic bile constituents with cholestatic liver injury; genotyping in patients with acquired cholestasis can identify genetic susceptibility to DILI [25, 26].

Some drugs (e.g., valproate, salicylate, antiretroviral agents) cause liver injury through mitochondrial toxicity; severe alteration of mitochondrial function in the liver may induce microvesicular steatosis and serious adverse effects such as lactic acidosis and rhabdomyolysis [27].

Risk Factors

Age

Age increases risk of liver injury from certain medications; examples include isoniazid, nitrofurantoin, diclofenac, and flucloxacillin (and historically halothane and troglitazone). The risk of isoniazid hepatotoxicity is higher in the old than the young, as noted in a US tuberculosis clinic; the age-specific incidence was higher in those over 50 years compared to the 25–34 age group [28]. The basis may be impaired hepatic function and decline in renal function with age and resultant higher hepatic drug concentration [29]. The high prevalence of polypharmacy in the geriatric population may be contributory. Cholestatic type of injury is more common in the old compared to hepatocellular type of injury [4, 29, 30]. Hepatotoxicity in geriatric patients may lead to fulminant hepatic failure and death, emphasizing the importance of a meticulous medication history.

Gender

A prospective trial by the DILI Network reported hepatocellular injury to be more common in women than men (65% vs. 35%), resulting from a single medication in 73% cases [31]. In a hepatology clinic, 56% with DILI were women [32]. This observation involved herbals, antiepileptics, and antidepressants drugs [33]; the etiology may be a higher prevalence of autoimmune diseases among women [34]. Women are especially predisposed to DILI from nitrofurantoin, sulfonamides, flucloxacillin, and minocycline; the differences in susceptibility between men and women to various medications perhaps relate to pharmacogenomics.

Drug Interactions

Incidence of adverse drug events (ADEs) increases with polypharmacy; some medications modify the hepatotoxic potential of others. Mechanisms include enzyme induction, reduction in bile flow, or competition with canalicular pathways for biliary excretion. Valproic acid hepatotoxicity increases with polypharmacy [35]. Addition of erythromycin provokes DILI through formation of reactive intermediaries during valproic acid metabolism.

Table 41.1 Nongenetic factors that predispose to DILI [28, 31–33]

Variable	Influence
Age	Age over 55 years
Gender	Females are at greater risk (are on more medications, more likely to seek health care or manifest autoimmune states)
Alcoholism	Enhances severity of acetaminophen-induced hepatotoxicity; alcohol mediates induction of hepatic CYP
Fasting state, malnutrition	may deplete hepatic glutathione, increasing risk
Obesity	Expression of CYP2E1 is increased
Preexisting liver disease	Influences ability to recover from DILI
Dosage of oral medications	Increase in dosage increases risk of DILI
History of hepatitis C or B	Increases susceptibility to DILI from anti-TB drugs and highly active antiretroviral therapy
Decline in renal function	May increase drug concentration in the liver
Diabetes mellitus	At risk for methotrexate-induced hepatotoxicity, by altering expression of hepatic CYP

Previous Drug Reactions

Prior history of ADE increases the risk of injury on reexposure to the same or structurally similar agents. This may be linked to cross-sensitivity and class effect; cross-sensitivity is observed between carbamazepine and phenytoin, halothane anesthetics, tricyclic antidepressants, and NSAIDs [36, 37]. It is essential to closely monitor hepatic function in those with a prior history of DILI.

Alcohol

Both acute alcohol consumption and chronic alcoholism decrease the dose threshold for acetaminophen hepatotoxicity [38]. Chronic alcohol ingestion modifies CYP2E1 activity and depletes hepatic glutathione levels. Chronic excessive alcohol consumption increases the risk of hepatic fibrosis in long-term users of methotrexate [39], as also isoniazid hepatotoxicity. The role of alcohol in idiosyncratic DILI is less clear; nor do prospective registries describe a significant association between alcohol consumption and severity of DILI [4].

Glutathione

To combat oxidative stress, the liver is well enriched with antioxidant mechanisms, such as micronutrients (e.g., vitamins E and C), thiol-rich proteins (e.g., metallothionein, ubiquinone), and glutathione (L-gamma-glutamyl-L-cyteine-glycine). The most important hepatic antioxidant is glutathione, with hepatocytes an exclusive site of synthesis. Hepatic levels of glutathione can be increased by enhancing the supply of cysteine, a precursor for glutathione synthesis; the mechanism is the cornerstone of thiol antidote therapy for acetaminophen (paracetamol) poisoning. Glutathione deficiency, common in malnutrition and chronic alcoholism, increases risk for drug-induced injury.

Coexisting Chronic Liver Disease

Data do not support withholding any medications in those coinfected with hepatitis B or C virus [40, 41]. Patients should be monitored with monthly LFTs and referred to specialists if liver enzyme elevations are three to fourfold [42]. The same risk applies to antituberculosis therapy [43]. The safety profile of statins in nonalcoholic fatty liver disease or in those with chronically elevated liver enzymes is generally favorable and demonstrated over a 10–16 year follow-up [44, 45].

Table 41.1 provides information on nongenetic risk factors.

Clinical Patterns of Liver Injury

Many drugs cause asymptomatic elevations in liver enzymes that are considered subclinical liver disease and are usually benign. DILI is a pattern of injury with characteristics that include biochemical, clinical, histologic, or a combination. Unpredictable hepatotoxic reactions can occur without warning, unrelated to dose, with variable latency periods, ranging from days to a year. Besides acute hepatic clinical presentations, some drugs cause chronic histological alterations, including vascular injury and neoplasms.

Dose-dependent injury occurs after hours and is characterized by zonal necrosis or microvesicular steatosis; examples include amiodarone, methotrexate, and acetaminophen [46].

Hepatocellular: Here the injury is similar to viral hepatitis and characterized by significant inflammation or reactive changes, apoptotic hepatocytes, hepatocyte degeneration, and cell death. Laboratory changes are characterized by marked aminotranferase elevations usually preceding increases in bilirubin and alkaline phosphatase levels. Zonal necrosis is usually from dose-dependent medications such as acetaminophen and carbon tetrachloride (zone 3). Nonzonal necrosis occurs with drugs that cause unpredictable idiosyncratic injury; examples are isoniazid, diclofenac, and methyldopa.

Beta adrenergic blockers, tetracyclines, sulfasalazine, and barbiturates are rarely associated with acute hepatitis.

Autoimmune hepatitis: Hypersensitivity or immunologic injury may be delayed or occur on repeated exposure to a drug and is associated with fever, rash, or eosinophilia. It is more rapid and severe with repeated exposure; examples include phenytoin, nitrofurantoin, minocycline, and HAART, while halothane is the prototype. With the antiretroviral agents, the mechanism involves significant immune reconstitution. Discontinuing the drug is followed by improvement within weeks. Corticosteroids are indicated in severe disease [47]. Rechallenge is risky and not recommended.

Cholestasis: Cholestatic DILI is the consequence of impaired bile acid transport and leads to hepatocellular or canalicular bile stasis with or without inflammation. High-dose estrogen, anabolic steroids, tamoxifen, and antimicrobials such as erythromycin estolate, amoxicillin-clavulanic acid, nafcillin, trimethoprim-sulfamethoxazole, and rifampin are incriminated [48]. Typical presentation is pruritus and jaundice with elevated alkaline phosphatase and bilirubin. Acute drug-induced cholestasis may lead to chronic cholestasis resembling primary biliary cirrhosis (PBC).

Steatosis and Steatohepatitis: Steatosis can be microvesicular or macrovesicular, based on droplet size; It is common due to high prevalence of obesity, metabolic syndrome, and alcohol use. Drugs that disrupt beta oxidation of lipids and oxidative energy production lead to steatosis [49]. Steatosis may remain asymptomatic or lead to steatohepatitis, a more concerning lesion that may go on to cirrhosis. Drugs that cause steatosis and steatohepatitis include amiodarone [50], tamoxifen, anti-retro viral drugs [51], valproic acid, tetracyclines, glucocorticoids, methotrexate and first-generation Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs), zidovudine, didanosine, and stavudine [52].

Granulomatous hepatitis: Granulomas dominate the inflammation are usually nonnecrotizing and found in portal and periportal areas and parenchyma. Incriminated drugs include allopurinol, phenytoin, carbamazepine and hydralazine, methimazole, and propyl-thiouracil. Differential diagnosis for granulomatous hepatitis includes fungal, atypical bacterial and mycobacterial infections, sarcoidosis, and PBC [53].

Drug-induced vascular injury: Vascular injury patterns are rare but diverse, usually classified by the vascular component most affected. Hepatic vein thrombotic occlusion also known as Budd Chiari syndrome may result from hormone therapy and can progress to noncirrhotic portal hypertension, liver failure, and death. Obstruction of small hepatic veins and sinusoids are the hallmark of sinusoidal obstruction syndrome (formerly termed veno-occlusive disorder), while dilatation and destruction of hepatic sinusoids is termed "peliosis hepatis". Vascular injury can result from chemotherapeutic agents such as busulphan, dactinomycin, and mitomycin, as also azathioprine, sex steroids, and vitamin A.

Neoplasia: Medications are associated with development of benign and malignant neoplasms. Benign tumors (adenoma) and malignant tumors (hepatocellular carcinoma) may be induced by long-term use of sex hormones. Data implicate androgens and estrogens in hepatocyte proliferation and as liver tumor inducers or promoters [54, 55].

Table 41.2 describes drugs predisposing to liver injury and their patterns.

Table 41.2 Drugs predisposing to liver injury in older adults

Drug class	Specific medication	Type of injury
Antibiotics	Amoxicillin/clavulanate	Cholestasis
	Flucloxacillin	Cholestasis
	Sulfonamides	Hepatocellular, granulomatous hepatitis
	Tetracyclines	Microvesicular steatosis
	Minocycline	Auto immune hepatitis
	Erythromycin	Cholestasis
	Clindamycin	Mixed
Antituberculosis	Isoniazid	Hepatocellular
	Rifampin	Hepatocellular
	Pyrazinamide	Hepatocellular
Antifungal	Ketoconazole	Hepatocellular
	Terbinafine	Cholestasis
Antiretrovirals	Nevirapine	Hepatocellular
	Ritonavir	Hepatocellular
Antiarrhythmics	Amiodarone	Steatohepatitis
	Quinidine	Granulomatous hepatitis
	Procainamide	Granulomatous hepatitis
Anti-inflammatory	Aspirin	Hepatocellular
	Ibuprofen	Mixed
	Acetaminophen	Hepatocellular
	Diclofenac	Chronic hepatitis
	Sulindac	Cholestasis
	Methotrexate	Fibrosis
	Allopurinol	Granulomatous and hepatocellular
Antihypertensives	ACE inhibitors	Mixed
	Irbesartan. losartan	Hepatocellular
	Hydralazine	Granulomatous hepatitis
	Diltiazem	Granulomatous hepatitis
Antiepileptics	Phenytoin	Hepatocellular, granulomatous
	Valproic acid	Steatohepatitis
	Carbamazepine	Granulomatous hepatitis
	Phenobarbital	Mixed

(continued)

Table 41.2 (continued)

Drug class	Specific medication	Type of injury
Antipsychotics	Sertraline	Hepatocellular
	Fluoxetine	Hepatocellular
	Paroxetine	Hepatocellular
	Trazodone	Mixed
	Respiridone	Hepatocellular
	Nefazodone	Hepatocellular
	Bupropion	Hepatocellular
Antidiabetic	Sulfonylureas	Hepatocellular
	Thiazolidinediones	Hepatocellular
Miscellaneous	Statins	Hepatocellular
	Estrogens	Cholestasis
	Tamoxifen	Mixed and steatohepatitis
	Phenothiazines	Mixed

Common Drugs and Supplements Associated with DILI in Older Adults

Acetaminophen

Acetaminophen (paracetamol), is used worldwide for its antipyretic and analgesic properties. Acetaminophen is the leading cause of ALF in the west. Acetaminophen is detoxified primarily through glucuronidation by UDP-glucuronosyl transferases (UGTs) and secondarily through sulfation by sulfotransferases (SULTs). Acetaminophen is metabolized by hepatic CYP450 (CYP2E1, CYP1A2, CYP3A4) to the toxic and highly reactive metabolite *N*-acetyl-*p*-benzoquinone imine (NAPQ1) [56]. Therapeutic doses of acetaminophen produce small amounts of NAPQ1, which in turn is rapidly conjugated by cysteine and mercaptate compounds and excreted in urine. Large doses of acetaminophen saturate glucuronidation pathways, with far more acetaminophen metabolized to NAPQ1, and resultant hepatotoxicity. Cimetidine minimizes the risk of damage by inhibiting the conversion of acetaminophen to its toxic metabolite.

Although acetaminophen is safe in usual therapeutic doses, hepatic and other organ damage occur with overdose from accumulated toxic metabolite. Alcohol consumption [57] and fasting lower the threshold for acetaminophen hepatotoxicity, by inducing the cytochrome P-450 system, increased formation of toxic metabolites, and depletion of glutathione. Liver damage is dose-dependent; while therapeutic doses are not hepatotoxic. A single dose of 7–10 grams of acetaminophen (14–20 extra strength) tablets can cause liver injury in the average size healthy adult. Prognosis is better when acetaminophen liver injury is treated with *N*-acetylcysteine within hours of ingestion [58, 59]. The stomach must be emptied with a wide bored gastric tube and blood levels of acetaminophen measured as a first step. In early 2011, the U.S. Food and Drug Administration has asked manufacturers to limit the strength of acetaminophen to 325 mg to limit the amount consumed; acetaminophen is often a constituent of several drug combinations, especially opioids. Also under consideration is a reduction in the maximum daily dose of acetaminophen when used long term [60] (Table 41.3).

Table 41.3 Acetaminophen-related liver injury [56–60]

Risk factors
Dosage and time of injury after ingestion
Acetaminophen is not hepatotoxic in therapeutic doses; ALF likely in the10–15 g/day range
Can occur at 4 g/day with coexisting malnutrition or chronic alcoholism, through glutathione depletion
Concomitant medications that induce the p450 system are a predisposition (e.g., isoniazid, phenytoin)
Clinical presentation
Phase 1 (0–24 h): Asymptomatic, anorexia, nausea, vomiting, malaise, and subclinical rise in AST/ALT levels begin in about 12 h
Phase 2 (18–72 h): right upper quadrant pain, anorexia, nausea, vomiting with continued rise in ALT/AST
Phase 3 (72–96 h): Centrilobular hepatic necrosis, abdominal pain, jaundice, coagulopathy, hepatic encephalopathy, renal failure, fatality
Phase 4 (4 days-3 weeks): Complete resolution of symptoms, resolution of organ failure
Management
Gastric lavage with a wide-bore tube performed if presentation within 4 h of ingestion
Activated charcoal, osmotic cathartics, or binding agents have little if any role
Acetaminophen blood levels are measured at presentation and repeated in 4–6 h, with the risk of liver injury estimated by reference to the Rumack-Matthew nomogram
Cysteine donors stimulate hepatic glutathione synthesis; *N*-acetylcysteine (NAC) is the principal antidote, and functions as a thiol donor. Significant hepatotoxicity is rare if administered within 16 h of drug ingestion
The standard oral dose of NAC is 140 mg/kg loading dose followed by 70 mg/kg every 4 h for 16 additional doses. IV NAC is used in UK
Liver transplantation is an option for severe liver failure
Prevention
Adherence to the recommended dosage guidelines
Lower doses in severe cardio respiratory disease, cirrhosis, and chronic alcoholism
The FDA and some manufacturers recommend a lower daily dose in view of common concurrent use of acetaminophen-drug combinations (e.g., opioids) and potential for adverse effects
With lower strength tablets, and limiting over-the-counter availability, acetaminophen may become a less common cause of liver failure

Antimicrobials

Antimicrobials are commonly used in geriatric practice. Worldwide, amoxicillin-clavulanic acid is one of the leading causes of antibiotic-induced DILI, usually acute and

cholestatic in pattern; risk factors are male gender, increasing age (over 55), and prolonged and repetitive use [61]. Flucloxacillin is a commonly reported cause for DILI in Europe, Scandinavia, and Australia [62]. Nitrofurantoin, a urinary antiseptic, is associated with acute and chronic hepatitis; presentations include hepatic granulomas, chronic hepatitis with autoimmune features, ALF, and cirrhosis [63, 64]. Sulfonamides cause acute and chronic hepatitis, cholestatic, granulomatous, or mixed reactions [65]; sulfonamide combinations: cotrimoxazole (sulfamethoxazole and trimethoprim) can cause prolonged cholestasis [66]; and quinolones such as trovafloxacin can cause fulminant hepatitis [67, 68]. Isoniazid causes mild, asymptomatic, and reversible elevations in AST and ALT, the risk higher with age. Regimens combining INH with rifampin or pyrazinamide are associated with higher incidence of hepatotoxicity [69–71].

Antihypertensives

Alpha methyldopa, an antihypertensive seldom used today, is associated with immune-allergic drug hepatitis and rarely cholestatic injury [72]; alpha methyl dopa is a classic example of bridging necrosis and cirrhosis and still used in many parts of the world. β-adrenergic blockers and calcium channel blockers rarely cause hepatotoxicity. Carvedilol [73], labetalol [74], and metoprolol can cause acute hepatitis-like picture, while diltiazem is linked to granulomatous hepatitis. Hydralazine causes a granulomatous hepatitis, reversible upon discontinuation of drug [75]. Angiotensin-converting enzyme inhibitor (ACEI)-induced liver disease is rare, but is relevant as the class is widely prescribed; examples include captopril, fosinopril [76], enalapril, and ramipril [77]; the picture is cholestatic, hepatocellular, or mixed hepatocellular, with resolution upon drug discontinuation. Of the angiotensin II receptor blockers, irbesartan [78], losartan [79], valsartan [80], and candesartan are implicated in causing acute hepatitis or cholestatic hepatitis.

Antiseizure Medications

Phenytoin causes severe acute cholestatic hepatitis [81], a hypersensitivity syndrome characterized by rash, fever, eosinophilia, and lymphadenopathy. Valproic acid causes a dose-related increase in liver function tests and rarely a serious idiosyncratic reaction not dose-dependent. Prevention involves adherence to prescribing guidelines and use of caution with valproic acid–drug combinations [35]. Carbamazepine can cause granulomatous hepatitis [82]. Levetiracetam (Keppra) is a relatively safe antiepileptic in chronic liver disease [83].

Nonsteroidal Anti-inflammatory Drugs

Aspirin occasionally causes elevated ALT levels and rarely progressive hepatic failure when blood salicylate concentrations exceed 25 mg/100 mL [84]. Diclofenac causes mild elevation of aminotransferases reflecting idiosyncratic toxicity, with or without cholestasis; the risk is higher in women and with age [85]. Bromfenac, a phenylacetic acid derivative, has been withdrawn because of associated fatal ALF [86]. Sulindac can cause cholestatic injury [87]; ibuprofen, can cause hepatocellular or mixed hepatocellular-cholestatic injury [88].

Neuropsychiatric Medications

Tacrine, a reversible choline esterase inhibitor, formerly used in Alzheimer's disease for cognitive benefits was associated with significant increase in ALT levels in 25% of patients, more in women, necessitating frequent monitoring of liver function [89]. It also caused abdominal discomfort and diarrhea and has been replaced by safer cholinesterase inhibitors. Tolcapone, a selective catechol-*o*-methyl transferase inhibitor used with cardidopa in Parkinson's disease, is associated with ALF, especially in older women [90], warranting close monitoring of liver function.

Statins

Statins are widely used today; the most common manifestation is asymptomatic elevations of serum ALT and AST levels that improve or completely resolve upon discontinuing or reducing the involved statin dose. DILI from statin use is overemphasized and benefits far outweigh risks. While monitoring of aminotransferases is recommended, the approach is unlikely to predict toxicity. Lovastatin [91], pravastatin [92], atorvastatin, and simvastatin [93] have been implicated in rare cases of cholestatic hepatitis. Atorvastatin can cause autoimmune hepatitis [94]. Niacin or nicotinic acid (3-pyridinecarboxylic acid) hepatic toxicity is dose-dependent in excess of 2 g daily [99]. Fibrates are rarely implicated. Individuals with elevated baseline liver enzymes are not at higher risk for hepatotoxicity from statins (Table 41.4).

Antidepressants

Selective serotonin reuptake inhibitors (SSRIs) have a better liver safety profile compared to tricyclic antidepressants; asymptomatic elevations of liver enzymes occur with fluoxetine and paroxetine [100, 101]. Tricyclic antidepressants (amitriptyline and imipramine) can cause prolonged cholestasis with recovery upon drug withdrawal; trazodone

Table 41.4 Statin-related liver injury [3, 44, 91–98]

Statins are generally safe for long-term use, with significant liver injury uncommon
Are safe for prevention of coronary artery disease, even in the setting of chronic liver damage
Statins can be safely used to treat hyperlipidemia in nonalcoholic fatty liver disease (NAFLD), with appropriate monitoring
Elevated baseline liver enzymes do not pose higher risk for statin hepatotoxicity
Chronic liver disease or compensated cirrhosis is not considered a contraindication for statins (recommendation of the Statin Safety Task Force of the National Lipid Association)
The most common liver injury is mild symptomatic elevations in ALT and AST
Elevation in AST (and, to a lesser extent, ALT) levels may be from muscle cell damage; resolution is usual with dosage reduction or discontinuing the drug
FDA labeling information recommends that liver enzyme blood tests be performed before and 12 weeks following the initiation of statins, or increase in dose, and periodically thereafter (every 3–6 months)
When aminotransferase levels are over three times upper normal, statins may be discontinued and levels reassessed
When transaminase elevation is persistent, statins should be withheld and screening initiated to exclude drug interactions (acetaminophen, NSAIDs, alcohol, herbal preparations, etc.) and underlying liver disease, before statins are considered the cause of DILI
Once levels return to baseline, may consider a lower dose or a different statin
Pravastatin may be less hepatotoxic than other statins; this may relate to its non-CYP-based metabolism and hydrophilic nature

is implicated in acute and chronic hepatocellular injury and cholestasis [102]; nefazodone, linked to sub-ALF, is no longer used [103].

Antidiabetic Drugs

Troglitazone (a thiazolidinedione) induced ALF occurred in older women and obese persons, necessitating withdrawal of the drug [104]. Serious liver injury appears rare with the second-generation thiazolidinediones, rosiglitazone, and pioglitazone [105]. Older sulfonylureas, such as chlorpropamide, have caused hepatocellular liver injury. Currently used agents such as tolazamide, glimepiride [106], and glibenclamide are rarely associated with cholestasis or cholestatic hepatitis. Rarely, antidiabetics cause liver injury; they include metformin, a first-line oral biguanide (idiosyncratic cholestasis) [107], repaglinide [108], acarbose, and human insulin.

Herbal and Dietary Supplements

Herbal medicines (sold as dietary supplements) are easily available over the counter and erroneously considered to be safe by many and are widely used by older adults along with prescription medications or even instead [109]. Intake of herbal medicines is consistently underreported and not elicited in the history and often consumed without professional supervision or monitoring. Herbal and dietary supplements (HDS) taken alone or in combination with other medications can cause DILI. Liver injury is either hepatocellular, cholestatic, or vascular in nature, with variable severity [110, 111]. Due to poor regulation and oversight of these products, there could be significant variations between the listed ingredients and contents of the supplement, including batch-to-batch differences. Among the many herbals, a few deserve mention. Chaparral (Larrea tridentata) is used as a dietary and "energy supplement" and causes cholestatic hepatiis, with long-term users developing end-stage liver disease requiring transplantation [112]. The postulated mechanism is inhibition of cyclooxygenase or cytochrome P450 or an immune-mediated mechanism. Dai-saiko-to intended for dyspepsia and gallstones is associated with acute hepatitis. Ma-huang, a Chinese herbal remedy, may cause hepatitis with serum autoantibodies (although in weak titers) mimicking autoimmune hepatitis. Saw palmetto used for benign prostatic hyperplasia is generally safe. However, a preparation of Serenoa repens Prostata has recently been associated with protracted cholestatic hepatitis [112] with antimitochondrial antibody positivity. It is the physician responsibility to obtain a history and discuss potential for adverse effects from the use of herbals and supplements [109, 113–115] (Table 41.5).

Diagnosis

A focused history including prescribed and nonprescribed medications, supplements, and herbal medications is the first step in all older adults. Abnormal liver function warrants consideration of DILI in the differential diagnosis, prior to needless tests and treatment. Information should detail as to when each medication had been initiated, including dosage, administration route, concomitant medications, alcohol consumption, and prior history of liver disease. If DILI is a consideration, revision of the drug regimen, including drug withdrawal, is the next step. It

Table 41.5 Herbals and liver injury [109–115]

Product	Comments	Type of injury
Atractylis gummifera	Antipyretic, diuretic	Hepatitis
Black cohosh	Menopausal symptoms	Fulminant hepatic failure
Chaparral	Weight loss, rheumatism, diarrhea	Mixed
Cascara	Laxative	Cholestasis
Comfrey	Herbal tea	Sinusoidal obstruction
Herbalife	Nutritional supplement	Cholestasis and fibrosis
Hydroxycut	Weight loss	Acute hepatitis
Kava	Anxiolytic	Mixed acute hepatitis, cholestasis
Greater celandine	Jaundice, hepatitis, IBS	Cholestasis
Green tea extract	Weight loss	Hepatitis
Germander	Weight loss	Acute hepatitis
Lipokinetix	Weight loss	Acute hepatitis
Mistletoe	Asthma, infertility	Hepatitis
Prostate	Lower urinary tract symptoms	Cholestasis
Valerian	Insomnia, headache	Hepatitis

Table 41.6 DILI: assessing the course of acute hepatitis as possibly a drug basis [116]

Cessation of drug	Very suggestive	Suggestive	Not suggestive	Inconclusive
YES	Decrease in ALT >50% within 8 days and normal in 30 days	Decrease in ALT >50% within 30 days	Variations in ALT within or after 30 days	
NO		Stable or Increase in ALT		Partial decrease of ALT or return to normal

Table 41.7 Extrahepatic manifestations in DILI [34]

Manifestation	Drug association
Allergy: fever, rash, eosinophilia	Phenytoin, dapsone, sulindac
Renal injury	Methoxyflurane, sulindac
Antinuclear antibodies	Alpha methyldopa, nitrofurantoin, minocycline
Gastrointestinal: ulcer, pancreatitis	Phenylbutazone, tetracycline
Bone marrow: aplastic anemia, thrombocytopenia	Phenytoin, phenylbutazone
Hemolytic anemia and jaundice	Dapsone, alpha methyldopa

might be the last drug initiated, although by no means this is certain. An International Consensus Meeting (1990) provides an approach to the diagnosis of drug-induced acute hepatitis and links the hepatic injury and liver enzymes levels to drug discontinuation [116] (Table 41.6).

Physical examination ascertains presence of fever, rash, arthritis, and jaundice, in addition to features of chronic liver disease and failure. History must include alcohol use, preceding episodes of hypotension or hypoxia, hypothermia, heart failure, and sepsis. Other causes of liver disease must be excluded with appropriate biochemical, serological, and radiological investigations.

DILI may be associated with extrahepatic systemic features (Table 41.7). Presence of fever, rash, and eosinophilia suggest drug hypersensitivity, although specific in vitro investigations with proven sensitivity and specificity are not available. Because most hepatic drug reactions are "dose independent," blood levels of drug or metabolite are seldom of diagnostic value; the exceptions being acetaminophen and aspirin-induced hepatitis.

Liver biopsy, although not indicated for most, is reserved for those with acute liver injury that fails to resolve following cessation of drug or supplement. Liver biopsy is valuable in certain situations: underlying liver disease, suspicion of autoimmune hepatitis despite negative serology, available clues for alternative explanations for liver injury, or a complex differential diagnosis that includes DILI. Liver biopsy identifies the pattern and degree of injury. The pathologist can classify the liver injury, aiding the clinician in differential diagnosis.

Management

With any clinical suspicion of DILI, the first step is to discontinue the causative drug(s). Liver injury is assessed and monitored with serial measures of liver function. Most cases improve upon withdrawal of the suspected medication(s). Spontaneous resolution occurs in most, but normalization of liver function may take days to months, while some progress to cirrhosis. Rechallenge is not advisable, since recurrent injury may be more severe than the initial insult, especially with immunologic

injury. DILI can be associated with significant mortality; presence of jaundice, coagulopathy, or encephalopathy may warrant hospitalization for close monitoring.

Hospitalized cases of severe DILI may be candidates for liver transplant because of potential poor outcomes. Attention may be paid to Hy's law [117]; the combination of severe acute hepatocellular injury with clinical jaundice (i.e., total biliribin >2.5 mgs/dL and three times elevation of ALT), with no other accountable reason (such as hepatitis), has been associated with poor prognosis and a case fatality rate of 10–50%. The observation is used by regulatory agencies to evaluate investigational drugs to demonstrate potential hepatototoxic signals during trials [117, 118].

Corticosteroids do not have a significant role in the treatment of most forms of DILI except in rare cases of drug-induced autoimmune hepatitis [47, 119].

Geriatric Patients Are Susceptible

Older individuals are subject to polypharmacy and are susceptible. Newer methods to predict injury prior to their occurrence must address predisposing factors and the emerging field of pharmacogenomics [120]. Several candidate genes conferring susceptibility to DILI have been identified. The primary physician and gastroenterologist have a huge task to monitor their patients to prevent and detect liver injury at the earliest [121]. An approach to prevention and management of DILI is provided in Table 41.8.

Table 41.8 An approach to drug-induced liver injury

Obtain a careful drug history
Current and past medication history
Use of herbal medications, nutritional supplements, and over-the-counter medications
Determine the precise dose, duration, and timing of drug ingestion
Determine a temporal relationship between exposure to known hepatotoxic agent and injury
If on multiple drugs, the most recently added drug prior to injury may be responsible
Criteria for DILI (Table 41.6) may be helpful
Exclude other causes of liver disease
Viral hepatitis
Alcoholism
Biliary abnormalities
Hemodynamic abnormalities: shock or heart failure and ischemic liver injury
Autoimmune liver
Hereditary diseases (such as hemochromatosis and Wilson's disease)
Steps following identification of a causative agent
Improvement occurs if offending drug is discontinued, although worsening may continue for weeks
Rechallenge is not prudent, since recurrence may be more severe, especially with immunologic drug injury
Hospitalize and closely monitor in presence of jaundice, coagulopathy, or encephalopathy
Steroids have little role in management (exception: autoimmune drug injury)
In severe cases of DILI, transplantation is an option
Prevention of DILI
Prevention is more important than treatment in drug-induced injury!
For dose-dependent hepatotoxins, adhere to dosage guidelines or monitor with blood levels
Clear communication between the physician and patient with recommendations on dose limitations help prevent most instances of liver injury
Polypharmacy must be addressed wherever possible
Providers must report suspected adverse effects to monitoring agencies during postmarketing surveillance of new drugs

Key Points

- DILI is common in the geriatric population, in part linked to the prevalence of polypharmacy in this age group.
- Abnormal liver function in the older adult, especially of new or unexplained onset, warrants consideration for a drug-associated basis.
- The role for herbal medications and dietary supplements in DILI must not escape attention, either on their own or in conjunction with other drugs.
- Patterns of liver injury differ markedly; the most common injuries are hepatocellular, cholestatic, and mixed patterns.
- Discontinuing the offending agent usually reverses the hepatic damage; the extent and time for resolution is highly variable.
- Common offenders include acetaminophen and antimicrobials.
- Liver transplantation has a role in severe liver injury if early referral takes place.
- Corticosteroids do not play a significant role in management.
- Ultimately, prevention and diagnosis of DILI is in the hands of the provider, with knowledge of geriatric pharmacology paramount.

References

1. Larrey D. Epidemiology and individual susceptibility to adverse drug reactions affecting the liver. Semin Liver Dis. 2002; 22:145–55.
2. Bell LN, Chalasani N. Epidemiology of idiosyncratic drug-induced liver injury. Semin Liver Dis. 2009;29:337–47.
3. Au JS, Navarro VJ, Rossi S. Review article: drug-induced liver injury—its pathophysiology and evolving diagnostic tools. Aliment Pharmacol Ther. 2011;10:1365–2036.

4. Ostapowicz G, Fontana RJ, Schiodt FV, et al. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. Ann Intern Med. 2002;137:947–54.
5. Reuben A, Koch DG, Lee WM. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology. 2010;52(6):2065–76.
6. Sgro C, Clinard F, Ouazir K, et al. Incidence of drug-induced hepatic injuries: a French population-based study. Hepatology. 2002;36:451–5.
7. Andrade RJ, Lucena MI, Fernandez MC, et al. Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period. Gastroenterology. 2005;129:512–21.
8. Daly AK, Day CP. Genetic association studies in drug-induced liver injury. Semin Liver Dis. 2009;29:400–11.
9. Wilke RA, Lin DW, Roden DM, et al. Identifying genetic risk factors for serious adverse reactions; current progress and challenges. Nat Rev Drug Discov. 2007;6:904–16.
10. Chalasani N, Bjornson E. Risk factors for idiosyncratic drug-induced liver injury. Gastroenterology. 2010;138(7):2246–59.
11. Tujios S, Fontana RJ, et al. Mechanisms of drug-induced liver injury: from bedside to bench. Nat Rev Gastroenterol Hepatol. 2011;8(4):202–11.
12. Cotreau MM, von Moltke LL, Greenblatt DJ. The influence of age and sex on the clearance of cytochrome P450 3A substrates. Clin Pharmacokinet. 2005;44:33–60.
13. Andrade RJ, Robles M, Ulzurrun E, et al. Drug-induced liver injury: insights from genetic studies. Pharmacogenomics. 2009;10:1467–87.
14. Walgren JL, Mitchell MD, Thompson DC. Role of metabolism in drug-induced idiosyncratic hepatotoxicity. Crit Rev Toxicol. 2005;35:325–61.
15. Huang YS. Genetic polymorphisms of drug-metabolizing enzymes and the susceptibility to antituberculosis drug-induced liver injury. Expert Opin Drug Metab Toxicol. 2007;3:1–8.
16. Shimizu Y, Dobashi K, Mita Y, et al. DNA microarray genotyping of N-acetyltransferase 2 polymorphism using carbodiimide as the linker for assessment of isoniazid hepatotoxicity. Tuberculosis (Edinb). 2006;86:374–81.
17. Huang YS, Chern HD, Su WJ, et al. Polymorphism of the N-acetyltransferase 2 gene as a susceptibility risk factor for antituberculosis drug-induced hepatitis. Hepatology. 2002;35:883–9.
18. Lucena MI, Andrade RJ, Martinez C, et al. Glutathione S-transferase m1 and t1 null genotypes increase susceptibility to idiosyncratic drug-induced liver injury. Hepatology. 2008;48:588–96.
19. Hautekeete ML, Horsmans Y, Van Waeyenberge C, et al. HLA association of amoxicillin-clavulanate–induced hepatitis. Gastroenterology. 1999;117:1181–6.
20. Daly AK, Donaldson PT, Bhatnagar P, et al. HLA-B*5701 genotype is a major determinant of drug-induced liver injury due to flucloxacillin. Nat Genet. 2009;41:816–21.
21. Aithal GP, Ramsay L, Daly AK, et al. Hepatic adducts, circulating antibodies, and cytokine polymorphisms in patients with diclofenac hepatotoxicity. Hepatology. 2004;39:1430–40.
22. Fredriksson L, Herpers B, Benedetti G, et al. Diclofenac inhibits tumor necrosis factor α-induced nuclear factor-κB activation causing synergistic hepatocyte apoptosis. Hepatology. 2011;53(6):2027–41.
23. Pauli-Magnus C, Meier PJ. Hepatobiliary transporters and drug induced cholestasis. Hepatology. 2006;44:778–87.
24. Ho RH, Kim RB. Transporters and drug therapy: implications for drug disposition and disease. Clin Pharmacol Ther. 2005;78:260–77.
25. Noe J, Kullak-Ublick GA, Jochum W, et al. Impaired expression and function of the bile salt export pump due to three novel ABCB11 mutations in intrahepatic cholestasis. J Hepatol. 2005;43:536–43.
26. Lang C, Meier Y, Stieger B, et al. Mutations and polymorphisms in the bile salt export pump and the multidrug resistance protein3 associated with drug-induced liver injury. Pharmacogenet Genomics. 2007;17:47–60.
27. Begriche K, Massart J, Robin MA, et al. Drug-induced toxicity on mitochondria and lipid metabolism: mechanistic diversity and deleterious consequences for the liver. J Hepatol. 2011;54(4):773–94.
28. Fountain FF, Tolley E, Chrisman CR, et al. Isoniazid hepatotoxicity associated with treatment of latent tuberculosis infection: a 7-year evaluation from a public health tuberculosis clinic. Chest. 2005;128:116–23.
29. Wynne HA, Cope LH, Mutch E, et al. The effect of age upon liver volume and apparent liver blood flow in healthy men. Hepatology. 1989;9:297–301.
30. Lucena MI, Andrade RJ, Kaplowitz N, et al. Phenotypic characterization of idiosyncratic drug-induced liver injury: the influence of age and gender. Hepatology. 2009;49:2001–9.
31. Chalasani N, Fontana RJ, Bonkovsky HL, et al. Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology. 2008;135:1924–34.
32. De Valle MB, Av Klinteberg V, Alem N, et al. Drug induced liver injury in a Swedish University hospital out-patient hepatology clinic. Aliment Pharmacol Ther. 2006;24:1187–95.
33. Fernandez-Liz E, Modamio P, Catalán A, Lastra CF, Rodriguez T, Mariño EL. Identifying how age and gender influence prescription drug use in a primary health care environment in Catalonia, Spain. Br J Clin Pharmacol. 2007;65:407–17.
34. Zimmerman HJ. Drug induced liver disease. In: Zimmerman HJ, editor. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, Williams & Wilkins; 1999. p. 427–50.
35. Gopaul S, Farrell K, Abbott F. Effects of age and polytherapy, risk factors of valproic acid (VPA) hepatotoxicity, on the excretion of thiol conjugates of (E)-2,4-diene VPA in people with epilepsy taking VPA. Epilepsia. 2003;44:322–8.
36. Lucena MI, Carvajal A, Andrade RJ, et al. Antidepressants induced hepatotoxicity. Expert Opin Drug Saf. 2003;2:1–14.
37. Andrejak A, Davion T, Gineston JL, et al. Cross hepatotoxicity between non-steroidal anti-inflammatory drugs. Br Med J (Clin Res Ed). 1987;295:180–1.
38. Schmidt LE, Dalhoff K, Poulsen HE. Acute versus chronic alcohol consumption in acetaminophen induced hepatotoxicity. Hepatology. 2002;35:876–82.
39. Malatjalian DA, Ross JB, Williams CN, et al. Methotrexate hepatotoxicity in psoriatics: report of 104 patients from Nova Scotia, with analysis of risks from obesity, diabetes and alcohol consumption during long term follow-up. Can J Gastroenterol. 1996;10:369–75.
40. Sulkowski MS, Thomas DL, Chaisson RE, et al. Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus. JAMA. 2000;283:74–80.
41. Sulkowski MS, Thomas DL, Mehta SH, et al. Hepatotoxicity associated with nevirapine or efavirenz-containing antiretroviral therapy: role of hepatitis C and B infections. Hepatology. 2002;35(1):182–9.
42. Bonacini M. Liver injury during highly active antiretroviral therapy: the effect of hepatitis C coinfection. Clin Infect Dis. 2004;38 Suppl 2:S104–8.
43. Ungo JR, Jones D, Ashkin D, et al. Antituberculosis drug-induced hepatotoxicity. The role of hepatitis C virus and the human immunodeficiency virus. Am J Respir Crit Care Med. 1998;157:1871–6.

44. Ekstedt M, Franzen LE, Mathiesen UL, et al. Statins in nonalcoholicfatty liver disease and chronically elevated liver enzymes: a histopathological follow-up study. J Hepatol. 2007;47:135–41.
45. Chalasani N, Aljadhey H, Kesterson J, et al. Patients with elevated liver enzymes are not at higher risk for statin hepatotoxicity. Gastroenterology. 2004;126(5):1287–92.
46. Dharmarajan TS, Pitchumoni CS, Kumar KS. Drug-induced liver disease in older adults. Pract Gastroenterol. 2001;25:43–60.
47. Czaja AJ. Drug-induced autoimmune-like hepatitis. Dig Dis Sci. 2011;56(4):958–76.
48. Chitturi S, Farrell GC. Drug-induced cholestasis. Semin Gastrointest Dis. 2001;12:113–24.
49. Cullen JM. Mechanistic classification of liver injury. Toxicol Pathol. 2005;33:6–8.
50. Kum LC, Chan WW, Hui HH, et al. Prevalence of amiodarone-related hepatotoxicity in 720 Chinese patients with or without baseline liver dysfunction. Clin Cardiol. 2006;29:295–9.
51. Miller KD, Cameron M, Wood LV, et al. Lactic acidosis and hepatic steatosis associated with use of stavudine: report of four cases. Ann Intern Med. 2000;133:192–6.
52. Bleeker-Rovers CP, Kadir SW, van Leusen R, et al. Hepatic steatosis and lactic acidosis caused by stavudine in an HIV-infected patient. Neth J Med. 2000;57:190–3.
53. Gaya DR, Thorburn D, Oien KA, et al. Hepatic granulomas: a 10 year single centre experience. J Clin Pathol. 2003;56:850–3.
54. Mays ET, Christopherson W. Hepatic tumors induced by sex steroids. Semin Liver Dis. 1984;4:147–57.
55. Giannitrapani L, Soresi M, La Spada E, et al. Sex hormones and risk of liver tumor. Ann N Y Acad Sci. 2006;1089:228–36.
56. Bessems JG, Vermeulen NP. Paracetamol (acetaminophen)-induced toxicity: molecular and biochemical mechanisms, analogues and protective approaches. Crit Rev Toxicol. 2001;31:55–138.
57. Schmidt LE. Age and paracetamol self-poisoning. Gut. 2005;54(5): 686–90.
58. Fontana RJ. Acute liver failure including acetaminophen overdose. Med Clin North Am. 2008;92(4):761–94.
59. Lee WM. Acetaminophen and the US Acute Failure Study Group: lowering the risks of hepatic failure. Hepatology. 2004;40(1): 6–9.
60. U.S. Food and Drug Administration. FDA Drug Safety Communication. Prescription acetaminophen products to be limited to 325 mg per dosage unit; boxed warning. www.fda.gov/Drugs/DrugSafety/ucm239821.htm. Accessed 14 March 2011.
61. Lucena MI, Andrade RJ, Fernández MC, et al. Determinants of the clinical expression of amoxicillin-clavulanate hepatotoxicity: a prospective series from Spain. Hepatology. 2006;44: 850–6.
62. Devereaux BM, Crawford DH, Purcell P, Powell LW, Roeser HP. Flucloxacillin associated cholestatic hepatitis. An Australian and Swedish epidemic? Eur J Clin Pharmacol. 1995;49(1–2): 81–5.
63. Koulaouzidis A, Bhat S, Moschos J, et al. Nitrofurantoin-induced lung- and hepatotoxicity. Ann Hepatol. 2007;6:119–21.
64. Peedikayil MC, Dahhan TI, Al Ashgar HI. Nitrofurantoin-induced fulminant hepatitis mimicking autoimmune hepatitis. Ann Pharmacother. 2006;40:1888–9.
65. Carson JL, Strom BL, Duff A, et al. Acute liver disease associated with erythromycins, sulfonamides, and tetracyclines. Ann Intern Med. 1993;119:576–83.
66. Windecker R, Steffen J, Cascorbi I, et al. Co-trimoxazole induced liver and renal failure. Eur J Clin Pharmacol. 2000;56:191–3.
67. Lazarczyk DA, Goldstein NS, Gordon SC. Trovafloxacin hepatotoxicity. Dig Dis Sci. 2001;46:925–6.
68. Lucena MI, Andrade RJ, Rodrigo L, et al. Trovafloxacin-induced acute hepatitis. Clin Infect Dis. 2000;30(2):400–1.
69. Tostmann A, Boeree MJ, Aarnoutse RE, et al. Antituberculosis drug-induced hepatotoxicity: concise up-to-date review. J Gastroenterol Hepatol. 2008;23(2):192–202.
70. Durand F, Bernuau J, Pessayre D, et al. Deleterious influence of pyrazinamide on the outcome of patients with fulminant or subfulminant liver failure during antituberculous treatment including isoniazid. Hepatology. 1995;21:929–32.
71. De Rosa HJ, Baldan HM, Brunetti IL, et al. The effect of pyrazinamide and rifampicin on isoniazid metabolism in rats. Biopharm Drug Dispos. 2007;28(6):291–6.
72. Maddrey WC, Boitnott JK. Severe hepatitis from methyldopa. Gastroenterology. 1975;68:351–60.
73. Hagmeyer KO, Stein J. Hepatotoxicity associated with carvedilol. Ann Pharmacother. 2001;35:1364–6.
74. Clark J, Zimmerman HJ, Tanner L. Labetalol hepatotoxicity. Ann Intern Med. 1990;113:210–3.
75. Jori GP, Peschile C. Hydralazine disease associated with transient granulomas in the liver: a case report. Gastroenterology. 1973;64: 1163–7.
76. Nunes AC, Amaro P, Mac as F, et al. Fosinopril-induced prolonged cholestatic jaundice and pruritus: first case report. Eur J Gastroenterol Hepatol. 2001;13:279–82.
77. Yeung E, Wong FS, Wanless IR, et al. Ramipril-associated hepatotoxicity. Arch Pathol Lab Med. 2003;127:1493–7.
78. Andrade RJ, Lucena MI, Fernandez MC, et al. Cholestatic hepatitis related to use of irbesartan: a case report and a literature review of angiotensin II antagonist-associated hepatotoxicity. Eur J Gastroenterol Hepatol. 2002;14:887–90.
79. Tabak F, Mert A, Ozaras R, et al. Losartan-induced hepatic injury. J Clin Gastroenterol. 2002;34:585–6.
80. Kiykim A, Altintas E, Sezgin O, et al. Valsartan-induced hepatotoxicity in a HBsAg positive patient. Am J Gastroenterol. 2003;98:507.
81. Altuntas Y, Ozturk B, Erdem L, et al. Phenytoin-induced toxic cholestatic hepatitis in a patient with skin lesions: case report. South Med J. 2003;96:201–3.
82. Mitchell MC, Boitnott JK, Arregui A, et al. Granulomatous hepatitis associated with carbamazepine therapy. Am J Med. 1981;71: 733–5.
83. Bilo L, Meo R, de Leva MF, et al. Levetiracetam in patients with epilepsy and chronic liver disease: observations in a case series. Clin Neuropharmacol. 2008;31(4):221–5.
84. O'Connor N, Dargan PI, Jones AL. Hepatocellular damage from non-steroidal anti-inflammatory drugs. QJM. 2003;96:787.
85. Boelsterli UA. Diclofenac-induced liver injury: a paradigm of idiosyncratic drug toxicity. Toxicol Appl Pharmacol. 2003;192:307–22.
86. Fontana RJ, McCashland TM, Benner KG, et al. Acute liver failure associated with prolonged use of bromfenac leading to liver transplantation. The Acute Liver Failure Study Group. Liver Transpl Surg. 1999;5:480–4.
87. Tarazi EM, Harter JG, Zimmermann HJ, et al. Sulindac associated hepatic injury: analysis of 91 cases reported to the Food and Drug Administration. Gastroenterology. 1993;104:569–74.
88. Javier Rodriguez-Gonzalez F, Montero JL, Puente J, et al. Orthotopic liver transplantation after subacute liver failure induced by therapeutic doses of ibuprofen. Am J Gastroenterol. 2002;97: 2476–7.
89. Watkins PB, Zimmerman HJ, Knapp MJ, et al. Hepatotoxic effects of tacrine administration in patients with Alzheimer's disease. JAMA. 1994;271:992–8.
90. Olanow CW, Watkins PB. Tolcapone: an efficacy and safety review. Clin Neuropharmacol. 2007;30:287–94.
91. Grimbert S, Pessayre D, Degott C, et al. Acute hepatitis induced by HMG-CoA reductase inhibitor, lovastatin. Dig Dis Sci. 1994;39:2032–3.

92. Hartleb M, Rymarczyk G, Januszewski K. Acute cholestatic hepatitis associated with pravastatin. Am J Gastroenterol. 1999;94:1388–90.
93. Ballare M, Campanini M, Catania E, et al. Acute cholestatic hepatitis during simvastatin administration. Recenti Prog Med. 1991;82:233–5.
94. Pelli N, Setti M, Ceppa P, et al. Autoimmune hepatitis revealed by atorvastatin. Eur J Gastroenterol Hepatol. 2003;15:921–4.
95. Ritzel U, Leonhardt U, Nather M, et al. Simvastatin in primary biliary cirrhosis: effects on serum lipids and distinct disease markers. J Hepatol. 2002;36(4):454–8.
96. Avins AL, Manos MM, Levin TR, et al. Lovastatin is not hepatotoxic to patients with pre-existing liver disease. Gastroenterology. 2006;130:A-595.
97. de Denus S, Spinler SA, Miller K, Peterson AM. Statins and liver toxicity: a meta-analysis. Pharmacotherapy. 2004;24(5):584–91.
98. Cohen DE, Anania FA, Chalasani N; National Lipid Association Statin Safety Task Force Liver Expert Panel. An assessment of statin safety by hepatologists. Am J Cardiol. 2006;97(8A): 77C–81.
99. McKenny JM, Proctor JD, Harris S, et al. A comparison of the efficacy and toxic effects of sustained vs. immediate-release niacin in hypercholesterolemic patients. JAMA. 1994;271:672–7.
100. Cai Q, Benson MA, Talbot TJ, et al. Acute hepatitis due to fluoxetine therapy. Mayo Clin Proc. 1999;74:692–4.
101. Benbow SJ, Gill G. Paroxetine and hepatotoxicity. BMJ. 1997;314:1387–8.
102. Fernandes NF, Martin RR, Schenker S. Trazodone-induced hepatotoxicity: a case report with comments on drug-induced hepatotoxicity. Am J Gastroenterol. 2000;95:532–5.
103. Aranda-Michel J, Koehler A, Bejarano PA, et al. Nefazodone-induced liver failure: report of three cases. Ann Intern Med. 1999;130:285–8.
104. Chojkier M. Troglitazone and liver injury: in search of answers. Hepatology. 2005;41:229–30.
105. Marcy TR, Britton ML, Blevins SM. Second-generation thiazolidinediones and hepatotoxicity. Ann Pharmacother. 2004;38: 1419–23.
106. Chounta A, Zouridakis S, Ellinas C, et al. Cholestatic liver injury after glimepiride therapy. J Hepatol. 2005;42:944–6.
107. Desilets DJ, Shorr AF, Moran KA, et al. Cholestatic jaundice associated with the use of metformin. Am J Gastroenterol. 2001;96:2257–8.
108. Lopez-Garcia F, Borras J, Verdu C, et al. Cholestatic hepatitis associated with repaglinide. Diabetes Care. 2005;28:752–3.
109. Yellapu RK, Mittal V, Grewal P, et al. Acute liver failure caused by 'fat burners' and dietary supplements: a case report and literature review. Can J Gastroenterol. 2011;25(3):157–60.
110. Schoepfer AM, Engel A, Fattinger K, et al. Herbal does not mean innocuous: ten cases of severe hepatotoxicity associated with dietary supplements from Herbalife products. J Hepatol. 2007;47: 521–6.
111. Stickel F, Patsenker E, Schuppan D. Herbal hepatotoxicity. J Hepatol. 2005;43:901–10.
112. Chitturi S, Farrell G. Herbal hepatotoxicity: an expanding but poorly defined problem. J Gastroenterol Hepatol. 2000;15: 1093–9.
113. Mei N, Guo L, Fu PP, et al. Metabolism, genotoxicity, and carcinogenicity of comfrey. J Toxicol Environ Health B Crit Rev. 2010;13(7–8):509–26.
114. Teschke R, et al. Kava hepatotoxicity–a clinical review. Ann Hepatol. 2010;9(3):251–65.
115. Sharma T, Wong L, Tsai N, et al. Hydroxycut (herbal weight loss supplement) induced hepatotoxicity: a case report and review of literature. Hawaii Med J. 2010;69(8):188–90.
116. Benichou C, Bankowski Z, Begaud B, et al. Criteria of drug-induced liver disorders. Report of an international consensus meeting. J Hepatol. 1990;11:272–6.
117. Reuben A. Hy's law. Hepatology. 2004;39(2):574–8.
118. Senior JR. Regulatory perspectives. In: Kaplowitz N, DeLeve LD, editors. Drug-induced liver disease. New York: Marcel Dekker; 2003. p. 739–54.
119. Giannattasio A, D'Ambrosi M, Volpicelli M, Iorio R. Steroid therapy for a case of severe drug-induced cholestasis. Ann Pharmacother. 2006;40:1196–9.
120. Kitzmiller JP, Groen DK, Phelps MA, Sadee W. Pharmacogenommic testing: relevance in medical practice. Why some drugs works in some patients but not in others. Cleve Clin J Med. 2011;78(4): 243–57.
121. Liss G, Rattan S, Lewis JH. Predicting and preventing acute drug induced liver injury: what's new in 2010? Expert Opin Drug Metab Toxicol. 2010;6(9):1047–61.

Gallbladder Disease

42

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Introduction

Gallbladder disease includes a wide range of presentations ranging from total asymptomatic to malignancy. Some disorders such as emphysematous cholecystitis and gallbladder cancer are common in the older age group. Geriatric patients are vulnerable to complications of cholelithiasis and associated morbidity and mortality. Treatment strategies are best individualized as comorbidity is a common association.

Cholelithiasis

Epidemiology

Gallstones are present in about 10% of the US population, with approximately 1,000,000 new cases of cholelithiasis diagnosed annually [1]. About 25% of adults older than 50 years develop gallstones. Cholelithiasis increases with age, to involve approximately 35% of women and 20% of men by the eighth decade of life. Gallstone disease increases overall morbidity and mortality [2].

Table 42.1 lists the common risk factors for cholelithiasis and include age, female sex, obesity, and heredity. In one study, tobacco, caffeine, and vegetarian diet did not affect the prevalence of gallstones, alcohol consumption demonstrated a protective effect [3]. A study in Northern India found a significantly increased risk associated with female gender, multiparity, genetic history, and males with diabetes [4].

Pathogenesis

Gallstones are of three types: cholesterol stones (70–80% of cases), black-pigment stones, and brown pigment stones. Several factors contribute to formation of cholesterol gallstones, including cholesterol supersaturation in bile, accelerated nucleation of cholesterol crystals, gallbladder hypomotility, and increased secretion of mucin by the gallbladder. Hypercholesterolemia predisposes to gallstone formation due to mutation in the CYP7A1 gene and a resultant decline in the enzyme cholesterol 7-hydroxylase [5]. Additionally, MDR3 gene mutations may result in defective phospholipid secretion into bile and cholesterol supersaturation [6]. Supersaturation by itself is insufficient to form gallstones. Nucleation of cholesterol monohydrate crystals is also important; the process is accelerated by either an excess of proneucleating or a deficiency of antinucleating factors.

Clinical Features

The vast majority of gallstones are asymptomatic and are found incidentally during abdominal imaging for other reasons. Symptoms may result from inflammation or obstruction in the cystic or common bile duct. The presentation may be biliary pain (sharp, right upper quadrant pain) and a crescendo-decrescendo course lasting 30–120 min with nausea and vomiting. Presentations associated with complications include cholecystitis, pancreatitis, obstructive jaundice, cholangitis, gangrenous gallbladder, or Mirrizzi's syndrome (where a stone impacted in the cystic duct causes inflammation and erodes into the common hepatic duct). A rare (0.3–0.5%) but serious complication of cholelithiasis is gallstone ileus, a complication more common in the old and female gender [7].

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Table 42.1 Risk factors for gallstones [3, 4]

Risk factor	Type of gallstone
Increasing age	Cholesterol stones
Gender (female >male)	Cholesterol stones
Demographic/genetic factors	Cholesterol stones
Obesity	Cholesterol stones
Rapid weight loss	Cholesterol stones
Total parenteral nutrition (TPN)	Cholesterol stones
Pregnancy	Cholesterol stones
Medications (oral contraceptive pills, estrogens, progesterones, clofibrate, ceftriazone, octreotide)	Cholesterol stones
Terminal ileal disease or resection	Cholesterol stones
Lipid abnormalities	Cholesterol stones
Cirrhosis	Black pigment stones
Chronic hemolysis	Black pigment stones
Duodenal diverticula	Black pigment stones
Biliary stricture	Brown pigment stones
Recurrent pyogenic cholangitis	Brown pigment stones

Less recognized presentations include cholecystocholedochal fistula and Bouveret's syndrome (a type of gallstone ileus where the stone is lodged in the duodenum or the stomach, resulting from a biliary-enteric fistula).

Diagnosis

Once gallstone disease is suspected based on the clinical presentation, differential diagnoses include peptic ulcer disease, nonsteroidal anti-inflammatory drug (NSAID)-induced ulcer disease, atypical reflux, sphincter of Oddi dysfunction, irritable bowel syndrome, pancreatitis, and other causes of acute abdominal pain. Since some of these diseases may coexist with cholecystitis, a detailed history and elucidation of symptoms is important. Physical examination and laboratory studies may be normal in patients with symptomatic cholelithiasis, but are abnormal in patients with complicated disease such as cholecystitis or common bile duct stones. Imaging studies are useful in diagnosis; the most sensitive tests are transabdominal ultrasound, endosonography (EUS), and magnetic resonance cholangiopancreatography. Oral cholecystography, currently obsolete, plain x-ray of the abdomen, and even computed tomography (CT) are less sensitive for the detection of gallstone disease.

Treatment

The presence of gallstones by itself is not an indication for intervention. The Group for Epidemiology and Prevention for Cholelithiasis (GREPCO) [8] studied the natural history of gallstones and found that symptomatic cholelithiasis developed in 12% of persons at 2 years and 26% of those by 10 years. Additionally, complications occurred in 3% of patients who were initially asymptomatic and in 6.5% of symptomatic patients at 10 years [8]. The recurrence of biliary pain after a symptomatic stone is very high; [9] hence, intervention is warranted in all patients who present with biliary pain or complications.

Treatment for symptomatic gallstone disease is cholecystectomy. With advances in anesthesia and surgical techniques, urgent cholecystectomy carries the same outcome in the old as in the young. Laparoscopic cholecystectomy is the standard of care, but open cholecystectomy may be needed in a small number of patients. Of note, while laparoscopic cholecystectomy in elderly patients is preferred to the open technique, it is associated with higher complication rates and longer lengths of hospital stay as compared to the younger population [10]. Further, an uncommon, but serious complication of cholecystectomy is bile duct injury. While the identified risk factors for this complication are acute cholecystitis, male sex, older age, and aberrant biliary anatomy, Asian race/ethnicity may be a risk factor in patients undergoing both laparoscopic and open cholecystectomies [11].

Natural Orifice Transluminal Endoscopic Surgery (NOTES) cholecystectomy is undergoing evaluation [12]. Patients with complicated disease, such as common bile duct pathology, require investigation with a cholangiogram.

Ursodeoxycholic acid (UCDA) a therapy used for dissolution of gallstones, has become nearly obsolete. Only a few patients with a functioning gallbladder and radiolucent stones <10 mm may experience complete dissolution, which may take up to 2 years of therapy [13]. Stones recur with cessation of medical therapy, and the drug is expensive. Recurrent choledocholithiasis after cholecystectomy is an indication for long-term treatment with UCDA.

It should be noted here that, while not a treatment, the use of long-term statin therapy (1–2 years or more) does reduce the risk of gallstone disease as the majority of gallstones originate from cholesterol-supersaturated bile [14].

Choledocholithiasis

Common bile duct stones are the most common source of biliary pain. Symptoms include biliary colic, jaundice, cholangitis, pancreatitis, or patients may be asymptomatic. Choledocholitiasis occurs in approximately 15–20% of the population with underlying cholelithiasis. Stones in the bile duct may also occur in 10% of patients without cholelithiasis and in 5% of patients status postcholecystectomy.

Acute Cholangitis

Acute cholangitis is a bacterial infection superimposed on an obstruction of the bile duct most commonly in the setting of choledocholithiasis. Charcot's triad is the symptom complex of jaundice, fever, and right upper quandrant pain that often occurs in cholangitis. Recent studies suggest that this triad occurs only in 15–20% of patients. Reynold's Pentad refers to the symptom complex of mental status changes and hypotension in combination with Charcot's triad. Patients present with mental status changes approximately 10–20% of the time and hypotension up to 30% of the time. In the setting of septic shock, the diagnosis can be missed up to 25% of the time. As such, awareness of these classic findings is paramount.

Treatment of Choledocholithiasis and Acute Cholangitis

Endoscopic sphincterotomy and stone extraction during endoscopic retrograde cholangiopancreatography (ERCP) has a success rate >90% and a complication rate of <5% for the removal of common bile duct stones. A common bile duct stone may also be extracted intraoperatively with common bile duct exploration. Though equivalent in success, common bile duct exploration is technically more challenging than ERCP, endoscopic sphincterotomy, and stone extraction. Because of the risks of ascending cholangitis and associated sepsis, it is generally recommended that a common bile duct stone be extracted whenever it is encountered.

Acute Cholecystitis

Epidemiology

Cholecystitis is the most common complication of gallstone disease occurring in 1–3% of patients with symptomatic gallstones. It typically affects young healthy women in comparison to acalculous cholecystitis, which affects critically ill elderly men. The overall mortality from a single episode ranges from <1% in young, healthy individuals to 10% in elderly or critically ill patients.

Pathogenesis

Acute cholecystitis occurs when a stone is chronically impacted (not transiently as in the case of biliary colic) in the cystic duct, gallbladder neck, or Hartman's pouch (outpunching of the gallbladder at the junction of the neck of the gall bladder and the cystic duct) [15]. In the majority of cases, gallbladder wall inflammation results from calculouscystic duct obstruction [15]. Inflammation results from several factors: mechanical; through intraluminal pressure and distention with resulting ischemia of the gallbladder mucosa and wall; chemical, through release of lysolecithin; and consequent bacterial inflammation.

Animal studies have demonstrated that cystic duct ligation alone is insufficient to cause acute cholecystitis [16, 17]. Lysolecithin, detectable in acute cholecystitis, is produced from lecithin, a normal bile constituent, by interaction with phospholipase A released from gallbladder mucosa following gallstone-induced trauma. Prostaglandins may play a role in propagation of the inflammatory process [18]. Bacteria can be cultured from bile in half the patients with acute cholecystitis, but infection is not the triggering event [19].

Clinical Features

Older adults do not always exhibit the classic symptoms, which include right upper quadrant or epigastric pain, nausea, and vomiting. Up to 75% of patients report prior biliary pain [20]. Pain associated with acute cholecystitis is of longer duration, usually lasting >6 h in comparison to biliary colic. Fever and leukocytosis are absent in up to 50% of elderly patients [21]. Jaundice, present in 40% of patients, may be caused by Mirizzi's syndrome. Mirizzi's syndrome refers to bile duct obstruction from a large stone(s) impacted in the cystic duct compressing transmurally on the bile duct or obstruction as a result of chronic inflammation from multiple stones in Hartman's pouch of the gallbladder that lead to fistula formation between the gallbladder and CBD resulting in obstruction. Murphy's sign is a relatively specific finding in acute cholecystitis, but its sensitivity is diminished in the elderly [22]. It is elicited by palpation of the area of the gallbladder fossa during inspiration; inspiratory arrest from discomfort is observed with descent of the gallbladder. A positive Murphy's sign in older adults is helpful, but a negative sign does not rule out acute cholecystitis. Untreated disease may result in gangrene, perforation, gallstone ileus, and cholecystoenteric fistulas [23].

Emphysematous Cholecystitis

Emphysematous cholecystitis afflicts men in their fifth to seventh decades, with a third to half being diabetic [24]. Emphysematous changes are a result of secondary infection of the gallbladder wall with gas-forming organisms, including *Clostridium welchii*, *Escherichia coli*, *Pseudomonas,* and *Klebsiella*. Abdominal wall crepitus may be elicited overlying the gallbladder. Unconjugated hyperbilirubinemia resulting from hemolysis due to clostridial infection can occur. Emphysematous cholecystitis may progress to gangrene, perforation, or other complications [25].

Complications of Cholecystitis

Prolonged obstruction can lead to gallbladder distention with colorless, mucoid fluid known as hydrops, resulting from absorption of bile pigments within the gallbladder. Gangrene and perforation may be a consequence of ischemia of the wall and patchy or complete tissue necrosis. Another complication of cholecystitis is fistula formation into an organ adjoining the gallbladder due to inflammation and adhesion formation. Fistulas commonly occur in the duodenum followed by the hepatic flexure of the colon, stomach or jejunum, abdominal wall, and renal pelvis. Gallstone ileus, a form of mechanical intestinal obstruction, results from passage of a large gallstone into the bowel lumen. Finally, calcium salts secreted into the gallbladder lumen may cause precipitation and diffuse, hazy opacification referred to as 'limey bile.' Although usually innocuous, cholesystectomy is recommended. Porcelain gallbladder can occur if calcium salt deposition occurs within the wall of a chronically inflamed gallbladder. Patients with porcelain gallbladder are prone to develop gallbladder cancer.

AIDS Cholangiopathy

AIDS cholangiopathy is a late complication caused by cytomegalovirus, *Cryptosporidium*, *Microsporium*, and *Mycobacterium avium* (details discussed in chapter 71).

Diagnosis

Ultrasonography is the most useful imaging modality in patients suspected to have acute cholecystitis. A sonographic Murphy's sign or focal gallbladder tenderness under the transducer has a positive predictive value >90% if gallstones are present, the patient is alert, and the operator is skillful [26]. Additional findings suggestive of acute cholecystitis include gallbladder wall thickening >4 mm and pericholecystic fluid. Ultrasound may fail to satisfactorily visualize the distal common duct.

Hepatobiliary scintigraphy (HIDA) scan is useful to exclude acute cholecystitis if the ultrasound is nondiagnostic. Technetium-labeled hepatic iminodiacetic acid is taken up by hepatocytes and excreted into bile. The test is positive if the gallbladder is not visualized, indicative of cystic duct obstruction. Sensitivity and specificity are 97 and 90%, respectively. Abdominal CT is useful in detecting complications of acute cholecystitis, especially pancreatic involvement, and to exclude other intra-abdominal pathology as the cause of symptoms.

Treatment

Patients diagnosed with acute cholecystitis should be admitted to the hospital and be provided intravenous rehydration. Antibiotics effective against gram-negative and anaerobic bacteria are initiated, although it is unclear if antibiotics are necessary in uncomplicated acute cholecystitis. The duration of antibiotic therapy is dependent upon clinical improvement [27].

The type and timing of definitive therapy depends upon symptom severity and the patient's surgical candidacy. If definitive therapy is not pursued during the initial presentation, the risk of recurrent symptoms is approximately 70%. Data in elderly patients with acute cholecystitis show that if cholecystectomy is not performed on initial hospitalization, the risk of recurrent episodes and readmission increases, as also associated costs [28]. Low-risk patients, defined as American Society of Anesthesiologists (ASA) class I and II, benefit from open or laparoscopic cholecystectomy [29]. Elective laparoscopic cholecystectomy carries lower morbidity and mortality as compared to open cholecystectomy [29–31]. Further, open cholecystectomy is associated with greater length of hospital stay and cost as compared with the laparoscopic technique [31]. In some surgical candidates, a cholecystostomy may be followed by delayed elective cholecystectomy at a later date. Further, gallstone extraction can be performed through the percutaneous catheter. Endoscopic transpapillary drainage procedure are palliative measures in those deemed nonsurgical candidates [32].

Acalculous Cholecystitis

Epidemiology

Acalculous cholecystitis, accounting for 10% of all cases, is an inflammatory process of the gallbladder and occurs in the absence of an obstructing gallstone. Most cases follow prolonged immobility, fasting, and hemodynamic instability. Predisposition is noted in underlying vascular disease, bone marrow transplant recipients, acquired immunodeficiency syndrome, and systemic vasculitides (Table 42.2) [33–37].

Pathogenesis

In a healthy patient, the gallbladder empties several times per day to rid it of concentrated bile. It refills with dilute bile, considered less noxious to the epithelium. The gallbladder does not get stimulated to contract and empty in patients in the fasting state, and hence, leads to concentration of bile within the gallbladder and subsequent noxious injury [38].

Table 42.2 Risk factors for acalulous cholecystitis [33, 39, 41, 45]

Elderly males
Burns
Cholesterol emboli
Coronary artery disease
Diabetes mellitus
Immunosuppression
Infections (e.g., *Vibrio*, *Candida*, *Salmonella*, *Campylobacter*, *Isospora*)
Major trauma
Mechanical ventilation
Medications (e.g., opiates, sunitinib (tyrosine-kinase inhibitor))
Multiple transfusions
Nonbiliary surgery
Sepsis/hypotension
Total parenteral nutrition
Vasculitis

Table 42.3 Ultrasonographic features suggestive of acalculous cholecystitis [37, 43–45]

Absence of gallstones or sludge
Thickening of the gallbladder wall >5 mm
Pericholecystic fluid
Positive Murphy's sign
Emphysematous cholecystitis with gas bubbles in the fundus (hampagne sign)
Frank perforation with abscess

Table 42.4 Reasons for false positive results on hepatobiliary scintigraphy in diagnosis of acalculous cholecystitis [37, 39, 41, 43–45]

Underlying liver disease: abnormal uptake and excretion of tracer
Fasting patients on TPN: gallbladder is maximally full due to inadequate contractions
Biliary sphincterotomy: preferential excretion of tracer into duodenum bypassing the gallbladder
Hyperbilirubinemia: impaired hepatic clearance of iminodiacetic acid compounds

Disturbances in the microcirculation of the gallbladder and release of specific mediators associated with tissue injury (Factor XII, prostaglandins) are also implicated [39]. Infection of the gallbladder with enteric organisms is probably secondary rather than a precipitating event [40].

Clinical Features

Acute acalculous cholecystitis carries a more progressive course compared to calculous cholecystitis. About half the patients have a complication such as gangrene, perforation, or empyema by the time the diagnosis is made. Unfortunately, the classic features of fever, right upper quadrant pain, Murphy's sign, and leukocytosis are less apparent in older adults. An elevated serum amylase or unexplained fever may be clues [41]. Abnormal liver function tests are more common in acalculous than calculous cholecystitis and include elevation of bilirubin, alkaline phosphatase, and transaminases. Up to 20% of patients develop jaundice secondary to extrinsic compression of the common bile duct from inflammation. Acalculous cholecystitis is a consideration in postoperative patients who develop jaundice [42]. Sepsis, peritonitis, and shock manifest in the setting of a complication. Due to the progressive nature of this disease and its occurrence in debilitated patients, mortality ranges from 10 to 50%, compared with a 1% mortality rate in calculous cholecystitis.

Diagnosis

Given the significant mortality in acalculous cholecystitis, timely diagnosis is important, with ultrasonography the mainstay radiologic modality for diagnosis [43–45]. Table 42.3 lists ultrasonographic features of acalculous cholecystitis; sensitivity rates for detecting acalculous cholecystitis are 67–92% and specificity rates >90% [44]. Sonographic Murphy's sign is operator-dependent and requires a cooperative patient.

The HIDA scan is employed if ultrasonography fails to provide a definitive diagnosis. False positive results occur for a number of reasons listed in Table 42.4. False negative tests can occur in acalculous disease since these patients do not have underlying cystic duct obstruction as a cause of the pathology; the gallbladder will fill despite presence of acalculous inflammation.

CT scanning detects gallbladder abnormalities suggestive of cholecystitis similar to ultrasonography. It can detect other intra-abdominal pathology that could account for the clinical manifestations if the gallbladder is normal. CT scanning has a disadvantage in that it is not portable to the bedside, especially for critically ill patients.

Treatment

Management includes prompt restoration of hemodynamic instability and use of antibiotics after blood cultures are obtained. Antibiotic therapy is directed towards enteric pathogens including *Bacteroides*, *Proteus*, *Pseudomonas*, *Enterococcus faecalis*, *E. coli,* and *Klebsiella* [45].

Cholecystectomy provides definitive therapy. Although a laparoscopic approach may be difficult due to inflammatory encasement, it is preferable in critically ill patients [37, 46]. Percutaneous cholecystosomy performed under radiologic guidance is advised in critically ill patients unfit for surgery. Complications from this intervention include peritonitis, catheter dislodgement, and

hepatic bleeding [47]. Definitive cholecystectomy is undertaken later when the patient is stable. Endoscopically placed nasocholecystostomy catheters are used in those unsuitable for percutaneous drainage (ascites, coagulopathy) [32].

Chronic Disorders

Chronic Cholecystitis

Chronic cholecystitis is a pathological term used to describe chronic inflammatory cell infiltration of the gallbladder seen in surgical specimens. It is believed to result from recurrent attacks of acute cholecystitis. However, this histopathologic finding does not necessarily correlate with symptoms [48]. The term chronic cholecystitis is at times used inappropriately for pain resulting from biliary dyskinesia.

Hyperplastic Cholecystoses and Adenomyomatosis

Hyperplastic cholecystoses are characterized by excessive proliferation of normal tissue components. Adenomyomatosis is a benign proliferation of the gallbladder surface epithelium with gland-like formations, extramural sinuses, transverse strictures, and/or fundal nodule formation.

Cholesterolosis and Gallbladder Polyps

Cholesterolosis occurs from abnormal deposition of lipid, and in particular, cholesteryl esters within macrophages in the lamina propria of the gallbladder wall. Gallbladder polyps occur in 5% of adults, predominantly in men. Cholecystectomy should be performed in symptomatic patients, those asymptomatic and over 50 years, polyps >10 mm in diameter or polyp growth on serial ultrasonography.

Gallbladder Cancer

Epidemiology

Gallbladder cancer is primarily a disease of the elderly. The National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Program data suggest that 75% of cases occur in the over 85-year-old age group [49]. Gallbladder cancer is the most common biliary tract cancer and is responsible for 4% of all cancer-related deaths. In the United States in 2009, 9,760 new cases of gallbladder cancer were diagnosed with 3,370 deaths [50]. Often, the diagnosis of gallbladder cancer is made late in its course. Gallbladder cancer spreads locally, with invasion to the liver, local lymph nodes, and peritoneal cavity. The 5-year survival rate for patient with locally advanced disease is approximately 42.5% and for distant disease is <1% [51].

Table 42.5 Risk factors for gallbladder cancer [49–51]

Native American, Hispanic, or Alaskan Native descent
Presence of gallstones
Gallstone size (stones >3 cm increase risk tenfold compared to stones <1 cm)
Porcelain gallbladder
Typhoid carriers
Gallbladder polyps
Obesity
Anomalous pancreatico-biliary junction or choledochal cyst
Carcinogens: nitosamine or azotoluene

Pathogenesis

Chronic inflammation is believed to play a central role in the development of gallbladder cancer. Risk factors are listed in Table 42.5. Gallstones are present in 70–90% of patients with gallbladder cancer. Despite the increased risk in patients with gallstones, the overall incidence of gallbladder cancer with cholelithiasis is only 0.5–3% [52]. The risk increases with larger gallstones. Gallstones may be a potential nidus for ongoing infection and inflammation. Abnormal pancreatico-biliary junctions (APBJ) are also implicated as a risk factor; a theory is that with the anatomic variant pancreatic juices may reflux into the bile duct leading to inflammatory reactions, biliary epithelial damage, and cyst formation.

Porcelin Gallbladder, a predisposition to gallbladder cancer, is characterized by intramural calcifications of the gallbladder wall. The lesion is usually asymptomatic and may be found incidentally on an abdominal X-ray or scan. Nonetheless, the finding has up to a 33% risk of gallbladder cancer. As such, porcelain gallbladder is an indication for prophylactic cholecystectomy.

Treatment

Adenocarcinoma accounts for 90% of gallbladder cancers, with the rest being squamous cell or other cancers. Treatment is dependent on presentation: malignancy suspected preoperatively because of symptoms, or malignancy diagnosed during cholecystectomy for presumed benign disease. Surgical management and chemotherapy for gallbladder cancer is best done through appropriate consultation.

Key Points

- The prevalence of gallstone disease increases with age.
- Gallbladder disease may be asymptomatic; symptomatic gallbladder disease includes acute cholecystitis, choledocolithiasis, ascending cholangitis, and acute pancreatitis.
- Older adults may not exhibit the classical manifestations of acute cholecystitis; prompt diagnosis and management helps minimize complications.
- Acalculous cholecystitis in the frail elderly is associated with significant mortality.
- Gallbladder cancer is primarily a disease of the elderly.

References

1. Schirmer BD, Winters KL, Edlich RF. Cholelithiasis and cholecystitis. J Long Term Eff Med Implants. 2005;15:329–38.
2. Ruhl CE, Everhart JE. Gallstone disease is associated with increased mortality in the United States. Gastroenterology. 2011;140:508–16.
3. Walcher T, Haenle MM, Mason RA. The effect of alcohol, tobacco and caffeine consumption and vegetarian diet on gallstone prevalence. Eur J Gastroenterol Hepatol. 2010;22:1345–51.
4. Unisa S, Jagannath P, Dhir V, Khandelwal C, Sarangi L, Roy TK. Population-based study to estimate prevalence and determine risk factors of gallbladder diseases in the rural Gangetic basin of North India. HPB (Oxford). 2011;13:117–25.
5. Pullinger CR, Eng C, Salen G. Human cholesterol 7α-hydroxylase (CYP7A1) deficiency has a hypercholesterolemic phenotype. J Clin Invest. 2002;110:109–17.
6. Rosmorduc O, Hermelin B, Poupon R. MDR3 gene defect in adults with symptomatic intrahepatic and gallbladder cholesterol cholelithiasis. Gastroenterology. 2001;120:1549–52.
7. Beuran M, Ivanov I, Venter MD. Gallstone ileus–clinical and therapeutic aspects. J Med Life. 2010;3:365–71.
8. Attili AF, De Santis A, Capri R, et al. The natural history of gallstones: the GREPCO experience. The GREPCO Group. Hepatology. 1995;21:655–60.
9. Thistle JL, Cleary PA, Lachin JM, Tyor MP, Hersh T. The natural history of cholelithiasis: the National Cooperative Gallstone Study. Ann Intern Med. 1984;101:171–5.
10. Cheng S, Chang Y, Liu C, et al. Factors associated with prolonged stay after laparoscopic cholecystectomy in elderly patients. Surg Endosc. 2008;22:1283–9.
11. Downing SR, Datoo G, Oyetunji TA, Fullum T, Chang DC, Ahuja N. Asian race/ethnicity as a risk factor for bile duct injury during cholecystectomy. Arch Surg. 2010;145:785–7.
12. Zorron R, Maggion LC, Pombo L. NOTES transvaginal cholecystectomy: preliminary clinical application. Surg Endosc. 2008;22:542–7.
13. May GR, Sutherland LR, Shaffer EA. Efficacy of bile acid therapy for gallstone dissolution—a meta-analysis of randomized trials. Aliment Pharmacol Ther. 1993;7:139–48.
14. Erichsen R, Froslev T, Lash TL, Pedersen L, Sorensen HT. Long-term statin use and the risk of gallstone disease: a population-based case-control study. Am J Epidemiol. 2010;173:162–70.
15. Indar AA, Beckingham IJ. Acute cholecystitis. BMJ. 2002;325:639–43.
16. Roslyn JJ, DenBesten L, Thompson Jr JE, Silverman BF. Roles of lithogenic bile and cystic duct occlusion in the pathogenesis of acute cholecystitis. Am J Surg. 1980;140:126–30.
17. Kaminski DL. Arachidonic acid metabolites in hepatobiliary physiology and disease. Gastroenterology. 1989;97:781–92.
18. Myers SI, Bartula L. Human cholecystitis is associated with increased gallbladder prostaglandin I2 and prostaglandin E2 synthesis. Hepatology. 1992;16:1176–9.
19. Cotton PB, Lehman G, Vennes J, et al. Endoscopic sphincterotomy complications and their management: an attempt at consensus. Gastrointest Endosc. 1991;37:383–93.
20. Rojas-Ortega S, Arizpe-Bravo D, Marin Lopez ER, Cesin-Sanchez R, Roman GR, Gomez C. Transcystic common bile duct exploration in the management of patients with choledocholithiasis. J Gastrointest Surg. 2003;7:492–6.
21. Parker LJ, Vukov LF, Wollan PC. Emergency department evaluation of geriatric patients with acute cholecystitis. Acad Emerg Med. 1997;4:51–5.
22. Adedeji OA, McAdam WA. Murphy's sign, acute cholecystitis and elderly people. J R Coll Surg Edinb. 1996;41:88–9.
23. Reiss R, Nudelman I, Gutman C, Deutsch AA. Changing trends in surgery for acute cholecystitis. World J Surg. 1990;14:567–71.
24. Mentzer Jr RM, Golden GT, Chandler JG, Horsley 3rd JS. A comparative appraisal of emphysematous cholecystitis. Am J Surg. 1975;129:10–5.
25. Sarmiento RV. Emphysematous cholecystitis. Report of four cases and review of the literature. Arch Surg. 1966;93:1009–14.
26. Trowbridge RL, Rutkowski NK, Shojania KG. Does this patient have acute cholecystitis? JAMA. 2003;289:80–6.
27. Kanafani ZA, Khalife N, Kanj SS. Antibiotic use in acute cholecystitis: practice patterns in the absence of evidence-based guidelines. J Infect. 2005;51:128.
28. Riall TS, Zhang D, Townsend CM, Kuo Y, Goodwin JS. Failure to perform cholecystectomy for acute cholecystitis in elderly patients is associated with increased morbidity, mortality, and cost. J Am Coll Surg. 2010;210:668–79.
29. Moyson J, Thill V, Simeons Ch, et al. Laparoscopic cholecystectomy for acute cholecystitis in the elderly: A retrospective study of 100 patients. Hepatogastroenterology. 2008;55:1975–80.
30. Ingraham AM, Cohen ME, Ko CY, Hall BL. A current profile and assessment of North American cholecystectomy: results from the American College of Surgeons National Surgical Quality Improvement Program. J Am Coll Surg. 2010;211:176–86.
31. Kuwabara K, Matsuda S, Ishikawa K, Horiguchi H, Fujimori K. Comparative quality of laparoscopic and open cholecystectomy in the elderly using propensity score matching analysis. Gastroenterol Res Pract. 2010;2010:490147.
32. Johlin Jr FC, Neil GA. Drainage of the gallbladder in patients with acute acalculous cholecystitis by transpapillary endoscopic cholecystotomy. Gastrointest Endosc. 1993;39:645–51.
33. Savoca PE, Longo WE, Zucker KA, McMillen MM, Modlin IM. The increasing prevalence of acalculous cholecystitis in outpatients. Results of a 7-year study. Ann Surg. 1990;211:433–7.
34. Wiboltt KS, Jeffrey Jr RB. Acalculous cholecystitis in patients undergoing bone marrow transplantation. Eur J Surg. 1997;163(7):519–24.
35. Nash JA, Cohen SA. Gallbladder and biliary tract disease in AIDS. Gastroenterol Clin North Am. 1997;26(2):323–35.
36. Kamimura T, Mimori A, Takeda A, et al. Acute acalculous cholecystitis in systemic lupus erythematosus: a case report and review of the literature. Lupus. 1998;7:361–3.
37. Kalliafas S, Ziegler DW, Flancbaum L, Choban PS. Acute acalculous cholecystitis: incidence, risk factors, diagnosis, and outcome. Am Surg. 1998;64:471–5.
38. Lee SP. Pathogenesis of biliary sludge. Hepatology. 1990;12(3 Pt 2):200S–5.
39. Barie PS, Eachempati SR. Acute acalculous cholecystitis. Gastroenterol Clin North Am. 2010;39:343–57.
40. Claesson BE. Microflora of the biliary tree and liver–clinical correlates. Dig Dis. 1986;4:93–118.

41. Cornwell 3rd EE, Rodriguez A, Mirvis SE, Shorr RM. Acute acalculous cholecystitis in critically injured patients. Preoperative diagnostic imaging Ann Surg. 1989;210:52–5.
42. Faust TW, Reddy KR. Postoperative jaundice. Clin Liver Dis. 2004;8:151–66.
43. Lameris JS, van Overhagen H. Imaging and intervention in patients with acute right upper quadrant disease. Baillieres Clin Gastroenterol. 1995;9:21–36.
44. Mirvis SE, Vainright JR, Nelson AW, et al. The diagnosis of acute acalculous cholecystitis: a comparison of sonography, scintigraphy, and CT. AJR Am J Roentgenol. 1986;147:1171–5.
45. Wang AJ, Wang TE, Lin CC, Lin SC, Shih SC. Clinical predictors of severe gallbladder complications in acute acalculous cholecystitis. World J Gastroenterol. 2003;9:2821–3.
46. Adams DB, Tarnasky PR, Hawes RH, et al. Outcome after laparoscopic cholecystectomy for chronic acalculous cholecystitis. Am Surg. 1998;64:1–6.
47. Spira RM, Nissan A, Zamir O, Cohen T, Fields SI, Freund HR. Percutaneous transhepatic cholecystostomy and delayed laparoscopic cholecystectomy in critically ill patients with acute calculus cholecystitis. Am J Surg. 2002;183:62–6.
48. Kalloo AN, Kantsevoy SV. Gallstones and biliary disease. Prim Care. 2001;28:591–606, vii.
49. Gloecker Ries LA, Reichman ME, Lewis DR. Cancer survival and incidence from the surveillance, epidemiology, and end results (SEER) program. Oncologist. 2003;8:541–52.
50. National Institute of Health: Gallbladder cancer. Available at http://www.cancer.gov/cancertopics/types/gallbladder/. Accessed May 2010.
51. Tsukada K, Kurosaki I, Uchida K, et al. Lymph node spread from carcinoma of the gallbladder. Cancer. 1997;80:661–7.
52. Williams CI, Shaffer EA. Gallstone disease: current therapeutic practice. Curr Treat Options Gastroenterol. 2008;11:71–7.

Acute Pancreatitis

43

C.S. Pitchumoni

Acute Pancreatitis

Introduction

Acute pancreatitis (AP) occurs in all ages and is increasing in incidence [1]. When older age itself is identified as an indicator of poor outcome, in most markers of prognosis, the epidemiological change is noteworthy [2–9]. Roughly 33% of the 200,000 patients admitted to hospitals in the US annually are over 65 years old [5]. Older age negatively influences outcome, either due to age-related decline in organ function and/or comorbid conditions [10–14]. Age over 70 alone carries a 19% risk of fatal outcome [14] and the risk increases further to 21% for those over 75 years [15–19].

AP represents a spectrum of diseases (a) ranging from a mild disease to a fatal form; (b) due to multiple etiological factors (Table 43.1), many readily detectable to obscure causes in the older adult (Table 43.2); and (c) affecting only the pancreas in its mildest form to multisystem disease. Longer life span and increasing prevalence of gallstones and obesity are contributory to the increased incidence of AP in the geriatric population, often in its severe form [5, 20]. Of the nearly 210,000 patients hospitalized in the US each year, 20% have severe AP (SAP) [21–24].

Definition of AP

AP is an acute inflammatory process of the pancreas characterized clinically by sudden onset of upper abdominal pain and biochemically by elevated serum levels of amylase and/or lipase. In mild AP, the mortality is less than 1% and in severe form it is 10% with sterile and 25% with infected pancreatic necrosis, respectively [23].

Two out of the three following features are required for the diagnosis of AP: abdominal pain, elevated levels of serum amylase and/or lipase at least three times the upper limit of normal, and characteristic findings of AP on computer tomography (CT) of the abdomen [24].

The widely quoted Atlanta Classification categorizes AP clinically as edematous (mild) or necrotizing by imaging studies [25]. A recent publication recommended a three-tier classification that includes an intermediate form or moderately severe AP [26]. A four-tier classification includes mild, moderate, severe, and critical AP [27]. The intermediate entity is associated with local complications, but no persistent organ failure [26]. A revision of the Atlanta Classification for better understanding of AP is under consideration [28] (Table 43.3).

Pathogenesis/Natural History

The pathogenesis involves premature intracinar activation of trypsinogen, a zymogen to trypsin, leading to necrosis that overwhelms the normal physiological protective mechanisms. Protective mechanisms include pancreatic secretory trypsin inhibitor (PSTI or SPINK1), mesotrypsin, enzyme Y, and trypsin itself, which splits and inactivates trypsin. Other protective nonspecific antiproteases are alpha-1-antitrypsin and alpha-2 macroglobulins in the pancreas. Normally, a small amount of trypsinogen may be prematurely activated to trypsin in the acinar cells, but inherent mechanisms protect the cell from necrosis. One of the cationic trypsinogen gene mutations well studied in the pathogenesis of hereditary pancreatitis alters the primary site for proteolytic activation [29, 30].

Once initiated, AP evolves in two stages. Stage one, which lasts about a week, is mostly functional; imaging studies may be normal. Multiple organ system failure in this stage is a result of systemic inflammatory response (SIRS) (Table 43.4), initiated by liberation of cytokines including platelet-activating factor, tumor necrosis factor (TNF-alpha), and various interleukins. Stage two may follow in about 10 days and is associated with morphologic changes resulting from pancreatic

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Table 43.1 Etiologic factors for acute pancreatitis (AP) in the older adult

Common
Gallstones
Alcohol
Drugs
Hypertriglyceridemia
Rare
Hypercalcemia
Obstruction of the ampulla of Vater, pancreatic adnocarcinoma, IPMN
Post-ERCP
Genetic
Pancreas divism
Trauma to abdomen
Viral (CMV, EBV, Mumps, Coxsackie B)
Parasitic (*Toxoplasma, Cryptosporidium, Ascaris, Clonorchis sinensis, Fasciola hepatica*)
Bacterial (Legionella)
Shock/ischemia/reperfusion injury (ICU pancreatitis)
Vasculitis
Duodenal diverticula
Choledochocele
Metastasis from primary tumor (lung, breast)
Abdominal and cardiac Surgery
Organophosphate poisoning
Idiopathic
Organ transplantation
Scorpion bite (in Trinidad)

Table 43.2 Obscure causes for acute pancreatitis (AP)

Microlithiasis
Ampullary tumors
Mucinous tumors of the pancreas (IPMN)
Undiagnosed chronic pancreatitis (early stages)
Anomalies of the pancreatic duct
Hereditary pancreatitis (initial episodes)
Sphincter of Oddi dysfunction
Choledochocele (type III choledochal cyst)
Annular pancreas
Anomalous pancreato-biliary junction
Duodenal diverticulum
Autoimmune (mostly chronic pancreatitis)

Even after completion of all tests, 15% of AP cases, an etiology is not identifiable

and/or peripancreatic necrosis and demonstrated in imaging studies. Nearly 80% of patients with AP improve without entering the second stage, while a small number may go on to a more protracted course lasting weeks to months [30]. The second peak of mortality is related to factors that include organ failure linked to pancreatic necrosis [30].

Table 43.3 Atlanta Classification of fluid collections, 1992 [25]

Acute fluid collection
Early in the course of AP
Lack of fibrous or granulation wall
Arise in or around pancreas
Pancreatic necrosis
Focal or diffiuse non viable pancreatc tissue
Usually associated with peripancreatic necrosis
Pancreatic abscess
Intra-abdominal collection of pus
Contains no or minimal pancreatic necrosis
Usually near the pancreas
Acute pseudocyst
Collection of pancreatic fluid
Enclosed by a fibrous wall or granulation tissue

Table 43.4 Systemic inflammatory response syndrome (SIRS) [24]

SIRS criteria
Temperature >38 or <36°C
Respiratory rate >20 breaths/minute or $PaCO_2$ <32 mmHg
Pulse >90 beats/minute
White blood cell count <4,000 cells/mm^3 or 12,000 cells/mm^3 or >10% immature bands

Note: SIRS is defined as the presence of 2 or more SIRS criteria

Epidemiology

Several observations have evolved pertinent to the epidemiology of AP in the geriatric age group. The overall apparent increase in the incidence of AP may be the result of an increased utility of serum pancreatic enzyme evaluations routinely in all emergency departments [18–20]. The incidence of AP ranges from 50 to 80 per 100,000 persons per year in the US [5] with a higher incidence in men [31, 32], reflecting the frequency of alcoholism in men [9]. As age advances, AP occurs increasingly: the incidence per 100,000 is <5–10, 10–30, and >20–30 in age groups <25 years, 25–60, and >60, respectively [32]. Several studies confirm that cigarette smoking increases the risk of both acute and chronic alcoholic pancreatitis [33, 34].

Gallstones as a cause of AP is observed in up to 55% of older patients [35]. In patients over 85 years, the incidence increases to 75% [36]. As a result of polypharmacy in older age, AP secondary to medications is a growing problem of undetermined frequency [37].

Etiological Factors

While AP results from multiple etiological factors, by itself, old age is not a risk factor. Gallstone disease is the most frequent cause of AP in the elderly. AP often occurs with small stones <5 mm in size since small stones pass easily

Table 43.5 Drug-induced pancreatitis in the older adult [37]

Medications implicated in acute pancreatitis in the elderly
Cardiovascular agents
Antihypertensives
ACE-I (Benzapril, captopril, enalapril, forinopril, lisinopril, moexipril, quinapril, ramipril, transolapril)
Diuretics (thiazide diuretics, loop diuretics, ethacrynic acid, furosemide)
Calcium channel blockers
Cholesterol-lowering agents
HMG-CoA reductase inhibitors [91] (fluvastatin, lovastatin, pravastatin, simvastatin,atorvastatin [92], rosuvastatin [92])
Fibrates (genfibrozil, fenofibrate)
Anti-platelets/thrombolytics
ASA, alteplase, anagrelide, dipyridamole, reteplase, streptokinase
Anti-srrhythmics
Smiodarone, mexiletine
Antibacterials [95]
Tetracyclines (doxycycline, demeclocycline, minocycline)
Macrolides (azithromycin, clarithromycin)
Quinolones (clatrofloxacin, ciprofloxacin, levofloxacin, norfloxacin, trovafloxacin)
Others (atovaquone, metronidazole [96], secnidazole [97], ertapenem, nitrofurantoin, trimethoprim/sulfamethoxazole, quinpristin/dalfopristin)
TNF-a inhibitors
Etanercept, infliximab
Anti-inflammatory agents
NSAIDS (diclofenac, ibuprofen, ketorolac, meloxicam, sulindac, mefenamic acid, nabumetone, naproxen, indomethacin [90], piroxicam)
COX-II inhibitors (celecoxib, rofecoxib)
Acetaminophen
Hypoglycemic agents
Incretin mimetic (exenatide) [93]
Glitazones (troglitazone, rosiglitazone, pioglitazone)
GI agents
PPIs (omeprazole, pantroprazole, rabeprazole)
Antacids (cimetidine, ranitidine)
IBD medications
Aminosalicylates (balsalazide, mesalamine, olsalazine, sulfasalazine)
Others (azathioprine [94], mercaptopurine)
Hormones
Steroids (cortisone, dexamethasone, fludrocortisone, methylprednisolone, prednisone)
Others (somatropin, octreotide)
Antineoplastic Drugs
L-asparaginase, 6-mercaptopurine, vincristine, vinblastine
Immunemodulators
Cyclosporine, glatiramer, interferon b-1B, interferon g-1B, mycophenolate, sirolimus, tacrolimus, thalidomide, PegInterferon a-2B

Table modified from Trivedi and Pitchumoni [37]

through the cystic duct to enter the common bile duct (CBD) and cause ampullary obstruction. In older adults, alcoholism is a less frequent cause of AP than in the younger age group. Alcoholism generally causes chronic pancreatitis, but some develop AP that does not progress to chronicity. Medications (diuretics, immunosuppressives, estrogens, and pain medications) (Table 43.5), metabolic disorders, surgical procedures, ischemia, and pancreatic tumors are other etiological factors. Prolonged fasting, total parenteral nutrition (TPN), and cephalosporin antibiotic therapy can cause microlithiasis.

Vasculitis, polyarteritis nodosa, cardiac surgery, transabdominal angiography, intraoperative shock, and hemorrhagic shock predispose to AP. In IBD, AP may occur due to the disease itself or result from medications used to treat the disease [38]. Ischemic pancreatitis may occur in clinical settings such as cardiopulmonary bypass, hemorrhagic shock, and organ transplantation. Hypercalcemia, both primary and secondary, is an unusual cause.

AP is the most common complication of ERCP, the incidence being 1.3–6.7%. Although the majority of patients with ERCP-induced pancreatitis have a mild disease course, a few develop severe AP [39]. ERCP, in general, has lost popularity solely as a diagnostic procedure.

Rarely, mild AP results from pancreatic cancer [40]. It is speculated that AP may be due to obstructed pancreatic ducts, local ischemia, or direct activation of pancreatic enzymes by neoplastic cells. When AP is the initial manifestation of pancreatic cancer, the diagnosis of cancer is delayed. Recognition of a potentially probable etiological factor such as a weak history of alcoholism, asymptomatic gallstone disease, or medication often causes pancreatic cancer to be overlooked. Intrapapillary mucin-producing tumor (IPMN) is a rare cause of AP. Metastatic tumors have been reported as a cause [41, 42].

The term "idiopathic" AP is used when recurrent AP occurs without a clear etiology despite a standard workup [43]. Biliary sludge, a viscous suspension in the gallbladder, may or may not be detected by routine abdominal ultrasound, suggesting that AP is idiopathic. The role of microlithiasis in causing idiopathic AP is quoted to vary from >60% in the earlier literature to less than 10% in the more recent publications. Elderly patients with an unknown etiology often present with more severe disease, higher mortality, and longer ICU stays [43]. Mutations of the cationic trypsinogen gene are known to cause recurrent AP which may appear idiopathic [44].

Diagnosis of Acute AP

1. Evaluation of abdominal pain

   The cardinal symptom of AP that leads to serum testing for amylase and/or lipase is the steady, boring upper abdominal pain radiating to back and chest and aggravated by food and associated with nausea and/or vomiting. Cognitive impairment, fear of a serious disease being diagnosed, or dulling of pain sensation either because of analgesic use for another cause or sensory impairment may impede the history and delay diagnosis.

Physical examination findings may also be atypical. Low-grade fever, tachycardia, abdominal tenderness, and muscular guarding are to be expected. Bowel sounds may be hypoactive because of ileus. Dyspnea may be prominent. Patients with severe AP may be pale, diaphoretic, and restless. Jaundice is infrequent but, when present, may indicate an impacted stone and, along with fever and shaking chills (Charcot's triad), may indicate cholangitis. Shock, unusual in early stages, and/or hypotension may be a sign of dehydration from blood loss (hemorrhagic pancreatitis) or albumin-rich fluid loss. In AP, accumulation of large quantities of fluid in the retroperitoneal space may occur from release of vasoactive kinins and active proteolytic enzymes into the circulation.

Many cardiac abnormalities may occur [45] (Table 43.6) that cause concern in older patients with comorbidity, cardiac arrhythmias being the most frequent. Abdominal tenderness, which is more objective than pain, can be influenced by lack of clear localization to the epigastric region. The differential diagnoses include ascending cholangitis, cholecystitis, choledocholithiasis, peptic ulcer, myocardial infarction, pancreatic cancer, bacterial pneumonia, and dissecting aneurysm. Cullen's sign (a bluish discoloration around the umbilicus) and Grey Turner's sign (blue–red–purple discoloration of flanks) are infrequent and nonspecific, but when present, are clearly markers of severity of AP. As a multisystem disease, AP in its severe form involves all organs (Table 43.7).

2. Laboratory Data

Blood tests help (a) establish the diagnosis of AP; (b) identify the etiological factor; and (c) assess the potential severity.

Elevated serum levels of amylase and/or lipase above 3 times the upper limit of normal are reliable indicators. One should be aware that serum levels of amylase or lipase neither indicate severity nor help in identifying the etiology of AP. In hypertriglyceridemic AP, the serum levels of amylase may be elevated only modestly or not at all. The determination of amylase activity is interfered with by severe hypertriglyceridemia. Once a diagnosis of AP is made, there is no indication to repeat the tests on a daily basis since the levels do not guide the course of the disease [45].

In clinical practice, there is no benefit in performing pancreatic isoenzyme levels. Further, there must be an awareness of spurious pancreatic enzyme elevations. There is growing evidence that false elevations of lipase are almost as frequent as those of amylase, and the often quoted specificity of lipase over amylase is questionable (Table 43.8).

Other laboratory tests help evaluate comorbid states, etiological factors (e.g., hypertriglyceridemia, hypercalcemia), and the severity of the disease. Hemoglobin, hematocrit, leukocyte and differential count, electrolytes, liver function tests, and BUN and creatinine are required in every patient. Repeating these tests in 24 h helps assess the prognosis of AP. Serum levels of AST, ALT, and ALP help in evaluating a biliary etiology.

Transient elevation of AST, ALT, and ALP can occur in biliary pancreatitis with a tendency to rapidly return to normal. Normal liver function tests do not totally exclude the possibility of a biliary etiology [46]. Fall in serum calcium and albumin levels in 48 h suggests severe AP. Hypocalcemia occurs in 25% of patients. Hyperglycemia in the absence of preexisting diabetes mellitus is a prognostic marker. A lipid profile is performed early in the course of pancreatitis. A triglyceride level of more than 1,000 mg/dL is seen in hyperlipidemic pancreatitis. Other markers of severity include elevated creatinine, BUN, and a quantitative CRP performed within 48 h (Table 43.9).

About 25% of patients overall and a larger number of older patients have hypoxemia. The decision to request

Table 43.6 Cardiac manifestations of (AP) [45]

Hemodynamic changes
Tachycardia
Low total peripheral resistance
Increased cardiac index
Hypovolemia
Decreased left ventricular stroke volume
Myocardial depression
Cardiac regional wall motion abnormalities
Impaired diastolic function
Decreased peak blood flow velocity
Electrocardiographic changes
Ventricular fibrillation
Bradycardia
Atrial flutter
Atrial fibrillation
Supraventricular premature contractions, ventricular ectopic arrhythmias
QRS prolongation
QT prolongation
Shortened PQ interval
Left bundle branch block
Right bundle branch block
Left anterior hemi-block
Nonspecific changes in repolarization
Decreased T-wave voltage
T-wave changes
ST-segment depression
ST-segment elevation
Pericardial changes
Pericardial effusion
Chylous pericardial effusion with tamponade
Fibrinous constrictive pericarditis

Table modified from Yegneswaran et al. [45]

Table 43.7 Complications of acute pancreatitis (AP) [45]

Systemic complications
Pulmonary
Early arterial hypoxia
Atelectasis, pneumonia, pleural effusion, and mediastinal abscess
Acute respiratory distress syndrome
Cardiac: shock, pericardial effusion, EKG changes, arrhythmias, SIRS
Hematologic: disseminated intravascular coagulation, thrombotic thrombocytopenic purpura/hemolytic uremic syndrome
Gastrointestinal: gastrointestinal bleeding (portal-splenic vein thrombosis, colonic infarction)
Renal: azotemia, oliguria
Metobolic: hyperkalemia, hypocalcemia, hypophosphatemia, hyperglycemia, hypertriglyceridemia, acidosis, elevation of free fatty acids, hypoalbuminemia
Central nervous system: psychosis, pancreatic encephalopathy, Purtscher-like retinopathy
Peripheral: fat necrosis (skin and bones), arthritis
Rhabdomyolysis
Pancreatic/peripancreatic complications
Acute fluid collection
Necrosis, sterile and infected
Pseudocyst
Infected pseudocyst/abscess
Local extrapancreatic complications
Involvement of contiguous organs (intraperitoneal hemorrhage, gastrointestinal bleeding, thrombosis of splenic vein, bowel infarction)
Obstructive jaundice
Colonic involvement (necrosis, stricture)
Abdominal compartment syndrome

Table 43.8 Conditions associated with elevation of serum amylase and/or lipase in the older adult

With abdominal pain	Without abdominal pain
Pancreatic causes	Malignancies of
Acute pancreatitis	Lung
Chronic pancreatitis (acute exacerbation)	Ovary
Trauma	Pancreas
Abdominal surgery	Colon
Intervention (ERCP)	Thymus
Nonpancreatic abdominal causes	Bone marrow
Mesenteric infarction	Breast
Intestinal obstruction	Tongue
Appendicitis	Esophagus
Systemic disorders (abdominal pain due to a nonpancreatic cause)	Stomach
Diabetic ketoacidosis	Small bowel
	Liver
	Other causes
	Renal failure
	Liver failure
	Shock
	ARDS
	Postburn
	Cardiac surgery
	Pneumonia
	Benign hyperlipasemia/ Hyperamylasemia

Table 43.9 Single markers of severity and comments [12, 26, 48, 49]

Obesity: BMI >30 is a poor prognostic marker
Ecchymosis (Cullen and Grey Turner signs); both signs are very rare
Admission hemoconcentration >44%: (lack of hemoconcentration denotes milder pancreatitis)
Failure to correct hemoconcentration to <44% within 24 h of hospitalization: suggests the need for early and adequate intravenous hydration
Serum creatinine >2 mg/dL on admission and failure to decline below 2 mg/dL with adequate fluid administration is a marker of volume depletion
Fasting blood glucose >125 mg/dL (in nondiabetics)
C-reactive protein >150 mg/L at 48 h after admission
Fall in serum calcium, albumin
CT scan of abdomen: not necessary in most, but is a good marker when used appropriately

arterial blood gas evaluation is a clinical one. Electrocardiographic abnormalities are interpreted based on the patient's prior history of cardiac disease as well as the awareness that AP has its own cardiovascular manifestations (Table 43.6) [45]. A chest X-ray, KUB radiograph, and abdominal sonogram to evaluate the gallbladder and biliary tree are required at admission (see algorithm, Fig. 43.1).

Severity Assessment

The window of opportunity to prevent organ system dysfunction early in the course of AP is very narrow [47]. The severity of AP can be determined by (a) any one of the multiple scoring criteria, (b) single markers of prognosis, and (c) by imaging studies. Since Ranson's initial report, a number of prognostic criteria have been developed utilizing clinical features, laboratory tests, imaging studies, and more complex approaches. In addition, a number of easily detectable single markers are identified in predicting the prognosis (Table 43.9). AP is not always just mild or severe since it is a dynamic process [26, 48]. Early identification of severity is important from the standpoint of transferring the patient to the ICU, assessing prognosis, and setting thresholds for specific interventions (vasopressors, ventilatory assistance, dialysis, therapeutic interventions). The measurement of parameters of SIRS on the first hospital day may provide important information required to assess severity [49].

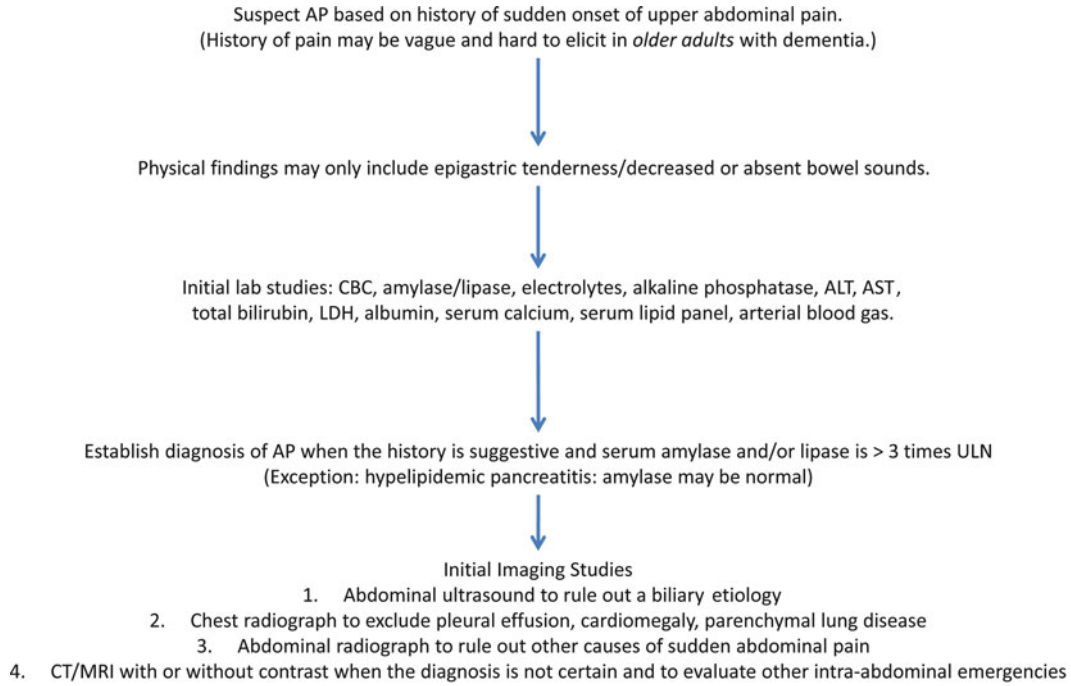

Fig 43.1 Initial evaluation and assessment of severity of acute pancreatitis (AP) [24, 35, 54]

This is particularly important in the older adult with AP who is vulnerable to organ system dysfunction.

1. Scoring Criteria
   Ranson's score (Table 43.10) is the most popular but has many limitations. Most hospitals do not perform all the 11 factors needed in the evaluation on days 1 and 2. However, presence of three or more factors indicates a higher risk for serious illness [50]. Another deficiency of the system is that scoring can be completed only after 48 h, delaying the crucial period of management.

   The APACHE II severity of disease classification is an excellent criterion, that includes a number of physiologic variables, age points, and chronic health points which can all be measured at admission or daily. Calculating APACHE II requires access to web-based calculators and all data that may not be available in many patients outside of the ICU. Death rates are less than 4% with scores <8 and 11–18% with scores of 8 or higher [24]. A score that increases in the first 48 h strongly predicts severe AP, and conversely, a score that decreases indicates mild disease. Ranson's and APACHE II scoring systems overscore elderly patients because older age is associated with more points [10].

   BISAP score (Table 43.11), proposed by Wu et al. [51], uses basic clinical and simple laboratory parameters available within hours of admission. The five-point scoring system uses blood urea nitrogen >25 mg/dL, impaired mental status, SIRS, age >60 years, and pleural effusion. Presence of three or more of the above factors correlates with a higher risk of death, organ failure, and pancreatic necrosis [52].

Table 43.10 Ranson's criteria [3]

	Nongallstone pancreatitis (1974)	Gallstone pancreatitis (1982)
At admission		
Age	>55 years	>70 years
White blood cell count	>16,000/μL	>18,000/μL
Serum glucose	>200 mg/dL	>220 mg/dL
Serum LDH	>350 IU/L	>400 IU/L
Serum AST	>250 IU/L	>250 IU/L
48 h after admission		
Fall in hematocrit	>10%	>10%
Fluid sequestration	>6 L	>4 L
Hypocalcemia	<8.0 mg/dL	<8.0 mg/dL
Hypoxemia	PO_2 <60 mmHg	PO_2 <60 mmHg
Increase in BUN after fluid hydration	>5 mg/dL	>2 mg/dL
Base deficit	>4 mEq/L	>5 mEq/L

2. Single Markers of Severity
   Many single markers of severity help to determine the prognosis (Table 43.9). Obesity, pleural effusion, and ecchymoses are features of severe AP. Hemoconcentration on admission, failure to correct hemoconcentration within

Table 43.11 Scoring system for Bedside Index of Severity in Acute Pancreatitis (BISAP) [98]

Score one point for each of the following criteria:
Blood urea nitrogen level >8.9 mmol/L
Impaired mental status
Systemic inflammatory response syndrome is present
Age >60 years
Pleural effusion on radiography

A score of more than three indicates an increased risk of death

Table 43.12 CT Severity Index [53, 54, 99]

CT grade	Points
A. Normal pancreas	0
B. Edematous pancreatitis	1
C. B plus mild extrapancreatic changes	2
D. Severe extrapancreatic changes including one fluid collection	3
E. Multiple or extensive extrapancreatic collections	4
Necrosis	
None	0
Less than one third	2
Greater than one third or less than one half	4
Greater than one half	6

24 h, elevated BUN, a creatinine level that does not decline with hydration, and falling serum calcium are easily identifiable laboratory abnormalities. Another serum marker is CRP, but its discriminating value is poor in the first 2 days after onset. Inflammatory markers IL-6, IL-8, TNF-alpha, PMN elastase, trypsinogen activation peptide, and procalcitonin are elevated in severe AP, but are not yet routine tests.

3. Imaging Studies

Radiological scoring systems correlate with clinical scores. Balthazar score based on CT examination of the abdomen is a good example. However, not all patients require CT soon after admission to evaluate the severity. A noncontrast-enhanced CT may provide information for severity assessment. When a contrast-enhanced CT is performed, another scoring system (CT severity index) can be used. This index assigns patients on the basis of CT grades (A–E) (Table 43.12) and the amount of necrosis (none, <30, 30–50, and >50%). Pancreatic necrosis is associated with a higher morbidity/mortality compared to edematous interstitial pancreatitis [53, 54]. MRI is comparable in the early assessment of AP. MRI/MRCP has an advantage over CT in detecting choledocholithiasis [55] CT scan changes may not be prominent in the first 48 h after onset of AP. Although pancreatic necrosis and pancreatic fluid collections are indicative of severe pancreatitis, many of these patients may not develop organ failure or infection [24, 56–58].

Abdominal film may be normal in AP, but dilated small bowel loops (sentinel loop) or "colon cut-off" sign are not pathognomonic of AP. Gallstones suggest an etiology for AP, and pancreatic calculi indicate chronic pancreatitis. The presence of pleural effusions indicate severity of AP and may identify cardiopulmonary problems. ARDS may be seen in severe AP.

An abdominal ultrasound is an essential early imaging study required in all patients to detect gallstones, rule out acute cholecystitis, and to identify a dilated CBD. EUS, MRCP, and/or endoscopic sphincterotomy and stone extraction may be needed based on ultrasound findings.

Computed tomography is not needed in the initial evaluation of a patient with AP when signs and symptoms are minimal. However, when the diagnosis is in doubt as it can be in the older adult, a CT, with or without contrast, may yield useful findings and help to exclude catastrophic intra-abdominal conditions. A CECT, if performed 72 h after the onset of the disease, is likely to show morphological changes. In interstitial pancreatitis, there is homogenous enhancement. CECT identifies areas of necrosis as well. When infected necrosis is suspected, fine needle aspiration helps to aspirate the necrotic material and perform a Gram stain and culture. CT also helps to identify fluid collection, splenic vein thrombosis, and splenic artery aneurysm.

Magnetic resonance imaging is a useful procedure to assess severity of AP and evaluate the CBD and CBD stones. Gadolinium, used as the contrast material for MRCP, is, however, not safe in patients with renal failure because of the potential complication of nephrogenic systemic sclerosis.

Differential Diagnosis

The differential diagnosis of AP includes peptic ulcer, gallstone disease, intestinal ischemia, dissecting aneurysm, mesenteric vascular occlusion, and myocardial infarction. Evaluation should be directed to exclude these causes, with the selection of tests based on the characteristic findings on presentation.

Management of AP

The principles of initial management of uncomplicated AP are straightforward. Almost all patients are kept NPO (non per os or nothing by mouth) to provide "rest to the pancreas;" appropriate management of pain and adequate hydration are also the mainstay of treatment. Routine use of nasogastric tube to keep the stomach empty is not necessary.

High rates of early readmission may occur after hospitalization for AP. Factors that promote readmission include: not performing a cholecystectomy during the initial hospital admission, continued alcoholism and cigarette smoking [59], discharge on less than a solid diet, and discharge with gastrointestinal symptoms [60].

1. Fluid Resuscitation
   Adequate early IV fluid resuscitation is the most important step in the initial management of AP [61, 62] to improve pancreatic microcirculation. Aggressive early fluid resuscitation assists in preventing the pathologic response of proinflammatory cytokines and vasoactive mediators, factors known to increase capillary permeability, vasospasm, and microthrombi. Considerations are paid to the rate, volume, and type of fluid [24, 56]. Pandol et al. [63] recommend that patients with severe volume depletion be started on 500–1,000 mL/h. Aggressive monitoring and reassessment of fluid needs at frequent intervals, as often as 1–2 h, are needed [63, 64]. In-hospital mortality was less in patients who received greater than one third of their initial 72 h fluid requirements within the first 24 h of hospitalization [62]. As a rough guide, patients with severe AP may require 5–10 L of fluid (200–400 mL/h) such as isotonic saline for the first few days [30].

   Aggressive fluid administration in the older adult is a clinical skill especially when the patient has comorbid conditions such as congestive cardiac or renal failure. Admission to ICU (or a step-down unit) for a day or two during the initial period is appropriate in the elderly with cardiac, pulmonary, or renal disease.
2. Pain Management
   When considering pain medications in the elderly, the agents should be based on knowledge of the metabolism of the drug, side effects, and toxicity. Meperidine is a drug that was once popular and is effective but has gone out of favor. Pharmacodynamic changes associated with aging result in a high risk for neurological adverse events including seizures. The metabolite of meperidine, normeperidine, accumulates with impaired renal function, causing the adverse effects. Alternative analgesics with less toxicity are preferred. Morphine, contrary to the older notion, neither increases biliary sphincter pressure nor worsens AP [65]. Nonnarcotic analgesics are an option.
3. Rest to the Pancreas
   In mild AP, oral feedings can be restored early within 3–7 days of hospitalization. Oral intake is encouraged, started early based on clinical improvement characterized by absence of pain, nausea and vomiting, and abdominal tenderness. Oral feeding with a diet rich in carbohydrates and proteins and low in fat (<30% of total energy intake) is preferred. Early oral feeding in mild AP is safe and may even accelerate recovery [66, 67]. There is no indication for proton pump inhibitors as a routine.
4. Enteral Nutrition
   The proposed mechanism of better clinical outcome with enteral nutrition is based on studies which have shown preservation of normal gut barrier function, thereby protecting against bacterial translocation [68]. The current recommendation is to initiate enteral nutrition in those with mild AP unless severe paralytic ileus is present [69]. Enteral nutrition is cheaper and does not cause metabolic or major complications such as line sepsis, which in turn may lead to fungal infection in AP. In the past, the preferred mode was TPN in severe AP. Emphasis has shifted to enteral nutrition by placing a nasojejunal tube. Tube feeding with peptide-based formulae is recommended [70]. In severe AP, a combination of enteral nutrition and TPN may be needed in early stages when enteral nutrition alone cannot provide adequate nutritional support. The placement of the tip of the tube in the jejunum avoids stimulation of duodenal hormones CCK and secretin and thereby pancreatic secretion [71–76]. Enteral nutrition initiated early, in comparison to TPN, results in a marked reduction in the risk of multiorgan system failure, infectious complications, and mortality [77, 78].

   Various formulations have been used for enteral nutrition. There is no recommendation for routine use of glutamine-rich "immunoenhancing" enteral formulas or probiotics at this time [79].
5. Prophylactic Antibiotic Therapy
   This is a controversial subject. The overwhelming opinion is not in favor of administering prophylactic antibiotics, even for sterile-necrotizing pancreatitis [24]. There is certainly no indication for antibiotics in patients with interstitial pancreatitis. The practice guidelines of ACG suggest that those with pancreatic necrosis who appear septic with leukocytosis, fever, or organ failure are candidates for antibiotic therapy, while an evaluation for a source of infection is in progress. If blood cultures and fine needle aspiration of necrotic area are negative for organisms, the recommendation is to discontinue antibiotics. Predisposition to gram positive and fungal sepsis is a complication of prophylactic antibiotic therapy [24, 80]. The studies that guide practice guidelines are not based solely on older adults and hence may have to be tailored to individual patient requirements. A recent guideline recommends the use of carbapenems, when indicated, at a dose of 1,500 mg/day for at least 14 days [66].
6. ERCP/EUS
   Endoscopic retrograde cholangiopancreatography (ERCP) is reserved only for those with dilated ducts, impacted stone, and in those associated with cholangitis or severe AP. Urgent ERCP sphincterotomy with stone extraction and/or stenting should be performed if cholangitis is suspected. ERCP is indicated to clear bile duct stones and in those who are poor candidates for cholecystectomy. Diagnostic ERCP must be definitely avoided. ERCP and sphincterotomy in the older adult with severe biliary AP are considerations.

   EUS is a noninvasive imaging modality to diagnose CBD stones and has the advantage of the imaging procedure being followed by ERCP and stone extraction if needed in the same sedation setting. MRCP is preferable when the

index of suspicion for a CBD stone is small. Claustrophobia, especially in the older adult, is a problem with MRCP. The overall sensitivity and specificity of MRCP to detect CBD stones are 94 and 98%, respectively [81–83].

7. Surgical Options in Acute Pancreatitis
   (a) Cholecystectomy
   In biliary AP, laparascopic cholecystectomy should be considered after recovery from an attack of AP during the same admission [66, 84]. In severe AP, cholecystectomy should be delayed until there is clinical recovery. Failure to perform cholecystectomy during the same admission is associated with a 25–30% chance for recurrence of AP [85].
   (b) Necrotizing AP
   Patients with sterile necrosis should be managed conservatively. Surgery is only rarely indicated, such as in multiorgan failure with failure of conservative therapy [86]. Surgery earlier than 14 days after the onset of AP is not recommended. Necrosectomy is the surgical procedure in infected pancreatic necrosis. Debridement of infected tissue is generally accomplished by open surgery, but endoscopic or percutaneous approaches are options [87].
   (c) Abdominal compartment syndrome
   Abdominal compartment syndrome (ACS) is associated with intra-abdominal hypertension (IAH) and noted to have a higher mortality, morbidity, and prolonged hospital stay. ACS is a recognized cause of multiple organ dysfunction in AP.

   IAH is defined as a sustained or repeated pathologic elevation of the intra-abdominal pressure (IAP) above 12 mmHg. ACS is described as the sustained elevation of IAP above 20 mmHg in combination with newly developed organ dysfunction. The typical symptoms of ACS in patients with AP include rapidly evolving multiple organ dysfunction syndrome (MODS), respiratory distress, hemodynamic compromise, and acute renal failure [88]. Early surgical decompression is associated with reduced mortality. Both subcutaneous fasciotomy and ultrasound-guided drainage of intra-abdominal and/or peripancreatic fluid collections seem to be safe and effective alternatives in the management of ACS [87, 89].
   (d) Pancreatic pseudocysts
   Not all pseudocysts require intervention. Pseudocysts which are symptomatic, expand on serial imaging studies, cause obstruction of adjacent organs such as duodenum or bile duct, or are infected require intervention, which may be endoscopic, percutaneous, or surgical [28].
   (e) Pancreatic abscess
   Surgical and percutaneous drainage are options, but surgical drainage should be performed immediately if percutaneous drainage fails [66].

Key Points

- Acute pancreatitis (AP) in the older adult results often from gallstones (sludge/microlithiasis) and less often from chronic alcoholism. Medications, neoplasms, and hyperlipidemia are other causes.
- Worldwide incidence of AP is increasing, really a result of routine serum amylase/lipase testing and increase in the prevalence of gallstone disease.
- Two out of three of the following are needed to diagnose AP: typical history of epigastric pain, elevation of serum levels of amylase/lipase >3 times the upper limit of normal, and CT changes. In the older adult; a history of abdominal pain may be difficult to obtain.
- An abdominal ultrasound helps diagnose a biliary etiology and to measure the CBD size to help determine management options.
- Abdominal CT examination with contrast is not needed in most cases initially. Early CT is essential when diagnosis is uncertain.
- Ranson's, APACHE II, Glasgow, SOFA, and BISAP scores and other single prognostic markers help to predict the severity of AP.
- There are two peaks of severity; the first peak occurs in the first few days when morphological changes are not noted (imaging studies may be normal).
- The second peak of severity occurs after the second week when complications such as pancreatic necrosis, sterile or infected, occur, resulting in multiorgan system dysfunction. Morphological changes on CECT are seen.
- Multiorgan dysfunction may be cardiac, pulmonary, renal, or metabolic.
- Initial management of AP warrants adequate intravenous hydration, NPO, and pain control. Meperidine is generally avoided in the elderly because of neuropsychiatric adverse effects.
- In patients with severe AP who need prolonged nutritional support, enteral feeding is preferred to parenteral nutrition.
- Surgical indications in AP include cholecystectomy (in the same admission), abdominal compartment syndrome, and infected necrosis.

References

1. Fagenholz PJ, Castillo CF, Harris NS, et al. Increasing United States hospital admissions for acute pancreatitis, 1988–2003. Ann Epidemiol. 2007;17(7):491–7.
2. Ranson JH, Rifkind KM, Roses DF, et al. Prognostic signs and the role of operative management in acute pancreatitis. Surg Gynecol Obstet. 1974;139(1):69–81.
3. Papachristou GI, Muddana V, Yadav D, et al. Comparison of BISAP, Ranson's, APACHE-II, and CTSI scores in predicting organ failure, complications, and mortality in acute pancreatitis. Am J Gastroenterol. 2010;105(2):435–41; quiz 42.

4. Rau B. Clinical assessment and biochemical markers to objectify severity and prognosis. In: Beger HG, Warshaw AL, Büchler MW, Kozarek RA, Lerch MM, Neoptolemos LP, Shirator KI, Whitcomb DC, Rau BM, editors. The pancreas: an integrated textbook of basic science, medicine, and surgery. 2nd ed. Oxford: Blackwell; 2009. p. 242–54.
5. Martin SP, Ulrich II CD. Pancreatic disease in the elderly. Clin Geriatr Med. 1999;15(3):579–605.
6. Taylor SL, Morgan DL, Denson KD, et al. A comparison of the Ranson, Glasgow, and APACHE II scoring systems to a multiple organ system score in predicting patient outcome in pancreatitis. Am J Surg. 2005;189(2):219–22.
7. Imrie CW, Benjamin IS, Ferguson JC, et al. A single-centre double-blind trial of Trasylol therapy in primary acute pancreatitis. Br J Surg. 1978;65(5):337–41.
8. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med. 1985;13(10):818–29.
9. Yadav D, Eigenbrodt ML, Briggs MJ, et al. Pancreatitis: prevalence and risk factors among male veterans in a detoxification program. Pancreas. 2007;34(4):390–8.
10. Uomo G. Inflammatory pancreatic diseases in older patients: recognition and management. Drugs Aging. 2003;20(1):59–70.
11. Uomo G, Talamini G, Rabitti PG, et al. Influence of advanced age and related comorbidity on the course and outcome of acute pancreatitis. Ital J Gastroenterol Hepatol. 1998;30(6):616–21.
12. Pitchumoni CS, Patel NM, Shah P. Factors influencing mortality in acute pancreatitis: can we alter them? J Clin Gastroenterol. 2005;39(9):798–814.
13. Fan ST, Choi TK, Lai CS, Wong J. Influence of age on the mortality from acute pancreatitis. Br J Surg. 1988;75(5):463–6.
14. Buscaglia JM, Kapoor S, Jagannath SB, et al. Disparities in demographics among patients with pancreatitis-related mortality. JOP. 2009;10(2):174–80.
15. Gardner TB, Vege SS, Chari ST, et al. The effect of age on hospital outcomes in severe acute pancreatitis. Pancreatology. 2008;8(3): 265–70.
16. Wig JD, Bharathy KG, Kochhar R, et al. Correlates of organ failure in severe acute pancreatitis. JOP. 2009;10(3):271–5.
17. Lowenfels AB, Maisonneuve P, Sullivan T. The changing character of acute pancreatitis: epidemiology, etiology, and prognosis. Curr Gastroenterol Rep. 2009;11(2):97–103.
18. Lindkvist B, Appelros S, Manjer J, Borgstrom A. Trends in incidence of acute pancreatitis in a Swedish population: is there really an increase? Clin Gastroenterol Hepatol. 2004;2(9): 831–7.
19. Yadav D, Ng B, Saul M, Kennard ED. Relationship of serum pancreatic enzyme testing trends with the diagnosis of acute pancreatitis. Pancreas. 2011;40(3):383–9.
20. Yadav D, Lowenfels AB. Trends in the epidemiology of the first attack of acute pancreatitis: a systematic review. Pancreas. 2006;33(4):323–30.
21. Russo MW, Wei JT, Thiny MT, et al. Digestive and liver diseases statistics, 2004. Gastroenterology. 2004;126(5):1448–53.
22. Gravante G, Garcea G, Ong SL, et al. Prediction of mortality in acute pancreatitis: a systematic review of the published evidence. Pancreatology. 2009;9(5):601–14.
23. Swaroop VS, Chari ST, Clain JE. Severe acute pancreatitis. JAMA. 2004;291(23):2865–8.
24. Banks PA, Freeman ML. Practice guidelines in acute pancreatitis. Am J Gastroenterol. 2006;101(10):2379–400.
25. Bradley III EL. A clinically based classification system for acute pancreatitis. Summary of the International Symposium on Acute Pancreatitis, Atlanta, GA, September 11 through 13, 1992. Arch Surg. 1993;128(5):586–90.
26. Vege SS, Gardner TB, Chari ST, et al. Low mortality and high morbidity in severe acute pancreatitis without organ failure: a case for revising the Atlanta classification to include "moderately severe acute pancreatitis". Am J Gastroenterol. 2009;104(3):710–5.
27. Petrov MS, Windsor JA. Classification of the severity of acute pancreatitis: how many categories make sense? Am J Gastroenterol. 2010;105(1):74–6.
28. Bollen TL, Santvort HC van, Besselink MGH et al. The Atlanta Classification of acute pancreatitis revisited. Brit J Surgery. 2007; 95(1):6–21.
29. Whitcomb DC, Gorry MC, Preston RA, et al. Hereditary pancreatitis is caused by a mutation in the cationic trypsinogen gene. Nat Genet. 1996;14(2):141–5.
30. Tenner S, Steinberg WM. Acute pancreatitis. In: Feldman M, Friedman LS, Brandt LJ, editors. Sleisenger and Fordtran's gastrointestinal and liver disease. Philadelphia: Elsevier; 2010. p. 959–76.
31. Lowenfels AB, Maisonneuve P. Epidemiologic and etiologic factors of pancreatic cancer. Hematol Oncol Clin North Am. 2002;16(1):1–16.
32. Vege SS, Yadav D, Chari ST. Pancreatitis. In: Talley NJ, Loke III GR, Saito YA, editors. GI epidemiology. 2007th ed. Oxford: Blackwell; 2007. p. 221–30.
33. Yadav D. Recent advances in the epidemiology of alcoholic pancreatitis. Curr Gastroenterol Rep. 2011;13(2):157–65.
34. Lindkvist B, Appelros S, Manjer J, et al. A prospective cohort study of smoking in acute pancreatitis. Pancreatology. 2008;8(1): 63–70.
35. Banks PA. Pancreatic disease in the elderly. Semin Gastrointest Dis. 1994;5(4):189–96.
36. Gloor B, Ahmed Z, Uhl W, Buchler MW. Pancreatic disease in the elderly. Best Pract Res Clin Gastroenterol. 2002;16(1):159–70.
37. Trivedi CD, Pitchumoni CS. Drug-induced pancreatitis: an update. J Clin Gastroenterol. 2005;39(8):709–16.
38. Pitchumoni CS, Rubin A, Das K. Pancreatitis in inflammatory bowel diseases. J Clin Gastroenterol. 2010;44(4):246–53.
39. Vege SS, Chari ST, Petersen BT, et al. Endoscopic retrograde cholangiopancreatography-induced severe acute pancreatitis. Pancreatology. 2006;6(6):527–30.
40. Mujica VR, Barkin JS, Go VL. Acute pancreatitis secondary to pancreatic carcinoma. Study group participants. Pancreas. 2000;21(4):329–32.
41. Blechacz B, Gores GJ. Tumors of the bile ducts, gallbladder, and ampulla. In: Feldman M, Friedman LS, Brandt LJ, editors. Sleisenger and Fordtran's gastrointestinal and liver disease. Philadelphia: Elsevier; 2010. p. 1171–83.
42. Stockland A, Baron TH. Endoscopic and radiologic treatment of biliary disease. In: Feldman M, Friedman LS, Brandt LJ, editors. Sleisenger and Fordtran's gastrointestinal and liver disease. Philadelphia: Elsevier; 2010. p. 1185–97.
43. Browder W, Patterson MD, Thompson JL, Walters DN. Acute pancreatitis of unknown etiology in the elderly. Ann Surg. 1993;217(5):469–74; discussion 74–5.
44. Whitcomb DC, Yadav D, Adam S, et al. Multicenter approach to recurrent acute and chronic pancreatitis in the United States: the North American Pancreatitis Study 2 (NAPS2). Pancreatology. 2008;8(4–5):520–31.
45. Yegneswaran B, Kostis JB. Pitchumoni CS. Cardiovascular manifestations of acute pancreatitis. J Crit Care. 2011;26(2):225e11–8. Epub 2010 Dec 23.
46. Dholakia K, Pitchumoni CS, Agarwal N. How often are liver function tests normal in acute biliary pancreatitis? J Clin Gastroenterol. 2004;38(1):81–3.
47. Chauhan S, Forsmark CE. The difficulty in predicting outcome in acute pancreatitis. Am J Gastroenterol. 2010;105(2):443–5.

48. Talukdar R, Vege SS. Classification of the severity of acute pancreatitis. Am J Gastroenterol. 2011;106(6):1169–70.
49. Singh VK, Wu BU, Bollen TL, et al. Early systemic inflammatory response syndrome is associated with severe acute pancreatitis. Clin Gastroenterol Hepatol. 2009;7(11):1247–51.
50. Stevens T, Parsi MA, Walsh RM. Acute pancreatitis: problems in adherence to guidelines. Cleve Clin J Med. 2009;76(12): 697–704.
51. Wu BU, Johannes RS, Sun X, et al. The early prediction of mortality in acute pancreatitis: a large population-based study. Gut. 2008;57(12):1698–703.
52. Singh VK, Wu BU, Bollen TL, et al. A prospective evaluation of the bedside index for severity in acute pancreatitis score in assessing mortality and intermediate markers of severity in acute pancreatitis. Am J Gastroenterol. 2009;104(4):966–71.
53. Balthazar EJ, Freeny PC, van Sonnenberg E. Imaging and intervention in acute pancreatitis. Radiology. 1994;193(2):297–306.
54. Balthazar EJ. Acute pancreatitis: assessment of severity with clinical and CT evaluation. Radiology. 2002;223(3):603–13.
55. Stimac D, Miletic D, Radic M, et al. The role of nonenhanced magnetic resonance imaging in the early assessment of acute pancreatitis. Am J Gastroenterol. 2007;102(5):997–1004.
56. Forsmark CE, Baillie J. AGA Institute technical review on acute pancreatitis. Gastroenterology. 2007;132(5):2022–44.
57. Mofidi R, Suttie SA, Patil PV, et al. The value of procalcitonin at predicting the severity of acute pancreatitis and development of infected pancreatic necrosis: systematic review. Surgery. 2009;146(1):72–81.
58. Rau B, Steinbach G, Baumgart K, et al. The clinical value of procalcitonin in the prediction of infected necrosis in acute pancreatitis. Intensive Care Med. 2000;26 Suppl 2:S159–64.
59. Yadav D, Hawes RH, Brand RE, et al. Alcohol consumption, cigarette smoking, and the risk of recurrent acute and chronic pancreatitis. Arch Intern Med. 2009;169(11):1035–45.
60. Whitlock TL, Repas K, Tignor A, et al. Early readmission in acute pancreatitis: incidence and risk factors. Am J Gastroenterol. 2010;105(11):2492–7.
61. Gardner TB, Vege SS, Pearson RK, Chari ST. Fluid resuscitation in acute pancreatitis. Clin Gastroenterol Hepatol. 2008;6(10): 1070–6.
62. Gardner TB, Vege SS, Chari ST, et al. Faster rate of initial fluid resuscitation in severe acute pancreatitis diminishes in-hospital mortality. Pancreatology. 2009;9(6):770–6.
63. Pandol SJ, Saluja AK, Imrie CW, Banks PA. Acute pancreatitis: bench to the bedside. Gastroenterology. 2007;132(3):1127–51.
64. Vege SS, Baron TH. Management of pancreatic necrosis in severe acute pancreatitis. Clin Gastroenterol Hepatol. 2005;3(2):192–6.
65. Chutka DS, Takahashi PY, Hoel RW. Inappropriate medications for elderly patients. Mayo Clin Proc. 2004;79(1):122–39.
66. Pezzilli R, Zerbi A, Di Carlo V, Bassi C, et al. Practical guidelines for acute pancreatitis. Pancreatology. 2010;10(5):523–35.
67. Sathiaraj E, Murthy S, Mansard MJ, et al. Clinical trial: oral feeding with a soft diet compared with clear liquid diet as initial meal in mild acute pancreatitis. Aliment Pharmacol Ther. 2008;28(6): 777–81.
68. Schwarz M, Thomsen J, Meyer H, et al. Frequency and time course of pancreatic and extrapancreatic bacterial infection in experimental acute pancreatitis in rats. Surgery. 2000;127(4):427–32.
69. Davies AR, Morrison SS, Ridley EJ, et al. Nutritional therapy in patients with acute pancreatitis requiring critical care unit management: a prospective observational study in Australia and New Zealand. Crit Care Med. 2011;39(3):462–8.
70. Meier R, Ockenga J, Pertkiewicz M, et al. ESPEN guidelines on enteral nutrition: pancreas. Clin Nutr. 2006;25(2):275–84.
71. Meier R, Beglinger C, Layer P, et al. ESPEN guidelines on nutrition in acute pancreatitis. European Society of Parenteral and Enteral Nutrition. Clin Nutr. 2002;21(2):173–83.
72. Mayumi T, Takada T, Kawarada Y, et al. Management strategy for acute pancreatitis in the JPN Guidelines. J Hepatobiliary Pancreat Surg. 2006;13(1):61–7.
73. Working Party of the British Society of Gastroenterology; Association of Surgeons of Great Britain and Ireland; Pancreatic Society of Great Britain and Ireland; Association of Upper GI Surgeons of Great Britain and Ireland. UK guidelines for the management of acute pancreatitis. Gut. 2005;54 Suppl 3:iii1–9.
74. Bank S, Singh P, Pooran N, Stark B. Evaluation of factors that have reduced mortality from acute pancreatitis over the past 20 years. J Clin Gastroenterol. 2002;35(1):50–60.
75. Greenwood JK, Lovelace HY, McClave SA. Enteral nutrition in acute pancreatitis: a survey of practices in canadian intensive care units. Nutr Clin Pract. 2004;19(1):31–6.
76. Heinrich S, Schafer M, Rousson V, Clavien PA. Evidence-based treatment of acute pancreatitis: a look at established paradigms. Ann Surg. 2006;243(2):154–68.
77. Hegazi R, Raina A, Graham T, et al. Early jejunal feeding initiation and clinical outcomes in patients with severe acute pancreatitis. JPEN J Parenter Enteral Nutr. 2011;35(1):91–6.
78. Cao Y, Xu Y, Lu T, et al. Meta-analysis of enteral nutrition versus total parenteral nutrition in patients with severe acute pancreatitis. Ann Nutr Metab. 2008;53(3–4):268–75.
79. Nathens AB, Curtis JR, Beale RJ, et al. Management of the critically ill patient with severe acute pancreatitis. Crit Care Med. 2004;32(12):2524–36.
80. Gotzinger P, Wamser P, Barlan M, et al. Candida infection of local necrosis in severe acute pancreatitis is associated with increased mortality. Shock. 2000;14(3):320–3; discussion 3–4.
81. Makary MA, Duncan MD, Harmon JW, et al. The role of magnetic resonance cholangiography in the management of patients with gallstone pancreatitis. Ann Surg. 2005;241(1):119–24.
82. Romagnuolo J, Bardou M, Rahme E, et al. Magnetic resonance cholangiopancreatography: a meta-analysis of test performance in suspected biliary disease. Ann Intern Med. 2003;139(7):547–57.
83. Howard TJ. As good as it gets: the study of prophylactic antibiotics in severe acute pancreatitis. Ann Surg. 2007;245(5):684–5.
84. Kimura Y, Takada T, Kawarada Y, et al. JPN Guidelines for the management of acute pancreatitis: treatment of gallstone-induced acute pancreatitis. J Hepatobiliary Pancreat Surg. 2006;13(1):56–60.
85. Hernandez V, Pascual I, Almela P, et al. Recurrence of acute gallstone pancreatitis and relationship with cholecystectomy or endoscopic sphincterotomy. Am J Gastroenterol. 2004;99(12): 2417–23.
86. Uhl W, Warshaw A, Imrie C, et al. IAP guidelines for the surgical management of acute pancreatitis. Pancreatology. 2002;2(6):565–73.
87. Mentula P, Hienonen P, Kemppainen E, et al. Surgical decompression for abdominal compartment syndrome in severe acute pancreatitis. Arch Surg. 2010;145(8):764–9.
88. De Waele JJ. Abdominal compartment syndrome in severe acute pancreatitis—when to decompress? Eur J Trauma Emerg Surg. 2008;34(1):11–6.
89. Dambrauskas Z, Parseliunas A, Maleckas A, et al. Interventional and surgical management of abdominal compartment syndrome in severe acute pancreatitis. Medicina (Kaunas). 2010;46(4):249–55.
90. Memis D, Akalin E, Yucel T. Indomethacin-induced pancreatitis: a case report. JOP. 2005;6(4):344–7.
91. Singh S. Drug induced pancreatitis might be a class effect of statin drugs. JOP. 2005;6(4):380; author reply 1.
92. Singh S, Nautiyal A, Dolan JG. Recurrent acute pancreatitis possibly induced by atorvastatin and rosuvastatin. Is statin induced pancreatitis a class effect? JOP. 2004;5(6):502–4.
93. Garg R, Chen W, Pendergrass M. Acute pancreatitis in type 2 diabetes treated with exenatide or sitagliptin: a retrospective observational pharmacy claims analysis. Diabetes Care. 2010;33(11): 2349–54.

94. Weersma RK, Batstra MR, Kleibeuker JH, van Dullemen HM. Are pancreatic autoantibodies associated with azathioprine-induced pancreatitis in Crohn's disease? JOP. 2008;9(3):283–9.
95. Noor MT, Radhakrishna Y, Kochhar R, et al. Bacteriology of infection in severe acute pancreatitis. JOP. 2011;12(1):19–25.
96. Nigwekar SU, Casey KJ. Metronidazole-induced pancreatitis. A case report and review of literature. JOP. 2004;5(6):516–9.
97. Slim R, Ben Salem C. Secnidazole-induced acute pancreatitis: a new side-effect for an old drug? JOP. 2010;11(1):85–6.
98. Wu BU. Prognosis in acute pancreatitis. CMAJ. 2011;183(6):673–7.
99. Ranson JH, Balthazar E, Caccavale R, Cooper M. Computed tomography and the prediction of pancreatic abscess in acute pancreatitis. Ann Surg. 1985;201(5):656–65.

Chronic Pancreatitis

44

Gaurav Aggarwal and Suresh T. Chari

Chronic Pancreatitis

Introduction

Chronic pancreatitis is characterized by chronic inflammation and fibrosis of the pancreas resulting in impaired exocrine and endocrine function [1]. In true acute pancreatitis, there is restitution of the gland to structural and functional normalcy after an acute attack, characterized by acute abdominal pain, elevated serum amylase/lipase, and morphological changes on imaging. In chronic pancreatitis, patients often experience attacks of clinical acute pancreatitis, but in contrast to true acute pancreatitis there is progressive structural and functional damage to the pancreas despite clinical recovery from the attacks. Despite the differences in the two entities, an emerging body of literature suggests that some patients with (recurrent) acute pancreatitis may progress to chronic pancreatitis [1].

Epidemiology

In the United States, pancreatitis was listed as the "first-listed diagnosis" in 72,000 hospital discharges and 101,000 ambulatory visits for patients aged ≥65 years in 2004 [2]. A survey in Japan revealed the prevalence of chronic pancreatitis in men between 65 and 69 years of age to be 115 per 100,000 population and in women aged 75–79 years to be 39.6 per 100,000 population [3]. A prospective survey of gastroenterologists in France yielded a crude prevalence of 26 per 100,000 and estimated that about 20% of chronic pancreatitis cases occurred in the over 65 year age group [4].

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Effects of Aging on the Pancreas

Studies of changes on exocrine pancreatic function with aging yield conflicting data. Early studies showed a 10–30% reduction in the volume, bicarbonate, and lipase in pancreatic juice in elderly patients [5]. In contrast, there was no difference in secretin stimulated pancreatic secretion between 25 older subjects and 30 young controls [6]. Experience with secretin stimulation tests over 10 years did not show a decrease in bicarbonate secretion with age [5]. These contradictory data may be due to differences in methodology and inadvertent inclusion of asymptomatic pancreatic disease. Regardless, even if there was some age related decline (10–30%), this would not be clinically relevant, since >90% of the pancreas has to be damaged to cause clinically evident exocrine insufficiency [7].

In contrast to the effects of age on function, marked changes in pancreatic structure occur with aging. Autopsy series reveal duct proliferation, lobular degeneration, and fatty infiltration [5, 8, 9]. Pancreatic lithiasis ranges from being absent in those <70 years to being present in 16% of patients >90 years [10]. Pancreatic lithiasis was found in the peripheral ducts upstream from sites of squamous metaplasia, was asymptomatic and was not associated with alcoholism or hypercalcemia [10]. Extensive parenchymal atrophy and fibrosis was also seen in areas upstream from the stones. Postmortem pancreatography performed by physicians trained in endoscopic retrograde cholangiopancreatography (ERCP) found ductal changes similar to those seen in chronic pancreatitis in 81% of older adults [11, 12]. However, histopathology in the same cases confirmed the findings to be age-related and not due to chronic pancreatitis [11]. The suggested ERCP criteria for the diagnosis of chronic pancreatitis in the elderly are summarized in Table 44.1 [12, 13].

Age-related pancreatic changes are also seen on endoscopic ultrasonography (EUS). In a prospective study of 120 patients without pancreatic disease, 39% patients >60 years had at least one EUS abnormality of chronic pancreatitis [14]. In this study, the presence of >3 EUS abnormalities,

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Table 44.1 ERCP criteria for diagnosis of chronic pancreatitis in the elderly (Adapted from Gloor et al. [12], Jones et al. [13])

Ductal obstruction and stricture
Gross irregularity of the main pancreatic duct
Presence of large cavities (>5 mm) (due to prestenotic ductal dilation)

ductal or parenchymal stones, ductal narrowing or dilation were more likely to represent disease than age-related changes [14]. Thus, caution should be exercised when interpreting ERCP and EUS findings in the geriatric patient.

Risk Factors

Idiopathic Chronic Pancreatitis

Most chronic pancreatitis with onset in the old are due to "late-onset" idiopathic disease, originally described as "senile" chronic pancreatitis by Amman et al. and characterized by an age of onset of 56 years, absence of pain, and early development of structural (diffuse calcifications) and functional (exocrine and endocrine) abnormalities [15, 16]. This is in contrast to "early-onset" idiopathic disease with a mean age of onset of 20 years, presence of pain and longer delay to the development of pancreatic abnormalities [16, 17].

Obstructive Pancreatitis

Obstruction of the main pancreatic duct (e.g., by an ampullary malignancy or cancer in the pancreatic head) can be an important cause in the elderly patient with new-onset chronic pancreatitis [12, 18]. This form of chronic pancreatitis differs from other varieties in the absence of calcifications and higher prevalence of a dilated pancreatic duct [18].

Alcoholic Chronic Pancreatitis

In the general population, alcohol is the most common cause of chronic pancreatitis, accounting for 70–80% cases; however in patients with onset of pancreatitis after the age of 65, alcohol is an exceedingly uncommon cause [19]. The risk increases with increasing dose (>4 drinks/day) and duration (>10 years) of alcohol consumption [20]. While alcohol appears to play an important role in the development of chronic pancreatitis, only 5–15% of alcoholics develop the disease, suggesting a role for cofactors such as genetics, tobacco, etc. [20].

Tobacco

While smoking is an independent risk factor for chronic pancreatitis, the damage to the pancreas is compounded by ongoing alcohol use [21].

Recurrent Acute Pancreatitis

Approximately 1 out of every 5 patients with acute alcoholic pancreatitis progresses to chronic pancreatitis [22].

Other Causes

- *Hereditary pancreatitis* is an uncommon cause of chronic pancreatitis. While mutations in the cationic trypsinogen gene (PRSS1) are most commonly associated with chronic pancreatitis, mutated cystic fibrosis gene (CFTR) and trypsin inhibitor (SPINK1) genes are being increasingly identified in patients with idiopathic chronic pancreatitis [23, 24].
- *Autoimmune pancreatitis (AIP)*: This entity is discussed in a separate section.
- *Tropical pancreatitis*: Although the life expectancy of patients with tropical pancreatitis has considerably improved, it is not yet a geriatric problem. The entity is common in southern India and is characterized by onset at young age, severe malnutrition, diabetes mellitus, and pancreatic calculi.

In summary, the etiology of chronic pancreatitis may be attributed to a complex interplay of environmental and genetic factors. The former include alcohol, tobacco and occupational chemicals, while the genetic factors include mutations in trypsin-controlling or cystic fibrosis genes [25].

Clinical Presentation

Abdominal pain, an uncommon symptom in late-onset idiopathic chronic pancreatitis, is often a major complaint in alcoholic chronic pancreatitis [12, 16]. The typical pain is epigastric, postprandial, radiates to the back, and is relieved by sitting up or leaning forward.

Pancreatic exocrine insufficiency is often the presenting symptom in patients with late-onset idiopathic chronic pancreatitis [16]. While protein and carbohydrate malabsorption might occur in advanced pancreatic insufficiency, they are generally less pronounced than fat malabsorption due to intact salivary amylase and brush border peptidases in most patients. Most patients with exocrine insufficiency present with greasy, foul-smelling stools (steatorrhea). Patients might also present with weight loss, malnutrition, fat-soluble vitamin deficiencies (Vitamin A, D, E, and K) and vitamin B12 deficiency (due to noncleavage of R-factor from vitamin B12, dependent on pancreatic function).

Endocrine pancreatic insufficiency ranges from mild to severe insulin-requiring diabetes.

Diagnosis

No single diagnostic test is adequately sensitive or specific for chronic pancreatitis in all patients. Age-related structural changes in the older adult may make the diagnosis even more difficult. A suggested diagnostic algorithm for chronic pancreatitis is outlined in Fig. 44.1.

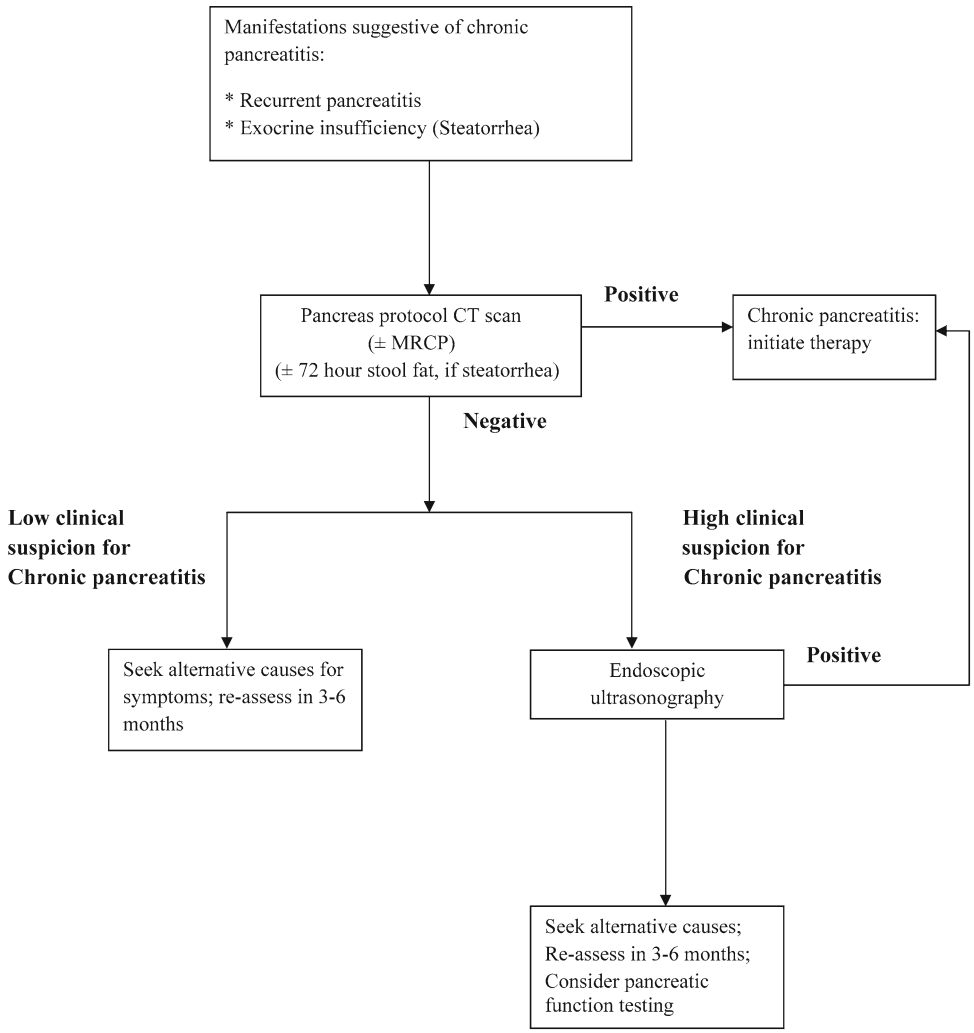

Fig. 44.1 Diagnostic algorithm for suspected chronic pancreatitis (Adapted from Etemad et al. [24])

Tests of function

- *Amylase and lipase levels*: Amylase and lipase levels are generally normal (due to fibrosis) and are not useful in the diagnosis of chronic pancreatitis.
- *Stool fat quantitation*: A 72-h fecal fat quantitation is useful in patients with steatorrhea. Patients with pancreatic insufficiency typically excrete >10–14 g of fat. Since exocrine pancreatic insufficiency develops only when <10% secretory capacity remains, this test is not useful in the diagnosis of early disease [7]. Further, the test is cumbersome in the elderly.
- *Stool elastase and chymotrypsin*: These tests are a measure of the secretion of elastase and chymotrypsin by the pancreas on random stool samples [26]. However, they provide yield only in the presence of steatorrhea, obviating their utility in the diagnosis of early disease [27].
- *Hormonal stimulation tests*: They measure pancreatic secretory capacity by collecting pancreatic fluid following stimulation with a secretagogue (e.g., secretin). Hormonal stimulation tests are considered the most sensitive tests (70–90%) for chronic pancreatitis [28]. While they detect early disease, there is a risk of complications from invasive endoscopic procedures [29].

Tests of structure

- *Plain radiography*: Diffuse calcifications in the pancreatic duct are very specific for chronic pancreatitis and often seen in elderly smokers with late-onset idiopathic disease [30] (Fig. 44.2).
- *Ultrasonography (USG)*: Transabdominal ultrasound has limited utility in evaluation of the pancreas due to interference by bowel gas and body fat [31].
- *Computed tomography (CT)*: CT has the advantage of adequate imaging regardless of body habitus, but carries risk of radiation exposure. However, the higher sensitivity (80–90%) and specificity (85%) for diagnosis of chronic pancreatitis justify its widespread use [32].
- *Magnetic resonance cholangiopancreatography (MRCP)*: MRCP is increasingly becoming the preferred test in the diagnosis of chronic pancreatitis since it can detect ductal

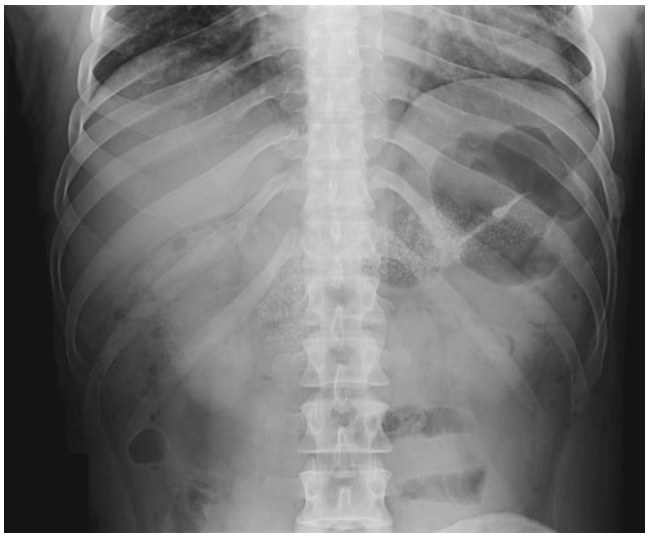

Fig. 44.2 Abdominal plain film in a patient with chronic pancreatitis with diffuse calcifications in the pancreas

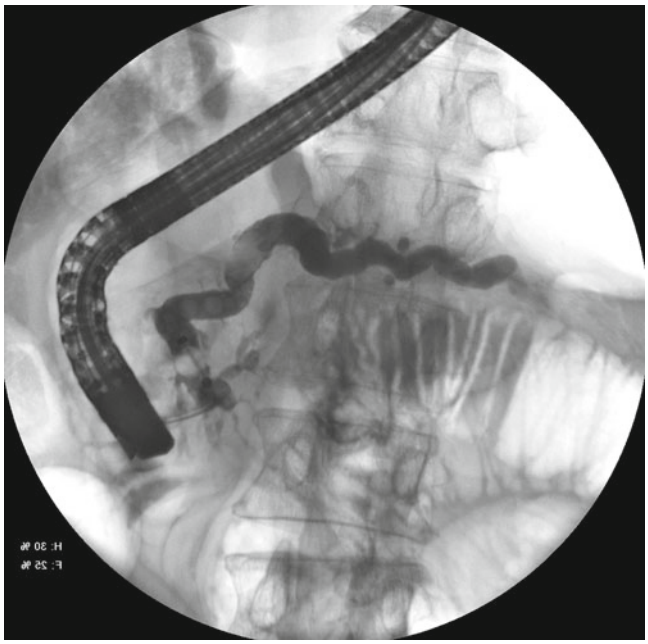

Fig. 44.3 Endoscopic retrograde cholangiopancreatography showing classic changes of chronic pancreatitis in an elderly patient (grossly irregular and dilated main pancreatic duct, dilated side branches, filling defects and stone in the main pancreatic duct)

abnormalities with a similar frequency to ERCP and avoids the risks associated with ERCP [33, 34].

- *Endoscopic retrograde cholangiopancreatography (ERCP)*: ERCP has the highest sensitivity (70–90%) and specificity (80–100%) for the diagnosis of chronic pancreatitis but carries a risk of complications [33]. As discussed earlier, ERCP findings of chronic pancreatitis in the older patient (Fig. 44.3) can be confounded by age-related changes in the normal pancreas [35, 36].
- *Endoscopic ultrasound (EUS)*: EUS criteria for diagnosis of chronic pancreatitis include ductal abnormalities (dilation, irregularity, calcification, etc.) and parenchymal abnormalities (cysts, hyperechoic foci, lobularity, etc.) [36, 37] (Fig. 44.4a, b, c) Besides aging, alcohol, smoking, and acute pancreatitis can all cause EUS abnormalities in the absence of chronic pancreatitis [14, 38]. EUS diagnosis is, therefore, heavily dependent on operator experience.

As chronic pancreatitis is a complex disease, EUS-based criteria for diagnosis have differed widely. A consensus study has established major and minor EUS based criteria for chronic pancreatitis in the "Rosemont Classification" [39]. Further, EUS may be complemented by digital imaging analysis and functional testing; EUS may also be used for celiac plexus blockade and ductal access techniques [40].

Treatment

Therapy for chronic pancreatitis is centered on the management of symptoms.

Abdominal Pain

Lifestyle modifications including abstinence from alcohol and cessation of smoking are associated with a reduction in pain [41]. Supplemental antioxidants (selenium, vitamin A, vitamin C, and vitamin E) have a modest effect on reducing pain [42]. However, most patients require some form of analgesia for pain control. When prescribing analgesics in the elderly, the strategy is to begin with nonnarcotic analgesics followed by low-potency opioids (e.g., tramadol) and finally higher-potency narcotics. The goal is to reduce pain to a manageable level and not complete alleviation. Since chronic pain can lead to depression which in turn exacerbates pain, there is a role for adjunct therapy such as antidepressants. Pancreatic enzymes help reduce pain only in small duct disease, women and those with idiopathic chronic pancreatitis [43]. Patients with worsening abdominal pain require evaluation for complications such as pseudocysts, cancer, stricture, etc.

Since the celiac plexus transmits nociceptive impulses from the pancreas to the spinal cord, blocking these signals (percutaneously, endoscopically, or surgically) can help treat pain in chronic pancreatitis. While EUS guided celiac plexus block (injecting steroids) is safer and more cost-effective than CT guided techniques, the pain relief is temporary. [44] A study of 90 patients showed pain relief in 55% at 4 weeks but by 24 weeks only 10% reported sustained benefit [45]. EUS guided celiac plexus block might be useful in the elderly since pain relief was more evident in those over age 45 years in the previously mentioned study, although its precise role is still evolving [45]. In patients with large duct disease and

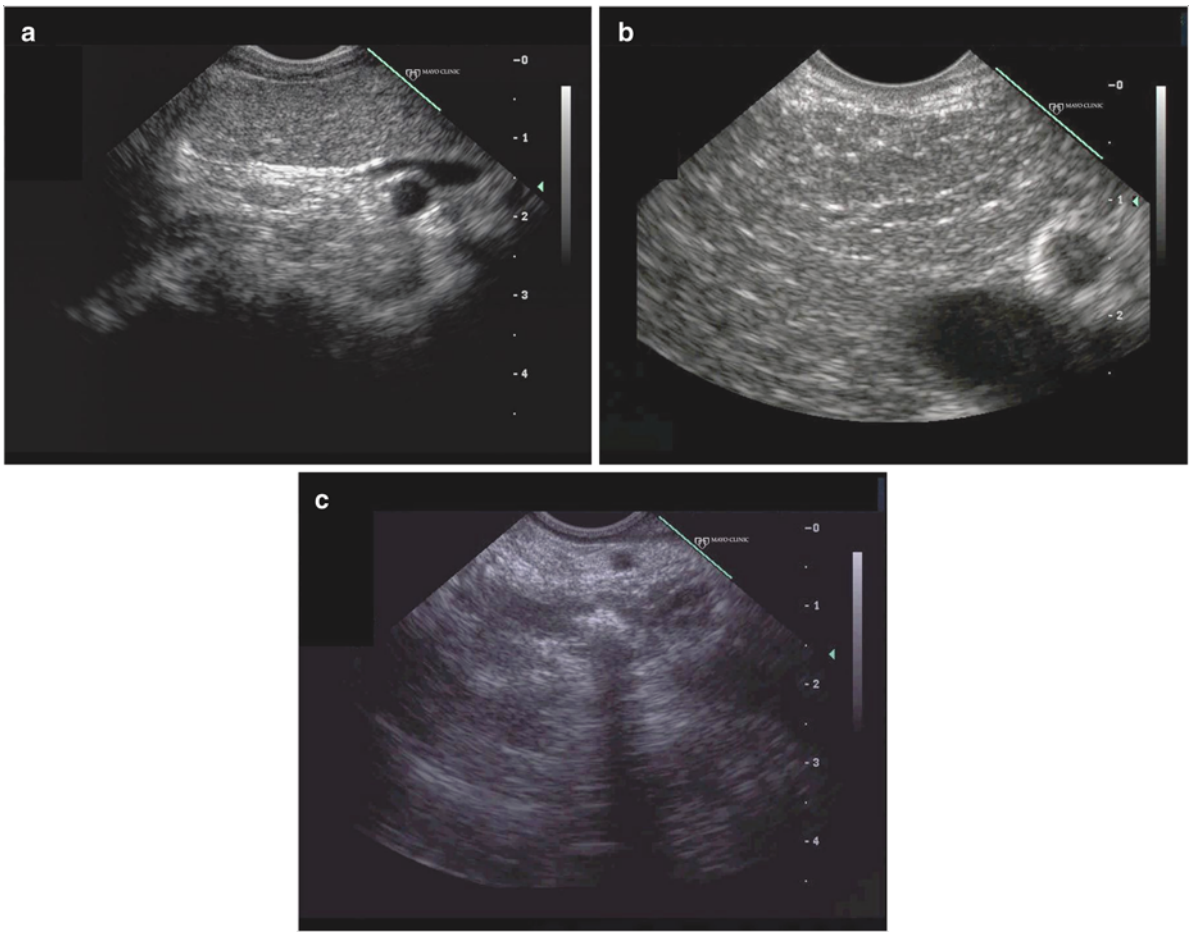

Fig. 44.4 EUS findings in chronic pancreatitis (Courtesy: Dr. Michael J. Levy, Mayo Clinic, Rochester, MN). (**a**) Normal pancreas. (**b**) Hyperechoic foci. (**c**) Dilated main pancreatic duct, intraductal calculus

evidence of pancreatic ductal obstruction (strictures or stones), endoscopic therapy with a pancreatic sphincterotomy with or without pancreatic stenting might be useful [46]. Surgical intervention with ductal drainage or pancreatic resection is reserved for medically refractory disease, suspected malignancy, and complications such as pseudocysts [47].

Steatorrhea

The mainstay of treatment for pancreatic steatorrhea is pancreatic enzyme supplementation. Lipase (30,000–50,000 IU) spread over each meal is generally adequate [28]. A smaller amount is required with snacks. If a non-enteric-coated formulation is selected, concomitant acid suppression (e.g., proton pump inhibitor or H_2 blocker) is necessary. In addition, fat-soluble vitamins should be replaced in patients with steatorrhea. In patients who do not respond, dietary restriction of fat to less than 20 g per day may help relief of steatorrhea, but prevents weight gain. Bacterial overgrowth may complicate steatorrhea and require treatment. Medium chain triglycerides (MCTs), which do not need lipase for absorption, are rarely required to treat pancreatic steatorrhea [28].

Diabetes Mellitus

Diabetes in chronic pancreatitis is usually insulin requiring. In addition, there is increased risk of hypoglycemia due to loss of glucagon secreting alpha cells.

Complications and approach to management are listed in Table 44.2.

Autoimmune Pancreatitis

AIP is a rare autoimmune disorder that is subclassified into two types, based on distinct pathological and clinical profiles [52]. Type 1 or lymphoplasmacytic sclerosing pancreatitis is characterized by infiltration of the pancreas by IgG4 positive plasma cells (Fig. 44.5a, b) and typically affects elderly men. Over 80% of patients with type 1 AIP are males, with >80% over age 50 [52]. Type 1 disease is also associated with a higher relapse rate as well as extrapancreatic involvement. In contrast, type 2 or idiopathic duct centric pancreatitis is characterized by a granulocytic epithelial lesion (GEL) with minimal IgG4 positive cells and affects younger patients

Table 44.2 Complications of chronic pancreatitis [48–51]

Complication	Cause	Presentation	Diagnosis	Treatment
Pseudocyst	Ductal disruption	Abdominal pain Bleeding Bowel/biliary obstruction Ascites (from disruption)	Imaging with USG, CT, MRI, EUS	No treatment, if asymptomatic Drainage, if symptomatic, enlarging or complicated
Biliary/duodenal obstruction	Inflammation or fibrosis in the head leading to compression	Jaundice Nausea, vomiting, abdominal pain	CT MRCP EGD	Surgical bypass or endoscopic stenting
Pancreatic fistulae and ascites	Ductal disruption, pseudocyst rupture	Abdominal pain Ascites	High amylase on paracentesis	TPN, NPO, octreotide Endoscopic stenting Surgery
Splenic vein thrombosis	Contiguous inflammation	Gastrointestinal bleeding from gastric varices	EGD USG with Doppler CT	No treatment if asymptomatic Endoscopic glue for bleeding Splenectomy is curative
Pseudoaneurysm	Enzymatic digestion of arterial wall	Bleeding	Urgent EGD CT Angiography	Angiographic embolization Surgery, if embolization fails
Pancreatic cancer	Highest risk in active smokers	No specific symptoms Abdominal pain, weight loss, jaundice	CA19-9 CT EUS	Surgery, if resectable

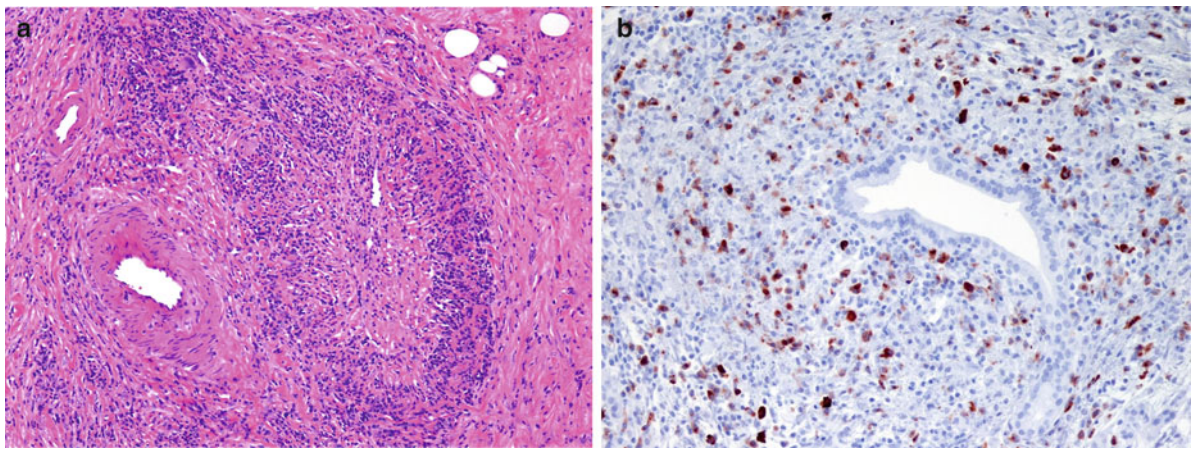

Fig. 44.5 Histopathololologic findings of autoimmune pancreatitis type I. (**a**) H & E stain shows lymphoplasmacytic infiltrate and storiform fibrosis surrounding a vein (obliterative phlebitis). (**b**) IgG4 immunostain shows diffuse increase in IgG4 in the gland

(affecting males and females equally). Type 2 disease rarely relapses or manifests with extrapancreatic disease but is associated with inflammatory bowel disease in 20–30% cases [52]. AIP typically presents with obstructive jaundice. Other manifestations include a pancreatic mass (at times mistaken for a carcinoma) and other organ involvement (sialadenitis, retroperitoneal fibrosis, lymphadenopathy, interstitial nephritis, etc.) [53]. The HISORt criteria (*H*istology, characteristic *I*maging (Fig. 44.6), elevated IgG4 on *S*erology, *O*ther organ involvement, *R*esponse to *t*reatment) are commonly used for diagnosis [54]. For inconclusive cases, a pancreatic biopsy might be necessary. Steroids are the mainstay of treatment. Patients who relapse on steroids or following steroid withdrawal may require immunosuppression (azathioprine, mycophenolate, cyclophosphamide, etc.) [53].

Key Points

- While alcohol is the most common cause of chronic pancreatitis in the general population, alcoholic pancreatitis rarely has its onset over age 60 years.
- Pancreatic cancer can mimic chronic pancreatitis in the elderly.
- There might be a latency of decades before chronic pancreatitis becomes clinically evident.

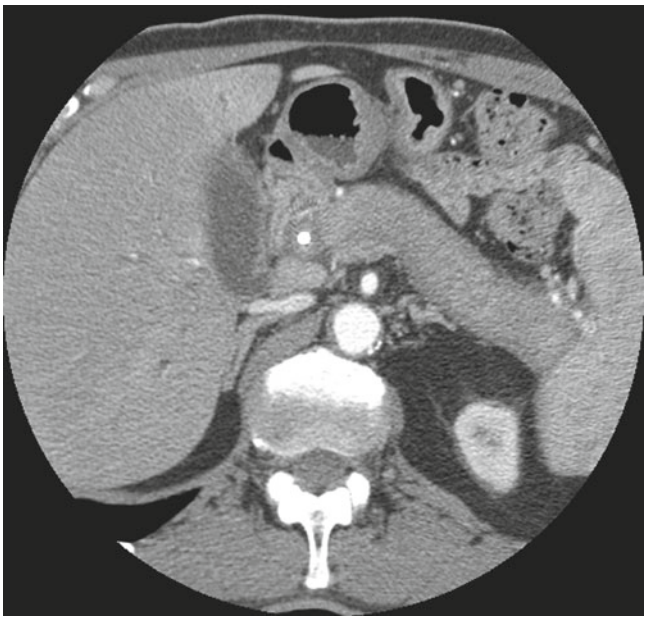

Fig. 44.6 Contrast-enhanced high resolution CT scan in a patient with autoimmune pancreatitis shows a diffusely enlarged gland with a rim like enhancement. This patient also had biliary involvement and underwent stent placement which is evident in this image

- Elderly patients often present with exocrine insufficiency without significant abdominal pain.
- Age-related changes in pancreatic structure can resemble the changes of chronic pancreatitis.
- Diffuse pancreatic calcifications on abdominal radiographs are specific for chronic pancreatitis but are generally seen in late stages of the disease.
- In early chronic pancreatitis, CT and MRI may be normal.
- EUS findings of chronic pancreatitis may be confounded by changes due to aging, alcohol, and smoking.
- Patients with chronic pancreatitis are at increased risk of pancreatic cancer.

References

1. DiMagno MJ, DiMagno EP. Chronic pancreatitis. Curr Opin Gastroenterol. 2010;26(5):490–8.
2. Everhart JE, Ruhl CE. Burden of digestive diseases in the United States Part III: Liver, biliary tract, and pancreas. Gastroenterology. 2009;136(4):1134–44.
3. Lin Y, Tamakoshi A, Matsuno S, et al. Nationwide epidemiological survey of chronic pancreatitis in Japan. J Gastroenterol. 2000;35(2):136–41.
4. Levy P, Barthet M, Mollard BR, et al. Estimation of the prevalence and incidence of chronic pancreatitis and its complications. Gastroenterol Clin Biol. 2006;30:838–44.
5. Ross SO, Forsmark CE. Pancreatic and biliary disorders in the elderly. Gastroenterol Clin North Am. 2001;30(2):531–45.
6. Gullo L, Priori P, Daniele C, et al. Exocrine pancreatic function in the elderly. Gerontology. 1983;29:407–11.
7. Di Magno EP, Go VLW, Summerskill WHJ. Relations between pancreatic enzyme output and malabsorption in severe pancreatic insufficiency. N Engl J Med. 1973;288:813–5.
8. Pitchumoni CS, Glasser M, Saran RM, et al. Pancreatic fibrosis in chronic alcoholics and nonalcoholics without clinical pancreatitis. Am J Gastroenterol. 1984;79:382–8.
9. Shimizu M, Hayashi T, Saitoh Y, et al. Interstitial fibrosis in the pancreas. Am J Clin Pathol. 1989;91:531–4.
10. Nagai H, Ohtsubo K. Pancreatic lithiasis in the aged. Gastroenterology. 1984;86:331–8.
11. Schmitz-Moorman P, Himmelmann GW, Folsch UR, et al. Comparative radiological and morphological study of human pancreas: Pancreatitis like changes in postmortem ductograms and their morphological pattern: Possible implications for ERCP. Gut. 1985;26:406–14.
12. Gloor B, Ahmed Z, Uhl W, et al. Pancreatic disease in the elderly. Best Pract Res Clin Gastroenterol. 2002;16(1):159–70.
13. Jones SN, McNeil NI, Lees ER. The interpretation of retrograde pancreatography in the elderly. Clin Radiol. 1989;40:391–6.
14. Rajan E, Clain JE, Levy MJ, et al. Age-related changes in the pancreas identified by EUS: a prospective evaluation. Gastrointest Endosc. 2005;61:401–6.
15. Ammann R, Sulser H. "Senile" chronic pancreatitis; a new nosologic entity? Studies in 38 cases. Indications of a vascular origin and relationship to the primarily painless chronic pancreatitis. Schweiz Med Wochenschr. 1976;106(13):429–37.
16. Layer P, Yamamoto H, Kalthoff L, et al. The different courses of early- and late-onset idiopathic and alcoholic chronic pancreatitis. Gastroenterology. 1994;107:1481–7.
17. Ammann RW, Buehler H, Muench R, et al. Differences in the natural history of idiopathic (nonalcoholic) and alcoholic chronic pancreatitis: a comparative long-term study of 287 patients. Pancreas. 1987;2:368–77.
18. Cavallini G, Frulloni L. Pathophysiology of chronic pancreatitis. In: Balthazar EJ, Megibow AJ, Pozzi RM, editors. Imaging of the pancreas. Berlin: Springer; 2009. p. 117–27.
19. Yang AL, Vadhavkar S, Singh G, et al. Epidemiology of alcohol-related liver and pancreatic disease in the United States. Arch Intern Med. 2008;168:649–56.
20. Yadav D, Papachristou GI, Whitcomb DC. Alcoholic pancreatitis. Gastroenterol Clin North Am. 2007;36:219–38.
21. Andriulli A, Botteri E, Almasio PL, et al. Smoking as a cofactor for causation of chronic pancreatitis: a meta-analysis. Pancreas. 2010;39:1205–10.
22. Yadav D. Recent advances in the epidemiology of alcoholic pancreatitis. Curr Gastroenterol Rep. 2011;13(2):157–65.
23. Bishop MD, Freedman SD, Zielinski J, et al. The cystic fibrosis transmembrane conductance regulator gene and ion channel function in patients with idiopathic pancreatitis. Hum Genet. 2005;118:372–81.
24. Etemad B, Whitcomb DC. Chronic pancreatitis. Diagnosis, classification, and new genetic developments. Gastroenterology. 2001;120:682–707.
25. Braganza JM, Lee SH, McCloy RF, et al. Chronic pancreatitis. Lancet. 2011;377(9772):1184–97.
26. Kein V, Teich N, Moesnner J. Clinical value of a new fecal elastase test for detection of chronic pancreatitis. Clin Lab. 2003; 49:209.
27. Lankisch PG. Now that fecal elastase is available in the United States, should clinicians start using it? Curr Gastroenterol Rep. 2004;6:126–31.
28. Chowdhury RS, Forsmark CE. Pancreatic function testing. Aliment Pharmacol Ther. 2003;17:733–50.
29. Domínguez-Muñoz JE. Pancreatic exocrine insufficiency: diagnosis and treatment. J Gastroenterol Hepatol. 2011;26 Suppl 2: 12–6.

30. Imoto M, DiMagno EP. Cigarette smoking increases the risk of pancreatic calcification in late-onset but not early-onset idiopathic chronic pancreatitis. Pancreas. 2000;21:115–9.
31. Ikeda M, Sato T, Morozumi A. Morphologic changes in the pancreas detected by screening ultrasonography in a mass survey, with special reference to main duct dilation, cyst formation, and calcification. Pancreas. 1994;9:508–12.
32. Choueiri NE, Balci NC, Alkaade S, et al. Advanced imaging of chronic pancreatitis. Curr Gastroenterol Rep. 2010;12(2):114–20.
33. Calvo MM, Bujanda L, Calderon A, et al. Comparison between magnetic resonance cholangiopancreatography and ERCP for evaluation of the pancreatic duct. Am J Gastroenterol. 2002;97:347–53.
34. Sandrasegaran K, Lin C, Akisik FM, et al. State-of-the-art pancreatic MRI. Am J Roentgenol. 2010;195(1):42–53.
35. Forsmark CE, Toskes PP. What does an abnormal pancreatogram mean? Gastrointest Endosc Clin N Am. 1995;5:105–24.
36. Gleeson FC, Topazian M. Endoscopic retrograde cholangiopancreatography and endoscopic ultrasonography for diagnosis of chronic pancreatitis. Curr Gastroenterol Rep. 2007;9:123–9.
37. Varadarajulu S, Eltoum I, Tamhane A, et al. Histologic correlates of noncalcific chronic pancreatitis by EUS: A prospective tissue characterization study. Gastrointest Endosc. 2007;66:501–9.
38. Yusoff IF, Sahai AV. A prospective, quantitative assessment of the effect of ethanol and other variables on the endosonographic appearance of the pancreas. Clin Gastroenterol Hepatol. 2004;2:405–9.
39. Catalano MF, Sahai A, Levy M, et al. EUS-based criteria for the diagnosis of chronic pancreatitis: the Rosemont classification. Gastrointest Endosc. 2009;69(7):1251–61.
40. Stevens T. Update on the role of endoscopic ultrasound in chronic pancreatitis. Curr Gastroenterol Rep. 2011;13(2):117–22.
41. Strum WB. Abstinence in alcoholic chronic pancreatitis. J Clin Gastroentrol. 1995;20:37–41.
42. Bhardwaj P, Garg PK, Maulik SK, et al. A randomized controlled trial of antioxidant supplementation for pain relief in patients with chronic pancreatitis. Gastroenterology. 2009;136:149–59.
43. Slaff J, Jacobson D, Tillman CR, et al. Protease-specific suppression of pancreatic exocrine secretion. Gastroenterology. 1984;87:44–52.
44. Gress F, Schmitt C, Sherman S, et al. Endoscopic ultrasound-guided celiac plexus block for managing abdominal pain associated with chronic pancreatitis: a prospective single center experience. Am J Gastroenterol. 2001;96(2):409–16.
45. Gress F, Schmitt C, Sherman S, et al. A prospective randomized comparison of endoscopic ultrasound- and computed tomography-guided celiac plexus block for managing chronic pancreatitis pain. Am J Gastroenterol. 1999;94(4):900–5.
46. Tringali A, Boskoski I, Costamagna G. The role of endoscopy in the therapy of chronic pancreatitis. Best Pract Res Clin Gastroenterol. 2008;22:145–65.
47. Warshaw AL, Buchler MW. Resection versus drainage in treatment of chronic pancreatitis. Gastroenterology. 2008;134:1606–7.
48. Habashi S, Draganov PV. Pancreatic pseudocyst. World J Gastroenterol. 2009;15(1):38–47.
49. Balachandra S, Siriwardena AK. Systematic appraisal of the management of the major vascular complications of pancreatitis. Am J Surg. 2005;190:489–95.
50. Morgan KA, Adams DB. Management of internal and external pancreatic fistulas. Surg Clin North Am. 2007;87:1503–13.
51. Lowenfels AB, Maisonneuve P, Cavallini G, et al. Pancreatitis and the risk of pancreatic cancer. N Engl J Med. 1993;328:1433–7.
52. Sah RP, Chari ST, Pannala R, et al. Differences in clinical profile and relapse rate of type 1 versus type 2 autoimmune pancreatitis. Gastroenterology. 2010;139:140–8.
53. Sugumar A, Chari ST. Diagnosis and treatment of autoimmune pancreatitis. Curr Opin Gastroenterol. 2010;26(5):513–8.
54. Chari ST. Diagnosis of autoimmune pancreatitis using its five cardinal features: introducing the Mayo Clinic's HISORt criteria. J Gastroenterol. 2007;42 Suppl 18:39–41.

Part X

Luminal Disorders

Oral Health in Older Adults

45

Mary S. Haumschild and Barbara G. Hammaker

Background and Significance

Demographic trends suggest that tooth loss in individuals in developed countries is on the decline and this direction is expected to continue; hence, the prevention and care for dental caries and periodontal disease are relevant. Even with the steady decline in edentulism, a fourth of older adults have lost their teeth. Tooth loss is associated with adverse psychological ramifications, such as loss of confidence, altered speech, embarrassment, discomfort, and avoidance of social dining. The interrelationship between oral health and general health is especially pronounced in older adults due to compromised chewing, eating, and nutrition. Impaired mastication and oral health are consistently associated with softer food choices, and lower intake of fiber and micronutrients [1]. Poor oral health is associated with impaired quality of life, and systemic illness.

The oral cavity consists of specialized hard and soft tissues that serve to function as a cohesive unit for the purposes of mastication, swallowing, and communication. Soft tissue structures include the tongue and taste buds, floor of the mouth, lining mucosa, attached gingiva, hard and soft palatal tissues, tooth pulp, tonsils, and the alveolar mucosa. Principle fiber groups composed of collagen and fibrin serve to brace the gingiva against the alveolar jawbone. The periodontal ligament is a highly specialized group of collagen fibers that firmly attach the tooth to the jaw, providing supportive, sensory, and nutritive functions to the tooth and surrounding alveolar bone. Hard tissues include tooth structures such as enamel, dentin (which houses the tooth's pulp), cementum, lamina dura, and alveolar bone. The teeth are innervated primarily by the trigeminal cranial nerve and receive blood and nutrients from surrounding bone [2].

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Access and Barriers to Care

The negative impact of poor oral health on the quality of life in older adults is a public health issue. Access to care may be affected by several barriers, commonly high costs associated with dental care, transportation to dental clinics, and disabilities that affect mobility. Although oral health problems are frequently encountered in older adults, other comorbidity gets a higher priority for care and treatment. Further, many older adults do not perceive a need for routine dentistry in the absence of pain. According to the Center for Disease Control and Prevention, only 58% of adults over age 65 had an annual dental visit in 2006 [3]. Dental insurance coverage is a strong correlate of dental care use in the aged. Dental insurance is typically provided as a benefit for working individuals, while retired persons are unlikely to have dental insurance. In addition, Medicare and Medicaid do not cover dental procedures. The rising costs of prescription drugs cause retirees to make a choice about where they will spend their health care dollars [1].

A qualitative study revealed that the major barriers to oral care for residents in long-term care facilities are lack of designated personnel, time constraints on nursing staff, poor oral hygiene and noncompliance among the residents, with low priority for daily mouth care [4]. Limitations resulting from being institutionalized are also a barrier. Residence in nursing homes for extended periods is associated with greater exposure to pathogens and unmet dental needs. Although there is paucity of high-level evidence, current data does suggest that oral care is important in reducing aspiration pneumonia in the elderly; poor oral hygiene is associated with the greatest risk, compounded by dysphagia, feeding problems, and decreased functional status [5].

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Table 45.1 Barriers to receiving dental care [1, 3]

Barriers	In home care	In institutions
High cost of dental care	X	X
Lack of dental insurance	X	X
No Medicare or Medicaid	X	X
Health care dollars spent on medications instead	X	
Transportation to dental office	X	X
Comorbid disorders have higher priority	X	X
Inadequate knowledge about oral care	X	X
Perception that dental care is not important	X	
Providers view oral care as lower priority		X

Oral decontamination using topical antimicrobial agents, such as chlorhexidine gluconate, with mechanical plaque control may reduce the rate of ventilator-associated-pneumonia (VAP). The Center for Disease Control and Prevention, the American Thoracic Society, and the Infectious Disease Society of America agree that poor oral health is a modifiable risk factor for VAP [6] (Table 45.1).

Oral-to-Systemic Health and Disease

Chronic systemic diseases share risk factors with oral diseases [7]. Oral manifestations are evident in several systemic disorders; cardiovascular, cerebrovascular, chronic lung and chronic kidney disease, diabetes, gastroesophageal reflux disease (GERD), immune deficient states and more. The link to this bidirectional relationship is inflammation [8]. Periodontal pathogens and inflammatory mediators pronounced in the oral cavity may gain access to the circulation leading to systemic effects [3]. Arthritis and periodontitis share proinflammatory pathways. Periodontal disease and inflammation interact to diminish oral function, quality of life, nutrition, and increase risk for systemic disease. Restricted dexterity compromises oral hygiene in the elderly with arthritis; the same occurs in stroke on the affected side. Oral infections and impaired salivary flow need to be promptly addressed in diabetics. Visual and hearing impairment cause difficulties in removal of the plaque biofilm, resulting in gingival inflammation [6].

Dental caries is defined as a localized, pathogenic process of external origin that involves softening of hard tissue surfaces, and proceeds to cavity formation. The caries process requires the presence of microorganisms such as *Mutans streptococci,* and *Lactobacilli,* in addition to a carbohydrate source and a susceptible tooth surface. Acid challenge results from the action of cariogenic bacteria in dental biofilm allowing these products to pass through microchannels in the enamel to penetrate into the underlying tooth dentin. Critical pH for tooth enamel is 4.5–5.0, and for cementum (root surface), 6.0–6.7. The incidence of root caries (decay of exposed root surfaces) is directly proportional to the amount of exposed root surfaces [2].

Longitudinal data suggests that caries (decay) is more prevalent in older adults than children; the latter are primary recipients of caries-prevention services. Currently, water fluoridation is the main caries-prevention program that benefits older adults by preventing decalcification and promoting recalcification of tooth surfaces [9]. Because of gingival (gum) recession, older adults are more prone to decay on the exposed root area adjoining the gumline. This underneath dentin is softer and lacks the protective hard enamel coating; therefore, it is affected by the plaque biofilm and can decay at a faster rate. Older adults should be taught to concentrate on cleaning at the gumline, without scrubbing this vulnerable area. For decay or caries prevention, they should limit sugar and fermentable carbohydrates because these foods and drinks cause a rapid drop in pH to acidic levels, which can last 20 min with each exposure and promote demineralization of dental enamel [10].

Factors that contribute to oral health problems in older adults include neurological disorders, dysphagia, adverse drug effects, past fluoride exposure, smoking, alcoholism, and inadequate prior preventive dental services. Physical limitations, common in the aged, often lead to suboptimal oral hygiene. The dexterity required for proper brushing and flossing decline with age. As a result, the elderly may depend on family and caregiver to maintain oral hygiene [1]. Preventive dentistry is crucial in the presence of Alzheimer's or other dementias; these patients may forget dental appointments, home care instructions, or the daily oral hygiene procedures, all components of their instrumental or basic activities of daily living. Access, mobility, and communication may be impaired with depression and memory loss. These patients may benefit from using adaptive floss aids, power toothbrushes, and oral irrigators. The patient should brush long enough with the proper 45° angle at gumline to remove the bacterial plaque. In addition, caregiver assistance may be required. Interdisciplinary communication between the dental and medical team helps manage complex dental and systemic issues [11].

Periodontal Inflammation and Gastrointestinal Disorders

Periodontal disease can be divided into two primary forms, gingivitis and periodontitis. In essence, both forms of this disease are direct inflammatory responses to dental biofilm. As dental biofilm accumulates at the cervical tooth surface adjacent to the gingival margin, a localized inflammatory reaction takes places, initiating a natural defense mechanism

by the host. As the biofilm continues to accumulate and age, more virulent strains of anaerobic bacteria begin to appear. Additionally, the host response becomes more clinically noticeable with the presence of redness, bleeding, and tissue edema. Eventually, the untreated lesion leads to exposed root surfaces as well as loose teeth [2].

Periodontal diseases are defined as a group of inflammatory disorders that affect the supporting ligaments and bone tissue in the mouth [12]. Emerging dental research suggests bacteria implicated in causing periodontal disease may play a role in triggering the immune system's inflammatory cascade mechanism [13]. This link may be due to shared proinflammatory cytokine expression common to both conditions. Implicated cytokines in periodontal inflammatory response are tumor necrosis alpha (TNF-a), interleukin 17 (IL-17), and interleukin 22 (IL-22); they also act on epithelial and fibroblast cells in systemic conditions such as Crohn's disease [14].

Treating the inflammatory component of the systemic disorder may help manage the periodontal problem [15]. Immune modulation is a therapeutic approach that down-regulates proinflammatory cytokine and up-regulates anti-inflammatory cytokines. Immune modulation therapy for Crohn's disease has shown promising results. Trials of intravenously administered antitumor necrosis factor-α antibody have shown dramatic responses in altering mucosal responses in patients with Crohn's disease. This response may be linked to the removal of tumor necrosis factor-α affecting T-helper 1-mediated cytokine production of interferon-γ, a key factor in Crohn's inflammation [16]. The therapeutic benefits of immune modulation may be a viable approach for treating periodontal disease [15].

The most common reason for tooth loss is periodontal disease. When this happens, there are several replacements for the natural teeth. A removable partial denture replaces only a few teeth. A complete denture replaces all of the teeth in the entire arch. A fixed bridge replaces only one or two teeth, attaches to natural teeth on either side of the missing tooth, and is not removable. An implant is composed of titanium and is placed during a surgical procedure. The implant is either restored with a crown over the titanium or an overdenture, which is a removable prosthesis that rests on retained natural teeth, following excessive bone loss, to give additional support while chewing.

Each prosthesis and the oral mucosa require daily oral care. Natural teeth should be cleaned with a disposable floss holder and power toothbrush if dexterity or arthritis is a problem. The denture should be placed in a plastic container with a fitted cover away from the bedside, so the patient will not accidently drink the solution when not fully alert at night. Warm water in the container with an effervescent tablet helps clean the denture or partial while the patient is asleep. Removal of the prosthesis at night helps rest the oral tissues. Oral cancer has been linked to ill-fitting dentures and partials. The sink may be lined with a face cloth to reduce breakage if the prosthesis is dropped; a brush made for either dentures or partials helps clean the prosthesis. Fixed bridges and implants should be flossed with a special threader [17].

Periodontal Health and Cardiovascular Disease

Chronic infections such as periodontal disease could be an initiating factor in the development of coronary artery disease (CAD). Periodontitis, as also bleeding sites and mobile teeth, is more frequent in those with CAD vs. controls. In part, this association may relate to inflammation, and the acute phase response causative in atherogenesis [18].

Oral Manifestations of Gastrointestinal Disorders

The link between gastrointestinal disorders and oral manifestations has been well elucidated. The most common oral manifestation of Crohn's disease is *apthosis*, a condition characterized by ulcerative, often painful lesions of oral free mucosal tissue. Less common manifestations include gingival hyperplasia, mucosal hyperplasia (nodular texture of buccal mucosa), diffuse gingival swelling, and angular cheilitis. While gingival hyperplasia is a less-often seen oral manifestation, it is one of the first diagnostic signs of Crohn's disease [19]. Patients with gastroesophageal reflux disease (GERD) may also present with erosion of hard tissue surfaces (enamel, cementum, and dentinal surfaces), nonspecific burning sensations, mucosal ulcerations, and alterations in taste perception [20, 21] (Table 45.2).

Table 45.2 Gastrointestinal disorders with oral manifestations [20, 21]

Crohn's disease	Aphthous ulcers, gingival hyperplasia, nodularity of buccal mucosa, angular cheiltis
GERD	Erythematous lesions in the palate, tonsillar area, uvula; erosion of hard tooth structure, xerostomia, altered taste perception
Gastic ulcers (*H. pylori* causative)	Pooling of H. pylori in recurrent aphthous ulcers, buccal mucosa, ventral surface of tongue; possible oral to oral transmission
Ulcerative colitis	Aphhthous ulcers, angular chelitis (less prominent than in Crohn's disease)
Chronic gastritis	Caries risk with overuse of chewable antacid tablets

Common Oral Mucosal Disorders in the Elderly

The elderly are commonly confronted with oral mucosal disease and lesions indicative of changes in systemic health. Oral cancer is the most significant oral mucosal lesion in older adults, increasing in frequency with age. The incidence and mortality rate for oral cancer is highest in individuals aged over 45 years. Sites for oral malignancy include lateral borders of the tongue, floor of the mouth, lips, buccal mucosa and posterior oropharnyx (tonsils). Most oral cancers are squamous cell lesions, but may include salivary, bone, or lymphoid cancers [22]. Furthermore, older adults are susceptible to opportunistic oral infections due to age and disease related changes in the oral cavity and immune system [23]. Infections in the oral cavity may be viral, fungal, or bacterial in origin. The most common viral infections are due to herpes simplex virus and varicella zoster virus. Bacterial infections are most often of periodontal or cariogenic origin. *Candida albicans* is the most common oral infection of fungal origin [22].

Gingivitis, an inflammation of the gingival unit (gums), may be the result of medication use, such as calcium channel blockers, phenytoin, and cyclosporins; gingivitis can predispose to caries and periodontitis. Treatment includes meticulous oral hygiene, including brushing and flossing after meals. Oral rinses with antimicrobials such as chlorhexidene 0.12% and antibiotics such as metronidazole or clindamycin may help [24].

Medications Affecting Oral Health

Medications cause adverse events affecting the oral cavity, the most common being xerostomia. Implicated medications causing xerostomia or interrupted saliva flow include anticholinergics, antipsychotics, antidepressants, anxiolytics, sedative, opioids, antihypertensives, diuretics, and nonsteroidal anti-inflammatory drugs [25]. It is incumbent upon health care professionals to review the patient's medical history, including drug history at each visit to ensure that the patient's dental health is not adversely affected by medications [26].

Certain antidepressant and antipsychotic medications have been associated with adverse drug reactions associated with movement disorders of the extrapyramidal system. Examples of agents that can cause unwanted dystonic effects include high-potency antipsychotic medications such as haloperidol, prochlorperazine, metochlopramide, thioridazine, resperidol and several others. While the incidence of reactions varies, the effects appear linked to the duration and dose of drug exposure. Manifestations are more common in females over 40 years, who take phenothiazines for 6 months to 2 years, or as long as 20 years. Dystonic manifestations include Parkinsonism, akathisia (increased compulsive motor activity), and tardive dyskinesia of the tongue, lips, face, and jaw [24].

It is estimated that nearly 400 medications may have antisialogogue properties and alter oral pH. Xerostomia coupled with lower pH can impair the normal protective mechanisms of saliva significantly, increasing the risk for carious lesions (decay), mucositis, or periodontal infection [23]. Salivary function does not decline with age, but salivary glands in older adults are more susceptible to damage than the young. Hence, xerostomia and hyposalivation are more common in older people [25] xerostomia is defined as oral dryness resulting from diminished or arrested salivary flow. Contrastingly, salivary gland hypofunction or hyposalivation is a condition of reduced salivary function [23]. Xerostomic symptoms may be comorbid with other oral conditions such as burning mouth syndrome, dysphagia, parageusia, or dysguesia. Antisialogogue states impair physical and psychosocial function. Patients may self-report symptoms ranging that are mild to embarrassment or substantial disruptions to daily living [25].

The role of salivary function in maintaining oral health cannot be understated. Saliva lubricates soft oral mucosal tissues, deters adhesion of bacteria to tooth structure, prevents gingival and mucosal ulcerations, buffers acids, aids in tooth remineralization, and assists in proper bolus formation [25]. Interruptions to saliva flow may affect speech, the proper fit of oral appliances, and may lead to altered taste perception [23]. Those on multiple medications stand to benefit from salivation status as part of routine assessment by their health care professionals [25]. Salivary hypofunction also results from chemotherapy or radiotherapy for cancer, and also conditions such as Alzheimer's disease, Sjogren's syndrome, thyroid disorders, diabetes, and systemic lupus. Local treatment strategies that provide transient relief from xerostomia include topical lubricants, coating agents, and saliva stimulants. Saliva-stimulating lozenges or gums, oral moisturizers, and saliva substitute products may provide a measure of relief from xerostomia [23] (Table 45.3). Salivary substitutes in gel form may help lubrication.

Bisphosphonates, which inhibit resorption of bone, are used in the management of osteoporosis. However, they are incriminated in disrupting the balanced osteoclast/osteoblast axis in the jaws with potential for osteonecrosis. A medical claims study of over 700,000 people suggested that oral administration of bisphosphonates decreases the risk of adverse bone outcomes, but IV administration significantly increases risk of osteonecrosis [27]. A relationship was found between IV use and inflammatory jaw conditions, and major jaw surgery for inflammatory conditions or various cancers. Cancer patients on intravenous bisphosphonates should be handled cautiously for invasive dental procedures [28].

Table 45.3 Adverse drug reactions involving the oral cavity [26]

Adverse effect	Group	Medication/agent name
Behavior-altering agents affecting dental hygiene	Psychotropic agents, antidepressants, centrally acting analgesics, antiepileptics	Phenytoin, valproic acid, sertraline
Agents that alter plaque biofilm composition and oral pH	Antifungal agents, antacid tablets, liquid and chewable forms of medications	Calcium carbonate, ystatin lozenges
Agents affecting salivary flow and oral pH	Cardiovascular agents, antidepressants, sedatives, central analgesics, anihistamines, antiallergy medications, antacids, bronchodilators, decongestants	Amlodipine, pseudoephedrine, diphenhydramine, cimetidine, omeprazole, albuterol
Lichenoid or erythematous lesions	NSAIDs, antiseizure medications, antibiotics, sulfonamides, diruretics, ACE inhibitors	Clindamycin, phenobarbital, captopril, phenytoin, ibuprofen
Altered taste	Antibiotics, cardiovascular agents, antidepressants, centrally acting agents, chlorhexadine products, ACE inhibitors	Beta-blockers (atenolol, metoprolol), dilitazem, nicotine patches
Agents causing angioedema	ACE inhibitors, angiotensin II receptor blockers, NSAIDS	Enalapril, lisinopril, losartan
Oral pigmentation	Tetracycline family	Minocycline
Gingival hyperplasia	Antiepileptics, cyclosporine	Phenytoin, cyclosporine
Affect clotting	Anticoagulant and antithrombic agents, NSAIDs, some herbals	Clopidogrel, warfarin, NSAIDs, *Ginkgo biloba*, ginger, ginseng, kava
Affect alveolar bone	Antiepileptics, corticosteroids, tetracyclines, bisphosphonates	Prednisone, phenytoin, valproic acid, ibuprofen, alendronate

Further, recent reports have also documented the possible link between oral bisphosphonates and bisphosphonate-related osteonecrosis of the jaw (BRONJ), characterized by painful areas of exposed bone in the oral cavity. Clinicians and prescribers need to be aware of this potential complication. Health care providers must weigh the risk vs. benefit ratio of using bisphosphonates for osteoporosis; the drug class also has a long half-life. Interdisciplinary collaboration between the medical and dental teams is paramount for good clinical outcomes. Patients on bisphosphonates must maintain good oral hygiene, and undergo regular dental checkups, including cleanings, to reduce dental or periodontal infections [29].

Key Points

- Healthy People 2020 objective is to increase the proportion of long-term care residents to utilize the oral health care system each year [30].
- Oral health is essential for communication, nutrition and host protection; age by itself does not impair oral health.
- Proper daily oral care, with prevention as the cornerstone, is the most crucial factor in improving oral health in older adults. Expert dental hygienists can train the nursing staff and facilitate oral care in hospitals and nursing homes.
- Older adults tend to be on numerous medications, rendering them susceptible to adverse effects involving the oral mucosa, appetite, or taste.
- The combination of systemic disease and its therapy, or medications by themselves predispose older adults to undesired manifestations and impaired quality of life.

References

1. Bailey R, Gueldner S, Ledikwe J, Smiciklas-Wright H. The oral health of older adults: An interdisciplinary mandate. J Gerontol Nurs. 2005;31:11–7.
2. Wilkins EM. The teeth. In: Wilkins EM, editor. Clinical practice of the dental hygienist. 10th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2009. p. 264–80.
3. Park DS. Challenges of delivering oral health care to older adults. New York State Dent J. 2009;75:36–40.
4. Wyatt CL, So FH, Williams PM, Mithani A, Zed CM, Yen EH. The development, implementation, utilization and outcomes of a comprehensive dental program for older adults residing in long-term care facilities. J Can Dent Assoc. 2006;72:419–27.
5. Terpenning M. Geriatric oral health and pneumonia risk. Clin Infect Dis. 2005;40:1807–10.
6. Boehm TK, Scannapieco FA. The epidemiology, consequences, and management of periodontal disease in older adults. J Am Dent Assoc. 2007;138(suppl):S26–33.
7. Petersen PE, Yamamoto T. Improving the oral health of older people: The approach of the WHO Global Health Programme. Community Dent Oral Epidemiol. 2005;33:81–92.
8. Haumschild MS, Haumschild RJ. The importance of oral health in long-term care. J Am Med Dir Assoc. 2009;10:667–71.
9. Griffin SO, Griffin PM, Swann JL, Zlobin N. New coronal caries in older adults: Implications for prevention. J Dent Res. 2005;84:715–20.
10. Towle JH. The elderly patient. In: Wilkins EM, editor. Clinical practice of the dental hygienist. 10th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2009. p. 818–31.
11. Scully C, Ettinger RL. The influence of systemic diseases on oral health care in older adults. J Am Dent Assoc. 2007;138(suppl):S7–14.
12. Craig RG, Kotanko P, Kamer AR, Levin NW. Periodontal diseases—modifiable source of systemic inflammation for the end-stage renal disease patient on haemodialysis therapy? Nephrol Dial Transplant. 2007;22:312–5.
13. Hammaker BG. Pharmacologic interventions for controlling the inflammatory cascade in periodontal disease. Access. 2010;24:19–20.

14. Liang SC, Tan X, Luxenberg DP, et al. Interleukin IL-22 and IL-17 are co-expressed by Th17 cells and cooperatively enhance expression of antimicrobial peptides. J Exp Med. 2006;203:2271–9.
15. Gaffen SL, Hajishengallis G. A new inflammatory cytokine on the block: Rethinking periodontal disease and the Th1/Th2 paradigm in the context of Th17 cells and IL-17. J Dent Res. 2008;87: 817–28.
16. Kantarci A, Hasturk H, Van Dyke TE. Host-mediated resolution of inflammation in periodontal diseases. Perio. 2006;40:144–63.
17. Ragalis K. The edentulous patient. In: Wilkins EM, editor. Clinical practice of the dental hygienist. 10th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2009. p. 832–44.
18. Sabine O, Geerts VL, Charpentier J, et al. Further evidence of the association between periodontal conditions and coronary artery disease. J Periodontol. 2004;31:402–11.
19. Mergulha OP, Magro F, Pereira P, et al. Gingival hyperplasia as a first manifestation of Crohn's disease. Dig Dis Sci. 2005;50: 1946–9.
20. DiFede O, Di Liberto C, Occhipinti G, et al. Oral manifestations in patients with gastroesophageal reflux disease: a single-center case-control study. J Oral Pathol Med. 2008;37:336–40.
21. Iamaroon A, Chaimano S, Linpisarn S, Pongsiriwet S, Phornphutkul K. Detection of *Helicobacter pylori* in recent apthous ulceration by nested PCR. J Oral Sci. 2003;45:107–10.
22. Ship JA, Mohammad AR. Geriatric oral medicine. htpp://www.geriatricoralhealth.org/topics/topic02/default.aspx. Accessed 7 Aug 2010.
23. Brosky ME. The role of saliva in oral health: Strategies for prevention and management of xerostomia. J Support Oncol. 2007;5:215–25.
24. Havales EB. Applied pharmacology for the dental hygienist. 6th ed. Maryland Heights, MO: Mosby Elsevier; 2011.
25. Weiner RC, Wu B, Crout R, et al. Hyposalivation and xerostomia in dentate older adults. J Am Dent Assoc. 2010;141:279–84.
26. Ciancio SG. Medications' impact on oral health. J Am Dent Assoc. 2004;135:1440–8.
27. Cartsos VM, Zhu S, Zavras AI. Bisphosphonate use and the risk of adverse jaw outcomes: a medical claims study of 714,217 people. J Am Dent Assoc. 2008;139(12):14–5.
28. Skrepnek GH, Seal B, Tangirala M, et al. Adverse events and intravenous versus oral bisphosphonate use in patients with osteoporosis and cancer in the U.S. Gen Dent. 2010;58:484–92.
29. Haumschild MS, Haumschild RJ. Postmenopausal females and the link between oral bisphosphonates and osteonecrosis of the jaw: A clinical review. J Am Ac Nurse Prac. 2010;22:534–9.
30. U.S. Department of Health and Human Services. Developing Healthy People 2020. Updated 30 Oct 2009. http://www.healthypeople.gov/hp2020/Objectives/TopicArea.aspx?id=38&TopicArea=Oral+Health. Accessed 19 Aug 2010.

Small Intestinal Bacterial Overgrowth Syndrome

46

T.S. Dharmarajan and C.S. Pitchumoni

Background

The aging population has resulted in a geriatric group ranging from the healthy to the frail, characteristically manifesting comorbid illness. While several chronic disorders in the aged can be diagnosed easily, some escape early diagnosis. Small intestinal bacterial overgrowth (SIBO) is defined as any condition in which part of the small bowel harbors for a long time bacterial counts over 10^5 Colony Forming Units/ml (CFU/ml) in the intestinal juice. SIBO is an entity that the aged are prone to, but often escapes diagnosis, partly due to its vague and nonspecific presentation. Also referred to as small bowel bacterial overgrowth (SBBO), it is an unrecognized, but common cause of malnutrition in the geriatric age group, resulting from the proliferation of bacteria in the otherwise normally sterile small intestine lumen [1, 2]. The bacterial proliferation deprives the host of macro- and micronutrients. The term SIBO refers to an increase or an alteration of the normal flora of the upper gastrointestinal (GI) tract and an overgrowth of colonic-type bacteria in the small intestine [3].

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Normal Gut Flora

In the healthy state, several defense mechanisms play a role in keeping gut bacterial counts close to normal; mechanisms include gastric acid secretion, normal intestinal motility, intestinal secretions with their bacteriostatic properties, and immunoglobulins in the intestinal mucosa. These defense mechanisms can be altered by systemic disease, surgery, fistulas or diverticuli, and medications. On the other hand, gut microbiota also contribute to useful functions such as trophic effects for the gut epithelium, immune function, fermentation of carbohydrates and prevention of growth of oppressive flora, amongst others.

Bacterial counts have become possible through a process of DNA sequencing; based on the technique used, the number of bacteria and variety change significantly. The epithelial surface of the small intestine is not colonized in health. As many as 500 or more different species of bacteria reside in the gut, but the majority are compromised of a few species. In healthy states, the upper gastrointestinal tract barring the oral cavity is low in bacterial activity, while at the lower end the colon is loaded with bacteria, the huge number also contributing to more than half the fecal mass [4, 5]. The oral cavity houses bacteria of several species that line the tongue, floor of mouth, cheek, and teeth; the bacteria are diverse even in good health, and predominantly anerobes. In the healthy state, protozoa and fungi contribute small numbers in the gut. The bacterial count is low in the duodenum and proximal jejunum, counts typically below 10^4 CFU/mL; here, counts above 10^5 CFU/mL are diagnostic of SIBO. While most bacteria in the small intestine are anerobes, there is a significant increase in aerobes at the cecal site. The large intestine lumen carries the highest load of bacteria, 99% of them anerobes, contributing to fecal mass. Table 46.1 provides an idea of bacterial flora and counts at different gut sites [4–6].

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Table 46.1 Microbiota in the human gastrointestinal tract [4–6]

Location	Bacterial counts	Type of bacteria
Oral cavity	High bacterial counts	Over 200 species. *Streptococcus, Actinomyces, Fusospirochetes, Neisseria, Lactobacillus, Veilonella*
Stomach	Below 10^3 CFU/mL	*Helicobacter pylori*, acid-tolerant lactobacilli
Duodenum	Below 10^4 CFU/mL	Lactobacilli, enterocci, anerobes both gram positive and facultative
Jejunum	Sterile to below 10^4 CFU/mL	Lactobacilli, enterococci, anerobes both gram positive and facultative
Ileum	Low counts increase to$10^{5–8}$ CFU/mL	Distal ileum shows marked increase in anerobes and coliforms
Colon	Over 10^{12}/content. Huge numbers, comprise half the fecal mass	Over 500 species, 99% are anerobes. *Bacteroides, Enterobacter, Clostridium, Enterococcus, Lactobacillus, Fusobacterium, Staphylococcus*

Table 46.2 SIBO: risk factors and predisposition

Aging is a predisposing factor
Disease states predisposing to SIBO
Gastroparesis and achlorhydria, if long standing
Stasis, any cause: blind loops, gastrocolic or enterocolic fistulae, stricture
Short bowel syndrome (e.g., ileocolic or jejunocolic anastamoses)
Postoperative: Billroth II, gastric bypass and other bariatric surgical procedures
Diverticular disease of duodenum or jejunum
Diabetes mellitus, Parkinson's disease (autonomic neuropathy)
Celiac disease
Crohn's disease
Scleroderma
Irritable bowel syndrome
Radiation enteritis
Cirrhosis liver and nonalcoholic steatohepatitis
Cancer of pancreas
Chronic pancreatitis
Chronic renal failure
Rheumatoid arthritis
Immune suppressed states
Medications and SIBO: beneficial or worsen
Use of immunosuppressive agents, a predisposition
Long-term use of PPIs, a predisposition
Warfarin requirements increase, because of vitamin K1 absorption
Antibiotics produce temporary relief in manifestations

Prevalence of Bacterial Overgrowth

The precise prevalence is not clear as the entity of SIBO is largely unsuspected and underdiagnosed. In most situations an alternate diagnosis is considered to be the explanation for the patient's manifestations. Ranges for SIBO in studies vary considerably from as low as 2.5% to as high as 90% in older adults with lactose intolerance [7]. Bacterial overgrowth does not spare persons of any body weight, with high prevalence in morbid obesity as noted in a recent study [8]. Based on specific risk factors in the individual, the prevalence of SIBO varies; its greater prevalence in older adults correlates well with age being a predisposition in association with the high frequency of comorbid disorders in the aged that are linked to SIBO.

Risk Factors and Predisposition to SIBO

Age predisposes to SIBO for several reasons. Older adults are more likely to have a decline in gastric acid due to gastric disease or use of acid neutralizing agents; we are in an era where the use of proton pump inhibitors ranges from established indications to redundancy; immune dysfunction from disease or use of medications such as steroids is common in the older adult; disease processes (Tables 46.2 and 46.3) which predispose to bacterial overgrowth are common in the elderly [9]. When healthy aged were compared to physically disabled older adults, with measures of physical activity and food intake, interestingly, not a single SBBO positive subject was detected by hydrogen breath test in the healthy group, in contrast to a fourth of the disabled elderly being SBBO positive [10]. Comparing the physically disabled and healthy older group further, there is no significant influence of SBBO on rice absorption [11].

Intestinal stasis irrespective of cause is a predisposition; stasis results from strictures, adhesions, blind loops, postoperative states (including Billroth II, gastric bypass surgery), fistulae, inflammatory bowel disease (Crohn's disease), diverticular disease of the small bowel, and motility disorders such as scleroderma and autonomic neuropathy of diabetes or Parkinson's disease. "Short bowel" syndrome allows transit of chime and undigested food, a substrate for bacterial growth. Type 1 diabetics with autonomic neuropathy have a higher prevalence of SIBO; further, SIBO positive diabetics also require higher daily insulin doses [12]. SIBO occurs more frequently is systemic sclerosis, present in 30 of 54 patients in a study; eradication of bacteria improved clinical features; orocecal transit time was slower in those with scleroderma (vs. controls), suggesting impaired motility as a basis for SIBO [13]. Gastroparetics with abdominal pain and bloating have a high likelihood of SIBO; in fact, 60% may have SIBO with pareisis of 5 years duration, irrespective of gender or etiology of paresis [14]. Gastropareisis is well known to occur in longstanding diabetics, but does not result solely from aging.

Table 46.3 Studies on SIBO

Symptomatic elders [9]
168 Patients, teaching hospital, UK
Median age 65, 106 females
Positive glucose breath test correlated with increasing age, low serum albumin, low serum B12, partial gastrectomy or right hemicolectomy, small bowel diverticulae and PPI use
Healthy vs. disabled adults [10]
Physical Fitness and Sports University Center, Japan
41 Healthy, mean age 74.6 years, vs. 42 disabled, mean age 78.8 years
SIBO not seen in healthy old, but present in 25% of disabled; no difference in food intake
Rice ingestion [11]
Physical Fitness and Sports University Center, Japan
15 disabled older adults, vs. 11 healthy older adults
5 of 15 disabled had SBBO; rice malabsorption seen in 1 of 11 healthy and 2 of 14 disabled, not significant
SBBO has no influence on rice absorption
Diabetics and autonomic neuropathy [12]
25 type I diabetics with normal autonomic tests vs. 25 type 1 diabetics with abnormal autonomic function
2 of 25 with normal autonomic had SIBO vs. 11 of 25 with abnormal autonomic function
Diabetics with autonomic dysfunction require more insulin
Nutrition [16]
Eight senior resident sites, Germany
294 subjects >61 years compared to ages 24–59
SIBO 15.6% in 61+ years vs. 5.9% in 24–59 years
SIBO associated with lower fiber, folic acid, B2 and B6 intake and weight loss
IBS and SIBO [18]
Medline and EMBASE search; Universities in the USA, Canada
1,921 subjects who met criteria for IBS
Pooled prevalence of +ve lactulose or glucose hydrogen breath test, and positive jejuna aspirate and culture
Pooled odds for +ve test for SIBO was 3.45 vs. prokinetic drugs may be beneficial in conditions such as scleroderma. Search controls
Cirrhosis liver and association [23]
40 patients with cirrhosis, Germany
Culture of jejuna aspirates provided diagnosis in 73#
Glucose breath hydrogen test sensitivity 27–52%, specificity 36–80%
Bone mineral density [26]
Physical Fitness and Sports University Center, Japan
33 disabled older adults vs. 17 healthy older adults
Z scores were not statistically different in the groups approximately 80 years old

Immune deficient states are common with age. Although age is associated with blunting of immune function, it is more likely that SIBO results from disease processes or immune suppressed states resulting from the medications used to treat disease. The presence of SIBO has been noted in pancreatic cancer treated with chemotherapy; the patient improved dramatically following administration of antibiotics [15].

In senior resident sites at Germany, SBBO was prevalent (by hydrogen breath test) in 15.6% of older adults compared to the 5.9% in the below 59 age group; those with SBBO consumed much less fiber and B vitamins, and manifested reduced body weight [16].

The relationship of SIBO with irritable bowel syndrome (IBS) deserves mention, for consideration as an association and in differential diagnosis. SIBO is present in a sizable proportion of patients with IBS, with older age and female gender predictors of SIBO [17]. The symptoms of constipation, diarrhea, and alternating patterns in IBS may be due to fermentation of methane in the gut and slow transit time causing constipation [18]. On the other hand, a large meta-analysis concluded that the prevalence of SIBO in IBS varied with criteria used to define a positive test, and was highest with breath testing [19]. SIBO is more likely to be present in diarrhea dominant IBS compared to the constipation dominant IBS [20].

Medication use has been associated with SIBO. The use of immunosuppressive agents has received attention. Often, PPI use meant to be short term, not uncommonly becomes long term in the treatment of gastroesophageal reflux disease (GERD) or nonerosive reflux disease (NERD); PPI therapy for 3 years in GERD was associated with SIBO in 50% of cases; this was eradicated by use of rifaximin in the majority who continued PPI therapy [21]. The findings prompt PPI use for a shorter term, or as step-down, or as on demand therapy. Interestingly, SIBO increases warfarin dose requirements through an increase in the dietary vitamin K1 absorption through damaged intestinal mucosa, rather than by increased intestinal vitamin K2 biosynthesis [22].

While the association of SIBO with cirrhosis of the liver is recognized, the pathophysiology is not clear [23]. SIBO has been associated with and implicated in the pathogenesis of nonalcoholic steatohepatits. As many as half the patients with celiac disease may have SIBO [24]. Chronic exocrine disorders of the pancreas have been linked to SIBO. Finally, it is likely that more than one predisposing factor may be present in an individual with SIBO.

Manifestations

Presentations in SIBO vary from the asymptomatic, presence of only nutrient deficiencies and the extreme of weight loss with failure to thrive. Classic manifestations include anorexia, bloating or flatulence, abdominal discomfort, pain, and diarrhea. Complaints in the old may not be typical and may even resemble gradual deterioration in health attributed falsely to aging; the patient may report improvement in the abdominal complaints following a recent antibiotic course prescribed for a respiratory or urinary infection.

Bacterial overgrowth leads to carbohydrate malabsorption by decreasing the disaccharidase enzymes in the brush border of the villi. Protein malabsorption, though not often clinically overt, is caused by decreased absorption of amino

acids and peptides probably secondary to mucosal damage. Steatorrhea, the major manifestation of SIBO, results from a decrease in primary bile acids which are deconjugated by the bacteria. Malabsorption of fat and fat-soluble vitamins results from bile acid deficiency. After lipolysis by pancreatic lipase and bicarbonate, the products of lipolysis normally undergo micelle formation in the presence of adequate bile acids. In SIBO, the concentration of bile acids (referred to as "crtical micellar concentration") in the jejunal lumen declines, with resultant steatorrhea.

Deficiencies of vitamins A, D, and E occur, while vitamin K deficiency is rare because of production of vitamin K by intestinal bacteria. While intestinal bacteria compete with the host and consume vitamin B12 resulting in low blood B12 levels, they synthesize folate, resulting in the unusual combination of low blood B12 levels but elevated folate [1].

The features of the predisposing condition such as systemic sclerosis or diabetes may be evident; on the other hand nutrient deficiencies (e.g., vitamin D or B12, calcium or iron) may be the basis for symptoms or signs unique to the nutrient. Lactose intolerance is common and may contribute to diarrhea.

While the differential diagnosis of SIBO includes several disorders, coexisting irritable colon may provide dilemmas in diagnosis or treatment. When diarrhea is of short duration, an infectious cause or an adverse drug effect may be the etiology in any age group; following their exclusion, differential diagnosis includes malabsorption of any etiology; SIBO and anatomic abnormalities predisposing to SIBO must be considered in any unexplained weight loss with or without malnutrition [25].

Studies demonstrate that malabsorption of rice does not necessarily occur in SIBO [11] nor is the bone mineral density affected [26]; these studies were from one center and compared small groups of healthy and disabled older adults.

Diagnosis

The gold standard with regard to diagnosis for SIBO remains poorly defined [3]. Although duodenal or jejunal aspirates and a variety of breath tests are available, they suffer variations in their performance and interpretation, leading to differing prevalence data for bacterial overgrowth [3]. There is also a lack of consensus with regard to optimal diagnostic criteria ("gold standard") for diagnosis of bacterial overgrowth [27].

The gold standard, though technically difficult, is culture of the upper small bowel aspirate which normally reveals concentrations of bacteria below 10^4 CFU/mL; concentrations of duodenal aspirate over 10^5 CFU/mL are diagnostic; similarity to colonic bacteria is even more confirmatory of SIBO. This method is time-consuming, invasive, and costly.

Breath tests vary, including in their sensitivity and are influenced by patient factors (capacity to produce methane and hydrogen), and life style (diet and smoking). Breath tests provide a noninvasive in vivo means to assess bacterial enzyme activities, organ functions, and transport processes [27–29]. The glucose hydrogen breath test is widely used; other tests are ^{14}C-glycocholic acid (produces ^{14}C-glycine) and ^{13}C-glycine hydrolase breath tests [28, 29]. Hydrogen breath tests assess carbohydrate malassimilation in SIBO, besides measuring orocecal transit time which is useful in diagnosis of motility disorders of the small intestine; glycine breath tests measure CO_2 in breath and substrate metabolism to assess gastric bacterial activity with *Helicobacter pylori* infection [28]; the test lacks sensitivity as some bacterial species lack cholylglycine hydrolase required to deconjugate glycine. The ^{14}C and ^{13}C-xylose breath tests involve radiation and measure labeled CO_2 in expired air. Xylose is a sugar that is absorbed without metabolism in the intestine.

The hydrogen breath test is safe and easy to perform in 2–3 h in the outpatient setting; it evaluates carbohydrate malabsorption. Breath samples analyze hydrogen concentration at baseline and every 30 min for 2 h; an earlier-than-expected rise of 20 parts per million (ppm) in breath over baseline at approximately 90 min is diagnostic of SIBO. The test is nonradioactive and has reasonable sensitivity and specificity, more so than the methane breath test. In the human, hydrogen and methane are produced in the large intestine only, but also in the small intestine in SIBO. Most of the hydrogen and methane is expelled by flatus and the rest in the breath [2]. In SIBO, the early increase in breath hydrogen within 90 min is due to metabolism by bacteria in small bowel. Glucose and lactulose are the sugars utilized for the test; lactulose is normally metabolized in the colon, giving it a peak hydrogen release in 3 h; but in SIBO, bacteria metabolize lactulose in the small bowel with hydrogen release in 90 min or less. Gut flora of some individuals produce methane and not hydrogen, while not all individuals produce methane; hence, it is better to measure both gases [1, 2].

In patients with cirrhosis, microbiological cultures of jejunal secretions are better for diagnosis than the glucose breath hydrogen test which correlates poorly with the gold standard for SIBO [23].

Duodenal biopsies in patients with SIBO confirmed by cultures and CFU counts demonstrate villous blunting as the only histopathology common to SIBO, compared to controls; as over half the biopsies in SIBO are unremarkable, one must consider SIBO as the explanation for GI manifestations even with normal duodenal biopsies [30].

Older adults tolerate the breath tests well; for reliable testing, the patient should not ingest high-fiber or carbohydrate-rich foods for a day prior to the test. Antibiotics in the recent past may negatively impact on the testing as the bacterial counts fall to low levels [1].

A test that once enjoyed popularity in the evaluation of patients with steatorrhea is the D-Xylose test; D-Xylose (normally not metabolized in the gut) excretion in the urine is marginally reduced because the sugar is consumed by the bacteria.

Additional tests to evaluate anemia or nutrient deficiencies and their cause may be warranted; fecal fat collection help confirm steatorrhea; radiological tests may help diagnose anatomic abnormalities such as diverticulae or fistulae.

Management

Treatment is supported by scant evidence, with most commonly used antibiotic regimens based on custom than from data derived from clinical trials [3]. Management of SIBO remains in large part primarily empiric, comprising antibiotic therapy and correction of nutritional deficiencies [31]. Nutritional support is essential to correct malnutrition.

The impact of probiotic yogurt administration for 4 weeks was studied in healthy older community subjects; normalization of the various cytokine responses and modulation of activation markers in blood phagocytes became more apparent in the group with positive breath test [32]. Although probiotics have been ascribed barrier-enhancing, antibacterial, and immune-modulator roles, their role in SIBO in humans requires further study [32].

Prokinetic drugs may be beneficial in motility disorders, such as scleroderma. Examples of these agents include octreotide, cisapride (withdrawn in the USA due to cardiac arrhythmias), metoclopramide, domperidone, and erythromycin; data is limited over their long-term efficacy.

Broad-spectrum antibiotics are the mainstay to help reduce bacterial overgrowth. Empirical use is often resorted to, without common agreement on choice. Quinolones such as norfloxacin (800 mg/day), ciprofloxacin (1,000 mg/day), amoxicillin/cavulinic acid (1,500 mg/day), metronidazole (750 mg/day), and tetracycline (1,000 mg/day) are options. More recently, rifaximin (600–1,200 mg/day), a nonsystemic, nonabsorbable antibiotic, has gained favor. The duration of therapy is about a week, though the initial course may be for 2 weeks, and repeated as required; improvement in manifestations is usually evident within days of therapy. Rotation of antibiotics may minimize resistance. The combination of rifampin with partially hydrolyzed guar gum appears more effective than rifampin alone in eradicating SIBO [33].

Recurrence after successful antibiotic therapy as shown by glucose breath test was 12.6, 27.5, and 43% and after 3, 6, and 9 months, respectively; recurrence was positively influenced by older age, prior appendectomy, and chronic use of PPIs [34]. Long-term use of antibiotic therapy is associated with its own problems: resistance, costs, and *Clostridium difficile* infection

Addressing the predisposing factors for SIBO would be ideal, but is not always practical. Conditions amenable for surgical correction include mechanical causes such as strictures, blind loops, or fistulae.

Special Considerations in the Elderly

As older adults high have a high prevalence for malnutrition and tend to suffer from chronic disorders, SIBO as the possible explanation is often lost in the myriad of alternate diagnostic possibilities. In any cause of malnutrition or weight loss that is not fully explained, it may be worthwhile entertaining and excluding the diagnosis of SIBO. Treatment not only has the potential to improve patient's well-being and quality of life but also avoids unnecessary costs and treatment for alternate erroneous diagnoses. Further, it is the geriatric age population that carries the background to develop unwanted gut bacterial overgrowth; they are the group subjected to courses of antibiotics, at times with questionable indications. The long-term use of PPIs is another area that continues to demonstrate a relationship to increased incidence of bacterial overgrowth [35], in fact suggesting the need to consider a step down or on-demand PPI therapy for an entirely different disorder, GERD [36]. Recent data suggest that SIBO and irritable bowel syndrome are common in chronic prostatitis (a disorder common in the old); and that patients with chronic prostatitis and SIBO may benefit from rifaximin therapy [37].

Key Points

- SIBO is an underrecognized cause of malabsorption in the geriatric population, commonly mistaken for other disorders.
- Age is a predisposing factor; however, additional comorbidity such as diabetes, systemic sclerosis, and stasis syndromes such as blind loops, diverticulae, and fistulae are more likely to be contributory.
- Medications that affect immune function and excessive use of PPIs are recognized causes.
- Diagnosis is based on linking manifestations to causative factors, utilizing duodenal or jejunal aspirate cultures, and breath tests.
- Management typically involves a short course of antibiotics; the use of probiotics needs further study.
- Recurrences follow months following antibiotic therapy, hastened and influenced by predisposing factors.

References

1. Elphick HL, Elphick DA, Sanders DS. Small bowel bacterial overgrowth. An under-recognized cause of malnutrition in older adults. Geriatrics. 2006;63(9):21–6.
2. Bures J, Cyrany J, Kohoutova D, et al. Small intestinal overgrowth syndrome. World J Gastroenterol. 2010;16(24):2978–90.
3. Quigley EM, Abu-Shanab A. Small intestinal bacterial overgrowth. Infect Dis Clin North Am. 2010;24(4):943–59.
4. Sears CL. A dynamic partnership: celebrating our gut flora. Anaerobe. 2005;5:247–51.
5. Guarner F, Malagelada JR. Gut flora in health and disease. Lancet. 2003;361(9356):512–9.
6. Hill MJ, Drasar BS. The normal colonic bacteria. Gut. 1975;16(4): 318–23.
7. Almeida JA, Kim R, Stoita A, et al. Lactose malabsorption in the elderly, role of small intestinal bacterial overgrowth. Scand J Gastroenterol. 2008;43:146–54.
8. Sabate JM, Jouet P, Harnois F, et al. High prevalence of small intestinal bacterial overgrowth in patients with morbid obesity: a contributor to severe hepatic steatosis. Obese Surg. 2008;18:371–7.
9. Elphick DA, Chew TS, Highham SE, et al. Small bowel bacterial overgrowth in symptomatic older people. Can it be diagnosed earlier? Gerontology. 2005;51(6):396–401.
10. Mitsui T, Shimaoka K, Goto Y, et al. Small bowel bacterial overgrowth is not seen in healthy adults, but is in disabled older adults. Hepatogastroenterology. 2006;53(57):82–5.
11. Mitsui T, Kagami H, Kinomoto H, et al. small bacterial overgrowth and rice malabsorption in healthy and physically disabled older adults. J Hum Nutr Diet. 2003;16(2):118–22.
12. Ojetti V, Pitocco D, Scarpellini E, et al. Small bowel bacterial overgrowth and type 1 diabetes. Eur Rev Med Pharmacol Sci. 2009; 13(8):419–23.
13. Parodi A, Sessarego M, Greco A, et al. Small intestinal bacterial overgrowth in patients suffering from scleroderma: clinical effectiveness of its eradication. Am J Gastroenterol. 2008;103(5):1257–62.
14. Reddymasu SC, McCallum RW. Small intestinal bacterial overgrowth in gastroparesis: are there any predictors? J Clin Gastroenterol. 2010;44(1):e8–13.
15. Bustillo I, Larson H, Saif MW. Small intestinal bacterial overgrowth: an undiagnosed cause of diarrhea in patients with pancreatic cancer. JOP. 2009;10(5):576–8.
16. Parlesak A, Klein B, Schecher K, et al. Prevalence of small bowel bacterial overgrowth and its association with nutrition intake in non-hospitalized older adults. J Am Geriatr Soc. 2003;51(6):768–73.
17. Reddymasu SC, Sostarich S, McCallum RW. Small intestinal bacterial overgrowth in irritable bowel syndrome: are there any predictors? BMC Gastroenterol. 2010;10:23.
18. Lee HR, Pimental M. Bacteria and irritable bowel syndrome: the evidence for small intestinal bacterial overgrowth. Curr Gastroenterol Rep. 2006;8(4):305–11.
19. Ford AC, Spiegel BM, Talley NJ, et al. Small intestinal bacterial overgrowth in irritable bowel syndrome: systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2009;7(12):1279–86.
20. Mann NS, Limoges-Gonzales M. The prevalence of small intestinal bacterial overgrowth in irritable bowel syndrome. Hepatogastroenterology. 2009;56(91–2):718–21.
21. Lombardo L, Foti M, Ruggia O, et al. Increased incidence of small intestinal bacterial overgrowth during proton pump inhibitor therapy. Clin Gastrenterol Hepatol. 2010;8(6):504–9.
22. Giuliano V, Bassotti G, Mourvaki E, et al. Small intestinal bacterial overgrowth and warfarin dose requirement variability. Thromb Res. 2010;126(1):12–7.
23. Bauer TM, Schwacha H, Steinbruckner B, et al. Diagnosis of small intestinal bacterial overgrowth in patients with cirrhosis of the liver: performance of the glucose breath hydrogen test. J Hepatol. 2000;33(3):382–6.
24. Rubio-Tapia A, Barton SH, Rosenblatt JE, et al. Prevalence of small intestinal bacterial overgrowth diagnosed by quantitative culture of intestinal aspirate in celiac disease. J Clin Gastroenterol. 2009;43: 157–61.
25. Holt PR. Diarrhea and malabsorption in the elderly. Gastroenterol Clin North Am. 2001;30(2):427–44.
26. Mitsui T, Shimaoka K, Takagi C, et al. Small bowel bacterial overgrowth may not affect bone mineral density in older people. Clin Nutr. 2005;24(6):920–4.
27. Abu-Shanab A, Quigley EM. Diagnosis of small intestinal bacterial overgrowth: the challenges persist. Expert Rev Gastroenterol Hepatol. 2009;3(1):77–87.
28. Braden B. Methods and functions: Breath tests. Best Pract Res Clin Gastroenterol. 2009;23(3):337–52.
29. Braden B, Lembcke B, Kuker W, et al. 13C-breath tests: current state of the art and future directions. Dig Liver Dis. 2007;39(9): 795–805.
30. Lappinga PJ, Abraham SC, Murray JA, et al. Small intestinal bacterial overgrowth; histopathological features and clinical correlates in an underrecognized entity. Arch Pathol Lab Med. 2010;134: 264–70.
31. Quigley EM, Querra R. Small intestinal bacterial overgrowth: roles of antibiotics, prebiotics and probiotics. Gastroenterology. 2006; 130(2 Suppl 1):S67–9.
32. Schiffrin EJ, Parlesak A, Bode C. Probiotic yogurt in the elderly with intestinal bacterial overgrowth: endotoxaemia and innate immune functions. Br J Nutr. 2009;101(7):961–6.
33. Furnari M, Parodi A, Gemignani L, et al. Clinical trial: the combination of rifampin with partially hydrolyzed guar gum is more effective than rifaximin alone in eradicating small intestinal bacterial overgrowth. Aliment Pharmacol Ther. 2010;32(8):1000–6.
34. Lauritano EC, Gabrielli M, Scarpellini E, et al. Small intestinal bacterial overgrowth recurrence after antibiotic therapy. Am J Gastroenterol. 2008;103(8):2031–5.
35. Lombardo L, Foti M, Ruggia O, Chiecchio A. Increased incidence of small intestinal bacterial overgrowth during proton pump inhibitor therapy. Clin Gastroenterol Hepatol. 2010;8(6):504–8.
36. Compare D, Pica L, Rocca A, et al. Effects of longterm PPI treatment on producing bowel symptoms and SIBO. Eur J Clin Invest. 2011;41(4):380–6.
37. Weinstock LB, Geng B, Brandes SB. Chronic prostatits and small intestinal bacerial overgrowth: effect of rifaximin. Can J Urol. 2011;18(4):5826–30.

Peptic Ulcer

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Isidor Segal

Introduction

A study of over 7,500 patients from the United Kingdom suggests that peptic ulcer disease (PUD) today affects predominantly an older age group. Patients with gastric ulcer are older than those with duodenal ulcer and the age group with PUD is higher than in earlier years. Hemorrhage appears to be the main complication. Patients respond well to acid-neutralizing therapy and the need for elective surgery has declined markedly [1]. The prevalence of PUD is on the increase in the geriatric population due to the use of non-steroidal anti-inflammatory drugs (NSAIDS), the prevalence of *Helicobacter pylori* infection coupled with increasing life expectancy. In the United Kingdom, gastrointestinal disorders are the third most common for patients over age 65 to seek primary health care; 40% of these consultations relate to the upper gastrointestinal tract [2]. The discussion focuses on the implications of PUD in the context of older adults.

Pathophysiology

Peptic ulcer results when the caustic effects of acid and pepsin in the gastrointestinal tract overwhelm the ability of the mucosa to resist those effects. Defensive elements that prevent or minimize damage to the gastroduodenal mucosa include preepithelial, epithelial, and subepithelial factors [3, 4].

Preepithelial factors include the mucus/bicarbonate barrier, mucoid cap, and surface active phospholipids. They impede contact between epithelial cells and noxious agents in the gastrointestinal lumen. When acid and pepsin breach the preepithelial defenses, other defense factors mitigate against acid/peptic injury. These epithelial defense mechanisms include acid-base transporters, release of growth factors, cellular resistance, and restitution factors, all of which facilitate prompt reconstitution of surface epithelium. The subepithelial factors comprise mucosal blood flow.

Gastric acid secretion levels are preserved with aging; however, the mucosal protective mechanisms such as prostaglandins become impaired by the aging process.

Etiology

H. pylori infection and NSAIDs constitute the common causes of peptic ulcer in the older adults [2]; the two may have a synergic effect. Less prominent risk factors include smoking and bisphosphonate use; the role of stress, diet, and alcohol is unclear.

H. pylori

H. pylori infection is present in 90–100% of patients with duodenal ulcer and 60–90% of those with gastric ulcer [5]. The prevalence of *H. pylori* increases with age in developed nations, while childhood *H. pylori* infection is common in developing nations. The prevalence of infection at 60 years is 50%, at which age it then plateaus [6]. Immigrants from the developing world have a high rate of infection and many have a high rate of not only *H. pylori* infection but resistant infection to the standard treatment of two antibiotics and high-dose proton pump inhibitors (PPIs) as a 7-day course.

H. pylori infection causes a chronic antral gastritis which may progress to intestinal metaplasia and atrophic gastritis, risk factors for stomach cancer and likely to increase with advancing age. In a study Pilotto et al. [7] found a significant reduction in the prevalence of chronic gastritis in patients treated for *H. pylori* and in whom the infection was successfully eradicated. Thus eradication of *H. pylori* may reduce gastric atrophy and intestinal metaplasia independently of age. Based on their findings, it may be best to eradicate *H. pylori* in the elderly.

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Nonsteroidal Anti-inflammatory Drugs

NSAIDs are an important risk factor for PUD, and especially associated with prepyloric ulcers. The use of NSAIDs increases significantly in those over age 60 years. In one study [4] NSAIDs were used by a third of patients over age of 65. Worldwide, perhaps 30 million people use NSAIDS on a daily basis [6]. Ingestion of aspirin and NSAIDS increases both the incidence and complications of ulcers. Interestingly, eradication of *H. pylori* before NSAID therapy reduces the occurrence of NSAID-induced peptic ulcers.

The pathogenesis of gastrointestinal injury from NSAID use is due primarily to the inhibition of prostaglandin synthesis in the gastric mucosa by NSAIDs. Prostaglandins protect the gastric mucosa by inhibiting gastric acid secretion, increasing mucosal blood flow, and promoting bicarbonate and mucus secretion. Inhibition of prostaglandin production renders the gastric mucosa vulnerable to injury from gastric acid, pepsin, and bile salts, leading to mucosal damage and ulceration. In the elderly, mucosal prostaglandin production may be decreased compared to younger patients [6]. Celecoxib, a cyclo-oxygenase-2 (COX-2) inhibitor, is believed to be associated with less gastrointestinal toxicity than traditional NSAIDs. Further, even low-dose aspirin, another risk factor, will nullify the safety profile of COX-2 inhibitors.

The evidence for peptic ulcer resulting from sole use of glucocorticoids is not strong; however in combination with NSAIDs the risk is higher than that for NSAIDs alone.

Cigarette smoking plays a role in the development of ulcers and their complications. Smoking causes delay in healing; there is also a correlation with likelihood of recurrence and the number of cigarettes smoked daily. A link to alcohol consumption is not clear, although alcohol has effects on acid secretion and gastric mucosa. A recent study revealed that a significant increased risk of gastrointestinal ulcer history is associated with older age, African-Americans, current and past smokers, former alcohol use, obesity, chronic obstructive lung disease, chronic kidney disease, coronary heart disease, and three or more doctor visits per year [8].

Clinical Features

The cardinal clinical features of peptic ulcer are epigastric pain, usually burning and nonradiating, occurring 1–3 h after a meal in gastric ulcer, while it may be relieved in duodenal ulcer. The pain often awakens the patient at night and is relieved by food or antacids. These classic symptoms are often absent in the elderly who may present in an atypical fashion; the symptoms may be nonspecific and non-localizing. Indeed the index manifestation may be a complication of PUD such as hemorrhage or perforation. Ulcer locations are most in the corpus and the pre-pyloric area, and ulcers are larger in the aged. In NSAID users, more often women, ulcers may be painless, associated with severe iron-deficiency anemia and bleeding, overt or occult. Overt bleeding is associated with high mortality.

Clinical features associated with peritonitis such as fever and leucocytosis may not be prominent or may be even absent in the elderly. Comorbid states such as dementia may make the diagnosis more difficult. The presence of coexisting myocardial, pulmonary, renal disease and diabetes mellitus is common.

Aside from the above, older adults who present with epigastric pain or discomfort should receive consideration for other extra-abdominal conditions such as a manifestation of coronary artery disease. It is essential that one does not miss a serious cardiac disorder in the quest for PUD. Overall diagnosis of peptic ulcer in the elderly differs from peptic ulcer in the younger age group. The atypical presentations emphasize the importance of obtaining a drug history, from the patient or a caregiver.

Gastrointestinal bleeding may be the presentation in the older age group; hematemesis is the manifestation in 50%, compared to a combination of hematemesis and melena in 20% [9]. Antecedent dyspepsia expected in younger patients may be absent in the older group. The patient may fail to differentiate hemoptysis from hematemesis. Unexplained syncope may be the manifestation of gastrointestinal bleeding in the elderly [9] and as such a decline in hemoglobin should raise a concern. Older adults with gastrointestinal bleeding are more likely to die during hospitalization compared to younger adults [10] and have a higher mortality rate even after hospital discharge. Factors predictive of poor outcome in PUD include older age, large transfusion requirements, and presence of comorbid illness.

Bleeding from PUD is a dramatic event with high mortality and cost in the aged; risk increases over age 65 and still more over 75 years. No anti-inflammatory drugs including selective COX-2 agents are completely safe; low-dose aspirin and even clopidogrel are associated with bleeding and mortality. Aspirin and other NSAIDs when used with clopidogrel in patients with prior coronary artery disease are more likely to have bleeding complications. Switching to COX-2 inhibitors following a bleed may not assure safety and concomitant PPI therapy is recommended [11].

Giant gastric ulcers (defined as size larger than 3 cm) are seen often in older patients; the course is aggressive and may manifest with bleeding, anorexia, and weight loss and emergency hospitalization. They are more likely to be located in the body of the stomach and may look malignant [12], but only a small number are cancerous. While there is a good response to acid-neutralizing agents, there is a tendency to recur. The condition may be a marker of poor health.

Complications

The most common complication of peptic ulcer in the elderly is hemorrhage followed by perforation, both more frequent than in the young. The complication rate of PUD in the over-70-year group is nearly 50% with a higher mortality rate than in the young [6]. Bleeding and perforation are associated with a mortality rate of 30% in those over age 65 [6]. The reasons for high mortality are increased occurrence of atypical presentation, delay in diagnosis, and presence of comorbidity.

Perforated peptic ulcer may present atypically in that symptoms may be nonspecific and non-localizing. A high degree of clinical suspicion is necessary. A rigid abdomen may not be evident. The patient may manifest delirium (acute confusional state) and shock may be evident. An X-ray of the abdomen or a CT scan may reveal air under the diagram; surgery may be immediately required.

Gastric outlet obstruction may be a rarer complication and the result of scarring or inflammation from an ulcer; manifestations include weight loss, vomiting, and early fullness following meals.

Diagnosis

In view of the atypical presentations, PUD with or without complications must be part of the differential diagnosis in the elderly presenting with vague abdominal pain associated with abnormal laboratory parameters. The gold standard for diagnosing gastric and duodenal ulcers is endoscopy. Double-contrast radiology should be performed only if there are absolute contraindications to endoscopy. Radiological testing is associated with higher false negative rate compared to endoscopy [6]. Endoscopy is safe in the elderly but awareness of the presence of comorbid disease such as coronary artery disease and a detailed drug history are essential. In a study of early vs. late endoscopy in 2,592 patients 66 years or older, with bleeding peptic ulcer, early endoscopy appears associated with increased efficiency of care, lower rates of surgery, and better control of hemorrhage; in the absence of contraindications, early endoscopy is recommended [13]. Testing for *H. pylori* and its eradication is essential.

The presence of multiple ulcers, atypical locations, and diarrhea should call for a measure of gastrin levels and consideration for Zollinger–Ellison syndrome.

Treatment

Treatment of peptic ulcer includes an overall comprehensive geriatric assessment that ensures multidimensional evaluation addressing etiology, risk factors, comorbidity, and the outcome [14]. Smoking should be stopped, as also alcohol consumption; the link to dietary alterations is not convincing.

PPI-based triple therapy for 7 days is highly effective for *H. pylori*-positive ulcers and to reduce ulcer recurrence. Anti-secretory drugs are also the treatment for NSAID- or aspirin-induced ulcers and to prevent ulcers in many older adults who must be on NSAIDs [14]. The drugs are well tolerated by older adults, but there is a need to be aware of the many side effects associated with long-term PPI therapy. Adverse effects with long term PPI therapy include malabsorption of iron and B12, increased predisposition to Clostridium difficile colitis, acute interstitial nephritis, bacterial overgrowth, hip fractures and more [15]. Eradication of *H. pylori* is superior to PPI maintenance therapy in treatment; the recurrence is higher if acid suppression alone is used. Eradication of *H. pylori* is also relevant as a long-term prevention strategy for cancer. Yet, healing takes longer in the aged compared to the young; a theory to explain the delayed healing is the circulatory incompetence to gastric mucosa from arteriosclerosis in the aged.

Gastrointestinal Bleeding

A multidisciplinary approach is appropriate in the management of gastrointestinal bleeding; admission to the intensive care unit may be a consideration. Initially resuscitation should ensure an adequate airway, volume restoration, nasogastric tube, and use of high-dose PPIs. Of interest is the fact, that long term antiplatelet therapy is known to be associated with peptic ulcer bleeding; this risk can be lowerer by eradication of H. pylori infection [16]. Management of bleeding is discussed in chapter 36.

Perforated Peptic Ulcer

The diagnosis is often delayed because of a paucity of classic clinical signs. Age and NSAID use are associated with perforation and a higher mortality rate. A more liberal use of radiological testing during early hospital stay is suggested. Perforated peptic ulcer [8] is associated with complications and mortality. Surgical approach to complications such as perforation has not changed despite the use of PPIs in treatment of PUD. The preferred surgical treatment is still simple closure, accompanied by treatment to eradicate *H. pylori*. A recent study [10] showed that increased patient age and therapeutic delay predicted outcome following surgical treatment of perforated ulcer. Morbidity and mortality can be reduced by earlier diagnosis and treatment, especially in the old, and by addressing treatment for coexisting medical illness, especially for perforated gastric ulcer [17].

Current Thoughts

Recently quadruple therapy includes two options: option one includes PPI and three antimicrobials (amoxicillin, metronidazole/tinidazole, and clarithromycin), and option two includes PPI, bismuth, tetracycline, and metronidazole. Standard triple therapy (PPI, amoxicillin, and clarithromycin) is better avoided owing to increasing resistance to this treatment [18]. Following bleeding, patients with cardiovascular disease requiring aspirin should restart within 7 days and ideally 1–3 days along with PPI [19].

Key Points

- Peptic ulcer is a disease today of an increasingly older population, with gastric ulcer patients likely to be older than those with duodenal ulcer.
- PUD in older adults may present atypically, or with the absence of pain, especially in those where the ulcer is associated with NSAID use.
- The most common etiological factors are *H. pylori* infection and NSAID use.
- The prognosis of PUD is poorer when associated with NSAID use due to associated anemia and other organ dysfunction related to NSAID use.
- Free perforation of peptic ulcer is more common in smokers and in the elderly.

References

1. Bardhan KD, Royston C. Time, change and peptic ulcer disease in Rotherham, UK. Dig Liver Dis. 2008;40(7):540–6.
2. Johnson RD, Singhal S, Bowling TE. Upper gastrointestinal disease in the elderly patient. Rev Clin Gerontol. 2005;15:175–85.
3. Cryer B, Spechler SJ. Peptic ulcer disease. In: Feldman M, Friedman LS, Brandt LJ, editors. Sleisenger and Fordtran's gastrointestinal and liver disease. Philadelphia: Saunders Elsevier; 2006. p. 1089–110.
4. Isenberg JI, McQuaid KR, Laine L, Walsh JH. Acid-peptic disorders (Chap. 61). In: Yamada T, Alpers DH, Yang CO, Powell DW, Silverstein FE, editors. Textbook of gastroenterology. Philadelphia: Lippincott Williams & Wilkins; 1995. p. 1347–430.
5. Seinala L, Ahvenainen J. Peptic ulcer in the very old patients. Gerontology. 2000;52(46):271–5.
6. Linder JD, Wilcox CM. Acid peptic disease in the elderly. Gastroenterol Clin North Am. 2001;30(2):363–74.
7. Pilotto A, Perri F, Leandro G, et al. Effect of *H. pylori* eradication on the outcome of reflux esophagitis and chronic gastritis in the elderly. Gerontology. 2006;52(2):99–106.
8. Garrow D, Delegge MH. Risk factors for gastrointestinal ulcer disease in the US population. Dig Dis Sci. 2010;55(1):66–72.
9. Farrell JJ, Friedman LS. Gastrointestnal bleeding in the elderly. Gastroenterol Clin North Am. 2001;30(2):377–404.
10. Bas G, Eryilmaz R, Okan I, Sahin M. Risk factors of morbidity and mortality in patients with perforated peptic ulcer. Acta Chir Belg. 2008;108:424–7.
11. Zullo A, Hassan C, Campo S, et al. Bleeding peptic ulcer in the elderly: risk factors and prevention strategies. Drugs Aging. 2007;24(10):815–28.
12. Raju GS, Bardhan KD, Phil D, et al. Giant gastric ulcer: its natural history and outcome in the H2RA era. Am J Gastroenterol. 1999;94:3478–86.
13. Cooper GS, Kou TD, Wong RC. Use and impact of early endoscopy in elderly patients with peptic ulcer hemorrhage: a population based analysis. Gastrointest Endosc. 2009;70(2):229–35.
14. Pilotto A. Optimal management of peptic ulcer disease in the elderly. Drugs Aging. 2010;27:545–58.
15. Desilets AR, Asal NJ, Dunican KC. Considerations for the use of proton pump inhibitors in older adults. Consult Pharm 2012;27(2):114–20.
16. Chan FK. Anti-platelet therapy and managing ulcer risk. J Gastroenterol Hepatol. 2012;27(2):195–9.
17. Di Carlo I, Toro A, Sparatore F, et al. Emergency gastric ulcer complications in elderly. Factors affecting the morbidity and mortality in relation to therapeutic approaches. Minerva Chir. 2006;61(4):325–32.
18. Rimbara E, Fischbach LA, Graham DY. Optimal therapy for *Helicobacter pylori* infections. Nat Rev Gastroenterol Hepatol. 2011;8:79–88.
19. Laine L, Jensen DM. Management of patients with ulcer bleeding. Am J Gastroenterol. 2012;107(3):345–60.

Irritable Bowel Syndrome

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Eamonn M.M. Quigley

Irritable Bowel Syndrome

Epidemiology of IBS and Related Symptoms in the Geriatric Age Group

Irritable bowel syndrome (IBS) is now recognized as a common disorder world-wide and, based on epidemiological studies largely derived from the "West" [1, 2], the "typical" patient with IBS is commonly thought to be a young adult female. Certain aspects of this stereotype may be inaccurate. Firstly, while female predominance is the norm in IBS in Europe and North America [1–3], this may not be the case in Asia [4, 5] and, secondly, IBS may not be the exclusive preserve of young adults [3]. Indeed, in a population survey performed almost 20 years ago the prevalence of IBS in a community population aged between 65 and 93 was estimated at 11% (using Manning criteria) [6]; a rate not dissimilar from that reported among a younger age group in the very same population using identical diagnostic criteria [7]. Furthermore, the prevalence rates for individual symptoms which may comprise IBS, frequent abdominal pain, chronic diarrhea and chronic constipation were even higher at 24%, 14% and 24%, respectively [2]. In a study among 70-year-old Danes, the prevalence of IBS ranged from 0 to 18% and from 4 to 32% among males and females, respectively, depending on IBS definition [8]; in the same population the prevalence of "important" abdominal pain was 11% among men and 19% among women [9].

There seems little doubt, therefore, that, not only does IBS occur in older adults, but also it is common in the geriatric age groups. Indeed, a systematic review of IBS epidemiology in North America concluded that there was little evidence for any significant age-related variation in IBS prevalence in North America [3]. In Asia, while there is some suggestion that IBS may be less common among those over 50 years of age, it is by no means rare in this age group [10]. Given the longevity of the Japanese population, studies from that country are of particular interest. Indeed, two out-patient studies from Japan reported a second peak in IBS prevalence in the elderly (the other peak was among adolescents in one study and among those aged 30–40 in the second) [11, 12]. The suggestion that there may be a fall-off in prevalence in IBS among the old was also evident in two community surveys, one from North America [13] and one from Western Europe [14]. IBS prevalence peaked in the age group 35–44 in North America and among 18–34 year olds in Europe at 25–29% and 12%, respectively. In the same surveys, prevalence rates for those over 65 were 6–13% and 7%, respectively. One interesting observation in this study was that those over 55 were about twice as likely to have medically diagnosed rather than undiagnosed IBS, whereas the reverse was true for those aged 18–34, suggesting, not surprisingly, that IBS-type symptoms may be more likely to trigger medical attendance and investigation among older subjects. In a study involving 123 general practices in the UK (incorporating 1,500 primary care physicians), where the overall incidence rates for IBS in males and females were 1.9 and 5.7 per 1,000, respectively, a fall-off in the incidence of IBS was evident among both men and women over the age of 75 [15].

These epidemiological findings need to be treated with caution as there would appear to be a distinct reluctance to make the diagnosis of IBS in geriatric patients; in a survey in the U.K. of 230 patients aged 65–94, among whom 22% had symptoms suggestive of IBS, a diagnosis of IBS had only been made in one [16]! What may be termed as IBS in a younger individual may well attract another label, such as "diverticular disease" in an older person. Good data on IBS prevalence in the geriatric population is awaited.

Once we get beyond these scanty and, perhaps, inaccurate, prevalence figures further details on the epidemiology of IBS in the elderly, mode of presentation, gender distribution

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or bowel habits become even harder to come by. Data from other sources may help to fill in the gaps. In particular, information on age-related prevalence rates for symptoms that may either form a part of the IBS spectrum or be associated with IBS may help provide a picture of IBS-type symptomatology in the elderly.

Though not a component of any definition of IBS, fecal incontinence may be associated with and may complicate IBS. In separate studies, the prevalence of incontinence among women increased from the third to the sixth decade and stabilized thereafter at around 20%, a rate that was twice the overall age-adjusted prevalence in that population [17]. Given the known association between bowel disturbances, including IBS, and fecal incontinence [18–20] one would not be surprised to find a high rate of incontinence among older IBS subjects. Indeed, these findings would suggest that fecal incontinence may be a consequence of long-standing IBS.

Constipation is generally more common in older subjects [21, 22], rising, in one large community study, from a prevalence rate of 9.2% to 14.5% and 20.6% among males aged under 50, between 50 and 70 and over 70 years of age, respectively. The corresponding values for females were 18.3%, 18.6% and 25%, respectively, suggesting that gender differences in constipation prevalence tend to disappear with advancing years [23]. Constipation in older adults may be contributed to by multiple factors and is not an inevitable consequence of aging; an assessment of bowel habits in healthy subjects in Sweden found no evidence of any age-related differences in stool frequency, defecatory symptoms or abdominal bloating [24].

In contrast, bloating a very common symptom in IBS, in general, does not appear to demonstrate age-related variations in prevalence, at least in community subjects [25].

Pathophysiology

There is little data on the pathophysiology of IBS or IBS-type symptoms in the old, as most studies have been performed in much younger patients. There is a suggestion that some changes occur in the colonic microbiota with age, with the numbers of *Bifidobacteria*, in particular, decreasing with advancing years. It must be stressed, however, that such findings were based on what would now be regarded as inadequate methodologies and, as modern molecular approaches are applied to the colonic microbiota in the elderly, its true complexity is becoming exposed [26]. To what extent any age-related changes reflect the effects of diet, therapeutic interventions, comorbid disease, not to mind their relevance to IBS or other functional symptoms, has yet to be determined.

The evidence that other aspects of gastrointestinal function such as motility, sensation or the operation of the gut-brain axis that are relevant to IBS undergo age-related changes is weak; most studies that have invoked such changes have largely failed to account for the many comorbidities in this population [27].

There is a suggestion that small intestinal bacterial overgrowth (SIBO) may play a role in the pathogenesis of IBS [28, 29]. Though this hypothesis has been criticized on a number of grounds in relation to IBS, in general [30–34], SIBO is more common among the elderly [35], and there is evidence to suggest that SIBO may be more common among older IBS subjects [36]. Further studies critically examining the prevalence of SIBO in older subjects with IBS-type symptoms would be interesting.

Challenges in Diagnosis

There is a distinct paucity of information on the presenting features of IBS in the elderly. In a study of 46 patients aged 65–94 with IBS compared to an age-matched non-IBS group, those with IBS were more likely to complain of lethargy, headaches, backache, chest pain and urinary frequency, suggesting that comorbidities well documented in younger IBS sufferers [15, 37] are also prevalent in the old [16].

The real challenge for the clinician dealing with suspected IBS in any age group lies in the fact that there is, as yet, no validated biomarker for this disorder [38]. IBS, in essence, comprises an aggregation of common gastrointestinal symptoms (abdominal pain or discomfort, altered bowel habits, bloating and/or distension), which are individually quite nonspecific but their occurrence in conjunction, in a recognizable and related pattern, facilitate a positive diagnosis. This led to the Rome criteria. Rome III defines IBS as follows:

> Recurrent abdominal pain or discomfort (an uncomfortable sensation not described as pain) at least 3 days per month in the last 3 months associated with two or more of the following:
> 1. Improvement with defecation
> 2. Onset associated with a change in frequency of stool
> 3. Onset associated with a change in form (appearance) of stool
>
> These criteria should have been fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis [39].

It must be stressed that the genesis of the Rome approach lay in research and their role may be limited in clinical practice [40]. Traditionally, the diagnosis of IBS has been made through a process of exclusion; i.e., organic disorders that could cause some or all of the symptoms that comprise IBS are sought for and ruled out through tests of varying invasiveness. This is obviously a costly and potentially dangerous approach. The relevant questions are, firstly, does a positive approach work and, secondly, do the criteria operate equally well to the elderly? The literature provides a reasonably robust response to the former but is virtually silent with respect to the latter question. Thus, there is a considerable body of literature to indicate that a clinical diagnosis of IBS made by one or other of the commonly applied criteria (Rome I, II or III, Manning) does have longitudinal integrity and is associated with a risk

for the "appearance" of new organic diagnoses which appears to be little different from that of control populations [41–44]. It must be stressed that these criteria have not been validated for reliability in older patients.

Pending further study on diagnostic criteria in a geriatric population, the clinician will, understandably, adopt a more cautious approach to the assessment of an older individual with IBS-like symptoms. It stands to reason that new-onset symptoms in an older person deserve special scrutiny. As in the young, the longevity of symptoms may serve as one valuable indicator of the likelihood of an underlying organic cause for symptoms. Given increasing prevalence of colon cancer with advancing years and the recommendation for colon cancer screening to commence in average risk individuals at age 50, there would be no argument with the use of colonoscopy in this age group [45]. Similarly, though the value of "alarm signs" has been supported in IBS, in general [46], the sensitivity and specificity of such symptoms as rectal bleeding, weight loss or fever for predicting organic disease has not been formally tested in the elderly.

One of the nightmares that haunts the clinician in assessing "the IBS patient" is, of course: "what could I be missing?" To address this question, some disorders that may occur at increased prevalence among the elderly will be discussed.

Depression

Depression is common in older adults, and may occur in association with disorders presenting with gastrointestinal manifestations, such as Parkinson's disease and chronic illnesses with prominent IBS-like symptomatology [47]. The interpretation of such presentations is complicated by the well-known comorbidity of IBS with depression and anxiety [48]; both have, indeed, been associated, in IBS, with female gender and increasing age [49]. The other trap for the unaware is that depression in the elderly may present with predominantly somatic, including gastrointestinal, symptoms in the absence of any classical depressive features [50].

Microscopic Colitis

Microscopic or lymphocytic colitis and the related disorder collagenous colitis are typically diagnosed in middle-aged to elderly females. While, superficially, there is the potential for confusion with diarrhea-predominant IBS, the predominance of watery diarrhea and the relatively mild nature of abdominal pain (if present) in the presenting symptomatology in the right demographic should alert the clinician and lead to the performance of colonoscopy with biopsies [51, 52].

Diverticular Disease/Diverticulosis

Diverticular disease, once a "hot" topic has virtually disappeared from the medical literature despite its high prevalence and clinical significance. In England, for example, over half a million hospital admissions (mostly emergencies) for diverticular disease were recorded over a 10-year period up to 2006; the 30-day mortality was 5% and the 1-year mortality 15% [53]. More staggering is the estimate that as many as 20% of those with diverticula (referred to as diverticulosis) will experience an inflammatory complication of the condition; when one realizes that as many as 60% of 70-year olds in the West harbor diverticula, the true prevalence of the condition becomes evident [54, 55]. While there should be no confusion between acute diverticulitis and IBS there are two areas of potential diagnostic difficulty at the intersection between IBS and diverticulosis.

The first of these relates to symptoms in the aftermath of an acute episode of diverticulitis. While a sizable proportion of patients with an acute episode of diverticulitis may suffer a recurrence, it is now evident that others may experience more chronic symptoms in the aftermath of acute diverticulitis. In one series, 25% of a total of 162 patients followed prospectively following a sigmoid colon resection for acute diverticulitis suffered chronic symptoms [56]. A pathological basis for these chronic symptoms was provided by the description of inflammatory changes around diverticula [57] and of a more frank process, peridiverticular colitis, or segmental colitis associated with diverticulosis (SCAD), in a minority [57–59].

The second issue is the much debated association between uncomplicated diverticular disease and gastrointestinal symptoms. Initially the term "symptomatic diverticular disease" was assigned to the combination of diverticula and lower gastrointestinal symptoms; others questioned this concept suggesting that it represented no more than the coincident occurrence of IBS in an individual who just happened to have sigmoid diverticula. While longitudinal studies suggest that the outcome for these patients (however defined) is benign [60], there is now some evidence to suggest that painful diverticular disease may, indeed, be a real entity related, at least in part, to ongoing inflammation and its effects on neuromuscular function in the colon [61–64].

The relationship between diverticula and IBS-type symptoms may be complex. While, the individual who harbors diverticula seems, in general, no more likely to experience gastrointestinal symptoms than those who do not [65], there appear to be a few individuals in whom a low grade inflammatory response may cause pain and related bowel dysfunction [66].

What then is the relationship between IBS and diverticular "disease?" That they are related is supported by evidence from a cross-sectional survey [67], which may simply reflect the sharing of common symptoms: pain and disturbed bowel habits. Comparative studies are few but do suggest some differences. Firstly, only a minority of symptomatic diverticular disease patients satisfy Rome II criteria [67, 68] and, secondly, symptom severity, as judged by a modified Patient Health Questionnaire 15 (PHQ-15) scale, appeared to be lower than in IBS, in one study [68]. However, the IBS and diverticular disease groups in the latter study were not age-matched. This is clearly an evolving area as diverticulosis attracts the research interest it deserves. Pending new data,

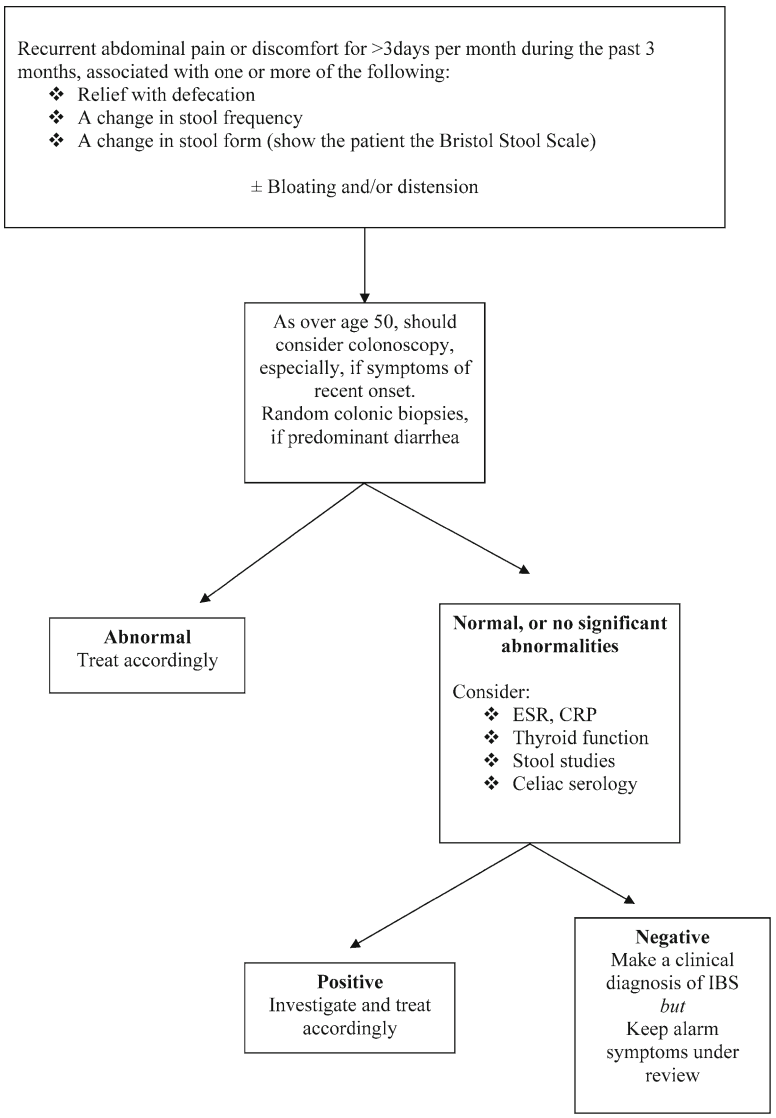

Fig. 48.1 Suggested approach to the older patient with irritable bowel syndrome (IBS)-type symptoms

the clinician needs to be alert to the possibility of diverticulitis and ongoing related inflammation as the latter may benefit from anti-inflammatory therapy.

Other Disorders

The prevalence of ischemic colitis, another disorder whose prevalence is age-related, is higher in those with IBS [69], though the nature of this relationship remains unclear. Diabetes and Type II diabetes, in particular, have reached epidemic proportions in the US and feature a number of gastrointestinal symptoms and complications. While diabetic gastroparesis and diarrhea feature prominently in textbooks, constipation and functional gastrointestinal complaints such as abdominal bloating/distension and IBS are actually the most common gastrointestinal symptoms in diabetics [70]. Polypharmacy is common in the elderly, especially in hospital and nursing home settings; many drugs cause gastrointestinal side effects and a medication side effect must always be considered in the assessment of the older patient with diarrhea or constipation. Finally, several neurological disorders common in the elderly may have associated gastrointestinal dysfunction; in some instances, such as Parkinson's disease, a gastrointestinal symptom, such as constipation, may dominate the patient's concerns [71].

Figure 48.1 presents an algorithmic approach to the older patient with IBS-type symptoms.

Management

Guidelines developed exclusively for the management of IBS in the geriatric population simply do not exist; so, for the most part, one's management strategy should follow that developed for IBS, in general (Table 48.1) [72]. In choosing drug therapy for the older patient, the clinician needs to be ever

Table 48.1 A summary of treatment approaches to IBS based on symptom pattern

Pain	Diarrhea predominant	Constipation predominant	Bloating
Certain probiotics seem to have global effects in IBS	Anti-diarrheals (no effect on pain)	Psyllium	Certain probiotics
Antispasmodics	Some probiotics	Osmotic laxatives (no effect on pain)	
Tricyclic anti-depressants (adverse effect: constipation)	Alosetron (beware of ischemic colitis)	Some probiotics	
Selective serotonin re-uptake inhibitors (SSRI's)	Rifaximin (not FDA approved for IBS)	Lubiprostone Prucalopride (available in Europe only and indicated for chronic constipation) Linaclotide (not yet approved)	

An individual may have more than one symptom and the symptoms may change over time. For further details see refs. [72, 74]

vigilant for the possibility of adverse events to which the elderly are more susceptible, including drug–drug interactions. While the management of constipation is addressed elsewhere [27, 73], two issues deserve emphasis: the risk of precipitating incontinence with the over-zealous use of laxatives and the likelihood of impaction and its attendant complications, such as stercoral ulceration, when constipation goes unrecognized and under-treated in the cognitively impaired or otherwise bowel insensitive individual. Needless to say, given the aforementioned discussion of depression and related psychopathology, the prompt recognition and appropriate management of such comorbidities is of paramount importance.

In conclusion, there is a real need to develop data on IBS in the geriatric population.

Key Points

- Irritable bowel syndrome (IBS) is common in the elderly but details of its epidemiology are scanty.
- Symptoms of IBS such as constipation and incontinence are also common in the elderly.
- Symptom-based diagnostic criteria for IBS have neither been developed nor validated in the elderly.
- Given the prevalence of comorbidity in the older subject, a lower threshold for investigation is appropriate and some disorders which are especially prevalent in this age group should feature prominently in the differential diagnosis in the right context.
- There are no treatment strategies for IBS that have been tailored specifically for the elderly; in managing the older patient with IBS, the potential for adverse effects, as well as drug–drug interactions needs to borne in mind.

References

1. Cremonini F, Talley NJ. Irritable bowel syndrome: epidemiology, natural history, health care seeking and emerging risk factors. Gastroenterol Clin N Am. 2005;34:189–204.
2. Choung RS, Locke III GR. Epidemiology of IBS. Gastroenterol Clin North Am. 2011;40:1–10.
3. Saito YA, Schoenfeld P, Locke GR. The epidemiology of irritable bowel syndrome in North America: a systematic review. Am J Gastroenterol. 2002;97:1910–5.
4. Lee OY. Prevalence and risk factors of irritable bowel syndrome in Asia. J Neurogastroenterol Motil. 2010;16:5–7.
5. Gwee K-A, Bak Y-T, Ghoshal UC, Gonlachanvit S, et al. Asian consensus on irritable bowel syndrome. J Gastroenterol Hepatol. 2010;25:1189–205.
6. Talley NJ, O'Keeffe EA, Zinsmeister AR, Melton III LJ. Prevalence of gastrointestinal symptoms in the elderly: a population-based study. Gastroenterology. 1992;102:895–901.
7. Talley NJ, Zinsmeister AR, Van Dyke C, Melton LJ. Epidemiology of colonic symptoms and the irritable bowel syndrome. Gastroenterology. 1991;101:927–34.
8. Kay L, Jorgensen T, Schultz-Larsen K. Colon symptoms in a 70-year-old Danish population. J Clin Epidemiol. 1993;46:1445–9.
9. Kay L, Jorgensen T, Schultz-Larsen K. Abdominal pain in a 70-year-old Danish population. An epidemiological study of the prevalence and importance of abdominal pain. J Clin Epidemiol. 1992;45:1377–82.
10. Gwee K-A, Lu CL, Ghoshal UC. Epidemiology of irritable bowel syndrome in Asia: something old, something new, something borrowed. J Gastroenterol Hepatol. 2009;24:1601–7.
11. Shinozaki M, Fukudo S, Hongo M, et al. High prevalence of irritable bowel syndrome in medial outpatients in Japan. J Clin Gastroenterol. 2008;42:1010–6.
12. Nakajima S. The spectra of functional gastrointestinal disorders (FGID) in a Japanese hospital outpatient department according to the Rome II integrative questionnaire. J Clin Gastroenterol. 2008;23 Suppl 2:S186–92.
13. Hungin APS, Chang L, Locke GR, et al. Irritable bowel syndrome in the United States: prevalence, symptom patterns and impact. Aliment Pharmacol Ther. 2005;21:1365–75.
14. Hungin AP, Whorwell PJ, Tack J, Mearin F. The prevalence, patterns and impact of irritable bowel syndrome: an international survey of 40 000 subjects. Aliment Pharmacol Ther. 2003;17:643–50.
15. Jones R, Latinovic R, Charlton J, Gulliford M. Physical and psychological co-morbidity in irritable bowel syndrome: a matched cohort study using the General Practice Research Database. Aliment Pharmacol Ther. 2006;24:879–86.
16. Agrawal A, Khan MH, Whorwell PJ. Irritable bowel syndrome in the elderly: an overlooked problem? Dig Liver Dis. 2009;41:721–4.
17. Bharucha AE, Zinsmeister AR, Locke GR, et al. Prevalence and burden of fecal incontinence: a population-based study in women. Gastroenterology. 2005;129:42–9.
18. Bharucha AE, Zinsmeister AR, Schleck CD, Melton LJ. Bowel disturbances are the most important risk factors for late onset fecal incontinence: a population-based study in women. Gastroenterology. 2010;139:1559–66.

19. Varma MG, Brown JS, Creasman JM, Thom DH, Van Den Eden SK, Beattie MS, et al. Fecal incontinence in females older than 40 years: who is at risk? Dis Colon Rectum. 2006;49:841–51.
20. Damon H, Schott AM, Barth X, et al. Clinical characteristics and quality of life in a cohort of 621 patients with faecal incontinence. In J Colorectal Dis. 2008;23:845–51.
21. McCrea GL, Miaskowski C, Stotts NA, et al. A review of the literature on gender and age differences in the prevalence and characteristics of constipation in North America. J Pain Symptom Manage. 2009;37:737–45.
22. Talley NJ, Fleming KC, Evans JM, et al. Constipation in an elderly community: a study of prevalence and potential risk factors. Am J Gastroenterol. 1996;91:19–25.
23. Choung RS, Locke III GR, Schleck CD, et al. Cumulative incidence chronic constipation: a population-based study 1988–2003. Aliment Pharmacol Ther. 2007;26:1521–8.
24. Walter SA, Kjellstrom L, Nyhlin H, et al. Assessment of normal bowel habits in the general adult population: the Popcol study. Scand J Gastroenterol. 2010;45:556–66.
25. Jiang X, Locke III GR, Choung RS, et al. Prevalence and risk factors for abdominal bloating and visible distention: a population-based study. Gut. 2008;57:756–63.
26. Claesson MJ, Cusack S, O'Sullivan O, et al. Composition, variability, and temporal stability of the intestinal microbiota of the elderly. Proc Natl Acad Sci U S A. 2011;108 Suppl 1:4586–91.
27. Gallagher PF, O'Mahony D, Quigley EMM. Treatment of chronic constipation in the elderly. Drugs Aging. 2008;25:807–21.
28. Pimentel M, Chow EJ, Lin HC. Eradication of small bowel bacterial overgrowth reduces symptoms of irritable bowel syndrome. Am J Gastroenterol. 2000;95:3503–6.
29. Pimentel M, Chow E, Lin H. Normalization of lactulose breath testing correlates with symptom improvement in irritable bowel syndrome: a double-blind, randomized, placebo-controlled study. Am J Gastroenterol. 2003;98:412–9.
30. Jones MP, Craig R, Olinger E. Small intestinal bacterial overgrowth is associated with irritable bowel syndrome: the cart lands squarely in front of the horse. Am J Gastroenterol. 2001;96:3204–5.
31. Hasler WL. Lactulose breath testing, bacterial overgrowth, and IBS: just a lot of hot air? Gastroenterology. 2003;125:1898–900.
32. Quigley EM. A 51-year-old with irritable bowel syndrome: test or treat for bacterial overgrowth? Clin Gastroenterol Hepatol. 2007;5:1140–3.
33. Vanner S. The small intestinal bacterial overgrowth. Irritable bowel syndrome hypothesis: implications for treatment. Gut. 2008;57:1315–21.
34. Ford AC, Spiegel BM, Talley NJ, Moayyedi P. Small intestinal bacterial overgrowth in irritable bowel syndrome: systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2009;7:1279–86.
35. Riordan SM, McIver CJ, Wakefield D, Bolin TD, Duncombe VM, Thomas MC. Small intestinal bacterial overgrowth in the symptomatic elderly. Am J Gastroenterol. 1997;92:47–51.
36. Reddymasu SC, Sostarich S, McCallum RW. Small intestinal bacterial overgrowth in irritable bowel syndrome: are there any predictors? BMC Gastroenterol. 2010;10:23.
37. Whitehead WE, Palsson O, Jones KR. Systematic review of the comorbidity of irritable bowel syndrome with other disorders: what are the causes and implications? Gastroenterology. 2002;122:1140–56.
38. Clarke G, Quigley EM, Cryan JF, Dinan TG. Irritable bowel syndrome: towards biomarker identification. Trends Mol Med. 2009;15:478–89.
39. Longstreth GF, Thompson WG, Chey WD, et al. Functional bowel disorders. Gastroenterology. 2006;130:1480–91.
40. Jellema P, van der Windt DAWM, Schellevis FG, van der Horst HE. Systematic review: accuracy of symptom-based criteria for diagnosis of irritable bowel syndrome in primary care. Aliment Pharmacol Ther. 2009;30:695–706.
41. Ford AC, Talley NJ, Veldhuyzen van Zanten SJ, et al. Will the history and physical examination help establish that irritable bowel syndrome is causing this patient's lower gastrointestinal tract symptoms? JAMA. 2008;300:1793–805.
42. Locke III GR. Natural history of irritable bowel syndrome and durability of the diagnosis. Rev Gastroenterol Disord. 2003;3 Suppl 3:S12–7.
43. Ruigomez A, Wallander MA, Johansson S, Rodriguez LAG. One-year follow-up of newly diagnosed irritable bowel syndrome patients. Aliment Pharmacol Ther. 1999;13:1097–102.
44. Gu H-X, Zhang Y-L, Zhi F-C, Jiang B, Huang Y. Organic colonic lesions in 3,332 patients with suspected irritable bowel syndrome and lacking warning signs, a retrospective case-control study. In J Colorectal Dis. 2011;26:934–40.
45. Rex DK, Johnson DA, Anderson JC, et al. American College of Gastroenterology guidelines for colorectal cancer screening 2009 [corrected]. Am J Gastroenterol. 2009;104:739–50.
46. Hammer J, Eslick GD, Howell SC, et al. Diagnostic yield of alarm features in irritable bowel syndrome and functional dyspepsia. Gut. 2004;53:666–72.
47. Levy RL, Olden KW, Naliboff BD, et al. Psychosocial aspects of the functional gastrointestinal disorders. Gastroenterology. 2006;130:1447–58.
48. Huang CQ, Dong BR, Lu ZC, et al. Chronic diseases and risk for depression in old age: a meta-analysis of published literature. Ageing Res Rev. 2010;9:131–41.
49. Addolorato G, Mirijello A, D'Angelo C, et al. State and trait anxiety and depression in patients affected by gastrointestinal diseases: psychometric evaluation of 1641 patients referred to an internal medicine outpatient setting. Int J Clin Pract. 2008;62:1063–9.
50. Alexopoulos GS, Borson S, Cuthbert BN, et al. Assessment of late life depression. Biol Psychiatry. 2002;52:164–74.
51. Pardi DS, Kelly CP. Microscopic colitis. Gastroenterology. 2011;140:1155–65.
52. Kao KT, Pedraza BA, McClune AC, et al. Microscopic colitis: a large retrospective analysis from a health maintenance organization experience. World J Gastroenterol. 2009;15:3122–7.
53. Jeyarajah S, Faiz O, Bottle A, et al. Diverticular disease hospital admissions are increasing, with poor outcomes in the elderly and emergency admissions. Aliment Pharmacol Ther. 2009;30:1171–82.
54. Stollman N, Raskin JB. Diverticular disease of the colon. Lancet. 2004;363:631–9.
55. Sheth AA, Longo W, Floch MH. Diverticular disease and diverticulitis. Am J Gastroenterol. 2008;103:1550–6.
56. Egger B, Peter MK, Candinas D. Persistent symptoms after elective sigmoid resection for diverticulitis. Dis Colon Rectum. 2008;51:1044–8.
57. West AB, Losada M. The pathology of diverticulosis coli. J Clin Gastroenterol. 2004;38(5 Suppl 1):S11–6.
58. Ierardi E, Hassan C, Zullo A, et al. Segmental colitis associated with diverticula: a rare clinical entity and a new challenge for the gastroenterologist. Dig Liver Dis. 2009;41:794–7.
59. Tursi A. Segmental colitis associated with diverticulosis: complication of diverticular disease or autonomous entity? Dig Dis Sci. 2011;56:27–34.
60. Salem TA, Molloy RG, O'Dwyer PJ. Prospective, five-year follow-up study of patients with symptomatic uncomplicated diverticular disease. Dis Colon Rectum. 2007;50:1460–4.
61. Simpson J, Neal KR, Scholefield JH, Spiller RC. Patterns of pain in diverticular disease and the influence of acute diverticulitis. Eur J Gastroenterol Hepatol. 2003;15:1005–10.
62. Simpson J, Scholefield JH, Spiller RC. Origin of symptoms in diverticular disease. Br J Surg. 2003;90:899–908.

63. Spiller R. How inflammation changes neuromuscular function and its relevance to symptoms in diverticular disease. J Clin Gastroenterol. 2006;40 Suppl 3:S117–20.
64. Simpson J, Sundler F, Humes DJ, et al. Post inflammatory damage to the enteric nervous system in diverticular disease and its relationship to symptoms. Neurogastroenterol Motil. 2009;21:847–58.
65. Kang JY, Firwana B, Green AE, et al. Uncomplicated diverticular disease is not a common cause of colonic symptoms. Aliment Pharmacol Ther. 2011;33:487–94.
66. Quigley EMM. Gut microbiota, inflammation and symptomatic diverticular disease. New insights into and old and neglected disorder. J Gastrointestin Liver Dis. 2010;19:127–9.
67. Jung H-K, Choung RS, Locke III GR, et al. Diarrhea-predominant irritable bowel syndrome is associated with diverticular disease: a population study. Am J Gastroenterol. 2010;105:652–61.
68. Spiller RC, Humes DJ, Campbell E, et al. The Patient Health Questionnaire 12 Somatic Symptom scale as a predictor of symptom severity and consulting behavior in patients with irritable bowel syndrome and symptomatic diverticular disease. Aliment Pharmacol Ther. 2010;32:811–20.
69. Hervé S, Beaugerie L, Bouhnik Y, et al. Irritable bowel syndrome is more frequent in patients hospitalized for ischaemic colitis: results of a case-control study. Neurogastroenterol Motil. 2009;21:1170–e102.
70. Quan C, Talley NJ, Jones MP, et al. Gastrointestinal symptoms and glycemic control in diabetes mellitus: a longitudinal population study. Eur J Gastroenterol Hepatol. 2008;20:888–97.
71. Quigley EMM. Gastrointestinal dysfunction in movement disorders. Semin Neurol. 1996;16:245–50.
72. American College of Gastroenterology Task Force on Irritable Bowel Syndrome, Brandt LJ, Chey WD, Foxx-Orenstein AE, Schiller LR, Schoenfeld PS, Spiegel BM, et al. An evidence-based position statement on the management of irritable bowel syndrome. Am J Gastroenterol. 2009;104(Suppl 1):S1–35.
73. Rao SSC, Go JT. Update on the management of constipation in the elderly: new treatment options. Clin Interv Aging. 2010;5:163–71.
74. Quigley EMM, Fried M, Gwee KA, et al. World Gastroenterology Organisation Global Guideline. Irritable bowel syndrome: a global perspective. http://www.worldgastroenterology.org/assets/downloads/en/pdf/guidelines/20_irritable_bowel_syndrome.pdf. Accessed 10 July 2011.

Intestinal Ischemia

49

Hazar Michael and C.S. Pitchumoni

Intestinal ischemia (II) represents a spectrum of diseases. The presentations, treatment and prognosis of II depend largely on the nature and location of ischemic disorders. The two major II are: ischemic colitis (IC), more common and with an overall better prognosis, and mesenteric ischemia (MI), less common, but with a much worse prognosis [1]. In general, vascular abdominal emergencies must be included in the differential diagnosis of older patients with nonspecific abdominal pain, even if the examination is not suggestive. In general, vascular abdominal emergencies must be included in the differential diagnosis of older patients with nonspecific abdominal pain, even if the examination is not suggestive. Most diagnoses are time sensitive, with integrity of organs at risk in the case of thromboembolic disease or aneurysms of the aorta with rupture and shock early diagnosis of II will more likely preserve the bowel and minimize the damage [2].

Pathophysiology

At rest the gut receives about 25% of the cardiac output, which increases to 35% after meal [1, 3]. The abdominal aorta provides blood supply to the small and large intestines through three branches: celiac axis (CA), superior mesenteric artery (SMA), and inferior mesenteric artery (IMA) (Table 49.1). An extensive network of collateral and intramural submucosal vessels protects the bowel from ischemia [1–3]. Despite this protection and multiple regulatory mechanisms, the bowel remains at risk for ischemia for a variety of reasons. Two watershed areas exist in the colon: one at the splenic flexure, between SMA and IMA, and the other at the rectosigmoid junction, between IMA and rectal arteries [1, 4]. The CA, SMA, and IMA differ in several aspects; the caliber and the take-off of the three arteries from the aorta differ and influence the likelihood of a specific artery getting occluded. The SMA is the most likely artery to be affected by an embolus or platelet thrombus due to its oblique origin from the abdominal aorta, while the CA originates perpendicular to the axis of the abdominal aorta.

When the blood supply to the bowel falls below the metabolic demand, ischemic injury will occur. The type of the ischemic injury depends on the size (small vs. large) and the affected blood vessel (artery vs. vein), as well as the duration and chronicity of the insult. Table 49.2 summarizes the spectrum of II [5]. The injury ranges from transient functional alternation to transmural infraction [6]. Multiple etiologic factors lead to decreased blood supply, with atherosclerosis, emboli, thrombus, and vasospasm the major players in the majority of cases [7]. Due to the increased incidence of atherosclerosis and cardiovascular disorders with aging; the elderly are at increased risk for developing II. Although controversial, in a UK study, risk factors for IC and acute MI did not necessarily concur; diabetes and prior cardiovascular surgery were associated with acute MI (AMI) but not IC [8]. In addition, II has been reported to occur from SMA syndrome, due to compression by an abdominal aorta aneurysm [9].

Ischemic Colitis

IC was first described in 1963 [10]. The true incidence is underestimated either due to misdiagnosis as other entities, especially infectious colitis mimic IC; alternatively other, individuals with mild symptoms may not seek medical attention [1, 11, 12]. In a recent review, the incidence of IC in the

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Table 49.1 Arterial supply to the digestive system [1, 2]

Vessel	Arterial branches	Supplied area
Celiac axis	Left gastric artery	Stomach
	Common hepatic artery	Duodenum
	Splenic artery	Pancreas and liver
Superior mesenteric artery	Anterior and posterior inferior pancreaticoduodenal arteries	Jejunum
	Middle colic artery	Ileum
	Right colic artery	Right colon to around mid-transverse colon
	Ileocolic artery	
	Jejunal and ileal branches	
Inferior mesenteric artery	Left colic artery	Distal transverse colon to superior rectum
	Multiple sigmoid branches	
	Superior rectal artery	
Internal iliac	Middle rectal artery	Mid to distal rectum
	Inferior rectal artery	

Table 49.2 The spectrum and frequency of intestinal ischemia [4–6]

Type	Frequency (%)
Ischemic colitis	75
Acute mesenteric ischemia	25
Focal segmental ischemia	<5
Chronic mesenteric ischemia	<5

general population ranged from 4.5 to 44 cases per 100,000 person-years [12, 13]. IC accounts for 1.28 ± 0.89 per 1,000 hospitalizations [6, 14, 15]. The entity results from transient colonic hypoperfusion, at presentation the colonic blood flow may be already normalized [1, 6, 11]. Although multiple risk factors for IC exist, aging is the most common risk factor; others include decreased cardiac output, systemic hypotension, splanchnic vasoconstriction, medications, and increased intracolonic or intra-abdominal pressure of any etiology [1, 4, 6, 11]. IC has been reported after a diagnostic colonoscopy on the basis of increased intracolonic pressure [16, 17]. Female gender, age more than 65 years, constipation-predominant irritable bowel syndrome and chronic obstructive pulmonary disease (COPD) have a two to four-fold increased risk for IC [12, 13]. The association of IC with COPD is not entirely clear, but may be related to small vessel disease secondary to chronic smoking [12]. IC is a well-known complication of abdominal aortic aneurysm (AAA) repair. Clinically significant IC is encountered in 1–3% of elective repair, and up to 14% in cases of rupture [18]. Aneurysm rupture, operative time more than 4 h and baseline renal insufficiency were independent risk factors for IC [18]. Patients who developed IC after AAA repair have up to 53% mortality at 1 month and a lower 2 year survival (35%) compared to those who do not develop IC after AAA repair (86%) [18]. It is controversial if endovascular repair decreases the incidence of IC compared to open repair [18, 19]. Multiple factors contribute to IC after AAA repair with IMA interruption, microembolization, and hypoperfusion the main offenders [19]. In contrast to most other type of IC, there is a high rate of colectomy (59%) with 60% surgical mortality in AAA repair patients who develop IC [18]. Besides AAA repair, IC can also complicate abdominal aortic dissection [20]. Table 49.3 summarizes causes of IC [12, 21–29].

Acute onset of crampy lower abdominal pain followed by diarrhea, which can be bloody, is the most common presentation [1, 6, 11]. On examination, there is usually manifest mild to moderate localized tenderness without peritoneal signs. Severe abdominal pain, massive rectal bleeding, or presence of peritoneal signs suggests an alternative diagnosis or full thickness necrosis and perforation. While WBC counts are elevated in the majority of cases, fever and metabolic acidosis are uncommon and signify a severe disease.

IC usually is a segmental disease. The left colon is the most affected area in IC [30]. The rectum is relatively spared due to its rich collateral circulation. Pancolonic involvement is encountered only in 2.8–7% of affected patients [15, 30]. The incidence of isolated right sided IC (IRSIC) is increasing, and currently accounts for 25% of all cases of IC [30, 31]. IRSIC can be a manifestation of MI and requires special attention. Figure 49.1 demonstrates the arterial supply to the colon and the distribution of IC.

The diagnosis of IC requires high clinical suspicion, utilizing a constellation of symptoms to complement physical and endoscopic findings. For patients with clinical suspicion of IC and no alarm features, the best diagnostic modality is a colonoscopy with endoscopic biopsy (Fig. 49.2). The earliest endoscopic findings are subepithelial hemorrhage and edema; ulcerations are seen after 24 h of presentation and necrosis in severe cases [15]. In those with alarm symptoms or findings, an imaging study is a must prior to endoscopy to rule out other disease entities or complications. Findings on imaging are nonspecific; further, imaging study can be normal in early

Table 49.3 Causes of ischemic colitis [1, 4, 5, 8, 11, 14, 30]

Systemic hypoperfusion	Small-vessel disease
Cardiac failure	Atherosclerosis
Septic shock	Diabetes
Hemorrhagic shock	Hypertension
Pancreatitis	Hyperlipidemia
Hypovolemia	Vasculitis
Diuretics	Systemic lupus erythematosus
Hemodialysis	Polyarteritis nodosa
Long-distance running	Wegner granulomatosis
Major cardiovascular surgery	Rheumatoid arthritis
Coronary artery bypass grafting	Radiation
Aorta repair	Amyloidosis
Snake venom	Iatrogenic
Anaphylaxis	Surgical
Colonic hypoperfusion	Colectomy with inferior mesenteric artery ligation
Colonoscopy	Endoscopic retrograde cholangiopancreatography-related mesenteric hematoma
Colonic obstruction including carcinoma	Drugs
Strangulated hernia	Alosetron (lotronex)
Thrombosis or embolism	Tegaserod
Congenital hypercoagulable state	Antihypertensive drugs
Factor V Leiden mutation	Digoxin
Prothrombin G20210A mutation	Cocaine
Protein C or S deficiency	Interferon-ribavirin
Antithrombin III deficiency	Nonsteroidal anti-inflammatory drugs
Acquired hypercoagulable state	Pseudoephedrine
Antiphospholipid syndrome	Psychotropic drugs
Anticardiolipin antibodies	Vasopressors
Lupus anticoagulation	Other causes
Disseminated intravascular coagulation	COPD
Oral contraceptive pills	Sickle cell disease
Paroxysmal nocturnal hemoglobinuria	
Arterial emboli (cardiac)	
Cholesterol emboli	

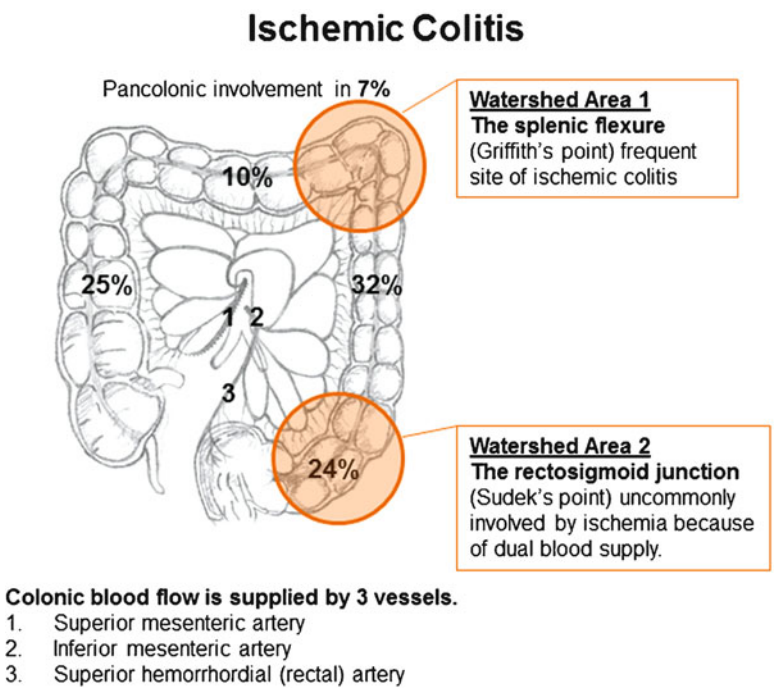

Fig. 49.1 Arterial blood supply to the colon and the distribution of ischemic colitis

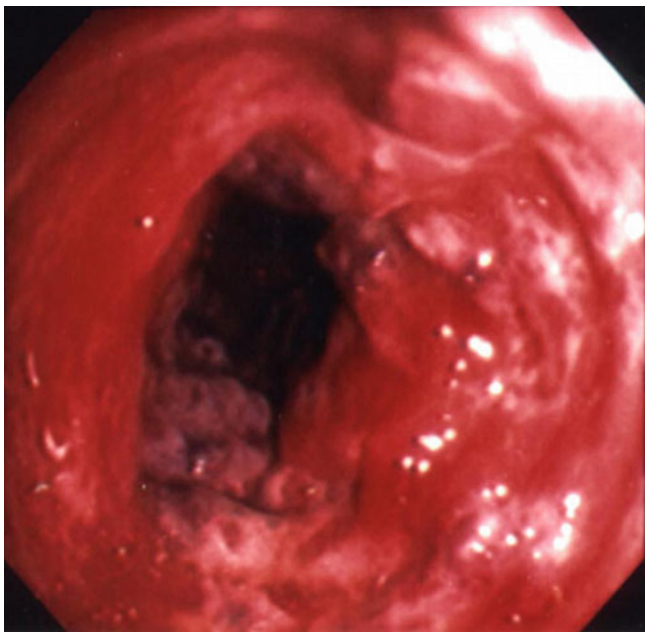

Fig. 49.2 Endoscopic view of sigmoid colon revealing circumferential mucosal edema, exudates and hemorrhage consistent with ischemic colitis

disease stages. While plain film of the abdomen may occasionally reveal thumb printing, a result of subepithelial hemorrhage and edema, its diagnostic value is limited and is being replaced largely with contrast computed tomography (CT) of the abdomen and pelvis. CT usually reveals segmental bowel wall thickness and in severe cases may reveal pneumatosis of the bowel wall or portal venous gas signifying bowel infarct [13, 22]. CT angiography (CTA) or mesenteric angiogram (MA) is not indicated for the majority of cases with IC, with IRSIC an exception.

Treatment of IC, generally, is medical and consists of keeping the patient NPO, hemodynamic stabilization, correcting the underlying causes if possible, and antibiotics for moderate to severe cases [1]. Surgery is needed in the minority of patients and usually reserved for those presenting with acute severe disease or a chronic complication such as stricture formation or for recurrence. The prognosis of IC usually is good, with a recurrence rate between 3 and 10% [1, 32]. Progression to chronic segmental colitis and stricture formation ranges from 0 to 17.9% and <1–20% respectively [15–32]. In one study only 12.9% had unfavorable outcome as defined by mortality and/or need for surgery [15]. Patients presenting with IRSIC have worse outcomes including at least a doubling of mortality rate and four to fivefold increased need for surgery [15, 30, 31]. End stage renal disease, COPD, hyperthyroidism, stroke, onset of IC after admission, abdominal pain without rectal bleeding, nonbloody diarrhea, peritoneal signs, intraperitoneal fluid on CT, delay in diagnosing IC till postoperative period, transmural necrosis, and mesenteric atherosclerosis in the resected specimen are predictors of worse outcomes [15, 30, 32–36]. In contrast presentation with rectal bleeding and nonsteroidal anti-inflammatory drug use predict better outcomes [32].

Mesenteric Ischemia

Based on the presentation MI may be termed AMI or chronic MI (CMI).

AMI

AMI develops following acute interruption to blood flow in the SMA. Table 49.4 summarizes the causes, frequency, and mortality rate in AMI [1]. Regardless of the etiology, the prognosis remains poor, with a mortality rate of 59–93%, largely due to the delay in the diagnosis [6].

Predisposing factors include age over 50 years, cardiac arrhythmia, decreased cardiac output, hypovolemia, and use of vasoactive drugs [1, 5]. Presenting symptoms are nonspecific, warranting a high index of suspicion to make the diagnosis. Abdominal pain is the most common presenting symptom, however, in an elder it may not be as obvious [1, 5]. An older adult may present with tachypnea or mental status changes [5]. Early on, the abdominal examination is benign without peritoneal signs. AMI should be considered in every older adult presenting with abdominal pain disproportionate to the physical findings, especially those with risk factors for AMI. Peritoneal signs, gastrointestinal bleeding, elevated lactic acid level, or abnormal plain film of the abdomen usually signifies an infarct and poor prognosis [1, 37].

Arterial thrombosis, due to the involvement of the SMA origin, has the worst prognosis. In mesenteric venous thrombosis (MVT) hematologic diseases and hypercoagulable state are common; here up to 50% of patients have a history of pulmonary embolism or deep venous thrombosis [38, 39]. Intra-abdominal inflammation and sepsis, cirrhosis and liver disease, sclerotherapy of esophageal varices, abdominal surgery, and blunt abdominal trauma can all lead to MVT [39, 40]. Due to the slower development of the occlusion in MVT, it tends to present less acutely than the arterial occlusion [39]. Colonic involvement with MVT and short bowel syndrome

Table 49.4 Causes, frequency, and mortality in acute mesenteric ischemia

Causes	Frequency (%)	Mortality (%)
Arterial embolism	40–50	70
Arterial thrombosis	25–30	90
Nonocclusive mesenteric ischemia	20–30	50–90
Mesenteric venous thrombosis	10	20–50

have substantial negative impact on short and long term survival [40]. Nonocclusive mesenteric ischemia (NOMI) results from mesenteric vasoconstriction and usually affects critically ill patients in the intensive care unit with poor splanchnic blood flow due to decreased cardiac output, hypovolemia, or use of vasoactive drugs including digoxin [7]. Abdominal pain may not be apparent and is absent in about 25%; ileus, gastrointestinal bleeding, or sepsis may be the presenting symptoms [39].

When AMI is suspected CT with contrast can be invaluable. CT findings in AMI can include: occlusion of any visceral artery, portomesenteric venous thrombosis, intestinal pneumatosis, portomesenteric venous gas, bowel wall thickening, bowel dilation, and solid organ infarct [41]. Multidetector row helical CT (MDCT) with biphasic mesenteric angiography can identify the vascular occlusion as well as its consequences. In a recent study of 79 patients with suspected AMI mesenteric undergoing MDCT angiography, the final diagnosis was AMI in 28 patients, with 96.4% diagnostic accuracy. The sensitivity, specificity, positive, and negative predictive values were 93%, 100%, 100%, and 94% respectively [42]. Further, the findings on MDCT can predict the prognosis of AMI [43]. Magnetic resonance angiography (MRA) is promising, but at present time, limited in availability and time consuming, is not widely used for AMI [1]. Selective MA remains the mainstay of the diagnosis of AMI [1, 5].

Treatment of AMI is complex and depends on the underlying cause and on the presence or absence of peritoneal signs. Prompt recognition and aggressive intervention play a substantial effect on outcomes. Early on attention is paid to resuscitation of fluid and electrolyte abnormalities coupled with correcting any feasible underling predisposing condition and the discontinuation of offending medications, such as vasoactive drugs [1, 5]. Broad-spectrum antibiotics should be initiated early due to the high risk of bacteria translocation and its potential to decrease the severity and the extent of ischemic injury [1, 5]. Glucagon decreases vasospasm, and may be a therapeutic consideration [1, 5]. After the initial imaging selective MA should be performed, and according to some experts, even if surgery is planned [6], to confirm the diagnosis and guide treatment. After the diagnostic portion of MA, the catheter should be left in place for papaverine infusion and possible follow-up serial angiograms [1, 6]. Papaverine is a vasodilator which can effectively treat the vasoconstriction, commonly occurring distal to the site of occlusion, and decrease the risk of reperfusion injury. In some studies papaverine infusion decreases the mortality rate from 70–90 to 40–50% [1]. Additional treatment depends on the underlying etiology. NOMI is treated according to the above-mentioned steps with surgery reserved only for those with peritoneal signs. In AMI the presence of peritoneal signs is an absolute indication for surgery. Surgery historically was the mainstay of treatment in AMI in those who are surgical candidates. At surgery dead bowels are resected and the blood flow resorted. Revascularization should be carried out prior to any resection to minimize the amount of resected bowel. Occasionally a second look surgery may be needed. In the last 2 decades interest had sparked in endovascular revascularization (ER) in the setting of AMI using a combination of thromboembolectomy and thrombolysis [44]. In a recent report on 70 patients with AMI in whom 81% received ER, and 87% success rate at revascularization, only 19% received immediate surgical intervention (ISI) [45]. Only 69% of ER group required laparotomy. The length of resected bowel, and acute renal and pulmonary failure were statistically better in patients treated by ER vs. ISI. Most importantly, the mortality rate in those with successful ER was statically better compared to those in whom ER failed or underwent ISI (36% vs. 50%, $P<0.05$). Anticoagulation therapy both in the acute and long term settings plays an important role in the treatment of MVT and results in decrease mortality and rethrombosis [1, 46].

CMI

It results from critical stenosis, ≥70%, most commonly from atherosclerosis, usually, of at least two of three mesenteric vessels [47]. The prevalence of mesenteric artery stenosis in the geriatric patients is high, and as much as 17.5% [48]. Due to abundant collaterals in the mesenteric circulation most obstruction is asymptomatic. Patients with CMI usually have diffuse atherosclerotic diseases and the risk factors to develop CMI generally speaking are those for developing atherosclerosis; less frequently it results from external compression, fibromuscular dysplasia, and vasculitis [49]. Typical symptoms include various types of postprandial abdominal pain, postprandial diarrhea, malabsorption, nausea, vomiting, fear of eating, and significant weight loss [1, 50]. Pain typically comes on following the ingestion of a meal and often predictable. Chronic dull abdominal pain usually signifies an advanced disease. Seventy percent of affected patients are female [47]. Differential diagnosis includes malignancy especially pancreatic and gastric cancer, peptic ulcer, and other disorders that cause abdominal pain.

Color duplex ultrasound is the screening method of choice for screening CMI with MRA and MDCT used to support the clinical diagnosis if the duplex is nondiagnostic [1, 50].

Treatment is usually recommended only for symptomatic patients either by ER by percutaneous transluminal angioplasty (PTA) with or without stent or surgical revascularization (SR). It appears that PTA with stent is superior to PTA alone [51]. In a recent analysis of publications over the last 20 years [52], SR was superior to ER in symptoms improvement, 5-year primary and assisted patency, and freedom of symptoms at 5 years (2.4, 3.8, 6.4, and 4.4 times more likely

respectively). Complication rate was 3.2 times more likely in SR but the difference in mortality was not statistically significant. Despite that ER remains an effective strategy. Therefore the choice of the revascularization method should be tailored to each individual patient anatomy, overall well-being and patient's preference as well as the local expertise.

Key Points

- IC is the most common form of II, but remains under diagnosed.
- Presence of peritoneal signs in any form of II is an absolute indication for immediate surgical intervention.
- Prognosis in IC is usually favorable; the majority recover uneventfully with low recurrence rate.
- IRSI and IC complicating abdominal aortic aneurysm (AAA) repair have worse prognosis with increased mortality and need for surgical intervention.
- The mortality rate of acute MI (AMI) remains high, warranting early recognition and aggressive intervention.
- Abdominal pain may not be evident in nonocclusive mesenteric ischemia (NOMI), requiring a high index of suspicion.
- Presentation of mesenteric venous thrombosis (MVT) tends to be less acute than arterial obstruction.
- Short and long term anticoagulation has a positive impact on the outcomes of MVT.
- Emerging improvement in diagnostic and interventional radiologic procedures will help early recognition, treatment, and prognosis of AMI.
- Presence of symptoms is mandatory to diagnose chronic MI (CMI).
- ER for CMI is effective with lower complication rate and is gaining increased popularity between physician and patients.

References

1. Cangemi JR, Picco MF. Intestinal ischemia in the elderly. Gastroenterol Clin North Am. 2009;38:527–40.
2. Lewiss RE, Egan DJ, Shreves A. Vascular abdominal emergencies. Emerg Med Clin North Am. 2011;29:253–72.
3. Vitin AA, Metzner JI. Anesthetic management of acute mesenteric ischemia in elderly patients. Anesthesiol Clin. 2009;27:551–67.
4. Stamatakos M, Douzinas E, Stefanaki C, et al. Ischemic colitis: surging waves of update. Tohoku J Exp Med. 2009;218:83–92.
5. Brandt LJ, Feuerstadt P. Intestinal ischemia. In: Feldman M, Friedman LS, Brandt LJ, editors. Sleisenger and Fordtran's gastrointestinal and liver disease. 9th ed. Philadelphia: W.B. Saunders; 2010: Chapter 114, electronic book.
6. Greenwald DA, Brandt LJ, Reinus JF. Ischemic bowel disease in the elderly. Gastroenterol Clin North Am. 2001;30:445–73.
7. Ozden N, Gurses B. Mesenteric ischemia in the elderly. Clin Geriatr Med. 2007;23:871–87.
8. Huerta C, Rivero E, Montoro MA, et al. Risk factors for intestinal ischemia among patients registered in a UK primary care database: a nested case-control study. Aliment Pharmacol Ther. 2011;33:969–78.
9. Okuyama Y, Kawakami T, Ito H, et al. A case of ischemic duodenitis associated with superior mesenteric artery syndrome caused by an abdominal aortic aneurysm. Case Rep Gastroenterol. 2011;5:278–82.
10. Boley SJ, Schwartz S, Lash J, et al. Reversible vascular occlusion of the colon. Surg Gynecol Obstet. 1963;116:53–60.
11. Theodoropoulou A, Koutroubakis IE. Ischemic colitis: clinical practice in diagnosis and treatment. World J Gastroenterol. 2008;14:7302–8.
12. Sreenarasimhaiah J. Diagnosis and management of ischemic colitis. Curr Gastroenterol Rep. 2005;7:421–6.
13. Higgins PD, Davis KJ, Laine L. Systematic review: the epidemiology of ischaemic colitis. Aliment Pharmacol Ther. 2004;19:729–38.
14. Brandt LJ, Boley SJ. AGA technical review on intestinal ischemia. American Gastrointestinal Association. Gastroenterology. 2000;118:954–68.
15. Montoro MA, Brandt LJ, Santolaria S, et al. Clinical patterns and outcomes of ischaemic colitis: results of the Working Group for the Study of Ischaemic Colitis in Spain (CIE study). Scand J Gastroenterol. 2011;46:236–46.
16. Dong Q, Wang Q, Li Y. Ischemic colitis after colonoscopy in a female patient. Am J Gastroenterol. 2009;104:2123–4.
17. Kao KT, Jain A, Sheinbaum A. Ischemic colitis following routine screening colonoscopy: a case report. Endoscopy. 2009;41 Suppl 2:E100.
18. Becquemin JP, Majewski M, Fermani N, et al. Colon ischemia following abdominal aortic aneurysm repair in the era of endovascular abdominal aortic repair. Vasc Surg. 2008;47:258–63.
19. Miller A, Marotta M, Scordi-Bello I, et al. Ischemic colitis after endovascular aortoiliac aneurysm repair: a 10-year retrospective study. Arch Surg. 2009;144:900–3.
20. Michael H, Brandt LJ, Hochsztein JG. Ischemic colitis complicating aortic dissection. Gastrointest Endosc. 2002;55:442–4.
21. Baixauli J, kiran RP, Delaney CP. Investigation and management of ischemic colitis. Cleve Clin J Med. 2003;70(11):920–34.
22. Elder K, Lashner BA, Al Solaiman F. Clinical approach to colonic ischemia. Cleve Clin J Med. 2009;76:401–9.
23. Halligan MS, Saunders BP, Thomas BM, et al. Ischaemic colitis in association with sigmoid carcinoma: a report of two cases. Clin Radiol. 1994;49:183–4.
24. Testini M, Marzaioli R, Gurrado A, et al. Massive mesenteric ischemia resulting from a giant strangulated umbilical hernia. Int Surg. 2007;92:296–9.
25. Punnam SR, Pothula VR, Gourineni N, et al. Interferon-ribavirin-associated ischemic colitis. J Clin Gastroenterol. 2008;42:323–5.
26. Dowd J, Bailey D, Moussa K, et al. Ischemic colitis associated with pseudoephedrine: four cases. Am J Gastroenterol. 1999;94:2430–4.
27. Kingsley DD, Schermer CR, Jamal MM. Rare complications of endoscopic retrograde cholangiopancreatography: two case reports. JSLS. 2001;5:171–3.
28. Krause R, Ameen V, Gordon SH, et al. A randomized, double-blind, placebo-controlled study to assess efficacy and safety of 0.5 mg and 1 mg alosetron in women with severe diarrhea-predominant IBS. Am J Gastroenterol. 2007;102:1709–19.
29. Lewis JH. The risk of ischaemic colitis in irritable bowel syndrome patients treated with serotonergic therapies. Drug Saf. 2011;34:545–65.
30. Brandt LJ, Feuerstadt P, Blaszka MC. Anatomic patterns, patient characteristics, and clinical outcomes in ischemic colitis: a study of 313 cases supported by histology. Am J Gastroenterol. 2010;105:2245–52.
31. Sotiriadis J, Brandt LJ, Behin DS, et al. Ischemic colitis has a worse prognosis when isolated to the right side of the colon. Am J Gastroenterol. 2007;102:2247–52.
32. Longstreth GF, Yao JF. Epidemiology, clinical features, high-risk factors, and outcome of acute large bowel ischemia. Clin Gastroenterol Hepatol. 2009;7:1075–80.

33. Ahn SE, Lee HL, Cho SC, et al. Is end stage renal disease a poor prognosis factor of ischemic colitis? Korean J Gastroenterol. 2009;53:235–8.
34. Paterno F, McGillicuddy EA, Schuster KM, et al. Ischemic colitis: risk factors for eventual surgery. Am J Surg. 2010;200: 646–50.
35. Reissfelder C, Sweiti H, Antolovic D, et al. Ischemic colitis: who will survive? Surgery. 2001;149:585–92.
36. Serralta de Colsa D, Arjona Medina I, García-Marín A, et al. Predictive factors of mortality in severe ischaemic colitis: postoperative analysis of 101 patients. Cir Esp. 2009;85:348–53.
37. Ritz JP, Runkel N, Berger G, et al. Prognostic factors in mesenteric infarct. Zentralbl Chir. 1997;122:332–8.
38. Martinez JP, Hogan GJ. Mesenteric ischemia. Emerg Med Clin North Am. 2004;22:909–28.
39. Burns BJ, Brandt LJ. Intestinal ischemia. Gastroenterol Clin North Am. 2003;32:1127–43.
40. Abu-Daff S, Abu-Daff N, Al-shahed M. Mesenteric venous thrombosis and factors associated with mortality: a statistical analysis with five-year follow-up. J Gastrointest Surg. 2009;13:1245–50.
41. Barajas Jr RF, Yeh BM, Webb EM, et al. Spectrum of CT findings in patients with atrial fibrillation and nontraumatic acute abdomen. AJR Am J Roentgenol. 2009;193:485–92.
42. Aschoff AJ, Stuber G, Becker BW, et al. Evaluation of acute mesenteric ischemia: accuracy of biphasic mesenteric multi-detector CT angiography. Abdom Imaging. 2009;34:345–57.
43. Moschetta M, Stabile Ianora AA, Pedote P, et al. Prognostic value of multidetector computed tomography in bowel infarction. Radiol Med. 2009;114:780–91.
44. Schoots IG, Levi MM, Reekers JA, et al. Thrombolytic therapy for acute superior mesenteric artery occlusion. J Vasc Interv Radiol. 2005;16:317–29.
45. Arthurs ZM, Titus J, Bannazadeh M, et al. A comparison of endovascular revascularization with traditional therapy for the treatment of acute mesenteric ischemia. J Vasc Surg. 2011;53: 698–705.
46. Cenedese A, Monneuse O, Gruner L, et al. Initial management of extensive mesenteric venous thrombosis: retrospective study of nine cases. World J Surg. 2009;33:2203–8.
47. White CJ. Chronic mesenteric ischemia: diagnosis and management. Prog Cardiovasc Dis. 2011;54:36–40.
48. Hansen KJ, Wilson DB, Craven TE. Mesenteric artery disease in the elderly. J Vasc Surg. 2004;40:45–52.
49. Zeller T, Macharzina R. Management of chronic atherosclerotic mesenteric ischemia. Vasa. 2011;40:99–107.
50. Zeller T, Rastan A, Sixt S. Chronic atherosclerotic mesenteric ischemia (CMI). Vasc Med. 2010;15:333–8.
51. Daliri A, Grunwald C, Jobst B, et al. Endovascular treatment for chronic atherosclerotic occlusive mesenteric disease: is stenting superior to balloon angioplasty? Vasa. 2010;39:319–24.
52. Gupta PK, Horan SM, Turaga KK, et al. Chronic mesenteric ischemia: endovascular versus open revascularization. J Endovasc Ther. 2010;17:540–9.

Inflammatory Bowel Disease

50

Jeffrey Raphael Abergel and Kiron M. Das

Introduction/Background/History

Inflammatory bowel disease (IBD) is a chronic, often debilitating illness. The three subtypes are Crohn's disease (CD), ulcerative colitis (UC), and indeterminate colitis. Crohn's disease can involve any part of the gastrointestinal tract. Ulcerative colitis and indeterminate colitis often involve the rectum and variable lengths of the colon. These three subtypes have overlapping features and similar treatments. Distinguishing between them may pose a clinical challenge. The diagnosis of indeterminate colitis is used for a patient with several characteristics of both Crohn's disease and ulcerative colitis. The definition and criteria of IBD have gone through multiple revisions as other conditions such as ischemic colitis, collagenous colitis, and lymphocytic colitis are now known to be distinct from IBD.

Though IBD usually afflicts patients in their 20s and 30s, a subgroup of patients are diagnosed after age 50. Key differences exist in diagnosis, treatment, and disease course between older and younger patients.

History

Crohn's disease was first described by the "Father of German Surgery" William Fabry in 1623 [1]. In 1932, it was categorized as a distinct entity by Crohn and his colleagues at the Mount Sinai Hospital who described a series of patients with terminal ileitis [2]. Ulcerative colitis was first noted by Samuel Wilks who delineated it from dysentery in 1859 [3]. Over the subsequent decades, physicians identified this entity more frequently. By 1909, 300 cases had been collected by the Royal Society of Medicine [4].

Epidemiology

IBD is more common in patients of Ashkenazi Jewish descent (from Eastern Europe and Russia) [5] and is relatively rare in African-American and Hispanic individuals [6]. However, due to a paucity of population-based epidemiologic studies, firm conclusions cannot be drawn [7].

The incidence and prevalence of IBD vary by region and both tend to be higher in the developed world. The incidence of UC in North America is between 2.2 and 14.3 cases per 100,000 person-years. For CD, the incidence ranges from 3.1 to 14.6 cases per 100,000 person-years. It is estimated that approximately 780,000 people in North America have UC, while 630,000 have CD [8]. Ulcerative colitis demonstrates a slight predilection for males, with an incidence of 8.2 cases per 100,000 patient years, compared to females with 5.9 cases per 100,000 patient years [9]. In CD, this trend is marginally reversed with a 1.2:1 female to male incidence ratio [10].

Earlier reports emphasize a bimodal incidence for IBD; the first peak occurring between age 21 and 30 and the second peak, between age 51 and 70 [11]. This second peak has recently come into question as several recent studies have failed to consistently demonstrate an increase in incidence after the age of 40.

A large retrospective study of residents of Minnesota demonstrated that in the seventh decade of life, the incidence rates for UC were 4.4 per 100,000 patient years in women and 10.5 cases per 100,000 patient years in men. In the third decade of life, the rates were 9.9 per 100,000 patient years in women and 14.1 cases in men [9]. In the same population, the incidence rates for CD were 4.1 per 100,000 patient years in the seventh decade of life, compared to a rate of 12.8 in the third decade of life [10]. No bimodal distribution was found in a number of other studies from Stockholm county Sweden (1997) [12], Northern France (2004) [13], Southern Germany (2008)

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[14], Korea (2009) [15], Australia (2010) [16], and China (2010) [17]. However, in a 2010 retrospective study from Uppsala county, Sweden, a second peak in UC incidence was noted in patients older than 60. This peak was more prominent in men than women [18]. A Japanese study indicates that the proportion of UC with "old age onset" has increased between 1981 and 2000 [19]. A large epidemiological study of nine European countries demonstrated a large peak in IBD-related hospitalizations in younger patients as well as a smaller peak in older patients [20]. The question of whether the incidence of IBD has a bimodal distribution thus remains open.

Pathogenesis

The pathogenesis of IBD is a topic of great complexity with significant interplay of genetics, environmental factors, and immune dysregulation. Autoimmunity has been emphasized in the pathogenesis of ulcerative colitis [21].

Genetic Factors

IBD demonstrates non-Mendelian heritability with CD having a stronger genetic component than UC. A person with a monozygotic twin who has UC incurs a 6–18% risk of developing this disease. The concordance rate for CD between monozygotic twins is significantly higher at 44–58% [22, 23]. First-degree relatives of patients with IBD have a 3–20 times higher risk of developing this disease [24]. Data suggest that the chance of a first-degree relative of an IBD patient developing the disease is 3.5–35 times higher than the general population [24, 25]. Crohn's disease acquired later in life appears to have less of a heritable component. Patients with symptom onset after the age of 40 are less likely than younger patients to have relatives with the disease [26, 27].

Recent advances have helped elucidate the genetic determinants that predispose patients to IBD. For instance, the IBD1 gene codes for the NOD2/CARD15 protein that regulates macrophage-signaling pathways [28]. Mutations in this gene are associated with a greater than 20-fold increase in the rate of developing CD [29, 30]. A large study from Germany evaluated different gene loci and found that patients with UC were more likely to have two particular MDR1 single nucleotide polymorphisms. This association only reached statistical significance in patients under the age of 46 [31]. A study of Japanese patients with UC evaluated the prevalence of polymorphism of the IL-1 receptor antagonist gene. This polymorphism was only associated with UC in patients diagnosed before the age of 30 [32]. A number of other gene mutations have been associated with a predisposition for IBD including IL-10 receptor [33], IL-23 receptor [34], and ATG16L1 [35, 36]. The distribution of these genes among different age groups has not yet been examined.

Environmental Factors

The incidence and prevalence of IBD tends to be lower in developing countries. As these places become more industrialized, disease incidence tends to increase to values closer to developed countries [8]. Additionally, immigrants from the developing world to the western world tend to have significant increase in incidence and prevalence of IBD. Immigrants from the Indian subcontinent to Great Britain acquired the risk of IBD of the native British population [37–39]. Several studies of collective farming communities in Israel have demonstrated that three different ethnic groups (Israeli Born, American/European Born, and African/Asian Born) have converging prevalences of both UC and CD [40, 41]. It is unclear if these findings are secondary to improved diagnostic techniques, more access to medical care, dietary changes, or fewer confounding diagnoses (such as infectious diarrhea). Interestingly, both within and between countries, there appears to be an increasing prevalence in the northern regions as compared with the southern regions. These findings were not adequately explained by differences in education or tobacco use. Factors that have been proposed as causes of the North–South gradient include diet, socioeconomic status, genetic variations, and climate [42, 43].

Tobacco use is a well-established environmental factor in CD, with smoking increasing the risk for developing this disease [44, 45]. Patients who continue smoking after surgery are two to three times as likely to experience a clinical recurrence and two and a half times more likely to require reoperation at 10 years [46]. The relationship between smoking and UC is more complex, with active smoking somewhat protective against the development of ulcerative colitis. However, former smokers are more likely to develop UC than the average population [44, 47]. One study confirmed that older patients with UC are more likely than younger patients to have used tobacco, though the likely presence of lead-time bias questions the finding [48].

Patients who underwent an appendectomy are protected against developing ulcerative colitis [49, 50]. This effect was only noted when the surgery was performed for an inflammatory process such as appendicitis. A meta-analysis from 2008 demonstrated that patients undergoing appendectomy were more likely to receive the diagnosis of Crohn's [51]. However, differences in diagnostic methods in some studies as well as the lack of statistical significance 5 years after the surgery make a connection less likely.

Immune Dysregulation

Though there are unanswered questions about the pathophysiology of CD, intestinal bacteria and the heightened immune response are certainly significant factors. One study revealed that specific bacterial DNA sequences resulted in a higher

rate of IgA seroreactivity in the intestinal specimens of CD patients (54%) compared to unaffected patients (4%) [52]. Patients with CD express antibodies to E. coli outer membrane porin C. This phenomenon is more frequent in patients with fibrostenosing disease and in those who require small bowel operations [53].

The autoimmune nature of ulcerative colitis has been established in a number of studies. Perinuclear antineutrophil cytoplasmic antibodies were found to be 92% specific in pediatric patients [54]. Patients with active UC have serum markers of antibody-dependent cell-mediated cytotoxicity which decrease significantly after total procto-colectomy [55]. Cytotoxic T-Cell lines derived from the peripheral blood leukocytes of UC demonstrated cytotoxicity against colonic epithelial cells [56]. Antibodies to a colonic epithelial protein, Tropomyosin Isoform 5, have been isolated from ulcerative colitis patients. Antibodies to a colonic epithelial protein, Tropomyosin Isoform 5, have been detected in the serum and colonic mucosa of patients with UC. These antibodies induce complement activation and the destruction of colonic epithelium [57].

Diagnosis

Endoscopic findings of IBD include mucosal granularity, erythema, edema, friability, and ulceration. Ulcerative colitis only involves the mucosal layer of the colon, whereas CD is a transmural disease involving all segments of the gastrointestinal tract. Rectal involvement can often help distinguish between CD and UC. Proctitis is a hallmark of UC, while the rectum can be spared in CD. The inflammation in CD is often patchy and segmental. UC usually has a more continuous distribution. Computerized Tomography is often useful for identifying complications of IBD such as fistulas, abscesses, perforations, and malignancies. Though CT scans are gradually replacing barium studies, the latter is quite useful for the identification and characterization of small intestinal and colonic strictures. Additionally, barium enema may be safer in older adults with chronic kidney disease as intravenous contrast is not needed. Colonoscopy with mucosal biopsies is the most common method for diagnosis of IBD. However, given the superficial nature of the tissue specimens obtained in this way, it often fails to distinguish between subtypes of IBD. Small bowel follow-through, CT enterography, and videocapsule endoscopy are a few modalities for diagnosing small bowel disease. These tests often help solve the diagnostic problem of differentiating CD from UC.

Additional diagnostic tests include specific antibodies such as p-ANCA, ASCA (IgG and IgA), anti-CBir1, and anti-OmpC. This panel can be helpful in the subset of patients in whom the diagnosis of IBD is in question. These blood tests are of particular use in elderly patients to distinguish between IBD and resistant infectious colitis (i.e.: *Clostridium difficile* colitis), recurrent diverticulitis, chronic ischemic colitis, and NSAID-induced colitis/enteritis. Distinguishing between these conditions is critical as the risks associated with IBD medications, surgery, and undertreatment are higher in older patients [58].

Crohn's Disease

Crohn's patients whose symptoms begin after age 40 have a shorter lag time between symptom onset and seeking medical attention. A diagnosis of CD is made earlier in older patients than in younger patients (1.8 years vs. 2.7 years), despite a higher rate of misdiagnosis with malignancy, ischemic colitis, or diverticulitis [26]. A small series of 22 patients found that the average delay until diagnosis in patients over 50 was 3.5 years [59]. Most presenting symptoms, including diarrhea, hematochezia, and weight loss, were present in similar frequencies of younger and older patients. However, abdominal pain/cramping was less common in older patients [26].

There are some differences between older and younger patients in the anatomical involvement of Crohn's disease. One study showed that 15.2% of patients diagnosed after age 40 had small bowel disease, while 42.3% had ileocolonic disease and 42.5% had colitis alone. The rate of colonic involvement was significantly higher in older patients compared to younger patients (Table 50.1) [27]. A different study which looked at 43 patients diagnosed after age 60 demonstrated small bowel disease in 30.2%, ileocolonic disease in 23.2%, and colonic disease in 41.9%. In the same study, older patients were more likely than younger ones to have "complex disease" manifested as strictures (44.2%) or penetrating/fistulizing disease (20.9%) [60].

Ulcerative Colitis

Significant differences are seen between patients diagnosed with UC after age 50 compared to their younger counterparts. Older patients are more likely to present with constipation and less likely to present with fever, weight loss, or diarrhea [61]. In contrast, another study found that older patients tended to present with more daily bowel movements than the

Table 50.1 Distribution of Crohn's disease in older adults

				Distribution		
References	Year	# of older patients	Age	Ileitis (%)	Ileocolitis (%)	Colitis (%)
Polito et al. [27]	1996	67	>40	15.2	42.3	42.5
Freeman [60]	2007	43	>60	30.2	23.2	41.9

Table 50.2 Distribution of ulcerative colitis in older adults

References	Year	*N*	Cutoff age	Comments
Zimmerman et al. [62]	1985	97	51	Higher rate of distal colonic involvement
Riegler et al. [48]	2000	1,705	NA	Colitis is more limited with advancing age. This might be due to a higher prevalence of women in the younger groups
Triantafillidis et al. [63]	2001	413	60	No significant differences in disease distribution
Fujimoto et al. [19]	2007	844	60	Older patients had milder colitis and proctitis
Lee et al. [61]	2010	455	40	Pancolitis was less common in older patients

young [62]. The severity and outcomes of the first episode of colitis in patients from both age groups were similar [63].

Some data indicate that a later age of diagnosis increases the risk of recurrence in the first year, whereas 2.5 years after diagnosis, there is a protective effect [64]. A Korean study found that 242 patients with ulcerative colitis diagnosed after age 40 had similar rates of hospital admission, relapse, and surgery when compared to younger patients [61].

Several studies have found that younger patients tend to have a greater disease extent [59, 61, 62], and a Japanese study noted that older patients tend to have milder colitis and proctitis compared to younger counterparts [19]. However, a relatively large percentage of veterans with UC had pancolitis (63%). A Greek study showed no statistically significant difference in disease distribution between older and younger patients (Table 50.2) [63]. Population-based epidemiological studies are required before conclusions can be drawn.

Treatment

Medical Treatment

Sulfasalazine and 5-Aminosalycilates

The oldest drug used in the treatment of IBD is sulfasalazine which was developed in early 1940s [65]. Subsequently, one of its two major metabolites, 5-amino salicylate (5-ASA), was found to be the therapeutic moiety [66] and the other metabolite, sulfapyridine, was discovered to be responsible for the majority of the side effects [67]. Several 5-ASA preparations also known as mesalamines were developed during the last 3 decades and have a more limited side effect profile. Due to their relatively few side effects and potential anti-cancer activity [68–70], they are the mainstay of therapy for mild-to-moderate UC. Some formulations are useful in patients suffering from CD as well. This class of medications works topically by inhibiting cyclooxygenase and thus blocking the production of proinflammatory prostaglandins. Sulfasalazine and 5-ASA derivatives also inhibit NF-κB, a mediator of cytokines [68, 70]. Additionally, these medications have been shown to suppress TC-22, a marker for colon cancer [71].

Though 5-ASA products are only minimally absorbed, they can still cause significant interactions with medications commonly used by older patients. The serum concentration of cardiac glycosides such as digoxin levels can decline while on these medications. Serum levels of digoxin should therefore be monitored more closely after starting sulfasalazine or a 5-ASA medication. 5-ASA derivatives may also increase the tendency to hemorrhage in patients taking heparin [66].

Mesalamine enemas are likely to be unsuitable for many elderly patients given the increased prevalence of pelvic floor disorders, rectal prolapse, and incontinence. The rate of fecal incontinence in the over-70 age group is approximately 15% [72]. Mesalamine suppositories and hydrocortisone foam are more likely to be well tolerated and should lead to higher levels of medication compliance.

Corticosteroids

Corticosteroids are frequently used as treatment for acute exacerbations of IBD. These medications inhibit production of TNF-alpha, IL-1, and IL-8. Much like 5-ASA derivatives, they inhibit NF-κB and proinflammatory prostaglandins [68]. Clinicians should aim to minimize the duration and dose of systemic corticosteroids in all patients as they cause significant morbid side effects. This goal is even more pressing in the elderly who at baseline are prone to osteoporosis, hyperglycemia, and cataracts. Corticosteroids can also worsen hypokalemia an issue that can be particularly problematic in older adults who take diuretics for fluid overload or hypertension [73, 74]. Budesonide is an oral corticosteroid that is used to treat small bowel CD; it has high first-pass hepatic metabolism and therefore more limited systemic side effects [68].

Crohn's patients older than 65 are equally likely to receive steroids for a flare than their younger counterparts. However, patients over 50 are at a higher risk for developing adverse reactions to steroids such as hypertension, hypokalemia, and altered mental status [75]. An Italian study of patients with UC over age 50 tended to have lower rates of corticosteroid use compared to those below age 25, although the age at diagnosis is unknown for these patients [48]. A Korean study confirmed these findings by demonstrating higher rates of corticosteroid administration in patients diagnosed earlier than age 40 [61]. These findings contradict two studies from the 1980s that found higher rates of systemic steroid use in patients diagnosed at a later age [62, 76]. One possible explanation of this discrepancy is evolving practices among clinicians, with today's gastroenterologists being more cautious regarding corticosteroid treatment in older patients.

Purine Analogs

6-Mercaptopurine (6-MP) and its pro-drug, azathioprine, are often used to induce and maintain remission in patients with CD, UC, and indeterminate colitis. They are powerful immunosuppressants that interfere with nucleic acid metabolism that promotes lymphocyte proliferation following antigenic stimulation [68]. All patients must have frequent blood tests to monitor for adverse reactions such as bone marrow suppression and hepatotoxicity. Elderly patients are more likely to have underlying liver and bone marrow disease, thus making them more susceptible to the side effects. Patients on purine analogs have an above average risk for developing lymphoproliferative disorders, and this effect appears to increase with age. In a prospective cohort study of almost 20,000 patients with IBD, age was found to be an independent predictor of the development of lymphoproliferative disease. The calculated hazard ratio was 1.06 per 1-year increase in age. The yearly incidence rate (per 1,000 patient years) for individuals older than 65 taking purine analogs was 5.41 as compared to 0.37 for patients under 50 and 2.58 for patients between age 50 and 65 [77].

Older patients should be warned that this class of medications could alter the effectiveness and side effects of vaccines. Azathioprine and 6MP can reduce the immune response to inactivated vaccines such as the influenza immunization and thus render them less efficacious. Live vaccines such as varicella should be avoided in patients taking these medications as they can lead to vaccine-related infections. Purine analogs may also reduce the anticoagulant effects of warfarin, a drug commonly used in older-age patients for deep vein thromboses, atrial fibrillation, and other ischemic disorders [78, 79].

Anti-tumor Necrosis Factor Drugs

In 1998, Infliximab, a monoclonal antibody against TNF-alpha, was approved by the FDA for use in patients with CD. It has since been approved for UC, ushering in a paradigm shift in the treatment of moderate-to-severe IBD. Infliximab and the other biologic agents, adalimumab and certolizumab (both of which have been approved by the FDA for the treatment of CD), function by inactivating the Tumor Necrosis Factor molecule [80–82]. This blocks the activation of the TNF-receptor, thereby preventing the release of this proinflammatory cytokine and T-cell activation [68]. Due to the alterations in patient's immune function, vaccines should not be administered in those who have received biologic agents in the past 3 months. Similar to purine analogs, vaccine-related infections can occur if live vaccines such as varicella are administered. Additionally, patients on anti-TNF agents are at risk for new heart failure as well as exacerbations of preexisting heart failure [68].

A recent large retrospective study from Italy suggested that elderly patients on anti-TNF therapy had a higher rate of infections and a higher mortality rate. Severe infections were noted in 11% of patients over 65 treated with infliximab or adalimumab. This is much higher when compared to the rate of severe infections in the elderly not on anti-TNF agents (0.5%) as well as patients under 65 who received these medications (2.6%). The same study demonstrated a significantly higher mortality rate for older patients on biologic agents. However, the study was retrospective and did not provide information regarding severity of disease in the different study groups [83]. Further prospective trials are needed for conclusions to be drawn.

Surgery

As the options for medical management of IBD increase, the percentage of patients requiring surgery diminishes. Despite this, surgery remains an integral part of management of refractory disease, malignancy, and complications such as perforation, obstruction, and fistulas. A retrospective study found no differences between surgery rates between older and younger UC patients [61]. A cross-sectional study of over 140,000 American patients with IBD confirmed this finding and noted a higher rate of undergoing surgery in UC patients younger than 65 compared to older patients (20.6% vs. 11.6%) [84]. In one study, Crohn's patients older than 40 had similar rates of surgery than their younger counterparts [26]. Two other studies, including the large cross-sectional study mentioned above, showed lower rates of operation in older patients with CD [63, 84]. It is important to note that all of these studies answer the question of whether older patients undergo surgery more often and not whether or not the severity of their illness warrants surgery more often. Older patients are more likely to have comorbidities that could be relative or absolute contraindications to potentially complicated operations. This almost certainly accounts for some older patients with IBD who do not undergo surgery (Table 50.3).

A study of 158 patients with ulcerative colitis who underwent operations helps elucidate the indications for surgery. Twelve percent of patients over 50 years of age underwent operations on an emergent basis for perforation, hemorrhage, or toxic colitis. When the surgical procedure was elective, 59% of patients had intractable disease, 27% were found to have a mass or stricture, and 14% had evidence of dysplasia on biopsies taken during colonoscopy. In 12.6% of the patients, dysplasia was discovered in the surgical specimen, while 6% were found to have invasive cancer [85].

A small study found that colonic involvement was more common in Crohn's patients older than 55 who underwent abdominal surgery when compared to younger patients. Small bowel and ileocecal resections were less common in older patients [86]. Another study found that all 5 of 22 Crohn's patients older than 50 who had colonic disease underwent surgery [59].

Overall, older IBD patients tend to have worse outcomes after surgery. Older patients were found to have a shorter lag time between symptoms and operation. Unfortunately, they

Table 50.3 Rates of surgery in older patients with inflammatory bowel disease

References	Year	*N*	Cutoff age	Crohn's or ulcerative colitis	Rate of surgery in older patients
Wagtmans et al. [26]	1998	445	40	Crohn's	Similar rates of surgery
Triantafillidis et al. [63]	2001	413	60	UC	Lower rate of surgery
Ananthakrishnan et al. [84]	2009	140,996	65	Both	Lower rate of surgery in both UC and CD
Lee et al. [61]	2010	455	40	UC	Similar rates of surgery

Table 50.4 Special features of IBD in the older adult

Variable	Comments
Second peak of IBD incidence in older adults	Though older data have demonstrated a second peak, newer studies are inconsistent [12–17] This may be secondary to improved diagnostic techniques
Genetic predispositions to IBD	Two SNPs associated with ulcerative colitis not seen in older patients [31, 32] Older Crohn's patients less likely to have affected relatives [26, 27]
Age-related differences in clinical manifestations	Older patients with Crohn's develop strictures and fistulas more frequently [60] Older ulcerative colitis patients are less likely to present with weight loss or fever [48, 61]
Considerations in treatment	Older patients are at risk for hyperglycemia, hypokalemia, hypertension, and lymphoma, all potential complications of certain IBD therapies [70, 72, 73, 75] Some vaccinations are contraindicated if on anti-TNF agents or purine analogs [76–80] These patients with pelvic floor disorders may tolerate enema therapy poorly
Outcomes	Older hospitalized patients have a higher mortality rate [82, 85] The elderly IBD patients have longer postoperative hospital stays and developed recurrent symptoms more quickly [26, 82] A higher rate of colorectal cancer is seen in older patients with IBD [87]

also developed recurrent symptoms of Crohn's disease more quickly after surgery when compared to younger patients (3.7 years vs. 5.8 years) [26]. On average, elderly patients also experience longer postoperative hospital stays [84].

Outcomes

A higher mortality rate was found in hospitalized IBD patients older than 65 when compared to their younger counterparts (odds ration 3.91) [84]. This finding was confirmed in a study from Scotland where patients with UC showed increasing mortality with age. The 3-year mortality rates were as follows: in age group below 50: 1.7%, 50–64: 10.6%, older than 65: 39.2% (Table 50.4) [87]. Several studies show conflicting results. A retrospective study of 295 patients demonstrated that patients diagnosed after age 50 were more likely than those diagnosed before age 30 to achieve steroid-free clinical remission (64% vs. 49%) [88]. Another study demonstrated a lower relapse rate in UC in those over 55. However, no information about the rates of immunomodulator or Anti-TNF agent administration was provided [15].

A retrospective study found an increased risk of colorectal cancer in patients diagnosed with UC after age 40. Older patients had UC for 10 years before developing malignancy, while younger patients had a 22-year interval between UC and cancer [89].

The extraintestinal manifestations of IBD are listed in Table 50.5 [90].

Key Points

- There are two peaks in incidence of inflammatory bowel disease (IBD), one between ages 21 and 30 and the other in older patients. Recent studies question a second peak of incidence.
- UC in older adults are less likely to present with weight loss and fever than younger individuals.
- Older patients with CD are more likely to develop strictures or fistula.
- Treatment of IBD in the elderly is complicated by a higher risk for infections, hyperglycemia, lymphoma, hypertension, and hypokalemia.
- Evidence for the distinctness of IBD in the elderly can be found in genetic studies. Two MDR1 single nucleotide polymorphisms as well as a polymorphism of the IL-1 receptor antagonist gene have been associated with development of UC. Crohn's patients older than 40 are less likely to have affected relatives indicating a weaker genetic influence.
- Overall, older IBD patients tend to have worse outcomes than younger patients. They are also at a higher risk of developing colorectal cancer.

Table 50.5 Extraintestinal manifestations of IBD [90]

Type	Extraintestinal manifestation	Features
Rheumatologic	Type 1 arthropathy	Asymmetric, pauciarticular, associated with active IBD
	Type 2 arthropathy	Symmetric, polyarticular, independent of IBD activity
	Axial arthropathy	Independent of IBD activity. Can be identical to anklyosing spondylitis
Metabolic bone diseases	Osteopenia	Prevalence of 40–50%. Corticosteroids are a risk factor
	Osteoporosis	Prevalence of 15%. Corticosteroids are a risk factor
	Osteomalacia	Mostly in CD patients especially after ileal resection
	Osteonecrosis	Most common in the hip. Corticosteroids are a risk factor
Dermatologic	Erythema nodosum	Up to 15% of patients with IBD. Raised, tender nodules on the extensor surfaces of the lower extremities. Usually correlates with disease activity
	Pyoderma gangrenosum	Pustule with central necrosis and ulceration, seen in the skin, more in lower legs. Correlation with disease activity not clear
	Oral aphthous ulcers	Occurs in 10–30% of patients
Ophthalmologic	Episcleritis	Acute redness and irritation of eyes without visual loss
	Scleritis	Severe eye pain and tenderness. Can result in vision impairment and retinal detachment
	Uveitis	Associated with rheumatologic and dermatologic manifestations of IBD. Presents with eye pain, erythema, and photophobia
Hepatobiliary	Primary sclerosing cholangitis	More common in UC patients. Presents with RUQ pain, jaundice, and weight loss. Elevated alkaline phosphatase is nearly universal. Diagnosed with ERCP, MRCP, or liver biopsy. High risk: cholangiocarcinoma and colorectal cancer
	Cholelithiasis	Prevalence of 25% in CD patients (mostly ileal disease)
Renal	Nephrolithiasis	Prevalence of up to 19% in IBD patients. Usually calcium oxalate stones, mostly in CD patients with ileal involvement
Miscellaneous	Secondary amyloidosis	Can result in kidney injury, cardiomyopathy, and neuropathy

- Older patients nevertheless experience disease characteristics that differ from their younger counterparts. It is conceivable that IBD in the elderly will be reclassified as a separate subtype with adjusted diagnostic and treatment recommendations.

References

1. No authors listed. Wilhelm Fabry (1560–1624)—the other Fabricus. JAMA. 1964;190:933.
2. Crohn BB, Ginzburg L, Oppenheimer GD. Regional ileitis. A pathological and clinical entity. JAMA. 1932;99(16):1323–9.
3. Wilks S. Morbid appearances in the intestine of Miss Bankes. Lond Med Times Gazette. 1859;2:264–5.
4. De Dombal FT. Ulcerative colitis: definition, historical background, aetiology, diagnosis, natural history and local complications. Postgrad Med J. 1968;44(515):684–92.
5. Roth MP, Petersen GM, McElree C, et al. Geographic origins of Jewish patients with inflammatory bowel disease. Gastroenterology. 1989;97(4):900–4.
6. Calkins BM, Lilienfeld AM, Garland CF, et al. Trends in incidence of ulcerative colitis and Crohn's disease. Dig Dis Sci. 1984;29(10):913–20.
7. Jackson JF, Kornbluth A. Do black and Hispanic Americans with inflammatory bowel disease (IBD) receive inferior care compared with white Americans? Uneasy questions and speculations. Am J Gastroenterol. 2007;102(7):1343–9.
8. Loftus Jr EV. Clinical epidemiology of inflammatory bowel disease: incidence, prevalence, and environmental influences. Gastroenterology. 2004;126(6):1504–17.
9. Loftus Jr EV, Silverstein MD, Sandborn WJ, et al. Ulcerative colitis in Olmsted County, Minnesota, 1940–1993: incidence, prevalence, and survival. Gut. 2000;46(3):336–43.
10. Loftus Jr EV, Silverstein MD, Sandborn WJ, et al. Crohn's disease in Olmsted County, Minnesota, 1940–1993: incidence, prevalence, and survival. Gastroenterology. 1998;114(6):1161–8.
11. Brandt LJ. Gastrointestinal disorders of the elderly. New York: Raven; 1984.
12. Lapidus A, Bernell O, Hellers G, et al. Incidence of Crohn's disease in Stockholm County 1955–1989. Gut. 1997;41(4):480–6.
13. Molinié F, Gower-Rousseau C, Yzet T, et al. Opposite evolution in incidence of Crohn's disease and ulcerative colitis in Northern France (1988–1999). Gut. 2004;53(6):843–8.
14. Ott C, Obermeier F, Thieler S, et al. The incidence of inflammatory bowel disease in a rural region of Southern Germany: a prospective population-based study. Eur J Gastroenterol Hepatol. 2008;20(9):917–23.
15. Jang ES, Lee DH, Kim J, et al. Age as a clinical predictor of relapse after induction therapy in ulcerative colitis. Hepatogastroenterology. 2009;56(94–95):1304–9.
16. Wilson J, Hair C, Knight R, et al. High incidence of inflammatory bowel disease in Australia: a prospective population-based Australian incidence study. Inflamm Bowel Dis. 2010;16(9):1550–6.
17. Zheng JJ, Zhu XS, Huangfu Z, et al. Prevalence and incidence rates of Crohn's disease in mainland China: a meta-analysis of 55 years of research. J Dig Dis. 2010;11(3):161–6.
18. Rönnblom A, Samuelsson SM, Ekbom A. Ulcerative colitis in the county of Uppsala 1945–2007: incidence and clinical characteristics. J Crohns Colitis. 2010;4(5):532–6.
19. Fujimoto T, Kato J, Nasu J, et al. Change of clinical characteristics of ulcerative colitis in Japan: analysis of 844 hospital-based patients from 1981–2000. Eur J Gastroenterol Hepatol. 2007;19(3):229–35.
20. Sonnenberg A. Age distribution of IBD hospitalization. Inflamm Bowel Dis. 2010;16(3):452–7.
21. Das KM, Biancone L. Is IBD an autoimmune disorder? Inflamm Bowel Dis. 2008;14 Suppl 2:S97–101.
22. Orholm M, Binder V, Sørensen TI, et al. Concordance of inflammatory bowel disease among Danish twins: results of a nationwide study. Scand J Gastroenterol. 2000;35(10):1075–81.

23. Halfvarson J, Bodin L, Tysk C, et al. Inflammatory bowel disease in a Swedish twin cohort: a long-term follow-up of concordance and clinical characteristics. Gastroenterology. 2003;124(7):1767–73.
24. Monsén U, Broström O, Nordenvall B, et al. Prevalence of inflammatory bowel disease among relatives of patients with ulcerative colitis. Scand J Gastroenterol. 1987;22(2):214–8.
25. Fielding JF. The relative risk of inflammatory bowel disease among parents and siblings of Crohn's disease patients. J Clin Gastroenterol. 1986;8(6):655–7.
26. Wagtmans MJ, Verspaget HW, Lamers CB, et al. Crohn's disease in the elderly: a comparison with young adults. J Clin Gastroenterol. 1998;27(2):129–33.
27. Polito JM, Childs B, Mellits ED, et al. Crohn's disease: influence of age at diagnosis on site and clinical type of disease. Gastroenterology. 1996;111(3):580–6.
28. Hanauer SB. Inflammatory bowel disease: epidemiology, pathogenesis, and therapeutic opportunities. Inflamm Bowel Dis. 2006;12 Suppl 1:S3–9.
29. Ogura Y, Bonen DK, Inohara N, et al. A frameshift mutation in NOD2 associated with susceptibility to Crohn's disease. Nature. 2001;411(6837):603–6.
30. Cuthbert AP, Fisher SA, Mirza MM, et al. The contribution of NOD2 gene mutations to the risk and site of disease in inflammatory bowel disease. Gastroenterology. 2002;122(4):867–74.
31. Fiedler T, Büning C, Reuter W, et al. Possible role of MDR1 two-locus genotypes for young-age onset ulcerative colitis but not Crohn's disease. Eur J Clin Pharmacol. 2007;63(10):917–25.
32. Nohara H, Inoue N, Hibi T, et al. Association between the interleukin-1 receptor antagonist polymorphism and ulcerative colitis with younger age at diagnosis. Immunol Lett. 2003;90(1):53–7.
33. Glocker EO, Kotlarz D, Boztug K, et al. Inflammatory bowel disease and mutations affecting the interleukin-10 receptor. N Engl J Med. 2009;361(21):2033–45.
34. Fisher SA, Tremelling M, Anderson CA, et al. Genetic determinants of ulcerative colitis include the ECM1 locus and five loci implicated in Crohn's disease. Nat Genet. 2008;40(6):710–2.
35. Hampe J, Franke A, Rosenstiel P, et al. A genome-wide association scan of nonysynonymous SNPs identifies a susceptibility variant for Crohn disease in ATG 16 L1. Nat Genet. 2007;39(2):207–11.
36. Rioux JD, Xavier RJ, Taylor KD, et al. Genome-wide association study identifies new susceptibility loci for Crohn's disease and implicates autophagy in disease pathogenesis. Nat Genet. 2007;39(5):596–604.
37. Probert CS, Jayanthi V, Pinder D, et al. Epidemiological study of ulcerative proctocolitis in Indian migrants and the indigenous population of Leicestershire. Gut. 1992;33(5):687–93.
38. Jayanthi V, Probert CS, Pinder D, et al. Epidemiology of Crohn's disease in Indian migrants and the indigenous population in Leicestershire. Q J Med. 1992;82(298):125–38.
39. Carr I, Mayberry JF. The effects of migration on ulcerative colitis: a three-year prospective study among Europeans and first- and second-generation South Asians in Leicester (1991–1994). Am J Gastroenterol. 1999;94(10):2918–22.
40. Zvidi I, Hazazi R, Birkenfeld S, et al. The prevalence of Crohn's disease in Israel: a 20-year survey. Dig Dis Sci. 2009;54(4):848–52.
41. Birkenfeld S, Zvidi I, Hazazi R, et al. The prevalence of ulcerative colitis in Israel: a twenty-year survey. J Clin Gastroenterol. 2009;43(8):743–6.
42. Shivananda S, Lennard-Jones J, Logan R, et al. Incidence of inflammatory bowel disease across Europe: is there a difference between north and south? Results of the European collaborative study on inflammatory bowel disease (EC-IBD). Gut. 1996; 39(5):690–7.
43. Sonnenberg A, McCarty DJ, Jacobsen SJ. Geographic variation of inflammatory bowel disease within the United States. Gastroenterology. 1991;100(1):143–9.
44. Mahid SS, Minor KS, Soto RE, et al. Smoking and inflammatory bowel disease. Mayo Clin Proc. 2006;81(11):1462–71.
45. Silverstein MD, Lashner BA, Hanauer SB, et al. Cigarette smoking in Crohn's disease. Am J Gastroenterol. 1989;84(1):31–3.
46. Reese GE, Nanidis T, Borysiewicz C, et al. The effect of smoking after surgery for Crohn's disease: a meta analysis of observational studies. Int J Colorectal Dis. 2008;23(12):1213–21.
47. Boyko EJ, Koepsell TD, Perera DR, et al. Risk of ulcerative colitis among former and current cigarette smokers. N Engl J Med. 1987;316(12):707–10.
48. Riegler G, Tartaglione MT, Carratú R, et al. Age-related clinical severity at diagnosis in 1705 patients with ulcerative colitis: a study by GISC (Italian Colon-Rectum Study Group). Dig Dis Sci. 2000;45(3):462–5.
49. Rutgeerts P, D'Haens G, Hiele M, et al. Appendectomy protects against ulcerative colitis. Gastroenterology. 1994;106(5):1251–3.
50. Andersson RE, Olaison G, Tysk C, et al. Appendectomy and protection against ulcerative colitis. N Engl J Med. 2001; 344(11):808–14.
51. Kaplan GG, Jackson T, Sands BE, et al. The risk of developing Crohn's disease after an appendectomy: a meta-analysis. Am J Gastroenterol. 2008;103(11):2925–31.
52. Sutton CL, Kim J, Yamane A, et al. Identification of a novel bacterial sequence associated with Crohn's disease. Gastroenterology. 2000;119(1):23–31.
53. Mow WS, Vasiliauskas EA, Lin YC, et al. Association of antibody responses to microbial antigens and complications of small bowel Crohn's disease. Gastroenterology. 2004;126(2):414–24.
54. Ruemmele FM, Targan SR, Levy G, et al. Diagnostic accuracy of serological assays in pediatric inflammatory bowel disease. Gastroenterology. 1998;115(4):822–9.
55. Das KM, Kadono Y, Fleischner GM. Antibody-dependent cell-mediated cytotoxicity in serum samples from patients with ulcerative colitis. Relationship to disease activity and response to total colectomy. Am J Med. 1984;77(5):791–6.
56. Yonamine Y, Watanabe M, Kinjo F, et al. Generation of MHC class 1-restricted cytotoxic T cell lines and clones against colonic epithelial cells from ulcerative colitis. J Clin Immunol. 1999;19(1):77–85.
57. Ebert EC, Geng X, Bajpai M, et al. Antibody to tropomyosin isoform 5 and complement induce the lysis of colonocytes in ulcerative colitis. Am J Gastroenterol. 2009;104(12):2996–3003.
58. Hussain SW, Pardi DS. Inflammatory bowel disease in the elderly. Drugs Aging. 2010;27(8):617–24.
59. Pappo I, Zamir O, Freund HR. Is Crohn's disease different in the elderly? Harefuah. 1997;132(2):86–8, 151.
60. Freeman HJ. Crohn's disease initially diagnosed after age 60 years. Age Ageing. 2007;36(5):587–9.
61. Lee JH, Cheon JH, Moon CM, et al. Do patients with ulcerative colitis diagnosed at a young age have more severe disease activity than patients diagnosed when older? Digestion. 2010;81(4):237–43.
62. Zimmerman J, Gavish D, Rachmilewitz D. Early and late onset ulcerative colitis: distinct clinical features. J Clin Gastroenterol. 1985;7(6):492–8.
63. Triantafillidis JK, Emmanouilidis A, Pomonis E, et al. Ulcerative colitis in the elderly: clinical patterns and outcome in 51 Greek patients. J Gastroenterol. 2001;36(5):312–6.
64. Romberg-Camps MJ, Dagnelie PC, Kester AD, et al. Influence of phenotype at diagnosis and of other potential prognostic factors on the course of inflammatory bowel disease. Am J Gastroenterol. 2009;104(2):371–83.
65. Das KM, Dubin R. Clinical pharmacokinetics of sulfasalazine. Clin Pharmacokinet. 1976;1:406–25.
66. Das KM, Sternlieb I. Salicylazosulfapyridine in inflammatory bowel disease. Am J Dig dis. 1975;20:971–6.

67. Das KM, Eastwood MA, McManus JP, et al. Adverse reactions during salicylazosulfapyridine therapy and the relation with drug metabolism and acetylator phenotype. N Engl J Med. 1973; 289(10):491–5.
68. McQuaid KR. Chapter 62: drugs used in the treatment of gastrointestinal disease. In: Katzung BG, Masters SB, Trevor AJ, editors. Basic & clinical pharmacology. New York: McGraw Hill Medical; 2009.
69. Velayos FS, Terdiman JP, Walsh JM. Effect of 5-aminosalicylate use on colorectal cancer and dysplasia risk: a systematic review and metaanalysis of observational studies. Am J Gastroenterol. 2005;100(6):1345–53.
70. Kao J, Kwok K, Das KM. Inducing and maintaining remission in ulcerative colitis: role of high-dose, extended release mesalamine. J Clin Gastroenterol. 2010;44(8):531–5.
71. Das KK, Bajpai M, Kong Y, et al. Mesalamine suppresses the expression of TC22, a novel tropomyosin isoform associated with colonic neoplasia. Mol Pharmacol. 2009;76(1):183–91.
72. Whitehead WE, Borrud L, Goode PS, et al. Fecal incontinence in US adults: epidemiology and risk factors. Gastroenterology. 2009;137(2):512–7, 517.e1–2.
73. Schacke H, Docke WD, Asadullah K. Mechanisms involved in the side effects of glucocorticoids. Pharmacol Ther. 2002;96(1):23–43.
74. Hoes JN, Jacobs JW, Verstappen SM, et al. Adverse events of low to medium-dose oral glucorticoids in inflammatory diseases: a meta-analysis. Ann Rheum Dis. 2009;68(12):1833–8.
75. Akerkar GA, Peppercorn MA, Hamel MB, et al. Corticosteroid-associated complications in elderly Crohn's disease patients. Am J Gastroenterol. 1997;92(3):461–4.
76. Jones HW, Hoare AM. Does ulcerative colitis behave differently in the elderly? Age Ageing. 1988;17(6):410–4.
77. Beaugerie L, Brousse N, Bouvier AM, et al. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. Lancet. 2009;374(9701):1617–25.
78. Singleton JD, Conyers L. Warfarin and azathioprine: an important drug interaction. Am J Med. 1992;92(2):217–9.
79. Kroger AT, Sumaya CV, Pickering LK, et al. General recommendations on immunization: recommendations of the ADvisory Committee on Immunization Practices (ACIP), MMWR. 2011; 60(2):1–64.
80. Sandborn W, Rutgeerts P, Reinisch W, et al. SONIC: a randomized double-blind, controlled trial comparing infliximab plus asathiprine in patients with Crohn's disease naive to immunomodulators and biologic therapy. Am J Gastroenterol. 2008;103:S436.
81. Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Gastroenterology. 2007;132: 52–65.
82. Schreiber S, Khaliq-Kareemi M, Lawrence IC, et al. Precise 2 study investigators: maintenance therapy with cerolizumab pegol for Crohn's disease. New Eng J Med. 2007;357(3):239–50.
83. Cottone M, Kohn A, Daperno M, et al. Advanced age is an independent risk factor for severe infections and mortality in patients given anti-tumor necrosis factor therapy for inflammatory bowel disease. Clin Gastroenterol Hepatol. 2011;9(1):30–5.
84. Ananthakrishnan AN, McGinley EL, Binion DG. Inflammatory bowel disease in the elderly is associated with worse outcomes: a national study of hospitalizations. Inflamm Bowel Dis. 2009;15(2): 182–9.
85. Longo WE, Virgo KS, Bahadursingh AN, et al. Patterns of disease and surgical treatment among United States veterans more than 50 years of age with ulcerative colitis. Am J Surg. 2003;186(5): 514–8.
86. Norris B, Solomon MJ, Eyers AA, et al. Abdominal surgery in the older Crohn's population. Aust N Z J Surg. 1999;69(3): 199–204.
87. Nicholls RJ, Clark DN, Kelso L, et al. Nationwide linkage analysis in Scotland implicates age as the critical overall determinant of mortality in ulcerative colitis. Aliment Pharmacol Ther. 2010;31(12):1310–21.
88. Ha C, Newberry R, Stone C, et al. Patients with late-adult-onset ulcerative colitis have better outcomes than those with early onset disease. Clin Gastroenterol Hepatol. 2010;8(8):682–7.
89. Karvellas CJ, Fedorak RN, Hanson J, et al. Increased risk of colorectal cancer in ulcerative colitis patients diagnosed after 40 years of age. Can J Gastroenterol. 2007;21(7):443–6.
90. Oikonomou I, Das KM. Extraintestinal manifestations of IBD. In: Bayless TM, Hanauer SB, editors. Advanced therapy in inflammatory bowel disease. Shelton, Conn: People's Medical Publishing House, USA;2011. p. 519–26.

Non-IBD and Noninfectious Colitis

51

Ole Haagen Nielson and Jakob Benedict Seidelin

Physiology Applicable to Rare Forms of Colitis in Older Adults

Diarrhea due to colitis in elderly persons might, apart from acute infectious colitis and chronic idiopathic inflammatory bowel disease (IBD), i.e., ulcerative colitis and Crohn's disease, be caused by microscopic colitis (MC), ischemic colitis, uremic colitis, radiation colitis, diverticular colitis, and drug-induced colitis. These rarer forms of colitis may be cumbersome for both patients and their physicians because the diagnostic process is often long and time-consuming. The pathophysiology and etiopathogenesis remain obscure, and the diagnosis frequently relies primarily on endoscopic findings combined with histopathologic evaluation of mucosal biopsies. In the absence of a definitive understanding of the etiopathogenesis, treatment is often empirical, and the lack of randomized, controlled trials makes it difficult to obtain valid evidence of therapeutic efficacy.

The aim of this chapter is to summarize the latest data on the pathophysiology, epidemiology, clinical features, and treatment of noninfectious, non-IBD forms of colitis found in older adults in order to provide a guideline for clinical use. The data on incidence is provided in Table 51.1.

Microscopic Colitis

MC is the generic term for the two distinct disease entities, collagenous colitis (CC) [1] and lymphocytic colitis (LC) [2] with unknown etiologies [3]. CC improves or resolves with diversion of the fecal stream and recurs after reestablishment of gut continuity, suggesting that luminal factors might contribute to the pathogenesis [4]. Precipitating factors include previous infection with *Yersinia enterocolitica*, *Clostridium difficile*-associated pseudomembranous colitis, various drugs, and malabsorption of bile acids [5, 6].

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Epidemiology

MC is a common cause of watery diarrhea in older people. The incidence is 7.1 per 10^5 inhabitants and 12.6 per 10^5 inhabitants for CC and LC, respectively, in the United States [7], i.e., similar to IBD. Patients are diagnosed at a median age of about 60 years, with a predominance of females (female:male ratio 7.5:1 for CC and 2.1:1 for LC) [8]. CC is associated with autoimmune diseases, such as Sjögren's syndrome, Raynaud's syndrome, rheumatoid arthritis, psoriasis, celiac disease, and hyper- or hypothyroidism [6].

Clinical Features

The primary symptom is profuse watery diarrhea which may severely affect the patients' daily activities and quality of life. The volume of diarrhea is associated with the intensity of lamina propria inflammation but not with the other histological hallmarks of CC [9]. Approximately 80% of cases resolve spontaneously after 3 years; MC is not associated with neoplasia development [10].

The histopathologic characteristics of MC are also found in ulcerative colitis and Crohn's disease, i.e., nodular lymphoid hyperplasia and hyalinized fibrosis [11]. However, with the proper clinical findings, the diagnosis can be reached with almost certainty. Thus, an inflammatory infiltrate in the lamina propria with an increased number of intraepithelial $CD8^+$ T lymphocytes exceeding 20% of the surface cells are common to CC (Fig. 51.1) as well as LC (Fig. 51.2) [12]. In CC, a diffusely distributed thickened collagenous band exceeding 10 μm is formed beneath the surface epithelium. Biopsies should be obtained from both the right and left colon, since involvement of the left colon is less frequent

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Table 51.1 Incidence of noninfectious colitis

Diagnosis	Incidence (per year)
Collagenous colitis	7.1/100,000 [7]
Lymphocytic colitis	12.6/100,000 [7]
Ischemic colitis	44/100,000 [18]
Uremic colitis	NA
Radiation colitis	NA
Diverticular colitis	3% of patients with diverticular disease [40]
Drug-induced colitis	NA

NA data not available

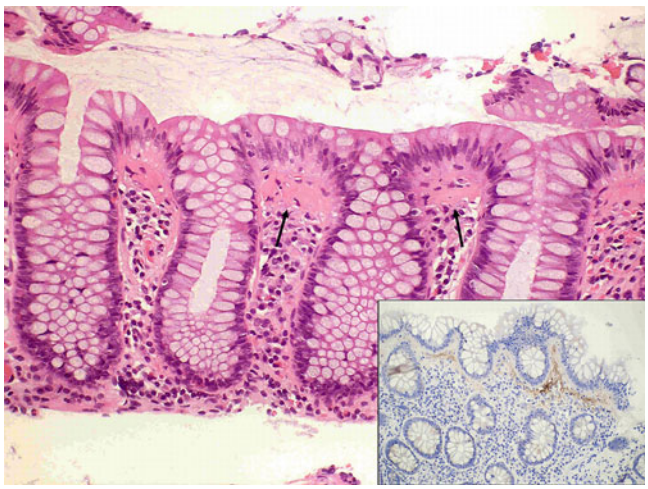

Fig. 51.1 Photomicrograph of colonic mucosa with collagenous colitis. A thickened layer of collagen is formed beneath the surface epithelium (*arrows*). Tenascin is incorporated into the collagen, which may be used to distinguish this layer from the normal basement membrane (*inset*). Hematoxylin & eosin, original magnification ×200, insert ×100

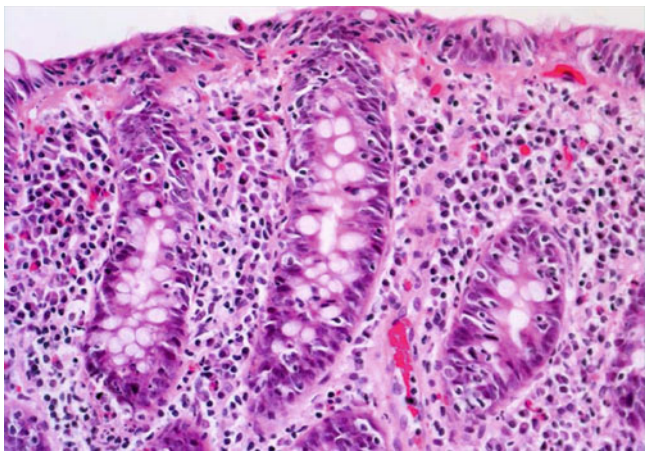

Fig. 51.2 Photograph of lymphocytic colitis showing the inflamed colonic mucosa infiltrated with significant amounts of cytotoxic lymphocytes in the epithelium. In this case, more than 40% of the cells in the epithelial layer are lymphocytes. The leukocyte infiltration in lamina propria is a mixture of lymphocytes, plasma cells, macrophages, eosinophil granulocytes, and occasionally, neutrophils. Hematoxylin and eosin, original magnification ×200

than involvement of the right colon, and thus biopsies obtained solely from the left colon will miss at least 10% of MC cases [13].

Treatment

Budesonide 9 mg/day for 8 weeks for CC yields clinical improvement in 81% of patients compared with 17% of patients receiving placebo [14]. Usually, therapy is discontinued after 6–8 weeks, but the high rate of recurrence, often requires long-term treatment with low-dose therapy (3 mg once daily or every second day). Somewhat weaker evidence for bismuth subsalicylate (Pepto Bismol; nine 262-mg tablets daily) and mesalamine in treating CC over a period of 8 weeks have been reported [14]. Prednisolone might induce remission in MC, but is not recommended due to better treatment alternatives [14].

In LC, 6 weeks of treatment with budesonide 9 mg/day may result in a clinical remission of 86% of patients compared with 48% receiving placebo [15]. Discontinuing NSAIDs and proton pump inhibitors is effective for symptom relief in a number of patients with MC [5].

Treatment of patients with azathioprine or 6-mercaptopurine has been suggested for patients with corticosteroid resistant MC, but no randomized studies demonstrate efficacy [16]. In patients who experience a relapse soon after a successful course of budesonide treatment, reintroduction of a lower dosage may be considered for a prolonged time interval (up to 1 year) [17]. In case of refractory MC surgery might rarely be necessary [17].

Ischemic Colitis

The incidence of ischemic colitis has increased in the United States and Western Europe from 5 to 44 cases per 10^5 person-years in the period from 1976 to 2001 [18], especially in females 65 years or older [18], possibly due to improved diagnostic methods. Causes of colonic ischemia include decreased cardiac output (from arrhythmias, hypotension or hypovolemia, arterial thrombosis or embolism), colonic obstruction caused by tumors, diverticulitis, peritoneal adhesions, medications, hypercoagulability states, vasculitis, intra-abdominal inflammatory or infectious processes, vascular surgery or can be found as a complication to endoscopic retrograde cholangiopancreatography caused by mesenteric hematoma.

Clinical Features

The diagnosis of fulminate ischemia requires a high degree of suspicion, and is considered in presentations with acute

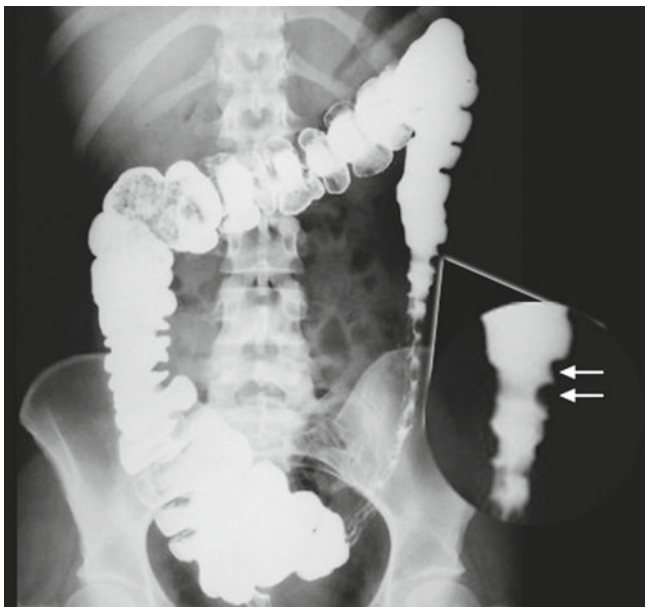

Fig. 51.3 The single-contrast barium enema examination of the ischemic colon demonstrates smooth-surfaced protrusions into the lumen (thumbprints), shown by *arrows*

abdominal pain, bloody stools, and hypotension. Radiologic findings in mild ischemic colitis range from none to bowel dilatation, air-filled intestinal loops, mural thickening, and loss of colonic haustrations. In 20–25% of patients "thumbprinting" of the colonic wall is seen [19] (Fig. 51.3). Endoscopic examination is the key to diagnosis; the endoscope is advanced no further than the affected area to avoid perforation.

Treatment

Acute ischemic colitis will reverse within 24–48 h in two-thirds of the patients, but endoscopic abnormalities may persist for up to 2 weeks. However, there is little evidence based data for management of this disorder; for persistent cases, surgery is often required [20, 21].

Uremic Colitis

This rare disorder, secondary to renal failure, possibly results from irritant effects of ammonia formed by the breakdown of increased urea in the intestinal secretions, although, the pathogenesis is not entirely clarified. It is frequently seen as a complication in hemolytic uremic syndrome (HUS), characterized by the triad of acute acquired Coombs-negative hemolytic anemia, thrombocytopenia, and renal dysfunction, including hematuria, proteinuria, and variable degree of renal failure. Often HUS is related to enteric pathogens (i.e., bacteria producing Shiga toxin or Shiga-like toxins) [22]; uremic colitis is characterized by hemorrhagic colonic mucosa.

While HUS usually occurs in children, critical gastrointestinal bleeding from uremic colitis may be observed among adult in-patients at rehabilitation centers [23]. Uremic colitis carries a high mortality of up to 20% [24].

The true incidence of uremic colitis is unknown. Risk factors include patient demographics, comorbidities and medication regimens; i.e., renal disease, diabetes, and use of anticoagulants, glucocorticoids, cyclosporine, long-term proton pump inhibitors, histamine 2 receptor antagonists or antibiotics, many capable of altering the normal protective gastrointestinal flora to colonization by enteric pathogens.

The institutionalized elderly residents may be at unique risk for uremic colitis, predisposed by a characteristic milieu with predisposition to serious gastrointestinal infections, e.g., dementia, fecal incontinence, and psychosis, in a setting of crowded living conditions and communal dining which facilitate behavioral patterns that allow person-to-person transmission of gastrointestinal pathogens.

Clinical Features

The onset of the uremic colitis is usually abrupt. The renal dysfunction displays a wide spectrum from minimal abnormalities to anuric renal failure with hypertension. The outcome of the renal disorder is extremely variable from complete recovery to irreversible chronic renal failure. The mechanism of uremic colitis may, however, differ from the colitis seen in patients at intensive care units. Although uremic colitis is suspected in patients with diarrhea, oliguria and anemia, a raised blood urea level might be falsely attributed to volume depletion secondary to diarrhea.

The cause of uremic colitis is often secondary to HUS caused by gastrointestinal infections with enterohemorrhagic *Escherichia coli* (EHEC), especially *E. coli 0157:H7* [25, 26]. Other pathogenic agents include *Shigella*, *Campylobacter jejuni*, and *C. difficile* [27].

Sigmoidoscopy or colonoscopy reveals friable mucosa with "touch bleeding," and is nonspecific. Endoscopies may additionally exclude rectal ulcer, a cause of acute lower gastrointestinal bleeding in the elderly with significant comorbidity. The histological findings are not similar to those seen in IBD [28].

Treatment

Treatment of uremic colitis is targeted to the causing factor, most often HUS. No pharmacologic prophylaxis for uremic colitis exists. The treatment of HUS is essentially supportive and requires fluid resuscitation and transfusion of blood and

hemodialysis when indicated [29]. In severe cases plasmapheresis combined with fresh frozen plasma replacement (plasma exchange) is recommended [26]. Plasmapheresis enables huge amounts of fresh frozen plasma to be given in a short time, and may also remove ammonia or yet unknown pathogenic factor(s).

Radiation Colitis

Chronic radiation-induced colitis usually develops 6 months to 5 years after oncologic regional radiotherapy [30]. The condition is usually self-limited, but the duration is highly variable, ranging from 3 months to 30 years [31].

Among 304 patients who had received a mean of 50.4 Gy pelvic radiation postoperatively for gynecologic malignancies, 4% developed acute enteritis, 6% had chronic enteritis, and 12% had chronic proctitis following a median latency of 2.1 years [32]. After 5 years 14% had proctitis and 7% enteritis in this series. Patient age and radiation dose are the only independent risk factors associated with complications to radiotherapy [32].

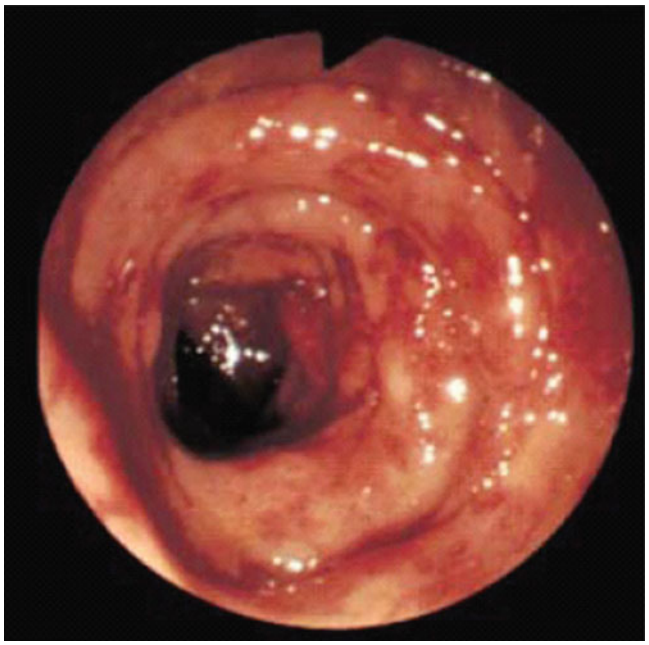

Fig. 51.4 Endoscopic picture of colonic telangiectatic lesions in radiation colitis

Clinical Features

Following abdominal irradiation, patients receiving more than 45 Gy of pelvic radiation may develop diarrhea and abdominal cramping [33]. Endoscopically, the colon shows diffuse hemorrhage or hyperemia with telangiectatic lesions (Fig. 51.4), or less frequently circumferential ulcers with a relatively sharp proximal and distal demarcation.

Treatment

No therapy stands out as clearly superior, and radiation colitis is rarely curable. The bile acid binding drug, cholestyramine, may be effective in preventing radiation-induced diarrhea if administered in dosages of 4 g three times a day prior to radiation therapy [34]. A low-residue diet combined with kaopectate (bismuth subsalicylate) or opiates, such as loperamide or diphenoxylate, may be sufficient for mild diarrhea. Aminosalicylates and prostaglandin-inhibiting compounds may also be considered [35]. In severe cases, oral steroids have been tried with limited success [36]. Sulfasalazine, glutathione, and antioxidants are sometimes tried, but their efficacy are unknown [37]. Radiation response modifiers (e.g., WR-2721, amifostine, and estrogen) have been tested in small studies but are not clinically useful. Severe fibrotic strictures are managed by resection and a primary anastomosis, which can be technically demanding due to adhesions in the pelvis and a higher risk for fistulas and anastomotic leaks [38]. Lactose intolerance and small bowel bacterial overgrowth may develop after radiation-induced intestinal damage, and the management of these problems might reduce symptoms for some patients [39].

Diverticular Colitis

In approximately 3% of persons with diverticular disease, the mucosa in the diverticular segments is inflamed [40]. This diverticular disease-associated segmental colitis, or diverticular colitis, is limited to the segments of the colon that harbor diverticulas [41]. The process is not synonymous with diverticulitis and does not share the same histopathologic features [42]. The pathogenesis of diverticular colitis is obscure; in some cases NSAIDs may be implicated, since patients with diverticular disease taking NSAIDs more often have bleeding [43].

Clinical Features

Diverticular colitis is often subclinical, and the condition therefore is likely to be under diagnosed, but the incidence and prevalence of the disease is unknown.

Patients may present with rectal bleeding, altered bowel habits, mucus discharge, and tenesmus [44, 45]. Typically, radiology shows only diverticular disease, whereas endoscopy may reveal changes ranging from mild, nonspecific inflammation with a granular appearance and erythema to florid inflammatory changes, including petechial bleeding or frank intramucosal hemorrhage with exudates and friability [44].

Treatment

No randomized, controlled clinical trials are available, but oral treatment with sulfasalazine or mesalazine and topical glucocorticoid enemas have been used with some success [46]. NSAIDs should be discontinued. A fiber-enriched diet has also been suggested [46]. Antibiotics are used by some clinicians, but without good scientific evidence. Surgical removal of the area with diverticulas will, given the close relationship with the colitides, relieve the patients of all symptoms [42, 44].

Drug-Induced Colitis

Medications are among the most frequent causes of diarrhea, contributed in large measure by polypharmacy in elderly [47]. The drugs most commonly associated with gastrointestinal adverse effects, including colitides, are the NSAIDs, in part due to their wide-spread use, but antibiotics, hormones, central nervous system agents, cardiovascular drugs, and chemotherapeutics all cause gastrointestinal symptoms.

Epidemiology

As drug-induced colitis appears secondary to drug use, the epidemiological data vary considerably. Gastrointestinal adverse drug reactions account for approximately 1/5 of all adverse drug reactions in nursing homes [48], and similar results have been found in other adult populations.

NSAIDs

Among NSAID users, serious lower gastrointestinal tract events account for approximately 40% of all reported significant gastrointestinal events [49]. NSAIDs can cause colonic inflammation, stricture formation, ulceration, bleeding, and perforation. The inflammation and ulceration inducing effects of NSAIDs are ascribed to their antiprostaglandin effect through inhibition of the cyclooxygenase pathway, leading to production of proinflammatory leukotrienes via the lipooxygenase pathway. The toxic effects to the colon might in fact be enhanced by enteric-coated formulations, which decrease side effects to the upper gastrointestinal tract, but deliver the active drug at the small intestine and colon.

Clinical Features and Treatment

NSAIDs commonly cause a nonspecific wide-spread colitis mimicking mild ulcerative colitis or Crohn-like segmental colitis [50]. Another presentation is sharply demarcated ulcers within macroscopically normal mucosa. NSAIDs may also cause wide-based circumferential stricture formation with a central pinpoint lumen. Ulcers and diaphragm-like structures are often found in the right side of the colon. Notably, NSAID colopathy is difficult to distinguish from IBD on histologic examination.

Although the majority of patients are asymptomatic, patients might present with diarrhea (which can be bloody), anemia, and abdominal pain. Others present with obstructive symptoms or symptoms of perforation and peritonitis. Cessation of NSAIDs results in healing of the colitis and NSAID associated ulcers within weeks, with improvement of symptoms. Strictures might persist after stopping NSAIDs and may require surgical resection of the involved segment. It is important to recognize that NSAIDs are implicated in specific IBDs including MC, Crohn's disease, and ulcerative colitis, and seem to play a role in the development of diverticular colitis [6, 43].

Antibiotics

Antibiotics are frequently associated with diarrhea and colitis. The cause is most likely alteration of the microbiome due to the antibiotic effects and growth of specific pathogens like *C. difficile*, which may cause pseudomembranous colitis with diarrhea, fever, and dehydration, especially in the old. *C. difficile* associated disease is described elsewhere in the book. Certain antibiotics, including ampicillin and tetracycline, are particularly prone to induce diarrhea, by yet unidentified drug-specific mechanisms.

The management of antibiotic-induced colitis includes cessation of the drug if possible or shifting to an antibiotic with a more limited spectrum or treatment of the specific infection, e.g., *C. difficile.*

Vasoactive Drugs

Drugs capable of inducing vasospasms, or in other ways lowering the splanchnic blood flow, may induce ischemic colitis. These include cocaine, amphetamine, ergotamine, and vasopressin analogues.

Laxatives

Laxatives may cause melanosis coli, a dark-brown discoloration of the colon following chronic use of anthraquinone containing laxatives (e.g., senna). The histopathology is characterized by lipofuscin-like pigment engulfed by the macrophages. The pigment is probably formed after ingestion of apoptotic epithelial cells and might thus be a marker of increased apoptosis rather than for laxative use per se.

Antineoplastic Drugs

Chemotherapies causing neutropenia may induce neutropenic colitis or necrotizing colitis caused by bacterial invasion of the mucosa due to the severe immunosuppressed states [51]. Patients present with fever, diarrhea, abdominal pain, and tenderness, which can evolve into rebound tenderness and abdominal guarding. The CT-scan of the abdomen will reveal dilated bowel loops with air-fluid levels, mural thumbprinting, and pneumatosis coli. Histopathologic examination shows bacterial overgrowth with limited inflammation. Incriminated drugs causing neutropenic colitis include adriamycin, cisplatin, cytarabine, cytosine arabinoside, 5-fluorouracil, mercaptopurine, thioguanine, and vincristine. Certain chemotherapeutic agents are specifically toxic to the intestinal mucosa, e.g., cytosine arabinoside.

Other Drugs

Microscopic colitis can be caused not only by NSAIDs, but also by lanzoprazole, ranitidine, flutamide, and ticlopidine [6].

Gold therapy may induce colitis by a hypersensitivity-like reaction characterized by peripheral eosinophilia and mucosal inflammation dominated by eosinophils in some cases [52]. The colitis typically starts during the first 3 months of gold treatment. Patients complain of profuse diarrhea, fever, and abdominal pain. The diarrhea can be bloody, and accompanied by anemia, leucocytosis and eosinophilia. Colonoscopy may reveal a diffusely inflamed colon, with ulcerations.

Local Effects of Drugs

Rectal administration of ergotamine has been associated with rectal ulcers, as have the use of NSAID suppositories. The symptoms include anal pain, soiling, and tenesmus; endoscopy shows a rectal ulcer, often mimicking the findings of the solitary rectal ulcer syndrome. Discontinuing the medication is the treatment. Anorectal stenosis, perforation and rectovaginal fistulas have been described as complications of rectal NSAID use, similar to the tendency to form diaphragm-like strictures elsewhere in the gastrointestinal tract [53].

Key Points

- Rarer forms of colitis among elderly persons, which include colitis not caused by infectious agents or chronic inflammatory bowel disease, pose a clinical challenge for the patient and clinician.
- Diagnostic and therapeutic principles are listed for microscopic colitis, ischemic colitis, uremic colitis, radiation colitis, and diverticular colitis. If drug-induced colitis is suspected, the specified drug should be discontinued immediately.
- Besides discontinuation of medications in drug-induced colitis and treatment of microscopic colitis, most therapeutic principles in management remain empirical.
- Individualized interdisciplinary discussions between primary physicians or geriatricians with gastroenterologists, radiologists, and pathologists are essential for the diagnosis and management of these overlooked disorders.
- Awareness and diagnosis of these rare forms of colitis in older adults may enhance the quality of their life.

References

1. Lindstrom CG. 'Collagenous colitis' with watery diarrhoea-a new entity? Pathol Eur. 1976;11:87–9.
2. Lazenby AJ, Yardley JH, Giardiello FM, Jessurun J, Bayless TM. Lymphocytic ("microscopic") colitis: a comparative histopathologic study with particular reference to collagenous colitis. Hum Pathol. 1989;20:18–28.
3. Levison DA, Lazenby AJ, Yardley JH. Microscopic colitis cases revisited. Gastroenterology. 1993;105:1594–6.
4. Jarnerot G, Tysk C, Bohr J, Eriksson S. Collagenous colitis and fecal stream diversion. Gastroenterology. 1995;109:449–55.
5. Chande N, Driman DK, Reynolds RP. Collagenous colitis and lymphocytic colitis: patient characteristics and clinical presentation. Scand J Gastroenterol. 2005;40:343–7.
6. Nielsen OH, Vainer B, Schaffalitzky de Muckadell OB. Microscopic colitis: a missed diagnosis? Lancet. 2004;364:2055–7.
7. Pardi DS, Loftus Jr EV, Smyrk TC, et al. The epidemiology of microscopic colitis: a population based study in Olmsted County, Minnesota. Gut. 2007;56:504–8.
8. Williams JJ, Beck PL, Andrews CN, Hogan DB, Storr MA. Microscopic colitis—a common cause of diarrhoea in older adults. Age Ageing. 2010;39:162–8.
9. Bo-Linn GW, Vendrell DD, Lee E, Fordtran JS. An evaluation of the significance of microscopic colitis in patients with chronic diarrhea. J Clin Invest. 1985;75:1559–69.
10. Mullhaupt B, Guller U, Anabitarte M, Guller R, Fried M. Lymphocytic colitis: clinical presentation and long term course. Gut. 1998;43:629–33.
11. Yantiss RK, Odze RD. Diagnostic difficulties in inflammatory bowel disease pathology. Histopathology. 2006;48:116–32.
12. Lazenby AJ. Collagenous and lymphocytic colitis. Semin Diagn Pathol. 2005;22:295–300.
13. Pardi DS, Smyrk TC, Tremaine WJ, Sandborn WJ. Microscopic colitis: a review. Am J Gastroenterol. 2002;97:794–802.
14. Chande N, Macdonald JK, McDonald JW. Interventions for treating microscopic colitis: a Cochrane Inflammatory Bowel Disease and Functional Bowel Disorders Review Group systematic review of randomized trials. Am J Gastroenterol. 2009;104:235–41.
15. Miehlke S, Madisch A, Karimi D, et al. Budesonide is effective in treating lymphocytic colitis: a randomized double-blind placebo-controlled study. Gastroenterology. 2009;136:2092–100.
16. Pardi DS, Loftus Jr EV, Tremaine WJ, Sandborn WJ. Treatment of refractory microscopic colitis with azathioprine and 6-mercaptopurine. Gastroenterology. 2001;120:1483–4.
17. Pardi DS, Kelly CP. Microscopic colitis. Gastroenterology. 2011;140:1155–65.

18. Higgins PD, Davis KJ, Laine L. Systematic review: the epidemiology of ischaemic colitis. Aliment Pharmacol Ther. 2004; 19:729–38.
19. Lefkovitz Z, Cappell MS, Lookstein R, Mitty HA, Gerard PS. Radiologic diagnosis and treatment of gastrointestinal hemorrhage and ischemia. Med Clin North Am. 2002;86:1357–99.
20. Diaz-Nieto R, Varcada M, Ogunbiyi OA, Winslet MC. Systematic review on the treatment of ischemic colitis. Colorectal Dis. 2011;13(7):744–7.
21. Longo WE, Ward D, Vernava III AM, Kaminski DL. Outcome of patients with total colonic ischemia. Dis Colon Rectum. 1997; 40:1448–54.
22. Tarr PI. Shiga toxin-associated hemolytic uremic syndrome and thrombotic thrombocytopenic purpura: distinct mechanisms of pathogenesis. Kidney Int Suppl. 2009;75:S29–32.
23. Hollenbeck M, Zawischa U, Passlick-Deetjen J, Kemmer F, Grabensee B. Haemolytic-uraemic syndrome in adults. Lancet. 1990;336:380.
24. Crosse BA, Naylor JR. Haemolytic-uraemic syndrome in adults. Lancet. 1990;335:1528–9.
25. Mead PS, Griffin PM. *Escherichia coli* O157:H7. Lancet. 1998;352:1207–12.
26. Reiss G, Kunz P, Koin D, Keeffe EB. *Escherichia coli* O157:H7 infection in nursing homes: review of literature and report of recent outbreak. J Am Geriatr Soc. 2006;54:680–4.
27. Mbonu CC, Davison DL, El-Jazzar KM, Simon GL. *Clostridium difficile* colitis associated with hemolytic-uremic syndrome. Am J Kidney Dis. 2003;41:E14.
28. Lin CC, Wang HP, Wu MS, Ho WC, Lee H, Lin JT. The etiology and clinical characteristics of acute lower gastrointestinal bleeding in patients hospitalized for comorbid illnesses. Hepatogas troenterology. 2006;53:395–8.
29. Allan A, Keighley MR, Thompson H. Beware of hemolytic uremic syndrome presenting as colorectal disease in adults. Report of two cases. Dis Colon Rectum. 1989;32:426–8.
30. Berthrong M, Fajardo LF. Radiation injury in surgical pathology. Alimentary tract. Am J Surg Pathol. 1981;5:153–78.
31. Berthrong M. Pathologic changes secondary to radiation. World J Surg. 1986;10:155–70.
32. Miller AR, Martenson JA, Nelson H, et al. The incidence and clinical consequences of treatment-related bowel injury. Int J Radiat Oncol Biol Phys. 1999;43:817–25.
33. Andreyev J. Gastrointestinal complications of pelvic radiotherapy: are they of any importance? Gut. 2005;54:1051–4.
34. Heusinkveld RS, Manning MR, Aristizabal SA. Control of radiation-induced diarrhea with cholestyramine. Int J Radiat Oncol Biol Phys. 1978;4:687–90.
35. Baughan CA, Canney PA, Buchanan RB, Pickering RM. A randomized trial to assess the efficacy of 5-aminosalicylic acid for the prevention of radiation enteritis. Clin Oncol (R Coll Radiol). 1993;5:19–24.
36. Kochhar R, Patel F, Dhar A, et al. Radiation-induced proctosigmoiditis. Prospective, randomized, double-blind controlled trial of oral sulfasalazine plus rectal steroids versus rectal sucralfate. Dig Dis Sci. 1991;36:103–7.
37. Kountouras J, Zavos C. Recent advances in the management of radiation colitis. World J Gastroenterol. 2008;14:7289–301.
38. Qadeer MA, Vargo JJ. Approaches to the prevention and management of radiation colitis. Curr Gastroenterol Rep. 2008;10: 507–13.
39. Wedlake L, Thomas K, McGough C, Andreyev HJ. Small bowel bacterial overgrowth and lactose intolerance during radical pelvic radiotherapy: an observational study. Eur J Cancer. 2008;44:2212–7.
40. Reinus JF, Brandt LJ. Vascular ectasias and diverticulosis. Common causes of lower intestinal bleeding. Gastroenterol Clin North Am. 1994;23:1–20.
41. Lamps LW, Knapple WL. Diverticular disease-associated segmental colitis. Clin Gastroenterol Hepatol. 2007;5:27–31.
42. Ludeman L, Warren BF, Shepherd NA. The pathology of diverticular disease. Best Pract Res Clin Gastroenterol. 2002; 16:543–62.
43. Goh H, Bourne R. Non-steroidal anti-inflammatory drugs and perforated diverticular disease: a case-control study. Ann R Coll Surg Engl. 2002;84:93–6.
44. Gore S, Shepherd NA, Wilkinson SP. Endoscopic crescentic fold disease of the sigmoid colon: the clinical and histopathological spectrum of a distinctive endoscopic appearance. Int J Colorectal Dis. 1992;7:76–81.
45. Peppercorn MA. Drug-responsive chronic segmental colitis associated with diverticula: a clinical syndrome in the elderly. Am J Gastroenterol. 1992;87:609–12.
46. Trivedi CD, Das KM. Emerging therapies for diverticular disease of the colon. J Clin Gastroenterol. 2008;42:1145–51.
47. Kyne L, Moran A, Keane C, O'Neill D. Hospital-acquired diarrhoea in elderly patients: epidemiology and staff awareness. Age Ageing. 1998;27:339–43.
48. Handler SM, Wright RM, Ruby CM, Hanlon JT. Epidemiology of medication-related adverse events in nursing homes. Am J Geriatr Pharmacother. 2006;4:264–72.
49. Laine L, Connors LG, Reicin A, et al. Serious lower gastrointestinal clinical events with nonselective NSAID or coxib use. Gastroenterology. 2003;124:288–92.
50. Price AB. Pathology of drug-associated gastrointestinal disease. Br J Clin Pharmacol. 2003;56:477–82.
51. Parfitt JR, Driman DK. Pathological effects of drugs on the gastrointestinal tract: a review. Hum Pathol. 2007;38:527–36.
52. Cappell MS. Colonic toxicity of administered drugs and chemicals. Am J Gastroenterol. 2004;99:1175–90.
53. Ballinger A. Adverse effects of nonsteroidal anti-inflammatory drugs on the colon. Curr Gastroenterol Rep. 2008;10:485–9.

Celiac Disease

52

C.S. Pitchumoni and Nancy Chen

Introduction

Celiac disease (CD), once considered solely a pediatric problem has become an entity to be included in the differential diagnosis of many presenting complaints in the older adult. CD also known as celiac sprue, nontropical sprue or gluten sensitive enteropathy, is a chronic small intestinal enteropathy characterized by an autoimmune response in genetically susceptible individuals affecting people of all ages worldwide [1, 2]. CD presents with a wide spectrum of manifestations ranging from the asymptomatic state to malabsorption, vitamin deficiencies, osteoporosis, and neurological disorders (Fig. 52.1). In the older adult, CD is a poorly recognized entity of growing clinical importance. Up to 34% of patients newly diagnosed with CD are older than 60 years of age [3].

Epidemiology

The earliest description of CD was in the first and second century AD [4]. In 1887, Samuel Gee (from England) described chronic diarrhea and failure to thrive as typical manifestations of CD in children. The management utilizing diet was first proposed [5].

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The prevalence of CD in Western population is estimated to be as high as 1% and has emerged as a major health problem that is underdiagnosed [6–13]. Population-based studies indicate the prevalence in the US to be in the range of 0.5–1.0% [14]. In European countries, prevalence ranges from 1 in 85 to 1 in 540, with 0.55% in adults [15, 16]. A centralized study of 29,212 participants from Europe tested for CD confirmed the prevalence in adults 30–64 years of age to be 2.4% in Finland, 0.3% in Germany, and 0.7% in Italy, with large unexplained differences in adults across European countries [17]. The prevalence of CD in North India is 1.04% [18]. The increasing prevalence is attributed to better diagnosis and true increase caused by various factors. Changes in infant feeding (ESPGHAN) [19, 20], frequent rotavirus infections, and other bacterial and parasitic infections are suspected to play a role. A Finnish study suggested that poorer socioeconomic conditions might protect against CD [21].

CD in the Older Adult

The true prevalence of CD in the older adult is difficult to estimate because many present atypically or have little or no symptoms [22]. There are two groups of celiacs: a group diagnosed in earlier life, and continue to do well decades later; and a group diagnosed in later life because of atypical presentations or late onset [23–25]. In the adult population, CD occurs in a bimodal distribution, with one peak in the fourth and fifth decade, predominantly in women, with a 2:1 to 3:1 female to male ratios and a second peak predominantly in men seen in the sixth and seventh decades of life [26–29]. The prevalence of CD confirmed by small intestinal mucosal biopsy results in the elderly population can be as high as 2.13%. In addition, in patients who are not biopsy candidates but are seropositive, the total prevalence in some reports may be as high as 2.45% [23, 24, 30–32].

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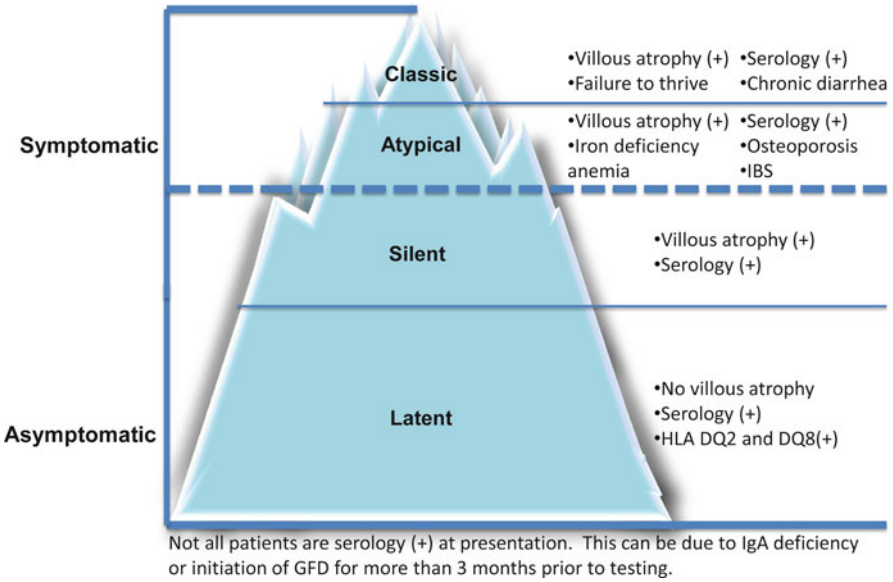

Fig. 52.1 The modified celiac iceberg [23, 39, 42, 47–51]

Genetics

The prevalence of CD is markedly increased in high-risk groups with family aggregations of specific genetic markers, HLA class II molecules (HLA-DQ2 and HLA-DQ8 haplotypes) [33]. About 90% of individuals carry the DQ2 heterodimer and practically all of the remaining patients express DQ8 [34]. First-degree relatives of individuals with biopsy-proven CD have villous atrophy on histology ranging from 4 to 12% [35]. Second-degree relatives also have an increased prevalence, defined only by serum antibody tests. Furthermore, the overall prevalence is higher in relatives of affected sibling pairs (17.2%) [36], monozygotic twins (75%), and HLA-identical siblings (40%) [37].

Clinical Presentation

There is a wide spectrum of symptomatology suggesting CD [38–46]. Based on the clinical features at presentation, histological and immunologic abnormalities, four types of clinical manifestations are presented as the celiac iceberg (Fig. 52.1) [28, 47–50].

Classic CD is seen in children and is characterized by diarrhea, failure to thrive, growth retardation, and malabsorption [42]. In contrast, the clinical presentation of CD in the adult population often can be atypical, manifesting as nonspecific extraintestinal symptoms or silent [51]. Surprisingly, data from a recent cohort study suggest the presentation of CD both clinically and histologically to be similar in young and old adults [52]. Diarrhea is the major presenting symptom in both groups. There is a similar prevalence of autoimmune disease, but thyroid disease and neuropathy are more prevalent in the elderly [52].

Frequent Presentations of CD in the Elderly

1. Anemia
   Anemia, usually secondary to iron deficiency, is often refractory to oral iron therapy and occurs in 60–80% of elderly patients with CD [31, 53–55]. It may also be multifactorial, with a lower prevalence of folate deficiency (about 10%) and B12 deficiency (about 5%) [53]. However, in addition to micronutrient deficiencies, inflammation may play a role as evidenced by the presence of anemia of chronic disease [53, 56, 57].
2. Osteoporosis
   Men more than women suffering with CD are at higher risk for osteoporosis [58]. Approximately 75% of patients with newly diagnosed CD have some degree of bone loss [58–64].
   Osteoporosis is mainly a result of long-term nutrient malabsorption. Vitamin D deficiency occurs in 68% of elderly patients. Calcium and vitamin D malabsorption can cause secondary hyperparathyroidism, which leads to a high rate of bone remodeling and bone loss. Deficiency of magnesium is common. It impairs the secretion and action of parathyroid hormone, resulting in osteopenia and skeletal fragility. Supplementation therapy decreases parathyroid hormone levels and improves bone mineral density (BMD) [3].
   The prevalence of osteopenia and osteoporosis is highest in newly diagnosed CD and when the disease is not in remission. The histological severity does not seem to be directly related to BMD [65, 66]. BMD improves following adherence to a gluten-free diet (GFD), vitamin D, and calcium supplements [65, 67, 68].

All patients with CD should be screened for osteoporosis. Further studies are needed to assess whether mass screening for CD in patients with osteoporosis is cost-effective [58].

3. Malnutrition
   Malabsorption contributes to malnutrition in the elderly [69]. Nutritional insufficiencies in CD often manifest as extraintestinal symptoms. Initial evaluation for newly diagnosed CD includes testing for iron, folate, calcium, and vitamin B12 deficiencies. Deficiency of fat-soluble vitamins (A, D, E, and K) is common. Other micronutrient deficiencies include magnesium, zinc, and copper. Clinical manifestations of vitamin A deficiency includes night blindness, conjunctival dryness, and keratomalacia [70]. Vitamin D malabsorption may result in osteomalacia, which clinically manifests as muscle weakness and musculoskeletal pain [71]. Calcium deficiency occurs in nearly 100% of patients with untreated CD [72] from malabsorption and downregulation of vitamin D regulating proteins (located in villous enterocytes) [73]. Manifestations of hypocalcemia such as tetany may occur. Low vitamin K levels detected by prolonged prothrombin time from decreased synthesis of clotting factors II, VII, IX, and X predispose to bruising, bleeding, and hemorrhage [74]. Zinc and copper deficiencies are common in untreated CD [75, 76]. Disturbed zinc metabolism can also result in vitamin A deficiency [75].
4. Celiac crisis
   Celiac crisis is a life-threatening syndrome often with a clear precipitating factor. The presentation includes profuse diarrhea and severe metabolic disturbances. Treatment with systemic steroids or oral budesonide should be considered [77, 78].
5. Obesity
   Patients with CD may be overweight or even obese [79–82]. Due to high BMI and silent presentation, these patients are handicapped by a delay in diagnosis and resultant increased morbidity and mortality. Weight gain may also occur following initiation of GFD and replacement of high-fat foods for gluten-containing products [79, 83–87].
6. Chronic pancreatitis
   Exocrine pancreatic insufficiency occurs in 20–40% of patients with untreated CD; it is usually mild and reversible after institution of a GFD [88, 89]. The coexistence of chronic calcific pancreatitis with CD has been documented [90–99].
7. Autoimmune disorders
   CD coexists with other autoimmune diseases [100]. Prevalence of CD was noted to be 1–19% in type 1 diabetes mellitus [101–105], 2–5% in autoimmune thyroid disorders [106], 3–7% in primary biliary cirrhosis [107–109], 0.4–6% in autoimmune hepatitis [110], and 19% in IBD [111, 112]. A common genetic predisposition with shared HLA haplotypes and non-HLA alleles is likely. Both CD and autoimmune thyroid disease are reported to be associated with the gene-encoding cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4). IgA autoantibodies against transglutaminase 2, present in the sera of patients with CD, react with transglutaminase 2 in thyroid tissue and contribute to the development of thyroid disease [113]. The length of exposure to gluten is associated with autoimmune disease, supporting a causal relationship between chronic gluten exposure and dysregulation of innate and adaptive immune mechanisms [114]. A higher prevalence of potential celiac disease has been noted in type 1 diabetes; the influence of genetic factors is questioned [115].
8. Dermatitis herpetiformis
   Dermatitis herpetiformis (DH), an intensely pruritic papulovesicular eruption located on the extensor surfaces of the elbows, knees, and trunk, occurs in about 25% of patients with CD and may be the initial presentation of gluten sensitivity in CD [116, 117]. DH has a 2:1 male to female ratio, with average age of presentation at 40 years [117, 118]. Unlike CD, patients with DH do not have an increase risk of malignancy, fractures, or mortality [119]. In contrast, autoimmune comorbidity is similar in both DH and CD [120]. The basis of therapy for DH is GFD, [121] with dapsone used for initial symptom suppression and flare [122].
9. Irritable bowel disease (IBS)
   ROME criteria used for the diagnosis of IBS can be fulfilled by several presenting symptoms of CD, and as such, leading to misdiagnosis of IBS in patients with underlying CD [123, 124]. Although the increased association between these two clinical entities remains unsettled, it is proposed to perform serologic testing on patients with diarrhea-predominant IBS or mixed-type IBS [2, 125].
10. Intususception
    Intussusception of small bowel is rare in healthy individuals. However, this may occur in older adults with CD warranting exclusion of adenocarcinoma [126].
11. Neurology
    Many rare neurological symptoms are associated with CD. In older adults with CD, neurological symptoms are mainly presented with neuropathy and ataxia [127–129].

Diagnosis

No one test can definitively diagnose or exclude CD in every individual. A comprehensive history must be obtained, along with a thorough physical examination. The clinician must be aware, understand, and look for the manifestations of CD.

The Diagnostic algorithm of CD is based on ESPGHAN criteria published in 1990 [130]. CD is diagnosed when typical small intestinal histopathological abnormalities defined as hyperplastic villous atrophy are noted in addition

Table 52.1 Serological tests for celiac disease [131–138]

Serologic antibody studies	Sensitivity (%)	Specificity (%)
IgA-tTG	98	95–99
IgA-EMA	90	95
IgA-AGA	70–85	70–90
IgG-DGP-AGA	65–94	99

tTG anti-human transglutaminase; *EMA* endomysial antibody; *AGA* anti-gladin antibody; *DGP* deamidated gladin peptide

Table 52.2 Modified Marsh classification of celiac disease [147]

Marsh type	Mucosal change
Marsh 0	Normal lymphocytosis
Marsh I	Intraepithelial lymphocytosis
Marsh II	Intraepithelial lymphocytosis and cypthyperplasia
Marsh III	Intraepithelial lymphocytosis, cypthyperplasia, and villous atrophy

to clinical remission on a strict GFD manifest by relief of symptoms. Serologic antibody studies include anti-human transglutaminase (tTG) test [131] and the endomysial antibody (EMA) immunofluorescence tests; both carry equivalent diagnostic accuracy, though EMA is more expensive than anti-tTG. The anti-gliadin antibody (AGA) test is less accurate. The newly emerged IgG and IgA antibody to deamidated gliadin peptides (DGP) has cross-linkage with tTG creating immunogenic epitopes enhancing antigenic presentation of gliadin [132, 133]. Some studies suggest that DGP-AGA has comparable diagnostic accuracy to IgA-tTG [134] and the combined search for IgA-tTG and IgG-DGP-AGA may provide the best diagnostic accuracy for CD [135, 136]. However, a recent meta-analysis shows IgA-tTG is more sensitive than DGP-AGA (Table 52.1) [137]. Not all patients have positive IgA-EMA or IgA-tTG at presentation [39]. IgA antibody deficiency is 10–15 times more common in CD than in normal health. When IgA deficiency is diagnosed, IgG-AGA and IgG-tTG or IgG-EMA test should be performed [138]. Tests to evaluate HLA-DQ2 and HLA-DQ8 are not an absolute requirement for diagnosis, although CD is highly unlikely when both are absent; HLA testing needs to be performed only once during the life time.

Initial negative serological tests do not exclude the development of disease later in life. It is important that all diagnostic tests to be performed while the patient is on a gluten-containing diet. In patients who are on a GFD for more than 3 months without a diagnosis, serological tests may be inconclusive necessitating a gluten challenge. The duration of gluten challenge and the quantity of gluten necessary to provoke a serological response are not clear [38].

Intestinal mucosal biopsy is the gold standard for diagnosis of CD [139, 140]. CD affects a highly variable portion of the small intestine, with above 95% of the cases involving the duodenum and a small percentage with duodenum sparing. Therefore routine biopsy may miss a small number with CD [141]. Wireless capsule endoscope (WCE) is a useful test for obtaining continuous images of the entire digestive tract and to exclude malignancy (see Chap. 24 for picture) [142–144].

Histology

Mucosal villous atrophy has long been considered the hallmark of CD and remains the gold standard in diagnosis [145, 146]. Histopathological changes in CD are characterized by typical architectural abnormalities. They are classified according to the modified Marsh classification (Table 52.2) [147].

Despite a good clinical response, abnormal endoscopic and histopathologic appearances persist in the majority of patients with CD treated with a GFD [148, 149].

A diagnosis of CD in the older adult is made with adequate histological and immunological evidence (Fig. 52.2). Unnecessary dietary restriction should be avoided in an individual who because of age, socioeconomic condition, and comorbidities may already have many limitations [150].

Management

The management of CD is a strict lifelong GFD which eliminates all forms wheat, rye, barley, and their derivatives. The accepted definition for gluten-free from the Codex Committee on Nutrition and Foods for Special Dietary Uses is as follows [151]: "gluten-free foods should not contain gluten higher than 20 mg/kg in total." Other studies suggest gluten intake in the range of 30–50 mg/day is safe when correlated to histology in the long-term [151, 152]. Individual variability must be borne in mind. Allowance of small or moderate amounts of uncontaminated oats in adult with disease remission is still controversial. However, this allowance can increase compliance to the diet by providing patients with more food alternatives and also improve the quality of life [153–155]. Patients should be referred to an experienced nutritionist at initial diagnosis and reassessment of the diet at each visit should be done to ensure GFD compliance [2, 156]. Lack of response to GFD means intentional or inadvertent consumption of gluten or the need to consider an alternate diagnosis. It is important to restrict lactose-containing foods for a few weeks until the intestine lactase levels are restored. Consumption of products such as yogurt, aged cheese, and iron containing foods is prudent.

There is an extensive list of gluten containing foods that should always be avoided. Patients should also steer clear from when not clearly labeled gluten-free. The patient should focus on what can be eaten as opposed to what cannot and on choosing naturally gluten-free products of high nutritional value (Table 52.3) [2]. The restrictive nature of a GFD is challenging. In older adults with existing comorbidity, dietary restriction can be extremely complicated. Unfortunately, at this time there is no alternate to a GFD.

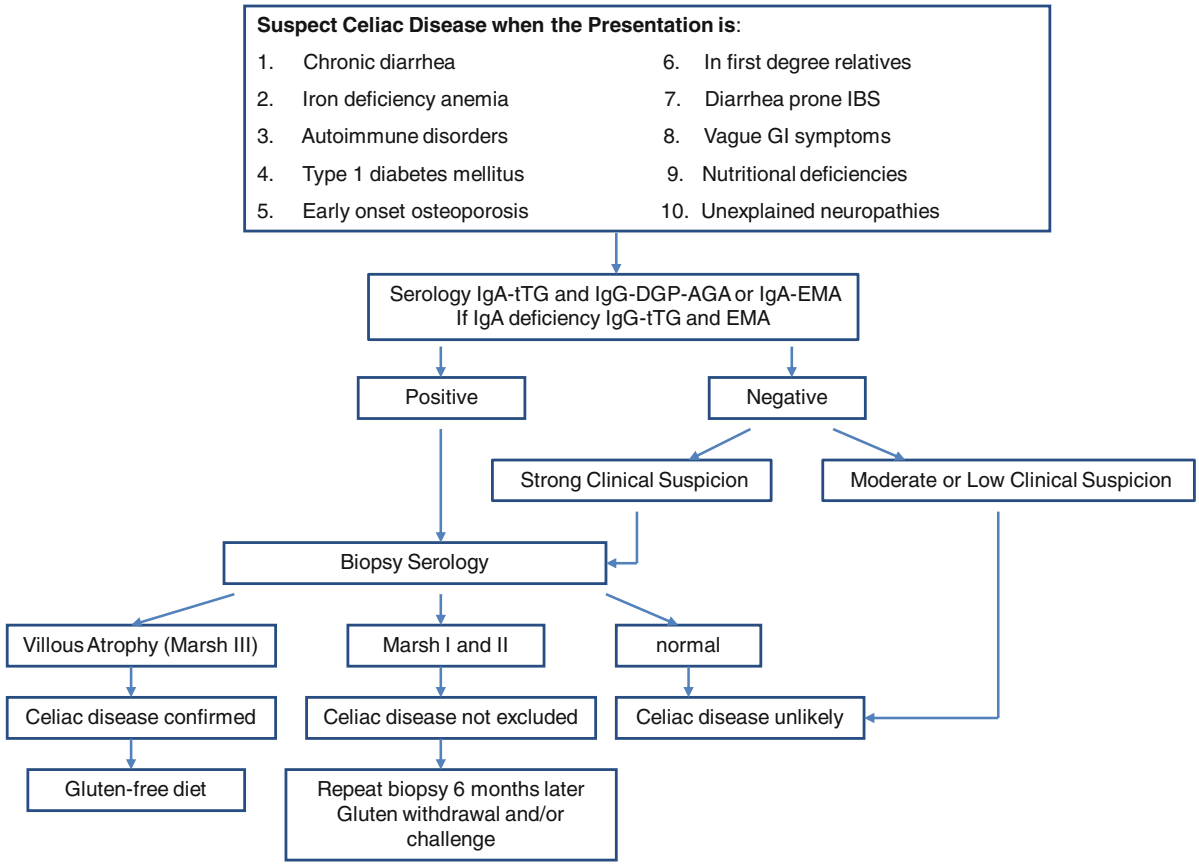

Fig. 52.2 Approach to celiac disease: a diagnostic algorithm

Table 52.3 Diet guide (adapted from Mayo Clinic (www.mayoclinic.com/health/gluten-free-diet/MY01140)

Always avoid	Avoid unless labeled "gluten free"	Allowed foods
Barley	Beers	Amaranth
Bulgur	Breads	Arrowroot
Durham	Candies	Buckwheat
Farina	Cakes and pies	Corn
Graham flour	Cereals	Cornmeal
Kamut	Cookies	Gluten-free flours (rice, soy, corn, potato, bean)
Matzo meal	Crackers	Hominy grits
Rye	Croutons	Polenta
Semolina	Gravies	Pure corn tortillas
Spelt (a form of wheat)	Imitation meats or seafood	Quinoa
Triticale	Oats	Rice
Wheat	Pastas	Tapioca
	Processed luncheon meats	Fresh meats, fish, and poultry (not breaded, batter-coated, or maintained)
	Salad dressings	Fruits
	Sauces (including soy sauce)	Most dairy products
	Self-basting poultry	Potatoes
	Soups	Rice
		Vegetables
		Wine and distilled liquors, ciders and spirits

New investigations aiming for easier and more comfortable treatment modalities are under active research. At present, several options are being investigated: these include enzyme supplementation (endoprolyl peptides, endoprotease B isoform 2), correction of the intestinal barrier defect against gluten entry, blocking of gliadin presentation by HLA blockers and tissue transglutaminase inhibitors, cytokines and anticytokines, modified gluten peptides, and stem cell transplantation [157–159].

Prognosis and Complications

Refractory CD

Refractory CD (RCD) is defined as the persistence of clinical and histological manifestations or recurrence after an initial adequate response, despite strict adherence to a GFD for more than 6–12 months [160]. This is diagnosed in a small percentage (1–5%) with adult-onset CD, especially in those over age 50 [161]. RCD type II has a poor short-term prognosis, increased mortality, and a close association with enteropathy-associated T-cell lymphoma [162–164]. RCD type I is relatively indolent, with good response to budesonide [165, 166]. Most recently, small intestinal release mesalamine has been found to be a safe and efficacious treatment option [167].

Malignancy and Mortality

Individuals with untreated CD have modest increase in overall risk of malignancy and mortality, especially if it is initially diagnosed late in the clinical course of the disease [25, 87, 168–170]. Clinical outcomes also depend on duration of exposure to gluten and the presence of RCD.

Increase in mortality is observed notably in autoimmune disease such as rheumatoid arthritis, connective tissue disease, and diabetes [171]. CD patients have a 30% overall increased risk of any malignancy [87, 168], specifically in gastrointestinal cancers [171] and lymphoproliferative cancer types [172] particularly enteropathy-associated T-cell lymphoma [173, 174]. The association of CD with increased mortality and malignancy is not universal. CD detected in an older population is not necessarily associated with increased risk of either malignancy or mortality. The longest follow-up study over 45 years shows the accumulated excess mortality does not occur until 25 years after the serum sampling date. When CD is diagnosed later in life, it may require a much longer follow-up for an increase in mortality to occur [1, 175]. It is important to note that both benign and malignant complications of CD do occur, but they can be avoided by early diagnosis and compliance with GFD [176]. Barring lymphoma, the frequency of malignant complications in CD appears much lower than indicated by earlier studies; further, although neurological or psychiatric conditions occur in CD, none are specifically associated with the disease [177]. A population-based study spanning over 25 years suggests that the mortality has not materially changed during the period; any excess mortality is attributed to deaths from cancer, digestive, and respiratory diseases [178]. As many deaths were from pneumonia, there is support for existing guidelines on the need to advise pneumococcal vaccination for those with celiac disease [178, 179].

Key Points

- Celiac disease is being increasingly recognized in the older adult.
- The diagnosis of celiac disease is established by serum antibody demonstration, small bowel mucosal histology, and response to gluten-free diet.
- The presentation of celiac disease in the older adults is likely to be atypical.
- Anemia is mostly attributed to iron deficiency and less often secondary to vitamin deficiency.
- Celiac disease may predispose to premature osteoporosis.
- Multiple vitamin and trace element deficiencies can result in CD.
- Celiac crisis is a life-threatening presentation with profuse diarrhea and metabolic disturbances.
- Refractory celiac disease is a serious condition, with significant morbidity.
- Several autoimmune disorders may coexist with celiac disease.
- The management of celiac disease includes strict adherence to a lifelong gluten-free diet and replacement of the nutrient deficiencies that occur with CD.
- There is a modest increase in intestinal T cell lymphoma in patients with CD.

References

1. Rubio-Tapia A, Murray JA. Celiac disease. Curr Opin Gastroenterol. 2010;26:116–22.
2. Crowe SE. Celiac disease. Ann Intern Med. 2011;154:ITC5-1.
3. Johnson MW, Ellis HJ, Asante MA, Ciclitira PJ. Celiac disease in the elderly. Nat Clin Pract Gastroenterol Hepatol. 2008;5:697–706.
4. Gasbarrini G, Miele L, Corazza GR, Gasbarrini A. When was celiac disease born?: the Italian case from the archeologic site of Cosa. J Clin Gastroenterol. 2010;44:502–3.
5. Losowsky MS. A history of coeliac disease. Dig Dis. 2008;26:112–20.
6. Dube C, Rostom A, Sy R, et al. The prevalence of celiac disease in average-risk and at-risk Western European populations: a systematic review. Gastroenterology. 2005;128:S57–67.
7. Cummins AG, Roberts-Thomson IC. Prevalence of celiac disease in the Asia-Pacific region. J Gastroenterol Hepatol. 2009;24:1347–51.

8. Catassi C, Ratsch IM, Gandolfi L, et al. Why is coeliac disease endemic in the people of the Sahara? Lancet. 1999;354:647–8.
9. Sood A, Midha V, Sood N, et al. Prevalence of celiac disease among school children in Punjab, North India. J Gastroenterol Hepatol. 2006;21:1622–5.
10. Bhattacharya M, Dubey AP, Mathur NB. Prevalence of celiac disease in north Indian children. Indian Pediatr. 2009;46:415–7.
11. Gomez JC, Selvaggio GS, Viola M, et al. Prevalence of celiac disease in Argentina: screening of an adult population in the La Plata area. Am J Gastroenterol. 2001;96:2700–4.
12. Pereira MA, Ortiz-Agostinho CL, Nishitokukado I, et al. Prevalence of celiac disease in an urban area of Brazil with predominantly European ancestry. World J Gastroenterol. 2006;12: 6546–50.
13. Remes-Troche JM, Ramirez-Iglesias MT, Rubio-Tapia A, et al. Celiac disease could be a frequent disease in Mexico: prevalence of tissue transglutaminase antibody in healthy blood donors. J Clin Gastroenterol. 2006;40:697–700.
14. Katz KD, Rashtak S, Lahr BD, et al. Screening for celiac disease in a North American population: sequential serology and gastrointestinal symptoms. Am J Gastroenterol. 2011;106(7):1333–9.
15. Virta LJ, Kaukinen K, Collin P. Incidence and prevalence of diagnosed coeliac disease in Finland: results of effective case finding in adults. Scand J Gastroenterol. 2009;44:933–8.
16. Barton SH, Kelly DG, Murray JA. Nutritional deficiencies in celiac disease. Gastroenterol Clin North Am. 2007;36:93–108; vi.
17. Mustalahti K, Catassi C, Reunanen A, et al. The prevalence of celiac disease in Europe: results of a centralized, international mass screening project. Ann Med. 2010;42:587–95.
18. Makharia GK, Verma AK, Amarchand R, et al. Prevalence of celiac disease in the northern part of India: a community based study. J Gastroenterol Hepatol. 2011;26:894–900.
19. Agostoni C, Decsi T, Fewtrell M, et al. Complementary feeding: a commentary by the ESPGHAN Committee on Nutrition. J Pediatr Gastroenterol Nutr. 2008;46:99–110.
20. Myleus A, Ivarsson A, Webb C, et al. Celiac disease revealed in 3% of Swedish 12-year-olds born during an epidemic. J Pediatr Gastroenterol Nutr. 2009;49:170–6.
21. Kondrashova A, Mustalahti K, Kaukinen K, et al. Lower economic status and inferior hygienic environment may protect against celiac disease. Ann Med. 2008;40:223–31.
22. Bardella MT, Trovato C, Cesana BM, et al. Serological markers for coeliac disease: is it time to change? Dig Liver Dis. 2001;33: 426–31.
23. Vilppula A, Collin P, Maki M, et al. Undetected coeliac disease in the elderly: a biopsy-proven population-based study. Dig Liver Dis. 2008;40:809–13.
24. Vilppula A, Kaukinen K, Luostarinen L, et al. Increasing prevalence and high incidence of celiac disease in elderly people: a population-based study. BMC Gastroenterol. 2009;9:49.
25. Ludvigsson JF, Montgomery SM, Ekbom A, Brandt L, Granath F. Small-intestinal histopathology and mortality risk in celiac disease. JAMA. 2009;302:1171–8.
26. Beaumont DM, Mian MS. Coeliac disease in old age: 'a catch in the rye'. Age Ageing. 1998;27:535–8.
27. Feighery C, Weir DG, Whelan A, et al. Diagnosis of gluten-sensitive enteropathy: is exclusive reliance on histology appropriate? Eur J Gastroenterol Hepatol. 1998;10:919–25.
28. Ferguson A, Arranz E, O'Mahony S. Clinical and pathological spectrum of coeliac disease—active, silent, latent, potential. Gut. 1993;34:150–1.
29. Swinson CM, Levi AJ. Is coeliac disease underdiagnosed? Br Med J. 1980;281:1258–60.
30. Campbell CB, Roberts RK, Cowen AE. The changing clinical presentation of coeliac disease in adults. Med J Aust. 1977;1:89–93.
31. Hankey GL, Holmes GK. Coeliac disease in the elderly. Gut. 1994;35:65–7.
32. Zipser RD, Patel S, Yahya KZ, Baisch DW, Monarch E. Presentations of adult celiac disease in a nationwide patient support group. Dig Dis Sci. 2003;48:761–4.
33. Tursi A, Elisei W, Giorgetti GM, et al. Prevalence of celiac disease and symptoms in relatives of patients with celiac disease. Eur Rev Med Pharmacol Sci. 2010;14:567–72.
34. Sollid LM, Markussen G, Ek J, et al. Evidence for a primary association of celiac disease to a particular HLA-DQ alpha/beta heterodimer. J Exp Med. 1989;169:345–50.
35. Rubio-Tapia A, Van Dyke CT, Lahr BD, et al. Predictors of family risk for celiac disease: a population-based study. Clin Gastroenterol Hepatol. 2008;6:983–7.
36. Gudjonsdottir AH, Nilsson S, Ek J, Kristiansson B, Ascher H. The risk of celiac disease in 107 families with at least two affected siblings. J Pediatr Gastroenterol Nutr. 2004;38:338–42.
37. Greco L, Romino R, Coto I, et al. The first large population based twin study of coeliac disease. Gut. 2002;50:624–8.
38. Cleo J, Libonati DMC. Recognizing celiac disease signs, symptoms, associated disorders & complications. Fort Washington: Gluten Free Works Publishing; 2007.
39. Green PH. The many faces of celiac disease: clinical presentation of celiac disease in the adult population. Gastroenterology. 2005; 128:S74–8.
40. Alaedini A, Green PH. Narrative review: celiac disease: understanding a complex autoimmune disorder. Ann Intern Med. 2005; 142:289–98.
41. Chand N, Mihas AA. Celiac disease: current concepts in diagnosis and treatment. J Clin Gastroenterol. 2006;40:3–14.
42. Farrell RJ, Kelly CP. Celiac sprue. N Engl J Med. 2002;346: 180–8.
43. Bardella MT, Fraquelli M, Quatrini M, et al. Prevalence of hypertransaminasemia in adult celiac patients and effect of gluten-free diet. Hepatology. 1995;22:833–6.
44. Kaukinen K, Halme L, Collin P, et al. Celiac disease in patients with severe liver disease: gluten-free diet may reverse hepatic failure. Gastroenterology. 2002;122:881–8.
45. Rampertab SD, Pooran N, Brar P, et al. Trends in the presentation of celiac disease. Am J Med. 2006;119(355):e9–14.
46. Jadallah KA, Khader YS. Celiac disease in patients with presumed irritable bowel syndrome: a case-finding study. World J Gastroenterol. 2009;15:5321–5.
47. Fasano A, Berti I, Gerarduzzi T, et al. Prevalence of celiac disease in at-risk and not-at-risk groups in the United States: a large multicenter study. Arch Intern Med. 2003;163:286–92.
48. Tommasini A, Not T, Kiren V, et al. Mass screening for coeliac disease using antihuman transglutaminase antibody assay. Arch Dis Child. 2004;89:512–5.
49. Kaukinen K, Collin P, Maki M. Latent coeliac disease or coeliac disease beyond villous atrophy? Gut. 2007;56:1339–40.
50. Collin P, Huhtala H, Virta L, et al. Diagnosis of celiac disease in clinical practice: physician's alertness to the condition essential. J Clin Gastroenterol. 2007;41:152–6.
51. Marmouz F. Adult coeliac disease. Eur Ann Allergy Clin Immunol. 2007;39:23–5.
52. Mukherjee R, Egbuna I, Brar P, et al. Celiac disease: similar presentations in the elderly and young adults. Dig Dis Sci. 2010;55:3147–53.
53. Harper JW, Holleran SF, Ramakrishnan R, et al. Anemia in celiac disease is multifactorial in etiology. Am J Hematol. 2007;82: 996–1000.
54. Carroccio A, Iannitto E, Cavataio F, et al. Sideropenic anemia and celiac disease: one study, two points of view. Dig Dis Sci. 1998;43:673–8.

55. Arnason JA, Gudjonsson H, Freysdottir J, et al. Do adults with high gliadin antibody concentrations have subclinical gluten intolerance? Gut. 1992;33:194–7.
56. Bergamaschi G, Markopoulos K, Albertini R, et al. Anemia of chronic disease and defective erythropoietin production in patients with celiac disease. Haematologica. 2008;93:1785–91.
57. Zamani F, Mohamadnejad M, Shakeri R, et al. Gluten sensitive enteropathy in patients with iron deficiency anemia of unknown origin. World J Gastroenterol. 2008;14:7381–5.
58. Mangione RA. Celiac disease and osteoporosis. Am J Health Syst Pharm. 2008;65:1601; author reply 2.
59. Meyer D, Stavropolous S, Diamond B, et al. Osteoporosis in a North American adult population with celiac disease. Am J Gastroenterol. 2001;96:112–9.
60. Ludvigsson JF, Michaelsson K, Ekbom A, Montgomery SM. Coeliac disease and the risk of fractures—a general population-based cohort study. Aliment Pharmacol Ther. 2007;25:273–85.
61. Vasquez H, Mazure R, Gonzalez D, et al. Risk of fractures in celiac disease patients: a cross-sectional, case-control study. Am J Gastroenterol. 2000;95:183–9.
62. Fickling WE, McFarlane XA, Bhalla AK, Robertson DA. The clinical impact of metabolic bone disease in coeliac disease. Postgrad Med J. 2001;77:33–6.
63. Thomason K, West J, Logan RF, et al. Fracture experience of patients with coeliac disease: a population based survey. Gut. 2003;52:518–22.
64. West J, Logan RF, Card TR, et al. Fracture risk in people with celiac disease: a population-based cohort study. Gastroenterology. 2003;125:429–36.
65. Mustalahti K, Collin P, Sievanen H, et al. Osteopenia in patients with clinically silent coeliac disease warrants screening. Lancet. 1999;354:744–5.
66. Kurppa K, Collin P, Sievanen H, et al. Gastrointestinal symptoms, quality of life and bone mineral density in mild enteropathic coeliac disease: a prospective clinical trial. Scand J Gastroenterol. 2010;45:305–14.
67. Fasano A, Catassi C. Current approaches to diagnosis and treatment of celiac disease: an evolving spectrum. Gastroenterology. 2001;120:636–51.
68. Sategna-Guidetti C, Grosso SB, Grosso S, et al. The effects of 1-year gluten withdrawal on bone mass, bone metabolism and nutritional status in newly-diagnosed adult coeliac disease patients. Aliment Pharmacol Ther. 2000;14:35–43.
69. Bolin T, Bare M, Caplan G, Daniells S, Holyday M. Malabsorption may contribute to malnutrition in the elderly. Nutrition. 2010;26:852–3.
70. Alwitry A. Vitamin A deficiency in coeliac disease. Br J Ophthalmol. 2000;84:1079–80.
71. Holick MF. Vitamin D deficiency: what a pain it is. Mayo Clin Proc. 2003;78:1457–9.
72. Molteni N, Bardella MT, Vezzoli G, et al. Intestinal calcium absorption as shown by stable strontium test in celiac disease before and after gluten-free diet. Am J Gastroenterol. 1995;90:2025–8.
73. Colston KW, Mackay AG, Finlayson C, et al. Localisation of vitamin D receptor in normal human duodenum and in patients with coeliac disease. Gut. 1994;35:1219–25.
74. Cavallaro R, Iovino P, Castiglione F, et al. Prevalence and clinical associations of prolonged prothrombin time in adult untreated coeliac disease. Eur J Gastroenterol Hepatol. 2004;16:219–23.
75. Scholmerich J, Wietholtz H, Buchsel R, et al. [Zinc and vitamin A deficiency in gastrointestinal diseases]. Leber Magen Darm. 1984;14:288–95.
76. Jameson S, Hellsing K, Magnusson S. Copper malabsorption in coeliac disease. Sci Total Environ. 1985;42:29–36.
77. Jamma S, Rubio-Tapia A, Kelly CP, et al. Celiac crisis is a rare but serious complication of celiac disease in adults. Clin Gastroenterol Hepatol. 2010;8:587–90.
78. Parry J, Acharya C. Celiac crisis in an older man. J Am Geriatr Soc. 2010;58:1818–9.
79. Dickey W, Kearney N. Overweight in celiac disease: prevalence, clinical characteristics, and effect of a gluten-free diet. Am J Gastroenterol. 2006;101:2356–9.
80. Owen DA, Thorlakson TK, Walli JE. Celiac disease in a patient with morbid obesity. Arch Intern Med. 1980;140:1380–1.
81. Semeraro LA, Barwick KW, Gryboski JD. Obesity in celiac sprue. J Clin Gastroenterol. 1986;8:177–80.
82. Cheng J, Brar PS, Lee AR, Green PH. Body mass index in celiac disease: beneficial effect of a gluten-free diet. J Clin Gastroenterol. 2010;44:267–71.
83. See J, Murray JA. Gluten-free diet: the medical and nutrition management of celiac disease. Nutr Clin Pract. 2006;21:1–15.
84. Adams KF, Schatzkin A, Harris TB, et al. Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. N Engl J Med. 2006;355:763–78.
85. Brar P, Kwon GY, Holleran S, et al. Change in lipid profile in celiac disease: beneficial effect of gluten-free diet. Am J Med. 2006;119:786–90.
86. West J, Logan RF, Card TR, et al. Risk of vascular disease in adults with diagnosed coeliac disease: a population-based study. Aliment Pharmacol Ther. 2004;20:73–9.
87. West J, Logan RF, Smith CJ, et al. Malignancy and mortality in people with coeliac disease: population based cohort study. BMJ. 2004;329:716–9.
88. Carroccio A, Iacono G, Montalto G, et al. Exocrine pancreatic function in children with coeliac disease before and after a gluten free diet. Gut. 1991;32:796–9.
89. Carroccio A, Iacono G, Lerro P, et al. Role of pancreatic impairment in growth recovery during gluten-free diet in childhood celiac disease. Gastroenterology. 1997;112:1839–44.
90. Regan PT, DiMagno EP. Exocrine pancreatic insufficiency in celiac sprue: a cause of treatment failure. Gastroenterology. 1980;78:484–7.
91. Pitchumoni CS, Thomas E, Balthazar E, Sherling B. Chronic calcific pancreatitis in association with celiac disease. Am J Gastroenterol. 1977;68:358–61.
92. Nanda R, Anand BS. Celiac disease and tropical calcific pancreatitis. Am J Gastroenterol. 1993;88:1790–2.
93. Arya S, Rana SS, Sinha SK, Nagi B, Bhasin DK. Celiac disease and chronic calcific pancreatitis with pancreas divisum. Gastrointest Endosc. 2006;63:1080–1.
94. Ludvigsson JF, Montgomery SM, Ekbom A. Risk of pancreatitis in 14,000 individuals with celiac disease. Clin Gastroenterol Hepatol. 2007;5:1347–53.
95. Pitchumoni CS. Pancreas in primary malnutrition disorders. Am J Clin Nutr. 1973;26:374–9.
96. Nordgren L, von Scheele C. Hepatic and pancreatic dysfunction in anorexia nervosa: a report of two cases. Biol Psychiatry. 1977;12:681–6.
97. Cox KL, Cannon RA, Ament ME, et al. Biochemical and ultrasonic abnormalities of the pancreas in anorexia nervosa. Dig Dis Sci. 1983;28:225–9.
98. Patel RS, Johlin Jr FC, Murray JA. Celiac disease and recurrent pancreatitis. Gastrointest Endosc. 1999;50:823–7.
99. Evans KE, Leeds JS, Morley S, Sanders DS. Pancreatic insufficiency in adult celiac disease: do patients require long-term enzyme supplementation? Dig Dis Sci. 2010;55:2999–3004.
100. Rashtak S, Marietta EV, Murray JA. Celiac sprue: a unique autoimmune disorder. Expert Rev Clin Immunol. 2009;5:593–604.

101. Buysschaert M, Tomasi JP, Hermans MP. Prospective screening for biopsy proven coeliac disease, autoimmunity and malabsorption markers in Belgian subjects with Type 1 diabetes. Diabet Med. 2005;22:889–92.
102. Mahmud FH, Murray JA, Kudva YC, et al. Celiac disease in type 1 diabetes mellitus in a North American community: prevalence, serologic screening, and clinical features. Mayo Clin Proc. 2005;80:1429–34.
103. Vicuna Arregui M, Zozaya Urmeneta JM, Martinez de Esteban JP, et al. [Study of celiac disease in adults with type 1 diabetes mellitus]. Gastroenterol Hepatol. 2010;33:6–11.
104. Cronin CC, Feighery A, Ferriss JB, et al. High prevalence of celiac disease among patients with insulin-dependent (type I) diabetes mellitus. Am J Gastroenterol. 1997;92:2210–2.
105. Sjoberg K, Eriksson KF, Bredberg A, et al. Screening for coeliac disease in adult insulin-dependent diabetes mellitus. J Intern Med. 1998;243:133–40.
106. Ch'ng CL, Jones MK, Kingham JG. Celiac disease and autoimmune thyroid disease. Clin Med Res. 2007;5:184–92.
107. Floreani A, Betterle C, Baragiotta A, et al. Prevalence of coeliac disease in primary biliary cirrhosis and of antimitochondrial antibodies in adult coeliac disease patients in Italy. Dig Liver Dis. 2002;34:258–61.
108. Kingham JG, Parker DR. The association between primary biliary cirrhosis and coeliac disease: a study of relative prevalences. Gut. 1998;42:120–2.
109. Volta U, Rodrigo L, Granito A, et al. Celiac disease in autoimmune cholestatic liver disorders. Am J Gastroenterol. 2002;97:2609–13.
110. Villalta D, Girolami D, Bidoli E, et al. High prevalence of celiac disease in autoimmune hepatitis detected by anti-tissue tranglutaminase autoantibodies. J Clin Lab Anal. 2005;19:6–10.
111. Tursi A, Giorgetti GM, Brandimarte G, Elisei W. High prevalence of celiac disease among patients affected by Crohn's disease. Inflamm Bowel Dis. 2005;11:662–6.
112. Yang A, Chen Y, Scherl E, et al. Inflammatory bowel disease in patients with celiac disease. Inflamm Bowel Dis. 2005;11: 528–32.
113. Naiyer AJ, Shah J, Hernandez L, et al. Tissue transglutaminase antibodies in individuals with celiac disease bind to thyroid follicles and extracellular matrix and may contribute to thyroid dysfunction. Thyroid. 2008;18:1171–8.
114. Ventura A, Magazzu G, Greco L. Duration of exposure to gluten and risk for autoimmune disorders in patients with celiac disease. SIGEP Study Group for Autoimmune Disorders in Celiac Disease. Gastroenterology. 1999;117:297–303.
115. Franzese A, Iafusco D, Spadaro R, et al. Potential celiac disease in type 1 diabetes: a multicenter study. Diabetes Res Clin Pract. 2011;92:53–6.
116. Reunala T. Dermatitis herpetiformis: coeliac disease of the skin. Ann Med. 1998;30:416–8.
117. Collin P, Reunala T. Recognition and management of the cutaneous manifestations of celiac disease: a guide for dermatologists. Am J Clin Dermatol. 2003;4:13–20.
118. Gawkrodger DJ, Blackwell JN, Gilmour HM, et al. Dermatitis herpetiformis: diagnosis, diet and demography. Gut. 1984;25: 151–7.
119. Lewis NR, Logan RF, Hubbard RB, West J. No increase in risk of fracture, malignancy or mortality in dermatitis herpetiformis: a cohort study. Aliment Pharmacol Ther. 2008;27:1140–7.
120. Reunala T, Collin P. Diseases associated with dermatitis herpetiformis. Br J Dermatol. 1997;136:315–8.
121. Rashtak S, Murray JA. Celiac disease in the elderly. Gastroenterol Clin North Am. 2009;38:433–46.
122. Nicolas ME, Krause PK, Gibson LE, Murray JA. Dermatitis herpetiformis. Int J Dermatol. 2003;42:588–600.
123. Korkut E, Bektas M, Oztas E, et al. The prevalence of celiac disease in patients fulfilling Rome III criteria for irritable bowel syndrome. Eur J Intern Med. 2010;21:389–92.
124. Ford AC, Chey WD, Talley NJ, et al. Yield of diagnostic tests for celiac disease in individuals with symptoms suggestive of irritable bowel syndrome: systematic review and meta-analysis. Arch Intern Med. 2009;169:651–8.
125. Brandt LJ, Bjorkman D, Fennerty MB, et al. Systematic review on the management of irritable bowel syndrome in North America. Am J Gastroenterol. 2002;97:S7–26.
126. Gonda TA, Khan SU, Cheng J, et al. Association of intussusception and celiac disease in adults. Dig Dis Sci. 2010;55:2899–903.
127. Green PH, Alaedini A, Sander HW, et al. Mechanisms underlying celiac disease and its neurologic manifestations. Cell Mol Life Sci. 2005;62:791–9.
128. Hernandez L, Green PH. Extraintestinal manifestations of celiac disease. Curr Gastroenterol Rep. 2006;8:383–9.
129. Rashtak S, Snyder MR, Pittock SJ, et al. Serology of celiac disease in gluten-sensitive ataxia or neuropathy: role of deamidated gliadin antibody. J Neuroimmunol. 2011;230:130–4.
130. Revised criteria for diagnosis of coeliac disease. Report of Working Group of European Society of Paediatric Gastroenterology and Nutrition. Arch Dis Child. 1990;65:909–11.
131. Zintzaras E, Germenis AE. Performance of antibodies against tissue transglutaminase for the diagnosis of celiac disease: meta-analysis. Clin Vaccine Immunol. 2006;13:187–92.
132. Dieterich W, Esslinger B, Trapp D, et al. Cross linking to tissue transglutaminase and collagen favours gliadin toxicity in coeliac disease. Gut. 2006;55:478–84.
133. Marietta EV, Rashtak S, Murray JA. Correlation analysis of celiac sprue tissue transglutaminase and deamidated gliadin IgG/IgA. World J Gastroenterol. 2009;15:845–8.
134. Vermeersch P, Geboes K, Marien G, et al. Diagnostic performance of IgG anti-deamidated gliadin peptide antibody assays is comparable to IgA anti-tTG in celiac disease. Clin Chim Acta. 2010;411:931–5.
135. Volta U, Granito A, Parisi C, et al. Deamidated gliadin peptide antibodies as a routine test for celiac disease: a prospective analysis. J Clin Gastroenterol. 2010;44:186–90.
136. Kaukinen K, Collin P, Laurila K, et al. Resurrection of gliadin antibodies in coeliac disease. Deamidated gliadin peptide antibody test provides additional diagnostic benefit. Scand J Gastroenterol. 2007;42:1428–33.
137. Lewis NR, Scott BB. Meta-analysis: deamidated gliadin peptide antibody and tissue transglutaminase antibody compared as screening tests for coeliac disease. Aliment Pharmacol Ther. 2010;31:73–81.
138. Kumar V, Jarzabek-Chorzelska M, Sulej J, et al. Celiac disease and immunoglobulin a deficiency: how effective are the serological methods of diagnosis? Clin Diagn Lab Immunol. 2002;9: 1295–300.
139. Green PH, Shane E, Rotterdam H, et al. Significance of unsuspected celiac disease detected at endoscopy. Gastrointest Endosc. 2000;51:60–5.
140. Walker MM, Murray JA. An update in the diagnosis of coeliac disease. Histopathology. 2011;59(2):166–79.
141. Murray JA, Rubio-Tapia A, Van Dyke CT, et al. Mucosal atrophy in celiac disease: extent of involvement, correlation with clinical presentation, and response to treatment. Clin Gastroenterol Hepatol. 2008;6:186–93; quiz 25.
142. Muhammad A, Pitchumoni CS. Newly detected celiac disease by wireless capsule endoscopy in older adults with iron deficiency anemia. J Clin Gastroenterol. 2008;42:980–3.
143. Culliford A, Daly J, Diamond B, et al. The value of wireless capsule endoscopy in patients with complicated celiac disease. Gastrointest Endosc. 2005;62:55–61.

144. Ciaccio EJ, Tennyson CA, Bhagat G, et al. Classification of video-capsule endoscopy image patterns: comparative analysis between patients with celiac disease and normal individuals. Biomed Eng Online. 2010;9:44.
145. Gonzalez S, Gupta A, Cheng J, et al. Prospective study of the role of duodenal bulb biopsies in the diagnosis of celiac disease. Gastrointest Endosc. 2010;72:758–65.
146. Walker MM, Murray JA, Ronkainen J, et al. Detection of celiac disease and lymphocytic enteropathy by parallel serology and histopathology in a population-based study. Gastroenterology. 2010;139:112–9.
147. Rostami K, Kerckhaert J, Tiemessen R, et al. Sensitivity of antiendomysium and antigliadin antibodies in untreated celiac disease: disappointing in clinical practice. Am J Gastroenterol. 1999;94: 888–94.
148. Lee SK, Lo W, Memeo L, Rotterdam H, Green PH. Duodenal histology in patients with celiac disease after treatment with a gluten-free diet. Gastrointest Endosc. 2003;57:187–91.
149. Rubio-Tapia A, Rahim MW, See JA, et al. Mucosal recovery and mortality in adults with celiac disease after treatment with a gluten-free diet. Am J Gastroenterol. 2010;105:1412–20.
150. Long KH, Rubio-Tapia A, Wagie AE, et al. The economics of coeliac disease: a population-based study. Aliment Pharmacol Ther. 2010;32:261–9.
151. Catassi C, Fabiani E, Iacono G, et al. A prospective, double-blind, placebo-controlled trial to establish a safe gluten threshold for patients with celiac disease. Am J Clin Nutr. 2007;85: 160–6.
152. Collin P, Thorell L, Kaukinen K, Maki M. The safe threshold for gluten contamination in gluten-free products. Can trace amounts be accepted in the treatment of coeliac disease? Aliment Pharmacol Ther. 2004;19:1277–83.
153. Storsrud S, Hulthen LR, Lenner RA. Beneficial effects of oats in the gluten-free diet of adults with special reference to nutrient status, symptoms and subjective experiences. Br J Nutr. 2003; 90:101–7.
154. Picarelli A, Di Tola M, Sabbatella L, et al. Immunologic evidence of no harmful effect of oats in celiac disease. Am J Clin Nutr. 2001;74:137–40.
155. Janatuinen EK, Kemppainen TA, Julkunen RJ, et al. No harm from five year ingestion of oats in coeliac disease. Gut. 2002;50: 332–5.
156. AGA Institute. AGA Institute medical position statement on the diagnosis and management of celiac disease. Gastroenterology. 2006;131:1977–80.
157. Selimoglu MA, Karabiber H. Celiac disease: prevention and treatment. J Clin Gastroenterol. 2010;44:4–8.
158. Lerner A. New therapeutic strategies for celiac disease. Autoimmun Rev. 2010;9:144–7.
159. Tennyson CA, Lewis SK, Green PH. New and developing therapies for celiac disease. Ther Adv Gastroenterol. 2009;2:303–9.
160. Rubio-Tapia A, Murray JA. Classification and management of refractory coeliac disease. Gut. 2010;59:547–57.
161. Cellier C, Delabesse E, Helmer C, et al. Refractory sprue, coeliac disease, and enteropathy-associated T-cell lymphoma. French Coeliac Disease Study Group. Lancet. 2000;356:203–8.
162. Culliford AN, Green PH. Refractory sprue. Curr Gastroenterol Rep. 2003;5:373–8.
163. Rubio-Tapia A, Kelly DG, Lahr BD, et al. Clinical staging and survival in refractory celiac disease: a single center experience. Gastroenterology. 2009;136:99–107; quiz 352–3.
164. Malamut G, Afchain P, Verkarre V, et al. Presentation and long-term follow-up of refractory celiac disease: comparison of type I with type II. Gastroenterology. 2009;136:81–90.
165. Daum S, Ipczynski R, Heine B, et al. Therapy with budesonide in patients with refractory sprue. Digestion. 2006;73:60–8.
166. Brar P, Lee S, Lewis S, et al. Budesonide in the treatment of refractory celiac disease. Am J Gastroenterol. 2007;102:2265–9.
167. Jamma S, Leffler DA, Dennis M, et al. Small intestinal release mesalamine for the treatment of refractory celiac disease type I. J Clin Gastroenterol. 2011;45:30–3.
168. Askling J, Linet M, Gridley G, et al. Cancer incidence in a population-based cohort of individuals hospitalized with celiac disease or dermatitis herpetiformis. Gastroenterology. 2002;123: 1428–35.
169. Peters U, Askling J, Gridley G, et al. Causes of death in patients with celiac disease in a population-based Swedish cohort. Arch Intern Med. 2003;163:1566–72.
170. Corrao G, Corazza GR, Bagnardi V, et al. Mortality in patients with coeliac disease and their relatives: a cohort study. Lancet. 2001;358:356–61.
171. Green PHR, Stavropoulos SN, Panagi SG, et al. Characteristics of adult celiac disease in the USA: results of a national survey. Am J Gastroenterol. 2001;96:126–31.
172. Green PH, Fleischauer AT, Bhagat G, Goyal R, Jabri B, Neugut AI. Risk of malignancy in patients with celiac disease. Am J Med. 2003;115:191–5.
173. Catassi C, Bearzi I, Holmes GK. Association of celiac disease and intestinal lymphomas and other cancers. Gastroenterology. 2005;128:S79–86.
174. Di Sabatino A, Corazza GR. Coeliac disease. Lancet. 2009;373: 1480–93.
175. Godfrey JD, Brantner TL, Brinjikji W, et al. Morbidity and mortality among older individuals with undiagnosed celiac disease. Gastroenterology. 2010;139:763–9.
176. Murray JA. The widening spectrum of celiac disease. Am J Clin Nutr. 1999;69:354–65.
177. Lewis NR, Holmes GK. Risk of morbidity in contemporary celiac disease. Expert Rev Gastroenterol Hepatol. 2010;4:767–80.
178. Grainge MJ, West J, Card TR, et al. Causes of death in people with celiac disease spanning the pre- and post- serology era: a polulation based cohort study from Derby, UK. Am J Gastroenterol. 2011;106:933–9.
179. Roshan B, Leffler DA, Jamima S, et al. The incidence and clinical spectrum of refractory celiac disease in a North American referral center. Am J Gastroenterol. 2011;106:923–8.

Diverticular Disease

53

C.S. Pitchumoni

Introduction

Described as early as the seventeenth century, colonic diverticulosis remained an obscure disease until the beginning of the twentieth century [1–3]. Diverticulosis, essentially a disease of the older adult, is expected to increase in prevalence with the change in demographics. The mere presence of diverticula is so common in the older adult that it is often ignored and labeled as "normal" for the age. The difference in the prevalence of diverticular disease (DD) in various parts of the world is striking. Until recently DD was relatively uncommon in Africa, Asia, and many parts of South America. Sir Dennis, an Irish surgeon who served for many years as a physician in Uganda, was impressed with the prevalence of the disease mostly in the Western countries and proposed that it is a malady of civilization [1, 2]. The data from developing nations is occasionally criticized as underestimated. Burkitt's hypothesis that diverticular disease is essentially a disease resulting from dietary fiber depletion is popular and convincing [4–8].

"Diverticulum," a word derived from Latin "diverter," means "to turn a different way." A diverticulum is a singular and abnormal outpouching or herniation of the lining of the colon wall, while two or more are known as "diverticula." Diverticulosis denotes the presence of uninflamed diverticula [5]. "Diverticular disease" is a clinical condition with abdominal symptoms associated with colonic diverticulosis. DD in turn may be complicated or noncomplicated. Colonic diverticulosis is a condition associated with multiple diverticula. Table 53.1 summarizes terminology pertinent to DD.

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Epidemiology

Colonic diverticulosis is a common radiological or endoscopic observation noted in 30% of those over 50 years, 50% in those over 70 years, and 66% in the over 85 years population [7, 9–14]. The exact prevalence of diverticulosis is difficult to document since the disorder is largely asymptomatic. Apparent increase in prevalence is attributed to findings from screening colonoscopy.

The onset of DD is typically noted in the sixth, seventh, and eighth decade of life [3]. Overall annual age-adjusted admissions for acute diverticulitis have increased in the United States from 120,500 in 1998 to 151,900 in 2005, a 26% increase. Elective operations for diverticulitis rose from 16,100 to 22,500 per year during the same period, a 40% increase. Poor outcomes in the elderly with emergency admissions were also noted [15, 16]. The epidemiology suggests that older age, the environment, and diet are factors that play a role in the pathogenesis of DD.

The burden of diverticular disease is estimated at $2.66 billion annually and is the fifth most important gastrointestinal disorder in terms of direct and indirect costs [3]. Recent increase in life expectancy, affluence, changes in dietary habits, and increased detection of diverticula with imaging and endoscopic studies in several Asian nations have resulted in an increased recognition of the disease [8, 17–23]. Right-sided diverticulosis is often seen in Asians.

Pathology

DD (see Table 53.2) mostly involves the sigmoid colon, and almost never the rectum. Based on the structure, a diverticulum may be classified as a true diverticulum if it involves all layers of the intestinal wall or a false diverticulum (pseudodiverticulum) when it has only the mucosal and submucosal layers herniated through a defect in the muscularis [9, 24–27]. The large majority of colonic diverticula on the left side of the colon are pseudo-diverticula. Diverticula herniate through

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Table 53.1 Terminology [3, 5, 8, 9]

1. Diverticulum: singular, derived from diverter (Latin) meaning "to turn a different way." Diverticula is the plural term
2. True diverticulum: protrusion involving all wall layers
3. False (pseudo) diverticulum: pulsion type herniation of mucosa and submucosa through a defect in the muscularis, e.g., colonic diverticula
4. Diverticulosis: presence of multiple diverticula, noninflamed diverticula and incidental finding in endoscopy or imaging studies
5. Diverticulitis: inflamed diverticula (change in bacterial flora, diminished venous outflow, and localized ischemia) Uncomplicated diverticulitis: includes phlegmon, peridiverticulitis (obstructed diverticulum with a cascade of events) Complicated diverticulitis: abscess, fistula, stricture, or full perforation

Table 53.2 Pathogenesis of colonic diverticulosis [9, 28, 69, 70]

1. Structural abnormalities in the colon Thickening of muscle wall (myochosis) shortening of the taenia (accordion like pleating of folds). Increased elastin deposition between the muscle walls
2. Motility disorder Higher resting postprandial luminal pressures Segmentation of colon Increased contraction amplitude Retropropagation of contractile waves
3. Dietary fiber deficiency Wide geographic variation in prevalence Consumption of low-fiber Western diet and association with slow transit time and low stool weight associated with increased intra-luminal pressure
4. Aging Reduction in the tensile strength of the colonic wall with age

the bowel wall at weak points in the circular muscle at sites where the main blood vessels transit to supply the colonic mucosa. The number of diverticula in patients varies from an isolated one to hundreds distributed diffusely. Generally, the size of each diverticulum is 5–10 mm in diameter, but may be as much as 2 cm. Giant colonic diverticula are considered a separate entity in which each diverticulum may be as large as 25 cm. In industrialized nations, the predominant form of DD is left-sided (90%) [3]. A curiosity that is not yet explained is the increased prevalence of right-sided diverticulosis in the Asian population. Right-sided diverticulosis is more likely to cause bleeding, whereas left-sided causes diverticulitis.

Abnormally increased intracolonic pressure in the sigmoid region and disordered colonic motility have long been implicated as pathogenic factors in DD [28]. Sustained segmental contraction results in increased intraluminal pressure leading to outpouching of the diverticula. Hypertonicity and colonic muscular hypertrophy probably precede diverticula formation. It is also possible that muscular changes occur after diverticular formation. Intermittent contractions divide the colonic lumen into a series of small compartments, comparable to "small bladders." The increased intracolonic pressure within these segments of sigmoid colon (increased phasic pressure activity) results in substantial outward force in the colonic wall, a prerequisite for diverticula formation. Protrusion of the mucosa occurs through points of weakness, located between the mesenteric and antimesenteric taenia, through which feeding blood vessels (vasa recta) penetrate the muscle layer. The mucosa of the remainder of the sigmoid colon, the nondiverticula mucosa, is normal. In a few cases the intervening mucosa shows features of ulcerative colitis or Crohn's disease, a form of segmental colitis associated with diverticular disease.

Colonic mucosa is extremely stretchable, allowing for easy herniation through the points of weakness in the wall. As age advances, the composition of collagen in the colonic wall changes and weakness develops. It is often stated that DD is a natural consequence of aging and not a discrete disease. In support of this is the observation that the majority of individuals (>80%) with DD have no symptoms or sequela.

An overlap in the pathology of inflammatory bowel disease (IBD) and diverticulitis is becoming more and more apparent, leading to a new view regarding the pathogenesis of diverticulitis. With the finding that chronic inflammation is part of the pathology of diverticulitis, mesalamine and other anti-inflammatory agents that are regularly used in the treatment of IBD have been examined in the management of DD [18, 29–34]. Visceral hypersensitivity, motor disturbance, fiber-depleted diet, and subtle mucosal inflammation are common factors in the pathogenesis [31]. DD is considered to be a form of enteric neuropathy and part of a spectrum of intestinal motility disorders.

Clinical Features

Asymptomatic Diverticular Disease

Diverticulosis is asymptomatic in the majority of patients; less than 20% experience symptoms, with little need for any specific therapy (Table 53.3). The role of a high fiber diet in preventing or reducing symptomatic disease is discussed in another chapter. Diets rich in red meat and fat are associated with a higher prevalence of the disease. There is no scientific proof to the long held belief that patients with diverticulosis should avoid nuts, corn, seeds and popcorn or that consumption thereof is associated with an increase risk of diverticulitis [35].

Symptomatic Uncomplicated Diverticular Disease

The pathogenesis of symptoms observed in a small number of patients is unclear. It has been observed that in patients

Table 53.3 Clinical spectrum of colonic diverticular disease [8–16, 45–49]

1. Asymptomatic diverticulosis: an incidental imaging finding
2. Symptomatic uncomplicated diverticular disease (SUDD)—associated with thickening of colonic muscle—mimics IBS
3. Bleeding diverticulosis
4. Diverticulitis Uncomplicated—perforation of a diverticulum Complicated—obstruction, free perforation, fistula, or abscess formation Recurrent diverticulitis—fistula, perforation, stricture
5. Incidental diverticulosis—overlapping other intracolonic disease such as colon polyps/cancer

with DD and a history of diverticulitis with episodes of recurrent abdominal pain and impaired bowel function, previous intestinal inflammation may play a role [36–38].

The presence of a chronic low-grade intestinal inflammation is hypothesized to induce a sensory-motor dysfunction, leading to symptom development and/or persistence [37, 38]. The concept is gaining strength in view of the recent observations in infectious enteritis and IBD. Constipation, IBD, and DD are common problems in older adults and may have a common pathogenic mechanism [28].

Although uncomplicated diverticular disease is mostly asymptomatic, a small number of patients suffer from nonspecific abdominal symptoms or recurrent attacks of left lower quadrant pain and bloating, exacerbated by eating and relieved by defecation, and indistinguishable from the symptoms of irritable bowel syndrome. It has been postulated that DD is a late complication of irritable bowel syndrome [39–41]. Muscular hypertonicity associated with diverticulosis and high-pressure contractions causes the recurrent pain. Obviously, one cannot be certain that the symptoms are from diverticula.

Symptomatic uncomplicated diverticular disease (SUDD) patients do not have fever, leukocytosis, or peritoneal signs. Tenderness of the left lower quadrant may be the only finding. No specific treatment is necessary for asymptomatic or painful DD. There is benefit from a prophylactic high fiber diet. A guaiac-positive stool or recurrent left lower quadrant pain should not be attributed to diverticular disease and requires a full colonoscopic examination. Colonoscopy may be difficult, but is not contraindicated in this setting.

The role of anticholinergics and antispasmodics is questionable, and in older adult men in particular, anticholinergics may cause retention of urine. Antibiotics and narcotic analgesics are not indicated in uncomplicated diverticular disease. Amino salicylic acid (5-ASA) is a newer modality of therapy based on the concept of "segmental colitis" [18, 33]. Probiotic therapy, discussed elsewhere, is a recent addition.

Complicated Diverticular Disease

Diverticulitis

Uncomplicated Diverticulitis

A complication of diverticulosis is diverticulitis, which can be classified as complicated or uncomplicated. In uncomplicated diverticulitis endoscopy with radiologic signs of diverticular inflammation are present without complications. By contrast, evidence of abscess, fistula or perforation accompanying endoscopic or radiologic signs of diverticular inflammation indicate complicated diverticulitis [42, 43].

About 10–25% of patients with DD eventually present with an episode of acute diverticulitis starting with occlusion of the diverticular neck by fecalith. The pathogenesis is similar to appendicitis [44–47]. Diverticulitis is inflammation of a diverticulum, which occurs as a consequence of gross or microscopic perforation with extra-luminal pericolic infection caused by extravasation of feces through the perforated diverticulum. The perforation may be walled off and localized. Macro-perforation is the one that leads to a large inflammatory mass. Stasis or obstruction in the narrow-necked pseudodiverticulum may lead to bacterial overgrowth and local tissue ischemia, similar to appendicitis. Sigmoid colon, being the segment with the highest incidence of diverticula, is the frequent site of clinical diverticulitis.

A patient with uncomplicated diverticulitis presents with left lower quadrant pain which may radiate to the suprapubic region, left groin, or back and may be associated with small volume diarrhea or constipation, low-grade fever, chills, anorexia, nausea, and vomiting. Urinary urgency and dysuria may be associated features. Absence of pain does not exclude the diagnosis. Rectal bleeding is not a feature of diverticulitis. Differential diagnosis includes Crohn's disease, cystitis, advanced colonic cancer, ovarian cyst with torsion, infectious colitis, and ischemic colitis [46]. With right-sided diverticular disease, observed more in the Asian population, acute appendicitis must be included in the differential diagnosis.

Physical examination reveals tenderness over sigmoid colon or across the hypogastrium. The distal colon may be palpable as a tender, rope-like mass. Involuntary muscle guarding indicates peritoneal irritation. On rectal examination a tender indurated area may be felt at the examining finger tip, and occasionally, a firm mass. Stool guaic may be trace-positive. Abdominal distention is associated with paralytic ileus or small bowel obstruction as a result of inflammatory reaction. Free perforation and peritonitis are to be diagnosed in presence of generalized distention and tenderness.

The symptoms may be atypical in the very old with immunodeficiency, chronic renal failure, and those on corticosteroids. These groups are also at a higher risk for complications, are less responsive to conservative therapy, and have higher postoperative complications and mortality compared with immunocompetent and younger patients [45, 48, 49].

Initial laboratory studies would include complete blood count, renal and liver function tests, blood cultures, and urinalysis. Imaging studies of the abdomen should be based on the clinical situation and may include plain X-ray (erect and supine abdominal film), ultrasound, and/or CT of the abdomen. Computed tomography of the abdomen is the right choice as the initial imagining study for diagnosis as it has a sensitivity of 93–97% and nearly 100% specificity. In addition, CT scan studies can evaluate the extent of the disease, diagnose deep pelvic abscesses, and help exclude alternate diagnoses such as acute appendicitis, small bowel obstruction, ovarian pathology, Crohn's ileitis, and ischemic colitis when diverticulitis is not present. Colonoscopy is a very useful procedure, but is generally not performed until after acute diverticulitis has resolved. Following treatment of diverticulitis with antibiotics, a gentle sigmoidoscopy, or better, a full colonoscopy should be performed to exclude coincidental colon cancer or polyp. Ultrasonography offers a low cost, noninvasive convenient option, but is less sensitive and operator-dependent. Barium enema is not an ideal option in the frail elderly [50].

Management of Uncomplicated Diverticulitis

The older patient with acute diverticulitis often needs hospitalization for appropriate fluid and intravenous antibiotic administration. Because of current longer life span, older patients are likely to have more comorbid conditions associated with a more hazardous course, and a higher cumulative risk of complicated episodes [51]. Comorbid conditions, severity of disease, and caregiver availability at home also determine the need for hospitalization. If a decision is made to treat as an outpatient, close follow-up is required to avoid delay in recognition of complications [48].

The principles of management include bowel rest, appropriate antibacterials, fluids and clear liquid diet, prevention of recurrent symptoms, and addressing infection or consequences of inflammation. The antibiotic coverage is for mixed aerobic and anaerobic infections, the most common organisms being *Escherichia coli*, *Streptococcus*, and *Bacteroides fragilis*. Current choices are antibiotics with broad-spectrum coverage such as amoxicillin/clavulanate, sulfamethoxazole/trimethoprim with metronidazole or a fluoroquinolone with metronidazole. If the patient is hospitalized, appropriate regimen would include IV aminoglycoside and metronidazole or a third-generation cephalosporin. Recent studies suggest that a poorly absorbed broad-spectrum antibiotic, such as rifaximin, is effective against both gram-negative and gram-positive aerobic bacteria for uncomplicated diverticular disease, in addition to dietary fiber supplementation [52].

Surgical treatment is usually not necessary; less than 10% of patients admitted to hospital with acute diverticulitis require surgery [53, 54]. The traditional advice in regard to surgical treatment for diverticulitis is to perform an elective sigmoid resection after two episodes of acute diverticulitis (or after a single episode in young patients) [55], or when complications such as colonic stenosis or fistulas occur. It is generally believed that the chance of recurrence after each episode is at least 33%. Recurrence of diverticulitis occurs in approximately one-third of patients, often within 1 year [56]. Recurrence is associated with increasing rates of perforation and other complications, as well as higher morbidity and mortality. Elective sigmoid resection can be performed as open surgery or laparoscopically.

Complicated Diverticulitis

Complications include abscess, fistula, intestinal obstruction, perforation, and peritonitis (see Tables 53.4 and 53.5).

Abscess

Abscess may follow an acute episode of diverticulitis. Spiking fever and leukocytosis may be present. Physical examination may demonstrate a tender mass in the left lower quadrant. On rectal examination, a tender mass may be palpated in the cul-de-sac.

Fistula

Extension of diverticulitis abscess formation may lead to a perforation of the colon into (1) enterocolic or colocolic fistula, (2) colo-vesical fistula, (3) colo-cutaneous fistula, (4) ischio-rectal abscess or perianal fistula, and (5) recto-vaginal fistula. CT scan of the abdomen, pelvis cystoscopy, contrast radiography, and methylene blue studies establish the diagnosis of fistula. Treatment is surgical.

Perforation and Peritonitis

Although any diverticulitis is the consequence of microperforation, occasionally a more severe perforation of colonic

Table 53.4 Presentation of diverticular disease [45–49]

Recurrent left lower quadrant pain
Lower gastrointestinal bleeding
Diverticulitis
Intestinal obstruction, diverticular stricture
Fistula: enterocolic or colocolic
Diverticular abscess
Perforated sigmoid diverticulitis with generalized peritonitis

Table 53.5 Stages of diverticulitis: Hinchey classification [71]

Stage I—diverticulitis with confined paracolic abscess
Stage II—diverticulitis with distant (pelvic, retroperitoneal) abscess
Stage III—diverticulitis with purulent peritonitis
Stage IV—diverticulitis with fecal peritonitis

wall may cause local or general peritonitis. It is rare to see free perforation of a diverticulum into the peritoneal cavity leading to a generalized peritonitis.

Intestinal Obstruction

The sigmoid colon is the most frequent site of stricture formation during or after diverticulitis. A loop of small bowel may get involved in the process leading to small bowel obstruction. The symptoms of intestinal obstruction may be sudden in onset or slow to develop. Fibrotic strictures develop after repeated episodes of diverticulitis. CT scan of the abdomen and barium studies help diagnose stricture and its location. Surgical resection of the involved segment is required. In any patient with colonic strictures underlying malignancy must be carefully ruled out by colonoscopy, which may also help in placing a temporary stent for decompression. Stenting, as a temporary measure to relieve colonic obstruction, also allows for bowel preparation and subsequent single-stage colonic resection [8, 57].

When there is microperforation, the inflammation is contained by pericolic fat and mesentery. Large perforations result in abscess, leading to an inflammatory mass that may extend to other organs.

Diverticular Bleeding

The features of bleeding from diverticula are: typically sudden in onset, painless, brisk and brief, massive, but generally self-limiting. Diverticulitis seldom coincides with bleeding. Occult bleeding and iron deficiency anemia are not features of DD. Nearly 40% of lower gastrointestinal bleeding is due to colonic diverticula, but bleeding complicates only 5% of all cases of colonic diverticulosis [58–60]. The bleeding is self-limiting in most, but persists in 20%, requiring emergency treatment. A second bleeding episode may occur in 22–38% of cases and a third recurrence may occur in up to 50% of patients [61]. The latter is the rationale for recommending surgery after a second episode.

Although most diverticula are located in the left colon, there is an observation that in more than one half of the cases the site of bleeding diverticula is in the proximal colon [62–64]. The use of NSAIDs may contribute to diverticular bleeding [65].

Pathophysiology

The diverticula typically pass through the bowel wall at weak points in the circular muscle layer where the blood vessels penetrate. Microangiography in surgical specimens from patients with bleeding diverticula shows intimal thickening and medial thinning of the vasa recta as it covers the dome of the diverticulum [48]. Only a few diverticula show this arterial change with venous changes not yet clear. Inflammation is not associated with diverticular bleeding. An increased risk of bleeding diverticula in NSAID users suggests that extrinsic factors may also play a role. Overall, those on NSAIDs have more complications from DD, and they are serious. The differential diagnosis includes vascular ectasias, infectious as well as idiopathic colitis, and neoplasms.

Diagnostic Studies

The principles of management of gastrointestinal bleeding, upper and lower, are discussed in another chapter. The clinical features of diverticular bleeding in the setting of an older adult help suspect a diverticular etiology for the lower gastrointestinal bleeding.

(a) The benefit of an emergency colonoscopy within 12–48 h of presentation is suggested by recent observations [66–68]. The preparation for emergent colonoscopy is with rapid oral load over 3–4 h or nasogastric purge with 1 L of polyethylene glycol solution until clear effluent is noted. Absence of diverticulosis by colonoscopy leads to a search for other sources for the bleed. The criteria used to diagnose diverticular bleeding include typical endoscopic findings, such as active bleeding, visible vessel, adherent clot, presence of fresh blood within one of more bowel segments and diverticular erosion. Unfortunately, using these criteria, a diagnosis of lower gastrointestinal bleeding can be attributed to diverticulosis in only 20% of cases. However, endoscopy permits therapeutic possibilities.

(b) If colonoscopy fails to accomplish a diagnosis, or is incomplete, or could not be preformed for any reason, a nuclear scan using technecticum-99m-tagged red blood cells is a choice. Red blood cells of the patient tagged with radioactive isotope are injected into the patient. The bleeding site is located with scanning. An advantage of radionuclide scanning is that the cells can circulate for 48 h. Repeated scanning can be performed when there is active bleeding if the initial scan is negative. Scanning is noninvasive, only localizing the site of bleeding, but does not determine its etiology.

(c) Angiography identifies the site of bleeding and offers opportunity for therapeutic embolization. However, it is complementary to colonoscopy, and influenced by available technical expertise.

Management

Initial management discussed earlier on gastrointestinal bleeding applies equally to diverticular bleeding. Assessment of volume and electrolyte status and replacement of fluids, electrolytes and packed red cells are essential components.

Therapeutic endoscopy plays an important role. Interventions with injection of epinephrine or bipolar coagulation may lead to decreases in re-bleeding and the need for surgical interventions. There is no marker that helps distinguish those patients who will stop bleeding spontaneously from those who will not.

Key Points

- Diverticulosis is an age-related anatomic abnormality.
- The prevalence of diverticulosis is over 60% in individuals over 80 years.
- Colonic mucosa herniates through the bowel wall at weak points where the main blood vessels enter, resulting in the disorder.
- Increased intracolonic pressure as a result of dietary fiber depletion, motility disorder, and age-related structural abnormalities contribute to pathogenesis.
- The clinical spectrum of diverticular disease ranges from asymptomatic (over 80%), symptomatic but uncomplicated, complicated diverticulitis, and bright red rectal bleeding.
- Diverticulitis is a result of microperforation which may be walled off or complicated.
- "Segmental colitis" is proposed as another mechanism for diverticulitis.
- Complications of diverticulitis include abscess, fistula, intestinal obstruction, perforation, and peritonitis.
- Uncomplicated diverticulitis can be treated with oral antibiotics as an outpatient, but some patients require hospitalizations, intravenous fluids, and antibiotics.
- Diverticular bleed is bright red and profuse, but self-limiting in most.

References

1. Trowell HC, Burkitt DP, Heaton KW. Dietary fibre, fibre-depleted foods and disease. London: Academic; 1985.
2. Painter NS, Burkitt DP. Diverticular disease of the colon: a deficiency disease of Western civilization. Br Med J. 1971;2:450–4.
3. Feagans J, Raskin J. Historical prospectives and the spectrum of diverticular disease. J Clin Gastroenterol. 2011;45:S3–6.
4. Ravikoff J, Korzenik J. The role of fiber in diverticular disease. J Clin Gastroenterol. 2011;45:S7–11.
5. Matrana MR, Margolin DA. Epidemiology and pathophysiology of diverticular disease. Clin Colon Rectal Surg. 2009;22:141–6.
6. Fisher N, Berry CS, Fearn T, Gregory JA, Hardy J. Cereal dietary fiber consumption and diverticular disease: a lifespan study in rats. Am J Clin Nutr. 1985;42:788–804.
7. Berry CS, Fearn T, Fisher N, Gregory JA, Hardy J. Dietary fibre and prevention of diverticular disease of colon: evidence from rats. Lancet. 1984;2:294.
8. Stollman N, Raskin JB. Diverticular disease of the colon. Lancet. 2004;363:631–9.
9. Van Patten K, West BA. The pathology of diverticular disease: practical considerations and controversies. J Clin Gastroenterol. 2011;45:S20–6.
10. Almy TP, Howell DA. Medical progress. Diverticular disease of the colon. N Engl J Med. 1980;302:324–31.
11. Parks TG. Natural history of diverticular disease of the colon. Clin Gastroenterol. 1975;4:53–69.
12. Fraser GA. A case of multiple jejunal diverticula causing chronic volvulus, and with associated megacolon. Br J Surg. 1964;51:333–7.
13. Chalmers K, Wilson JM, Smith AN, Eastwood MA. Diverticular disease of the colon in Scottish hospitals over a decade. Health Bull (Edinb). 1983;41:32–41.
14. Floch MH, Bina I. The natural history of diverticulitis: fact and theory. J Clin Gastroenterol. 2004;38:S2–7.
15. Etzioni DA, Mack TM, Beart Jr RW, Kaiser AM. Diverticulitis in the United States: 1998–2005: changing patterns of disease and treatment. Ann Surg. 2009;249:210–7.
16. Strong SA. Acute diverticulitis. J Clin Gastroenterol. 2011;45:S62–9.
17. Segal I, Solomon A, Hunt JA. Emergence of diverticular disease in the urban South African black. Gastroenterology. 1977;72:215–9.
18. Tursi A, Papagrigoriadis S. Review article: the current and evolving treatment of colonic diverticular disease. Aliment Pharmacol Ther. 2009;30:532–46.
19. Chia JG, Wilde CC, Ngoi SS, Goh PM, Ong CL. Trends of diverticular disease of the large bowel in a newly developed country. Dis Colon Rectum. 1991;34:498–501.
20. Rajendra S, Ho JJ. Colonic diverticular disease in a multiracial Asian patient population has an ethnic predilection. Eur J Gastroenterol Hepatol. 2005;17:871–5.
21. Kang JY, Dhar A, Pollok R, Leicester RJ, Benson MJ, Kumar D, et al. Diverticular disease of the colon: ethnic differences in frequency. Aliment Pharmacol Ther. 2004;19:765–9.
22. Goenka MK, Nagi B, Kochhar R, Bhasin DK, Singh A, Mehta SK. Colonic diverticulosis in India: the changing scene. Indian J Gastroenterol. 1994;13:86–8.
23. Kastuar S, Narayanan S, Kastuar S, Pitchumoni CS. Prevalence and pattern of colonic diverticular disease in asymptomatic Indian immigrants in the U.S.A. Pract Gastroenterol. 2010;34(12):12–5.
24. Whiteway J, Morson BC. Elastosis in diverticular disease of the sigmoid colon. Gut. 1985;26:258–66.
25. Kelly JK. Polypoid prolapsing mucosal folds in diverticular disease. Am J Surg Pathol. 1991;15:871–8.
26. Morson BC. The muscle abnormality in diverticular disease of the sigmoid colon. Br J Radiol. 1963;36:393–406.
27. West AB, Losada M. The pathology of diverticulosis coli. J Clin Gastroenterol. 2004;38(5 Suppl 1):S11–6.
28. Singh S, Rao SSC. Colonic motility in the pathogenesis of diverticular disease. J Clin Gastroenterol. 2011;45:S15–9.
29. Floch MH. The microbatome and intestinal microflora in diverticular disease. J Clin Gastroenterol. 2011;45:S12–4.
30. Wang RY, Nicholas TJ, Michael PF. Overlap: irritable bowel syndrome, inflammatory bowel disease, and diverticular disease. J Clin Gastroenterol. 2011;45:S36–42.
31. Lenza C, Das KM. Mesalamine in the treatment of diverticular disease. J Clin Gastroenterol. 2011;45:S53–61.
32. Trivedi CD, Das KM. Emerging therapies for diverticular disease of the colon. J Clin Gastroenterol. 2008;42:1145–51.
33. Di Mario F, Aragona G, Leandro G, Comparato G, Fanigliulo L, Cavallaro LG, et al. Efficacy of mesalazine in the treatment of symptomatic diverticular disease. Dig Dis Sci. 2005;50:581–6.
34. Rogler G, Andus T. Cytokines in inflammatory bowel disease. World J Surg. 1998;22:382–9.
35. Strate LL, Liu YL, Syngal S, Aldoori WH, Giovannucci EL. Nut, corn, and popcorn consumption and the incidence of diverticular disease. JAMA. 2008;300:907–14.
36. Cheskin LJ, Lamport RD. Diverticular disease. Epidemiology and pharmacological treatment. Drugs Aging. 1995;6:55–63.
37. Neal KR, Hebden J, Spiller R. Prevalence of gastrointestinal symptoms six months after bacterial gastroenteritis and risk factors for development of the irritable bowel syndrome: postal survey of patients. BMJ. 1997;314:779–82.
38. Colecchia A, Sandri L, Capodicasa S, Vestito A, Mazzella G, Staniscia T, et al. Diverticular disease of the colon: new perspectives in symptom development and treatment. World J Gastroenterol. 2003;9:1385–9.
39. Tursi A, Brandimarte G, Elisei W, Giorgetti GM, Inchingolo CD, Danese S, et al. Assessment and grading of mucosal inflammation

in colonic diverticular disease. J Clin Gastroenterol. 2008;42: 699–703.
40. Tursi A, Brandimarte G, Elisei W, Giorgetti GM, Inchingolo CD, Aiello F. Faecal calprotectin in colonic diverticular disease: a case-control study. Int J Colorectal Dis. 2009;24:49–55.
41. Tursi A. Diverticular disease: what is the best long-term treatment? Nat Rev Gastroenterol Hepatol. 2010;7:77–8.
42. Tursi A. Antibiotics and probiotics in the treatment of diverticular disease. J Clin Gastroenterol. 2011;45:S46–52.
43. Tursi A, Brandimarte G, Giorgetti G, Elisei W, Maiorano M, Aiello F. The clinical picture of uncomplicated versus complicated diverticulitis of the colon. Dig Dis Sci. 2008;53:2474–9.
44. Livingston EH, Fomby TB, Woodward WA, Haley RW. Epidemiological similarities between appendicitis and diverticulitis suggesting a common underlying pathogenesis. Arch Surg. 2011; 146:308–14.
45. Touzios JG, Dozois EJ. Diverticulosis and acute diverticulitis. Gastroenterol Clin North Am. 2009;38:513–25.
46. Jacobs DO. Clinical practice. Diverticulitis. N Engl J Med. 2007;357:2057–66.
47. Assifi MM, Hines OJ. Appendicitis equals diverticulitis: a challenge to traditional dogma. Arch Surg. 2011;146:315.
48. Comparato G, Pilotto A, Franze A, Franceschi M, Di Mario F. Diverticular disease in the elderly. Dig Dis. 2007;25:151–9.
49. Fox J, Stollman N. Diverticular disease of the colon. In: Feldman M, Friedman L, Brandt L, editors. Sleisenger and Fordtran's gastrointestinal and liver disease (chap. 117). 9th ed. Philadelphia, PA: Saunders Elsevier; 2010.
50. Ambrosetti P, Jenny A, Becker C, Terrier TF, Morel P. Acute left colonic diverticulitis—compared performance of computed tomography and water-soluble contrast enema: prospective evaluation of 420 patients. Dis Colon Rectum. 2000;43:1363–7.
51. Klarenbeek BR, Samuels M, van der Wal MA, van der Peet DL, Meijerink WJ, Cuesta MA. Indications for elective sigmoid resection in diverticular disease. Ann Surg. 2010;251:670–4.
52. Latella G, Pimpo MT, Sottili S, Zippi M, Viscido A, Chiaramonte M, et al. Rifaximin improves symptoms of acquired uncomplicated diverticular disease of the colon. Int J Colorectal Dis. 2003;18:55–62.
53. Kohler L, Sauerland S, Neugebauer E. Diagnosis and treatment of diverticular disease: results of a consensus development conference. The Scientific Committee of the European Association for Endoscopic Surgery. Surg Endosc. 1999;13:430–6.
54. Wong WD, Wexner SD, Lowry A, Vernava III A, Burnstein M, Denstman F, et al. Practice parameters for the treatment of sigmoid diverticulitis—supporting documentation. The Standards Task Force. The American Society of Colon and Rectal Surgeons. Dis Colon Rectum. 2000;43:290–7.
55. Stollman NH, Raskin JB. Diagnosis and management of diverticular disease of the colon in adults. Ad Hoc Practice Parameters Committee of the American College of Gastroenterology. Am J Gastroenterol. 1999;94:3110–21.
56. Rafferty J, Shellito P, Hyman NH, Buie WD. Practice parameters for sigmoid diverticulitis. Dis Colon Rectum. 2006;49:939–44.
57. Tamim WZ, Ghellai A, Counihan TC, Swanson RS, Colby JM, Sweeney WB. Experience with endoluminal colonic wall stents for the management of large bowel obstruction for benign and malignant disease. Arch Surg. 2000;135:434–8.
58. Peura DA, Lanza FL, Gostout CJ, Foutch PG. The American College of Gastroenterology Bleeding Registry: preliminary findings. Am J Gastroenterol. 1997;92:924–8.
59. Longstreth GF. Epidemiology and outcome of patients hospitalized with acute lower gastrointestinal hemorrhage: a population-based study. Am J Gastroenterol. 1997;92:419–24.
60. Zuckerman GR, Prakash C. Acute lower intestinal bleeding. Part II: etiology, therapy, and outcomes. Gastrointest Endosc. 1999;49:228–38.
61. McGuire Jr HH. Bleeding colonic diverticula. A reappraisal of natural history and management. Ann Surg. 1994;220:653–6.
62. Wong SK, Ho YH, Leong AP, Seow-Choen F. Clinical behavior of complicated right-sided and left-sided diverticulosis. Dis Colon Rectum. 1997;40:344–8.
63. Stollman NH, Raskin JB. Diverticular disease of the colon. J Clin Gastroenterol. 1999;29:241–52.
64. Reinus JF, Brandt LJ. Vascular ectasias and diverticulosis. Common causes of lower intestinal bleeding. Gastroenterol Clin North Am. 1994;23:1–20.
65. Wilcox CM, Alexander LN, Cotsonis GA, Clark WS. Nonsteroidal antiinflammatory drugs are associated with both upper and lower gastrointestinal bleeding. Dig Dis Sci. 1997;42:990–7.
66. Jensen DM, Machicado GA, Jutabha R, Kovacs TO. Urgent colonoscopy for the diagnosis and treatment of severe diverticular hemorrhage. N Engl J Med. 2000;342:78–82.
67. Van Os EC, Gostout CJ, Geller A, Ahlquist DA, Batts KP, Wolff BG. Band ligation-assisted endoscopic resection of a flat rectal adenoma containing infiltrating adenocarcinoma. Gastrointest Endosc. 1997;45:322–4.
68. Pilichos C, Bobotis E. Role of endoscopy in the management of acute diverticular bleeding. World J Gastroenterol. 2008;14:1981–3.
69. Ludeman L, Warren BF, Shepherd NA. The pathology of diverticular disease. Best Pract Res Clin Gastroenterol. 2002;16:543–62.
70. Mimura T, Emanuel A, Kamm MA. Pathophysiology of diverticular disease. Best Pract Res Clin Gastroenterol. 2002;16:563–76.
71. Hinchey EJ, Schaal PG, Richards GK. Treatment of perforated diverticular disease of the colon. Adv Surg. 1978;12:85–109.

Clostridium dif cile-Associated Diseases

54

C.S. Pitchumoni and T.S. Dharmarajan

Introduction

The spectrum of antibiotic-associated diarrheal disorders includes the mild but common antibiotic-associated diarrhea (AAD), the rare but dramatic hemorrhagic colitis and *Clostridium difficile*-associated diseases (CDAD). *C. difficile*, causative agent of the most common nosocomial infection of the gastrointestinal tract is responsible for 10–20% cases of AAD, depending on the type of antibiotic and individual susceptibility [1]. In the older adults CDAD has emerged as the most frequent nosocomial infection with substantial morbidity, mortality, and economic burden to healthcare.

AAD is a frequent side effect of many antibiotics, usually self-limited, and can be treated by discontinuing the offending antibiotic. AAD is often caused by alterations of gut microflora resulting in mild diarrhea secondary to intestinal carbohydrate and/or bile acid metabolism and not associated with any colonic mucosal lesions. Antibiotic (ampicillin)-associated hemorrhagic colitis has recently been recognized to be the result of *Klebsiella oxytoca* infection and will not be discussed in this chapter.

The spectrum of CDAD ranges from mild diarrhea to pseudomembranous colitis (PMC), complicated by toxic megacolon, caused by toxins A and B, and produced by a spore-forming obligate anaerobic bacillus. The organism is part of the normal fecal flora of many infants, 5% of healthy adults, and 10% or more of hospitalized adults without diarrhea who have received antibiotics or chemotherapeutic agents [1]. Since the understanding of *C. difficile* as the main etiologic factor for PMC in 1974, this anaerobic spore-forming bacterium has emerged as the leading cause of nosocomial diarrhea in adults [2–11]. Since 2000 there have been reports of epidemics of *C. difficile* in the United States, Canada, and Europe associated with a hypervirulent strain with characteristics of excess toxin production in vitro and resistance to clindamycin and quinolones [12, 13].

Epidemiology: Past and Present

In the United States, the incidence varies from 1 to 20 per 1,000 hospital admissions, the higher rate being in bone marrow transplant recipients and those who underwent cardiothoracic surgery [14]. Recently several institutions worldwide have reported an increase in the incidence of CDAD [13, 15–17] attributed to changing demographics of hospitalized patients, infection control policies, antibiotic use patterns, and emergence of more virulent strains of the organisms. There is a notable rise in community-acquired cases in comparison to nosocomial-acquired infections in the past. CDAD occurs when the patients have a decline in their natural gastrointestinal flora that allows for toxin production and proliferation of *C. difficile*.

The importance of CDAD in the geriatric population is gaining momentum because of the increase in recurrence rates, treatment failures, complications, and mortality [18]. The occurrence of CDAD in individuals without exposure to antibiotics is puzzling.

The epidemiological characteristics of CDAD vary markedly depending on the antibiotic prescribing patterns, endemic strains, and criteria used to define CDAD [19, 20]. The clinical index of suspicion associated with the frequency with which the presence of toxins A and B are assayed in stools of suspected patients influence epidemiological studies [1, 21].

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C. difficile infection occurs when a susceptible host ingests the spores of the organism which colonize the large bowel and release the two protein exo-toxins that cause colitis [21, 22]. The heat-resistant spores are normally resistant to gastric acid; healthy adults are protected from colonization and disease by normal gut flora and by antibody to toxin A.

Risk Factors for CDAD

Antibiotic use is the major risk factor for CDAD. Ampicillin or amoxicillin, cephalosporins, clindamycin, and fluoroquinolones are most frequently associated with CDAD, though most antibiotics, including metronidazole and rifaximin which are used to treat CDAD are also known to be causative [23].

Other than age, comorbid conditions requiring care in the intensive care setting, cancer, hypoalbuminemia, chronic obstructive lung disease, and chronic kidney disease increase the risk for CDAD. Hospitalization and residence in nursing homes or rehabilitation facilities are predisposing factors [24].

Individuals over 65 years have a tenfold higher risk of contracting *C. difficile* during outbreaks [25]. Nasogastric tube feeding, severe leukocytosis, and hypoalbuminemia are associations with increased mortality [18].

Recent data suggest prolonged proton pump inhibitor (PPI) therapy to be an independent risk factor for CDAD [26–28]. Because *C. difficile* spores are generally acid-resistant, the influence of acid suppression on the occurrence of CDAD is unclear. Other risk factors include white race and underlying inflammatory bowel disease (IBD) [29]. Patients with ulcerative colitis have higher rates of *C. difficile* infection compared to Crohn's disease. Patients with IBD with *C. difficile* infection encounter increased morbidity, longer length of stay, and increased mortality. Exacerbation of IBD requires exclusion of CDAD almost as a rule. Risk factors for CDAD are listed in Table 54.1.

Table 54.1 Risk factors for *Clostridium difficile*-associated disease [2, 16, 34, 43, 45]

1. Advanced age		
2. Comorbid conditions	Intensive care unit stay	
	Preadmission residence in nursing home	
	Preadmission nasogastric or enteral feeding (particularly postpyloric)	
	Handling tube feed by healthcare workers	
	Contamination of tube feeding	
	Low fiber content of formulas	
	Enemas and stool softeners	
	Mechanical ventilation	
	Chronic obstructive lung disease	
	Immunosuppression	
	Chronic renal failure	
	Cancer and anti-neoplastic drugs: examples: doxorubicin, cisplastin, cyclophosphamide, 5-fluoracil, chlorambucil, and methotrexate	
	Gastrointestinal surgery	
	NSAID use	
3. Reduced gastric acidity	Prolonged use of H2 receptor antagonists or PPIs	
4. Antimicrobial agents	Frequently associated	Ampicillin
		Amoxicillin
		Cephalosporin
		Clindamycin
		Quinolones
	Occasionally associated	Penicillins, other than ampicillin
		Sulfonamides
		Erythromycin
		Trimethoprim
	Rarely or never associated	Parental aminoglycosides
		Tetracycline
		Chloramphenicol
		Metronidazole
		Intravenous vancomycin
5. Failure to follow institution-specific infection control policies		
6. Exposure to infected roommate		

Bacteriology: The New Virulent Strain

C. difficile produces two cytopathic and enteropathic virulent factors, toxin A (or Tcd A) and toxin B (or Tcd B). Toxin A is an inflammatory enterotoxin that induces fluid secretion, increases mucosal permeability, and causes enteritis and colitis. Toxin B is an extremely potent toxin. Toxins A and B are structurally similar and most pathogenic strains produce both toxins [30]. These toxins are encoded by two genes, Tcd A and Tcd B, that map to a 19.6 kb pathogenicity locus (Pa loc) consisting additional regulatory genes [30]. However, clinically relevant toxin A-negative, toxin B-positive (A–, B+) strains of *C. difficile* that cause diarrhea and colitis in humans have been isolated [31, 32]. A third toxin—a binary toxin designated CDT (actin-specific ADP—ribosyl trasferase) is found in 1–16% of patients with CDAD; the role of the above toxin in the pathogenesis of CDAD is not clear [33, 34]. Outbreaks demonstrating a new toxic strain of *C. difficile* have been reported [6, 35, 36] influenced by antimicrobial use patterns, increased virulence or resistance among strains and failure in infection control measures. Infection with the highly virulent NAP1/027 strain characterized by fluoroquinolone resistance and higher levels of toxin production than the conventional strains causes a threefold higher mortality rate than matched controls with less virulent strains [22, 25]. The effects of host immune responses are important but they are not well studied.

Clinical Manifestations of CDAD

CDAD encompasses a wide spectrum of clinical manifestations ranging from asymptomatic carriers and those with mild brief self-limited diarrhea, to severe diarrhea, colitis and diarrhea complicating underlying IBD, septic shock, toxic mega colon including need for total colectomy to fatal CDAD. The onset of symptoms is usually within 48 h of infection. Although hospitalized patients are generally infected within 3 weeks of hospitalization, delayed onset of CDAD may occur up to 2–3 weeks after infection has been reported [11, 37]. Toxic megacolon must be suspected when the transverse colonic diameter is greater than 6 cm, a disorder associated with systemic toxicity; mortality can be as high as 64%. Severe CDAD mimics ischemic colitis, IBD, intra-abdominal sepsis, and diverticulitis. The pathogenesis of CDAD involves multiple steps. Initially there is disruption of the normal colonic bacterial flora with use of antibiotics or anti-neoplastic agents, followed by colonization with toxigenic *C. difficile* that elaborates the two toxins A and B resulting in mucosal injury.

Diagnosis

Demonstration of *C. dif cile* Toxins

Diagnostic studies looking at toxins A and/or B include enzyme immunoassay (EIA) and cell culture toxicity assay performed on stool samples. EIA or tissue culture cytotoxicity assay are considered the gold standard for diagnosis. The sensitivity of these tests ranges from 63 to 94% and specificity ranges from 75 to 100%. Both toxins A and B are to be tested and detected in CDAD. Atypical strains produce one of the two toxins. The absence of toxin in the stool in the initial assay does not rule out CDAD. Stool assays for *C. difficile* toxin have significant false negative rates. Detection of toxigenic *C. difficile* in stool samples by real-time polymerase chain reaction (PCR) for the diagnosis of CDAD has turnaround time of less than 4 h and is more sensitive than EIA [38]; however, the test is not available for routine use. The detection for *C. difficile* toxin in IBD patients is challenging and testing of multiple stool samples is needed [8].

Sigmoidoscopy and Colonoscopy

Endoscopic examination is not mandatory in the diagnosis of CDAD. Sigmoidoscopy may be normal in mild cases; alternatively, the characteristic pseudomembrane may be seen as yellow or white plaques 2–4 mm in diameter. Since pseudomembranes may be proximal and beyond the reach of the sigmoidoscope, colonoscopy may be required to detect proximal pathology [39]. The histology in severe cases shows focal ulceration of the colonic mucosa associated with the eruption of purulent material containing inflammatory cells and necrotic debris that covers the area of ulceration, and termed "summit" or "volcano" lesions. The ACG guidelines [2] recommend endoscopy in the following situations:

- When rapid diagnosis is needed and test results are delayed or insensitive tests are used.
- When the patient has an ileus and stool is not available
- When another colonic disease is being considered and can be diagnosed through endoscopy.

C. dif cile Culture

Although in general, culture is not required to diagnose CDAD and is not specific for toxin-producing strains, in special cases culture permits strain typing.

Table 54.2 provides options for diagnosis.

Table 54.2 Diagnosis of *C. difficile* infection [57, 58]

Options
Fecal culture
Slow, but most sensitive and specific
Good for epidemiological studies
Screening enzyme immunoassay
Sensitive but less specific
Detects *C. difficile* glutamate dehydrogenase (GDH)
Enzyme immunoassay for toxins A and B
Variably sensitive, more specific compared to GDH assay
Tests may combine toxin assay with GDH detection
Cell culture cytotoxicity
Detects stool cytotoxin activity
Sensitive, specific, but difficult to perform and slow
Polymerase chain reaction (PCR)-based assays
Detects gene targets within the locus of *C. difficile*
Sensitive, specific, but expensive
Remarks
Testing by EIA and PCR is performed utilizing liquid stools
Repeat stool testing within days does not increase diagnostic yield and is discouraged
Testing in asymptomatic patients is not useful, including use as a test of cure
Stool cultures in general are essential for epidemiological studies

Table 54.3 Preventive strategies for *C. difficile* infection [57, 58]

Use of antibiotics
Restrict the use of antibiotics, including the number of antimicrobials, and their frequency and duration of use
Hospitals and long-term care institutions must use antibiotic stewardship to monitor antibiotic use
The use of narrow spectrum antibiotics as a general rule is encouraged
Infection control measures
Policies for infection control must be in place and updated as indicated
Hand hygiene through meticulous hand washing with soap and water is most important; compliance needs to be monitored. Alcohol-based gels are ineffective
Gloves and gowns must be used when entering a room with an infected patient
Patients with CDAD should be placed in isolation rooms or cohorted
Cleansing the room and environment entails the use of chlorine or sporicidal agents

Treatment of CDAD

Permanent cure of CDAD warrants reestablishment of normal fecal flora, eliminating *C. difficile*. The principles of management include [40]:

(a) Preventive measures
(b) Treatment of initial mild disease
(c) Treatment of recurrences
(d) Treatment of complications and surgery in CDAD

Preventive Measures

Institutional Steps

Attempts to control CDAD require prudent use of antimicrobials, prevention of nosocomial infection, and ongoing surveillance. An important step that has shown considerable benefit in reducing the incidence of CDAD in healthcare facilities is enforcement of the practice of meticulous hand washing with soap and water by all healthcare providers and the practice of contact precautions using sterile gown and gloves while caring for patients. It must be emphasized that CDAD is a disease spread by spores, and hence alcohol-based hand sanitizers are ineffective.

A well-established hospital-wide infection control program, phenolic disinfection for environment cleaning, disinfection of rooms with a spore killing bleach, disposable medical equipments, and periodic education programs are all mandatory steps for the control of CDAD [41].

Physician Education

Clindamycin, cephalosporin, and fluroquinolones are the antibiotics determined to be associated with the highest risk for CDAD. Metronidazole, vancomycin, and aminoglycosides have a lower risk [6, 16, 25]. Restrictive antibiotic policies such as antibiotic stewardship are a needed step [42, 43]. Since the evidence for a role of PPIs is mounting, and PPI overuse is frequent, it is prudent to be cautious with the excessive and prolonged use of PPIs, especially in high-risk patients. Antidiarrrheal agents and narcotics should be avoided in patients with symptomatic CDAD because of their potential to induce toxic mega colon.

Table 54.3 suggests preventive strategies to control *C. difficile* infection.

Treatment of Initial Disease

Patients with mild disease characterized by minimal diarrhea are managed conservatively by discontinuing the inciting antibiotic. In acutely ill patients with suspected CDAD, treatment should be initiated while stool test results are pending and in suspected severe cases despite negative stool assays [22]. Those with more severe diarrhea may require oral metronidazole or vancomycin therapy with supportive measures. While oral vancomycin is the only FDA-approved treatment for CDAD, metronidazole is generally the drug of choice because of its low cost and acceptable efficacy in most cases. Certainly, it is the recommended drug for mild to moderate cases. Metronidazole provides effective therapy with a reported response rate of 95–100%. The oral adult dose for metronidazole is 500 mg thrice daily or 250 mg four times daily for 10–14 days; the intravenous dose is 500 mg four

times a day for 10–14 days. Symptoms resolve in >90% of patients within a week. Documented hypersensitivity is rare, but a contraindication for metronidazole therapy. Metronidazole may increase the toxicity of warfarin, lithium and phenytoin, through drug–drug interaction; these are drugs that older adults may be on. Disulfiram reaction may occur if alcohol is ingested during metronidazole therapy. Oral vancomycin is the treatment if metronidazole therapy fails or is contraindicated. Vancomycin is the first line of treatment in patients with severe *C. difficile* disease [44].

The new strain of *C. difficile* is associated with a decreased response to metronidazole and a high rate of recurrence [8, 44–48]. The recommended dose of vancomycin is 500 mg four times a day; a lower dose of 125 mg four times a day also results in drug concentrations in the colon well above the MIC for *C. difficile* and good clinical outcomes.

Treatment of Recurrences

Recurrent *C. difficile* infection is unrelated to organism resistance to the specific medication used in initial therapy. Recurrence is a result of re-infection through the same spores or a different strain of *C. difficile* from the environment. Although the mechanism of persistent carrier state is poorly understood [49], the diagnosis of recurrence should be confirmed with a stool toxin assay (Table 54.4).

CDAD recurs in about 20% of patients within 2–4 weeks of remission following the first episode. Risk factors for recurrence are not clear; a meta-analysis identified certain factors: continued use of antibiotics after diagnosis of CDAD ($P<0.0001$), use of antacids ($P=0.019$), and older age ($P=0.0012$) [50, 51]. Multiple recurrences may occur. It is standard teaching to treat the first recurrence with a second course of the same drug used in treatment of the first episode. In view of the changing epidemiology, this approach needs to be reevaluated [8].

Table 54.4 Recurrent CDAD [57, 58]

Relapses occurring within 1–2 weeks after stopping antibiotic treatment or increasing stool frequency over 2 consecutive days
Recurrent episodes of spores germinating may be re-infections and not recurrence
If relapse occurs following a second course of treatment, rule out other causes for diarrhea, the patient could be an asymptomatic carrier
Repeat stool toxin assays are not indicated after treatment if the patient is asymptomatic
About 50% of patients have positive stool assays up to 6 weeks following completion of treatment
Initial treatment is the same as for the first episode; second or subsequent recurrence is treated with vancomycin with a pulsed/tapering dose

Prolonged tapering or pulsed dose of oral vancomycin 125 mg four times a day for 1 week, three times a day for a week, every other day for a week, and finally every 3 days for 2 weeks may be one approach. Other antimicrobials are investigational. Rifaximin 200 mg three times a day for 3 days [52] and nitazoxamide [8] are currently being evaluated. Other nonantibiotic investigational agents include tolevamer, a toxin-binding polymer, anion-binding resins, cholestyramine and colestipol for initial infection as well as relapse. These resins have the advantage of not altering the normal colonic flora.

When a patient has more than two recurrences prior to therapy, the diagnosis should be confirmed by stool assay. Other causes including postinfectious irritable bowel syndrome may mimic recurrences.

A newly approved macrocyclic antibiotic, fidaxomicin, in doses of 200 mg twice daily for 10 days was noninferior to vancomycin 125 mg orally; a significantly lower rate of recurrence was associated with fidaxomicin and the drug was well tolerated [53, 54].

Case reports suggest efficacy of intravenous immunoglobulin therapy. Studies are under way on the use of monoclonal antibodies and fecal enemas (or stool transplant) from a healthy donor to patients with recurrent CDAD [55, 56]. Although it is not yet the standard of care, it has attracted much attention.

Acute Fulminant Infection

Acute fulminant disease in the older adult is associated with a high mortality rate. Severe disease occurs during the initial infection or first recurrence [22]. In patients with impending toxic megacolon, temporarily diarrhea may improve or be absent.

If paralytic ileus is prominent, intravenous metronidazole is likely to result in sufficient concentrations in the feces and inflamed colon; intracolonic administration of vancomycin is useful in some; where colonic perforation is imminent it is prudent to stop oral and rectal therapy [57, 58]. Despite lack of data, higher doses of vancomycin (500 mg in 100 mL saline four times daily) may be prudent via oral or rectal route [58]. In addition, oral feeds may be withheld and substituted for parenteral nutrition. Surgical consult should be obtained since a small number of patients require emergency colectomy.

Predictors of fatal outcome are poorly defined and controversial. Older age, low albumin, postorgan transplantation, higher APACHE II score, higher ASA class, preexisting pulmonary or renal disease, use of steroids, evidence of toxic mega-colon, and higher WBC counts are all factors to be considered.

Surgery in CDAD

In patients with fulminant disease and toxic mega colon, emergency subtotal colectomy is a consideration. It is an extremely difficult decision to choose surgery for a disease which, until recently, was considered medically manageable. Systemic signs of severe infection such as fever, leukocytosis, severe abdominal pain, toxic mega colon, shock requiring vasopressors, lack of response to medical therapy, peritoneal sepsis, and perforation are indications for surgery [59, 60].

It is prudent to consider early surgery in at-risk patients such as those aged more than 65 years with comorbidities and marked leukocytosis [61]. The goal for surgical intervention is to operate before elevation of serum lactate and white blood cell counts or multi-organ failure develops. Subtotal colectomy is associated with a better outcome than hemi-colectomy [60].

Probiotics

The topic of probiotics is covered in chapter 11. *C. difficile*, being an opportunistic infection, colonizes the colon only after the normal colonic bacterial flora has been altered by antibiotics. Treatment with *Saccharomyces boulardii*, a non-pathogenic yeast at 1 g/day for 4 weeks along with oral vancomycin (2 g/day for 10 days), compared to the group on vancomycin plus placebo, produced a significantly lower rate of recurrence (16.7% vs. 50%) [62].

Current evidence supports the efficacy of *S. boulardii* in the prevention of antibiotic-associated recurrent CDAD in adults, whereas *Lactobacillus rhamnosus* (LGG) is useful in the treatment of AAD in children. Based on the observation that recurrences are reflections of the host immune response, IV immunoglobin (IVIG) has been tried [63]. A vaccine has been developed to promote production of antitoxin A antibody [64].

Special Considerations in Older Adults

Guidelines from the Australasian Society for Infectious Diseases for the diagnosis and treatment of *C. difficile* infection mention that *C. difficile* is the most common cause of healthcare-associated and AAD; it appears that hypervirulent strains have also hit Australia; the strategies for management of CDAD are similar to those in the United States [57, 58].

"*C. difficile* now is a different disease than it was in 1995," with mutations of the bacterium transforming a rare nosocomial infection to one that can spread from hospitals to community and infect healthy individuals with few risk factors [65]. *C. difficile* infections have surpassed methicillin-resistant *Staphylococcus aureus* infections in at least one group of community hospitals. New therapies may be on the horizon, including the use of two novel neutralizing fully human monoclonal antibodies against toxin A and B for secondary prevention of infection as a single infusion; in the antibody group recurrent infection developed in 7%, compared to 25% of the placebo group, for a reduction of 72% [66]. Thus far only antibiotics have been the mainstay of treatment for an antibiotic-associated condition, and so the no-antibiotic approach offers hope; it is relevant that in the study the mean age was 64 years (range 20–101 years), and as age more than 65 years is associated with risk of recurrence by a factor of 6, older patients will benefit from secondary prevention [67].

Further, the hypervirulent mutations of *C. difficile* infections tend to spread rapidly in long-term care facilities which are vulnerable to importation of strains as residents are typically admitted from referral sources; clonal infections due to cross-contamination from asymptomatic residents and carriers can occur quickly, necessitating strategies for prevention and control in the nursing home environment [68]. The entire staff requires to be educated; in this regard the housekeepers (most "invisible" of healthcare workers) can play an important role [68]. In a Veterans hospital, transfers within the past month from an affiliated long-term care site played a significant role in development of outbreaks [69]. Recent data underscore the need to consider the role of asymptomatic colonized patients in *C. difficile* transmission in healthcare settings [70].

Older adults suffer from vague upper gastrointestinal complaints that are often treated with PPIs (as stated earlier); PPI use during incident *C. difficile* treatment was associated with 42% increased risk of recurrence in a large study [71].

In summary, the epidemiology of CDAD has changed over the decade, with a dramatic worldwide increase in incidence. The incidence of treatment failures has increased emphasizing the need for alternate agents [72]. Infection control measures are key to preventing horizontal transmission of infection [72]. They include implementation of infection control policies in hospitals and institutions to enforce hand hygiene and the appropriate use of antibiotics in general [73]. Further studies will help define the role for doxycycline in protecting against the development of *C. difficile* infection [74]. Immune based strategies relying on active vaccination or passive monoclonal antibody administration are the focus of intense research [75].

Key Points

- Antibiotic-associated diarrhea occurs in over 5% of patients receiving antibiotics.
- *Clostridium difficile*-associated diseases (CDAD) relating to antibiotic use is currently among the most common health facility-acquired infections.

- *Clostridium difficile* is an aerobic spore-forming bacillus that produces at least two toxins A and B.
- Major risk factors for CDAD include age over 65, chronic kidney disease, tube feeding, gastric surgery, immune suppressed states, hospitalization, and recent antibiotic use.
- Epidemics of a new virulent toxic strain (NAP1/B1) have emerged.
- Diagnosis of CDAD is made by stool toxin assay and sigmoidoscopy or colonoscopy.
- CDAD may be mild to severe, recurrent, resistant to treatment, and associated with serious complications.
- Prevention is the key: CDAD an example of an antibiotic-induced condition, requiring antibiotics for a cure. In general, the judicious use of antibiotics is recommended.
- Effective isolation measures and education of staff in general.
- Hand hygiene, patient isolation, and cleansing the environment are relevant preventive measures.
- Metronidazole or vancomycin given orally is the recommended initial therapy.

References

1. Bartlett JG. *Clostridium difficile*: history of its role as an enteric pathogen and the current state of knowledge about the organism. Clin Infect Dis. 1994;18 Suppl 4:S265–72.
2. Fekety R. Guidelines for the diagnosis and management of *Clostridium difficile*-associated diarrhea and colitis. American College of Gastroenterology, Practice Parameters Committee. Am J Gastroenterol. 1997;92:739–50.
3. Tedesco FJ, Barton RW, Alpers DH. Clindamycin-associated colitis. A prospective study. Ann Intern Med. 1974;81:429–33.
4. Thomas C, Stevenson M, Riley TV. Antibiotics and hospital-acquired *Clostridium difficile*-associated diarrhoea: a systematic review. J Antimicrob Chemother. 2003;51:1339–50.
5. Surawicz CM. Treatment of recurrent *Clostridium difficile*-associated disease. Nat Clin Pract Gastroenterol Hepatol. 2004;1:32–8.
6. Thomas C, Riley TV. Restriction of third generation cephalosporin use reduces the incidence of *Clostridium difficile*-associated diarrhoea in hospitalised patients. Commun Dis Intell. 2003;27(Suppl):S28–31.
7. Aslam S, Musher DM. An update on diagnosis, treatment, and prevention of *Clostridium difficile*-associated disease. Gastroenterol Clin North Am. 2006;35:315–35.
8. Ananthakrishnan AN, Guzman-Perez R, Gainer V, et al. Predictors of severe outcomes associated with Clostridium difficile infection in patients with inflammatory bowel disease. Aliment Pharmacol Ther. 2012;35(7):789–95.
9. Bartlett JG. Historical perspectives on studies of *Clostridium difficile* and *C. difficile* infection. Clin Infect Dis. 2008;46 Suppl 1:S4–11.
10. Bartlett JG, Gerding DN. Clinical recognition and diagnosis of *Clostridium difficile* infection. Clin Infect Dis. 2008;46 Suppl 1:S12–8.
11. McFarland LV. Update on the changing epidemiology of *Clostridium difficile*-associated disease. Nat Clin Pract Gastroenterol Hepatol. 2008;5:40–8.
12. Kuipers EJ, Surawicz CM. *Clostridium difficile* infection. Lancet. 2008;371:1486–8.
13. Pepin J, Valiquette L, Alary ME, et al. *Clostridium difficile*-associated diarrhea in a region of Quebec from 1991 to 2003: a changing pattern of disease severity. CMAJ. 2004;171:466–72.
14. Lai KK, Melvin ZS, Menard MJ, et al. *Clostridium difficile*-associated diarrhea: epidemiology, risk factors, and infection control. Infect Control Hosp Epidemiol. 1997;18:628–32.
15. Archibald LK, Banerjee SN, Jarvis WR. Secular trends in hospital-acquired *Clostridium difficile* disease in the United States, 1987–2001. J Infect Dis. 2004;189:1585–9.
16. McDonald LC, Killgore GE, Thompson A, et al. An epidemic, toxin gene-variant strain of *Clostridium difficile*. N Engl J Med. 2005;353:2433–41.
17. Loo VG, Poirier L, Miller MA, et al. A predominantly clonal multi-institutional outbreak of *Clostridium difficile*-associated diarrhea with high morbidity and mortality. N Engl J Med. 2005;353:2442–9.
18. Moshkowitz M, Ben-Baruch E, Kline Z, et al. Risk factors for severity and relapse of pseudomembranous colitis in an elderly population. Colorectal Dis. 2007;9:173–7.
19. Gaynes R, Rimland D, Killum E, et al. Outbreak of *Clostridium difficile* infection in a long-term care facility: association with gatifloxacin use. Clin Infect Dis. 2004;38:640–5.
20. Zheng L, Keller SF, Lyerly DM, et al. Multicenter evaluation of a new screening test that detects *Clostridium difficile* in fecal specimens. J Clin Microbiol. 2004;42:3837–40.
21. Riegler M, Sedivy R, Pothoulakis C, et al. *Clostridium difficile* toxin B is more potent than toxin A in damaging human colonic epithelium in vitro. J Clin Invest. 1995;95:2004–11.
22. Leffler DA, Lamont JT. Treatment of *Clostridium difficile*-associated disease. Gastroenterology. 2009;136:1899–912.
23. Surawicz CM. Antibiotics and *Clostridium difficile*: cause and cure. J Clin Gastroenterol. 2007;41:1–2.
24. Pepin J, Saheb N, Coulombe MA, et al. Emergence of fluoroquinolones as the predominant risk factor for *Clostridium difficile*-associated diarrhea: a cohort study during an epidemic in Quebec. Clin Infect Dis. 2005;41:1254–60.
25. Pepin J, Valiquette L, Cossette B. Mortality attributable to nosocomial *Clostridium difficile*-associated disease during an epidemic caused by a hypervirulent strain in Quebec. CMAJ. 2005;173:1037–42.
26. Dial S, Alrasadi K, Manoukian C, et al. Risk of *Clostridium difficile* diarrhea among hospital inpatients prescribed proton pump inhibitors: cohort and case-control studies. CMAJ. 2004;171:33–8.
27. Dial S, Delaney JA, Barkun AN, et al. Use of gastric acid-suppressive agents and the risk of community-acquired *Clostridium difficile*-associated disease. JAMA. 2005;294:2989–95.
28. Dial S, Delaney JA, Schneider V, et al. Proton pump inhibitor use and risk of community-acquired *Clostridium difficile*-associated disease defined by prescription for oral vancomycin therapy. CMAJ. 2006;175:745–8.
29. Redelings MD, Sorvillo F, Mascola L. Increase in *Clostridium difficile*-related mortality rates, United States, 1999–2004. Emerg Infect Dis. 2007;13:1417–9.
30. Cohen SH, Tang YJ, Silva Jr J. Analysis of the pathogenicity locus in *Clostridium difficile* strains. J Infect Dis. 2000;181:659–63.
31. Brazier JS, Stubbs SL, Duerden BI. Prevalence of toxin A negative/B positive *Clostridium difficile* strains. J Hosp Infect. 1999;42:248–9.
32. Drudy D, Harnedy N, Fanning S, et al. Isolation and characterisation of toxin A-negative, toxin B-positive *Clostridium difficile* in Dublin, Ireland. Clin Microbiol Infect. 2007;13:298–304.
33. Geric B, Rupnik M, Gerding DN, et al. Distribution of *Clostridium difficile* variant toxinotypes and strains with binary toxin genes among clinical isolates in an American hospital. J Med Microbiol. 2004;53:887–94.
34. Goncalves C, Decre D, Barbut F, et al. Prevalence and characterization of a binary toxin (actin-specific ADP-ribosyltransferase) from *Clostridium difficile*. J Clin Microbiol. 2004;42:1933–9.

35. Impallomeni M, Galletly NP, Wort SJ, et al. Increased risk of diarrhoea caused by *Clostridium difficile* in elderly patients receiving cefotaxime. BMJ. 1995;311:1345–6.
36. O'Connor D, Hynes P, Cormican M, et al. Evaluation of methods for detection of toxins in specimens of feces submitted for diagnosis of *Clostridium difficile*-associated diarrhea. J Clin Microbiol. 2001;39:2846–9.
37. McFarland LV, Beneda HW, Clarridge JE, et al. Implications of the changing face of *Clostridium difficile* disease for health care practitioners. Am J Infect Control. 2007;35:237–53.
38. Peterson LR, Manson RU, Paule SM, et al. Detection of toxigenic *Clostridium difficile* in stool samples by real-time polymerase chain reaction for the diagnosis of *C. difficile*-associated diarrhea. Clin Infect Dis. 2007;45:1152–60.
39. Johal SS, Hammond J, Solomon K, et al. *Clostridium difficile* associated diarrhoea in hospitalised patients: onset in the community and hospital and role of flexible sigmoidoscopy. Gut. 2004;53: 673–7.
40. Gerding DN, Muto CA, Owens Jr RC. Treatment of *Clostridium difficile* infection. Clin Infect Dis. 2008;46 Suppl 1:S32–42.
41. McMullen KM, Zack J, Coopersmith CM, et al. Use of hypochlorite solution to decrease rates of *Clostridium difficile*-associated diarrhea. Infect Control Hosp Epidemiol. 2007;28:205–7.
42. McNulty C, Logan M, Donald IP, et al. Successful control of *Clostridium difficile* infection in an elderly care unit through use of a restrictive antibiotic policy. J Antimicrob Chemother. 1997;40: 707–11.
43. Carling P, Fung T, Killion A, et al. Favorable impact of a multidisciplinary antibiotic management program conducted during 7 years. Infect Control Hosp Epidemiol. 2003;24:699–706.
44. Zar FA, Bakkanagari SR, Moorthi KM, et al. A comparison of vancomycin and metronidazole for the treatment of *Clostridium difficile*-associated diarrhea, stratified by disease severity. Clin Infect Dis. 2007;45:302–7.
45. Pepin J, Alary ME, Valiquette L, et al. Increasing risk of relapse after treatment of *Clostridium difficile* colitis in Quebec, Canada. Clin Infect Dis. 2005;40:1591–7.
46. Musher DM, Aslam S, Logan N, et al. Relatively poor outcome after treatment of *Clostridium difficile* colitis with metronidazole. Clin Infect Dis. 2005;40:1586–90.
47. Gerding DN. Metronidazole for *Clostridium difficile*-associated disease: is it okay for mom? Clin Infect Dis. 2005;40:1598–600.
48. Bartlett JG. Narrative review: the new epidemic of *Clostridium difficile*-associated enteric disease. Ann Intern Med. 2006;145: 758–64.
49. Maroo S, Lamont JT. Recurrent *Clostridium difficile*. Gastroenterology. 2006;130:1311–6.
50. Karas JA, Enoch DA, Aliyu SH. A review of mortality due to *Clostridium difficile* infection. J Infect. 2010;61:1–8.
51. Garey KW, Sethi S, Yadav Y, et al. Meta-analysis to assess risk factors for recurrent *Clostridium difficile* infection. J Hosp Infect. 2008;70:298–304.
52. Jodlowski TZ, Oehler R, Kam LW, et al. Emerging therapies in the treatment of *Clostridium difficile*-associated disease. Ann Pharmacother. 2006;40:2164–9.
53. Louie TJ, Miller MA, Mullane KM, et al. Fidaxomicin versus vancomycin for *Clostridium difficile* infection. N Engl J Med. 2011;364:422–31.
54. Miller M. Fidaxomicin (OPT-80) for the treatment of *Clostridium difficile* infection. Expert Opin Pharmacother. 2010;11(9): 1569–78.
55. Persky SE, Brandt LJ. Treatment of recurrent *Clostridium difficile*-associated diarrhea by administration of donated stool directly through a colonoscope. Am J Gastroenterol. 2000;95:3283–5.
56. van Nispen Tot Pannerden CM, Verbon A, Kulpers EJ. Recurrent *Clostridium difficile* infection: what are the treatment options? Drugs. 2011;71(7):853–68.
57. Cheng AC, Ferguson JK, Richards MJ, et al. Australasian Society for Infectious Diseases guidelines for the diagnosis and treatment of *Clostridium difficile* infection. Med J Aust. 2011;194:353–8.
58. Cohen SH, Gerding DN, Johnson S, et al. Clinical Practice Guidelines for *Clostridium difficile* infection in adults: 2010 update by the Society for Healthcare (SHEA) Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). Infect Control Hosp Epidemiol. 2010;31(5):431–55.
59. Longo WE, Mazuski JE, Virgo KS, et al. Outcome after colectomy for *Clostridium difficile* colitis. Dis Colon Rectum. 2004;47:1620–6.
60. Koss K, Clark MA, Sanders DS, et al. The outcome of surgery in fulminant *Clostridium difficile* colitis. Colorectal Dis. 2006;8:149–54.
61. Surawicz CM. Does emergency colectomy reduce mortality in patients with *Clostridium difficile*-associated disease? Nat Clin Pract Gastroenterol Hepatol. 2007;4:542–3.
62. Surawicz CM, McFarland LV, Greenberg RN, et al. The search for a better treatment for recurrent *Clostridium difficile* disease: use of high-dose vancomycin combined with *Saccharomyces boulardii*. Clin Infect Dis. 2000;31:1012–7.
63. McPherson S, Rees CJ, Ellis R, et al. Intravenous immunoglobulin for the treatment of severe, refractory, and recurrent *Clostridium difficile* diarrhea. Dis Colon Rectum. 2006;49:640–5.
64. Aboudola S, Kotloff KL, Kyne L, et al. *Clostridium difficile* vaccine and serum immunoglobulin G antibody response to toxin A. Infect Immun. 2003;71:1608–10.
65. Voelker R. Increased *Clostridium difficile* virulence demands new treatment approach. JAMA. 2010;303:2017–8.
66. Lowy I, Molrine DC, Leav BA, et al. Treatment with monoclonal antibodies against *Clostridium difficile* toxins. N Engl J Med. 2010;362:197–205.
67. Kyme L. *Clostridium difficile*—beyond antibiotics. N Engl J Med. 2010;362:264–5.
68. Vrtis MC. The *Clostridium difficile* epidemic: a potential disaster for long term care. Ann Long Term Care. 2008;16(7):19–24.
69. Guerrero DM, Nerandzic MM, Jury LA, et al. *Clostridium difficile* infection in a department of Veterans Affairs long-term care facility. Infect Control Hosp Epidemiol. 2011;32:513–5.
70. Lanzas C, Dubberke ER, Lu Z, et al. Epidemiological model for *Clostridium difficile* transmission in healthcare settings. Infect Control Hosp Epidemiol. 2011;32:553–61.
71. Linsky A, Gupta K, Lawler EV, et al. Proton pump inhibitors and risk for recurrent *Clostridium difficile* infection. Arch Intern Med. 2010;170(9):772–8.
72. Ananthakrishnan AN. *Clostridium difficile* infection: epidemiology, risk factors and management. Nat Rev Gastroenterol Hepatol. 2011;8(1):17–28.
73. Gerding DN, Johnson S. Advances in pathogenesis, diagnosis and management of CDI. *Clostridium difficile* infection in 2010. Nat Rev Gastroenterol Hepatol. 2011;8:67–8.
74. Doernberg SB, Winston LG, Deck DH, Chambers HF. Does doxycycline protect against development of Clostridium difficile infection? Clin Infect Dis. 2012 May 4; ahead of print.
75. Rebeaud F, Bachmann MF. Immunization strategies for Clostridium difficile infections. Expert Rev Vaccines. 2012;11(4):469–79.

Gastrointestinal Infections

55

David V. Alcid

Gastrointestinal infections are common in the geriatric population and the presentation is often subtle or atypical. Several predisposing factors in the aged, in addition to a background of comorbidity and diminished physiological reserves, cause the aged to become susceptible. The defense may be immune and nonimmune. Alterations in systemic immunity involve adaptive (antigen-specific) immunity involving cell-mediated and humoral immune responses and innate immunity. Both quality and proportion of T helper and T suppressor cells decline with age. Secretory IgA antibodies are T cell-dependent and may be altered, further contributed by a decline in Peyer's patches which generate the immune response. Besides a decline in T cell and B cell function, there is reduced T Cell CD28 expression with age. An increase in autoantibodies also occurs. Proneness to infections is also contributed by nonimmune mechanisms. These include a decline in gastric acidity contributed to by disorders such as chronic gastritis or by agents that reduce gastric acidity, delayed gastric emptying, alterations in small intestinal motility with bacterial overgrowth, and other factors. Infections due to opportunistic pathogens may not be recognized as the elderly are not considered to be immunocompromised. Yet, in spite of atypical presentations, infections in the old must be recognized at an early stage and treated to reduce morbidity and mortality [1–8].

General Principles

The utilization of antibiotics and knowledge of sensitivity or resistance based on suspected organism (Table 55.1) and the use of empiric antibiotics for enteric infections in the elderly may be relevant in certain situations (Table 55.2). Dosing of antimicrobial agents must be adjusted for renal function. It is worth recognizing that older adults with a normal serum creatinine value may in fact have a lower than expected glomerular filtration rate (GFR); this is particularly true in the frail old with low muscle mass. As a general rule, it is relevant to assess renal function in older individuals through the use of an acceptable formula. Indiscriminate use of antibiotics with failure to adjust drug dosage for several factors matters. Variables that need to be considered include renal and hepatic function, body weight, body fat, and fluid status. Treatment should never be worse than the disease; the use of injudicious antimicrobials and consequent *Clostridium difficile* infections is an example. Some of the adverse drug effects (such as vertigo, renal failure) may be irreversible and could render the frail old disabled. Use of antimicrobials is always a supplement to several basic steps in management such as the maintenance of hemodynamic stability through prompt and aggressive replacement of appropriate fluids and electrolytes. Earlier hospitalization and critical management may be necessary earlier in older adults.

Host Defense

Normally, the majority of ingested microorganisms never reach the small bowel because of the inhibitory effect of gastric acid (pH < 4). Administration of acid-reducing agents can result in a reduction of the infecting dose of cholera and salmonella. Increased susceptibility to *Giardia lamblia, Strongyloides stercoralis,* and *Diphyllobothrium latum* is observed in patients with achlorhydria or hypochlorhydria. Many older people have a decline in gastric acid from age-associated disease and even more likely from acid-reducing agents; consequentially, the old are highly susceptible to enteric pathogens

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Table 55.1 Gastrointestinal infections and antibiotic sensitivity

Drug	*Salmonella*	*Shigella*	*Yersinia*	*E. coli*	*Vibrio*	*Campylobacter*
Ciprofloxacin[a]	a++++	++++	++++	++++	+++	a+++
Azithromycin	++++	+++	+++	++++	+++	+++
Sulfa/trimethroprim	+++	+++	+++	+++	+++	+++
Ceftriaxone	++++	++++	++++	++++	+++	+++
Rifaximin[b]	–	–	–	++++	–	–
Erythromycin	–	–	–	–	–	++++

[a]Majority of *Salmonella* and *Campylobacter* from Asia are resistant to ciprofloxacin
[b]Contraindicated in the presence of fever or bloody stools

Table 55.2 Empiric antimicrobials in older adults

Indications for early institution of antimicrobials prior to establishing a diagnosis
High fever
Bloody diarrhea
Presence of shock or hypotension without an obvious explanation such as bleeding
Alteration in mentation or delirium, unexplained by other basis

Pathogenesis

Enteric pathogens cause disease by production of toxigenic enterotoxins or through invasion of epithelial cells resulting in tissue destruction and ulceration (invasive). Some pathogens produce toxins outside the host, while other organisms are ingested and produce toxins in the intestinal tract. Invasive pathogens attack, penetrate, and destroy mucosal cells. Pathogens like *Escherichia coli* 0157:H7, *Shigella*, and *Vibrio parahemolyticus* produce toxins (Shiga toxin or Shiga-like toxin) that are cytotoxic to cultured cell lines. Several strains of *E. coli* (0157:H7, EPEC) can attach to the mucosa and induce secretory diarrhea through increase in intracellular calcium (signal transduction) [9–11].

C. difficile-associated diarrhea and Helicobacter pylori infections are addressed elsewhere in this text.

General Manifestations

Patients infected by toxigenic (enterotoxin) pathogens are usually afebrile, nontoxic looking. Obvious clinical signs may be absent. In the frail elderly, subtle clinical manifestations are common and may be limited to just a change in functional status. The presentation may be decline in function, new onset of confusion, incontinence, falls, decreased mobility, or failure to cooperate, all from infection

Toxigenic pathogens usually affect the small bowel; diarrhea is usually voluminous with crampy abdominal pain. Illness is self-limited and the patient improves in 3–10 days. Invasive pathogens, on the other hand, are frequently accompanied by systemic features such as fever and malaise. The colon and rectum may be involved, therefore the presentation may include tenesmus and urgency, with small but frequent bowel movements. Blood and mucus may be present. Most infections are self-limited, but treatment with appropriate antibiotics addressing suspected organisms decreases the duration of illness (Table 55.1).

Acute Syndromes

The incubation period of diseases due to ingestion of preformed enterotoxin, as with *Staphylococcus aureus* and *Bacillus cereus*, are short, usually just hours. Foods implicated in *S. aureus* outbreaks are salads, pies, gravy, cakes, and mayonnaise. Contaminated foods are normal in color, odor, and taste. Grains (rice) are normally contaminated with *B. cereus* spores and prolonged heating will in fact facilitate growth of the organism with resultant toxin production. The symptoms for both organisms are identical: nausea, vomiting, headache, and occasionally, mild diarrhea. The illness is self-limited, usually lasting about 24 h, and treatment is supportive. Diagnosis is made by history and/or demonstration of the organism by culture of the suspected food or vehicle. Therapy is supportive.

Abdominal Cramps, Diarrhea, Low Grade or No Fever, Changes in Mental Status

The major etiologic agents for this syndrome are *E. coli, Vibrio species, B. cereus, Clostridium perfringens*, *Rotavirus, and Norovirus*. Symptoms include watery diarrhea and cramps, with no tenesmus or urgency. Vomiting and fever (>102°F) occur infrequently, the presence of which probably excludes these pathogens. Illness usually lasts 24–48 h and

treatment is primarily supportive with use of oral rehydrating solutions, although the duration of illness (*E. coli* and *Vibrio*) can be shortened by antibiotics [12, 13].

Shiga Toxin-Producing Gram negatives

Syndrome due to *E. coli* strains, and other gram negatives, produce Shiga-like (verotoxin), a cytotoxin designated SLT I and/or II. While most commonly the etiology is O157: H: 7 (36%), other gram negatives can cause the same syndrome. Outbreaks result from ingestion of contaminated beef products and water or other food contaminated by farm animal feces (Table 55.3). Person-to-person transmission can occur, with 8% of close contacts of infected patients developing the syndrome and at risk for Hemolytic Uremic Syndrome (HUS) (Table 55.4). Shiga toxin producing *E. coli*-associated HUS carries serious sequelae (Table 55.5). The diagnosis is made by demonstrating Shiga toxin from the stool [14].

Invasive Pathogens Presenting as Fever, Abdominal Cramps, Diarrhea

The major etiologic considerations for this syndrome are *Salmonella, Shigella, Campylobacter jejuni, Yersinia enterocolitica,* and *V. parahemolyticus*. Clinical presentations are identical for all pathogens. Incubation period is around 16–72 h; stools may contain mucus and blood. Systemic symptoms (fever, malaise) are the rule, with vomiting in 35–80% of patients. These pathogens usually affect the colon/rectum, with resultant tenesmus and urgency. Illnesses usually resolve within 2–10 days, and earlier with appropriate antibiotic therapy. *Campylobacter* is worldwide in distribution and a commensal in the gastrointestinal tract of cattle, sheep, swine, dogs, cats, rodents, and fowl. Most infected animals serve as chronic asymptomatic carriers. Infection results either from direct contact with an infected animal or ingestion of poorly cooked contaminated meat. *Campylobacter* species are usually susceptible to erythromycin and azithromycin. *Y. enterocolitica* has a natural reservoir in cattle, pigs, rodents, rabbits, horses, dogs, and cats. Infection results from direct contact or food-borne, through contaminated water or milk products; a unique complication is mesenteric lymphadenitis, which may be misdiagnosed as acute appendicitis. The recommendation would be to treat the elderly with antimicrobial agents such as ciprofloxacin. For each disease, prevention strategies and microbiology related evidence-based guidelines should be adopted. In addition, to minimize the spread of gastrointestinal infections through endoscopic procedures, appropriate methodology for endoscope reprocessing must be followed, although the guidelines are not consistent [15–22].

Table 55.3 Transmission of Shiga toxin producing *E. coli*

Ground beef	43%
Milk	4%
Other beef products	6%
Noncattle sources: apple cider, fermented sausages, mayonnaise, salads	6%
Water	6%
Person-to-person infectious dose of 50–100 organism/mL	20%

Table 55.4 Clinical presentation of Shiga toxin producing *E. coli*

Urgency or tenesmus, with small quantity of bloody stool
Hemolytic uremic syndrome
Thrombotic thrombocytopenic Purpura
Diarrhea, mild, watery, and frequently bloody

Table 55.5 Sequele of Shiga toxin producing *E. coli*

Poor outcome (11%)
End stage renal disease (3.6%)
Cerebrovascular disease (brain infarcts) (3.6%)
Chronic renal disease and hypertension
Proteinuria, with reduced renal function (51%)

Listeriosis

Listeriosis, a serious food-borne infection, carries a high 30% mortality rate. The disease primarily affects older adults, especially those immuno-compromised. *Listeria monocytogenes* is commonly found in soil and water; animals can carry the bacterium without appearing ill and contaminate foods of animal origin, such as meats and dairy products. Listeriosis usually presents with muscle aches, sometimes preceded by diarrhea or other gastrointestinal symptoms. Almost everyone diagnosed with listeriosis has "invasive" infection, where the bacteria spread beyond the gastrointestinal tract. Symptoms, in addition to fever and myalgia, may include headache, stiff neck, confusion, loss of balance, and convulsions. In particular, those vulnerable to serious illness include the elderly, the immunocompromised such as posttransplant recipients and following chemotherapy or corticosteroids, cancer, diabetes, alcoholism, liver, and kidney disease. Persons with AIDS are almost 300 times more susceptible to listeriosis than people with normal immune systems. Prevention is addressed through several measures; these include avoiding ingestion of processed meats such as cold cuts unless heated to 165°F; washing hands after handling hot dogs, luncheon meats, and deli meats; and avoiding ingestion of soft cheeses, unless made with pasteurized milk. Canned and shelf stable tuna, salmon, and other fish products are safe to eat.

The clinical diagnosis is confirmed only after isolation of *L. monocytogenes* from an infected site, such as blood or stool (or other sources). *L. monocytogenes* can be isolated readily using routine media. Serological tests are unreliable and not recommended at the present time [23, 24]. Treatment involves the use of ampicillin and sulfa/trimethoprim in those allergic to penicillin

Travelers Diarrhea

Depending on the area visited, 21–100% of travelers may develop acute diarrhea. The pathogens implicated may vary. Symptoms develop 3–15 days after arriving in the area and include malaise, abdominal cramps, and watery diarrhea, and occasionally, nausea and vomiting. The illness is usually self-limited, lasting 1–5 days, but some continue to be sick for 5–10 days. Individuals on H2 blockers and PPI are at increased risk for traveler's diarrhea, due to a decline in protection offered by normal gastric acidity. Hence, older adults on acid reducers must be considered for prophylactic antibiotics instead of preemptive therapy [25–29].

Noroviruses

Noroviruses (genus *Norovirus,* family *Caliciviridae*) are a group of single-stranded RNA, nonenveloped viruses that cause acute gastroenteritis. The most common manifestations include diarrhea, vomiting, and abdominal pain. Norovirus is highly contagious and can spread from person to person, through the fecal-oral route. Norovirus is now recognized as the leading cause of food-borne disease outbreaks in the United States. Outbreaks are common in the institutional settings, such as nursing homes, cruise ships, and dormitories. Acute gastroenteritis due to norovirus is a serious illness, more so in those unable to drink enough fluids to replace losses from vomiting or diarrhea. Treatment is primarily supportive, and there is no lasting immunity [30–34].

Cryptosporidium parvum Infection

Infection secondary to *Cryptosporidium parvum* is increasingly being recognized as an important pathogen in the elderly and causes significant morbidity and mortality from dehydration, with poor outcomes. This pathogen is frequently associated with chronic diarrhea in patients with AIDS. It is an often unrecognized pathogen in the elderly and the diagnosis missed as testing for cryptosporidium requires a specific test not routinely offered by the laboratory. Older patients need to be tested for cryptosporidium specifically since treatment differs from that offered for other causes of diarrhea. Diagnosis is made by acid fast smear of the stool or direct fluorescent stain using monoclonal antibodies against cryptosporidium. Azithromycin has been used with some success [35–38].

Intraperitoneal, Hepatic, and Splenic Abscess

Secondary peritonitis develops when the peritoneal cavity is contaminated by organisms from a ruptured viscus. The microbial flora always reflects the source. A colonic leak such as from the appendix, diverticuli, or malignancy is almost always secondary to mixed aerobes and anaerobes. Peritonitis from a biliary source is usually secondary to aerobic gram negatives and enterococci, as anaerobes are uncommon pathogen in the biliary tract. Untreated or unrecognized peritonitis usually results in abscess formation and extends to other organs such as the liver or spleen. Symptoms of peritonitis and visceral abscess may be subtle or absent in the elderly. The presentation may be prolonged fever lasting over 2 weeks, without an evident etiological diagnosis after usual tests, referred to as fever of unknown origin (FUO). The only manifestations of FUO in the elderly, besides fever, may be lethargy and altered mental status (delirium). The evaluation of FUO in the geriatric age group must include an abdominal ultrasound or computerized tomography to exclude an abscess or infected fluid collection in the liver, spleen, kidneys, and the subphrenic or pelvic areas. Malignant disorders, including lymphomas, abdominal tuberculosis, and drug-induced fever, are considerations in the differential diagnosis of prolonged fever when an etiology is not readily apparent. In addition to surgical drainage of the abscess, management includes antimicrobial therapy to address aerobes and anaerobes. There is no clinical evidence that a specific antibiotic or combination is superior to others. Choices and combinations include: penicillin/β-lactamase inhibitors (piperacillin/tazobactam), carbapenemases (imipenem, ertapenem), ampicillin/metronidazole/ciprofloxacin, cefoxitin, and in the penicillin allergic patient, aztreonam/metronidazole.

Unlike liver abscess, a splenic abscess usually results from hematogenous spread. The organisms involved differ form those in liver abscess, the most common being *S. aureus* and *Streptococcus milleri.* The clinical picture of splenic abscess is identical to liver abscess. Treatment is directed towards *S. aureus* and *S. milleri, Streptococcus anginosus*; vancomycin may be started empirically, with further specific therapy based on susceptibility of the offending organism.

Gastrointestinal infections in the older adult require prompt recognition of the illness, a decision on the need for and choice of antibiotics and stabilization of the patient with other measures to address unstable hemodynamic status and loss of electrolytes and water. Tuberculosis must be a consideration when the cause of fever is an enigma. Delay in

Table 55.6 Characteristics of ORS* (oral rehydrating solutions)

Product	CHO	Na	K	HCO_3	mOsm/L
WHO ORS*	20	90	20	30	310
Cera lyte	40	70	20	10	240
Gatorade	45	20	3	3	330
Colas	50–150	2	0.1	13	550
Tea	0	0	0	0	5
Chicken soup	0	250	5	0	450

decision making may lead to adverse outcomes. A choice of oral solutions for hydration is provided in Table 55.6; often, oral fluids may be all that is required. Intravenous fluid administration is dealt with another chapter.

Key Points

- Gastrointestinal infections are common in the geriatric population; the presentation may differ in the old, with fever and leukocytosis less prominent; instead delirium, failure to thrive and hemodynamic instability are more common
- Knowledge of common infections in the practice setting enables earlier recognition of possibilities and allows for empiric antibiotic therapy; this approach favors better outcomes.
- At the same time, inappropriate broad spectrum antimicrobials can lead to adverse effects, where the consequence may be worse than the primary infection for which antibiotics are used.
- If antibiotics are used, the dose should be tailored to organ function and to the individual.
- In addition, prompt recognition of unstable hemodynamic status warrants use of oxygen, fluids, and electrolytes by an appropriate route.
- When the cause is not apparent, unusual causes such as an intra-abdominal abscess, tuberculosis, and lymphoma may be considered in the differential diagnosis as for fever of unknown origin.

References

1. Goronzy JJ, Fulbright JW, Crowson CS, Poland GA, et al. Value of immunological markers in predicting responsiveness to influenza vaccination in elderly individuals. J Virol. 2001;75:12182–7.
2. Meyer KC. Aging. Proc Am Thorac Soc. 2005;2:433–9.
3. Vergis EN, Brennen C, Wagener M, Muder RR. Pneumonia in long term care: a prospective case control study of risk factors and impact on survival. Arch Intern Med. 2001;161:2378–81.
4. Ratnake RN. Diarrhea in old age. In: Pilotto A, Malfertheiner P, Holt PR, editors. Aging and the gastrointestinal tract. New York: Karger; 2003. p. 187–99.
5. Berman P, Hogan DB, Fox RA. The atypical presentation of infection in old age. Age Aging. 1987;16:201–7.
6. Leonard J, Marchall JK, Moayyedi P. Systematic review of the risk of enteric infection in patients taking acid suppression. Am J Gastroenterol. 2007;102:2047–56.
7. Neal KR, Scott HM, Slack RC, et al. Omeprazole as a risk factor for campylobacter gastroenteritis: case-control study. BMJ. 1996;312(7028):414–5.
8. Flores J, Okhuysen PC. Genetics of susceptibility to infection with enteric pathogens. Curr Opin Infect Dis. 2009;22(5):471–6.
9. Thielman MN, Guerrant RL. Acute infectious diarrhea. N Engl J Med. 2004;350:38–47.
10. DuPont HL. Guidelines on acute infectious diarrhea in adults. Am J Gastroenterol. 1997;92:1962–75.
11. Guerrant RL, Van Gilder T, Steiner TS, et al. Practice guidelines for the management of infectious diarrhea. Clin Infect Dis. 2001;32:331–51.
12. Bresee J, Widdowson M, Monroe S, et al. Foodborne viral gastroenteritis: challenges and opportunities. Clin Infect Dis. 2002;35:748–53.
13. Bender JB, Smith KE, McNees AA, et al. Emerging Infections Program FoodNet Working Group: Factors affecting surveillance data on *Escherichia coli* O157 infections collected from FoodNet sites, 1996–1999. Clin Infect Dis. 2004;38 Suppl 3:S157–64.
14. Musher DM, Musher BL. Contagious acute gastrointestinal infections. N Engl J Med. 2004;351:2417–27.
15. Martin SJ, Yost RJ. Infectious diseases in the critically ill patients. J Pharm Pract. 2011;24(1):35–43.
16. Campylobacter Sentinel Surveillance Scheme Collaborators. Ciprofloxacin resistance in *Campylobacter jejuni:* case-case analysis as a tool for elucidating risks at home and abroad. J Antimicrob Chemother. 2002;50(4):561–8.
17. Engberg J, Neimann J, Nielsen EM, et al. Quinolone-resistant *Campylobacter* infections: risk factors and clinical consequences. Emerg Infect Dis. 2004;10:1056–63.
18. Kassenborg HD, Smith KE, Vugia DJ, et al. Fluoroquinolone-resistant *Campylobacter* infections: eating poultry outside of the home and foreign travel are risk factors. Clin Infect Dis. 2004;38 Suppl 3:S279–84.
19. Kuschner RA, Trofa AF, Thomas RJ, et al. Use of azithromycin for the treatment of *Campylobacter* enteritis in travelers to Thailand, an area where ciprofloxacin resistance is prevalent. Clin Infect Dis. 1995;21(3):536–41.
20. Muscarella LF. Inconsistencies in endoscope-reprocessing and infection-control guidelines: the importance of endoscope drying. Am J Gastroenterol. 2006;101(9):2147–54.
21. Agrawal D, Muscarella LF. Delayed reprocessing of endoscopes. Gastrointest Endosc. 2011;73(4):853–4.
22. Chang HG, Tserenpuntsag B, Kacica M, et al. Hemolytic uremic syndrome incidence in New York. Emerg Infect Dis. 2004;10:928–31.
23. Ramaswamy V, Cresence VM, Rejitha JS, et al. Listeria—review of epidemiology and pathogenesis. Microbiol Immunol Infect. 2007;40:4–13.
24. Farber JM, Peterkin PI. Listeria monocytogenes, a food-borne pathogen. Microbiol Mol Biol Rev. 1991;55(3):476–511.

25. Kean BH. The diarrhea of travelers to Mexico. Summary of five-year study. Ann Intern Med. 1963;59:605–14.
26. DuPont HL, Ericsson CD. Prevention and treatment of traveler's diarrhea. N Engl J Med. 1993;328(25):1821–7.
27. Tjoa WS, DuPont HL, Sullivan P, et al. Location of food consumption and travelers' diarrhea. Am J Epidemiol. 1977;v106(1):61–6.
28. Gorbach S, Edelman R. Travelers' diarrhea: National Institutes of Health Consensus Development Conference. Rev Infect Dis. 1986;8 Suppl 2:S109–233.
29. Singh E, Redfield D. Prophylaxis for travelers' diarrhea. Curr Gastroenterol Rep. 2009;11(4):297–300.
30. Widdowson MA, Cramer EH, Hadley L, et al. Outbreaks of acute gastroenteritis on cruise ships and on land: identification of a predominant circulating strain of Norovirus-United States, 2002. J Infect Dis. 2004;190(1):27–36.
31. Drinka PJ. Norovirus outbreaks in nursing homes. J Am Geriatr Soc. 2005;53(10):1839–40.
32. Lin H, Ng S, Chan S, et al. Institutional risk factors for norovirus outbreaks in Hong Kong elderly homes: a retrospective cohort study. BMC Public Health. 2011;11:297.
33. Lopman BA, Reacher MH, Vipond IB, et al. Clinical manifestation of norovirus gastroenteritis in heath care settings. Clin Infect Dis. 2004;39(3):318–24.
34. Wu HM, Fornek M, Schwab KJ, et al. A norovirus outbreak at a long-term-care facility: the role of environmental surface contamination. Infect Control Hosp Epidemiol. 2005;26(10):802–10.
35. White Jr AC. Cryptosporidiosis (*Cryptosporidium hominis*, *Cryptosporidium parvum*, other species). In: Mandell GL, Bennett JE, Dolin R, editors. Principles and practice of infectious diseases. 6th ed. Philadelphia: Elsevier Churchill Livingstone; 2005. p. 3215–28.
36. MacKenzie WR, Hoxie NJ, Proctor ME, et al. A massive outbreak of cryptosporidium infection transmitted through the public water supply. N Engl J Med. 1994;331:161–7.
37. Chappell CL, Okhuysen PC, Sterling CR, et al. Infectivity of *Cryptosporidium parvum* in healthy adults with pre-existing anti-C. *parvum* serum IgG. Am J Trop Med Hyg. 1999;60: 157–64.
38. Neill MA, Rice SK, Ahmad NV, Flanigan TP. Cryptosporidiosis: an unrecognized cause of diarrhea in elderly hospitalized patients. Clin Infect Dis. 1996;22:168–70.

Anal Incontinence

56

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Introduction

Anal incontinence (AI) is the involuntary loss of either flatus, mucous, liquid stool, or solid stool, leading to social and hygienic issues. It is socially unacceptable to pass flatus or stool in public, and this leads to embarrassment, especially when unforeseen. Fecal incontinence is the second most common cause of institutionalization in the geriatric age group, negatively impacting quality of life and degree of care required [1].

The physician must differentiate true incontinence from pseudoincontinence, the latter referring to soiling, frequency, and urgency. Pseudoincontinent situations may arise from prolapsed mucosa, hemorrhoidal disease, or inflamed rectal mucosa as observed with gastroenteritis, inflammatory bowel disease, or irritable bowel syndrome. Patients with pseudoincontinence usually have an intact sphincter mechanism.

Epidemiology

The prevalence of AI varies widely, as the literature often excludes flatus for statistical analysis. The National Health and Nutrition Examination Survey (NHANES) cross-sectional survey of fecal incontinence in noninstitutionalized adults revealed that 8.3% of noninstitutionalized adults reported fecal incontinence at least once in the previous 30 days [2]. Liquid stool was the most common form of incontinence, with solid stool incontinence more prevalent among women than men. Diarrhea appeared significantly associated with a risk of fecal incontinence.

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While women are more likely to experience AI [3, 4], there appears to be equal gender involvement in the noninstitutionalized [2, 5, 6]. The NHANES data suggested that 51.0% of women and 46.2% of men reported incontinence to flatus at least once in the previous month. The high rates may have included patients with recent infectious colitis, unlikely to encounter incontinence again.

Age remains an important risk factor for fecal incontinence [2, 5]. Noninstitutionalized adults over age 60 manifest increasing rates of fecal incontinence, increasing further beyond age 70–75. Risk factors include watery stools, over 21 bowel movements per week, poor self-rated health, and urinary incontinence. Factors influencing the occurrence of fecal incontinence in women include obesity (BMI >30 kg/m^2), sedentary lifestyle, and presence of at least one chronic illness.

Healthcare providers should be proactive in determining the presence of AI [6]. Physicians should directly ask their patients if they experience symptoms of AI and determine reasons for underreporting.

The Physiology of Continence

A multitude of factors determine continence (Table 56.1) including stool consistency, colonic transit, rectal capacity and compliance, rectal sensation, the rectoanal inhibitory reflex, and the sphincter apparatus consisting of the internal and external anal sphincters as well as the puborectalis and levator ani muscles. As gastrointestinal contents proceed distally through the intestines, 8–9 L of water absorption contributes to forming stool with a volume of 200–300 mL. With decreased colonic transit time, as in infectious colitis, inflammatory bowel disease, or short bowel syndrome, the stool has more fluidity when reaching the rectum. This may lead to urgency and soiling in otherwise healthy individuals without prior anorectal disease.

Stool reaching the rectum distends it to maintain a low intraluminal pressure. While this rectal reservoir maintains continence, it is unclear if a decrease in rectal capacity leads

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Table 56.1 Mechanisms of anal continence

Sphincter apparatus
Internal anal sphincter (80% resting tone)
External anal sphincter
Levator ani (ileococcygeus, pubococcygeus)
Puborectalis
Rectal compliance
Rectum distends with stool
Rectoanal inhibitory reflex
Rectal sensation
Temperature, pain, pressure, friction receptors
Stool consistency
Increased transit time ≥ more formed
Decreased transit time ≥ more loose

Table 56.2 Causes of anal incontinence

Sphincter injury
Obstetric
Vaginal delivery
Midline episiotomy
Forceps delivery
Anorectal surgery
Lord's procedure
Manual dilatation of the anal canal
Lateral internal sphincterotomy
Hemorrhoidectomy
Fistulotomy
Traumatic
Pelvic fracture
Anatomic abnormalities
Descending perineum
Rectal prolapse
Rectocele
Disease-related
Inflammatory bowel disease
Radiation proctitis
Infectious diarrhea
Diabetes
Multiple sclerosis
Stroke
CNS neoplasms
Dementia
Muscular disorders
Congenital lesions
Amyloidosis

to incontinence or vice versa (incontinence leads to a decrease in rectal capacity) [7]. Patients with altered mental status, such as dementia, stroke, and encephalitis may experience overflow incontinence. Since altered mentation may prevent sensing distention, the rectum continues to distend resulting in higher intraluminal pressures.

The mechanism of continence is partially explained by the rectoanal inhibitory reflex (RAIR). Stool or air causes the rectum to distend. Although the rectum itself does not have stretch receptors, the puborectalis and levator ani muscles sense the rectal fullness, causing temporary relaxation of the internal anal sphincter and contraction of the external sphincter to allow discrimination between gas and liquid vs. solid stool. Once this occurs, the internal sphincter contracts again [8].

The internal anal sphincter is a thickening of the smooth muscle of the rectum and is usually contracted, accounting for 80% of the resting anal sphincter tone. The external anal sphincter on the other hand is composed of striated muscle and accounts for 20% of the resting anal sphincter tone along with the levator ani and puborectalis muscles. In addition to the RAIR, the external anal sphincter involuntarily contracts when changing from a sitting to standing position and in response to increased intra-abdominal pressure. As one may guess, the external anal sphincter voluntarily contracts in a cognitively intact person when the situation is not appropriate for defecating.

The puborectalis muscle is also important in defecation. This muscle partially wraps around the posterior aspect of the anal sphincter, forming a U-shaped sling. The resting tone of the puborectalis–levator ani complex maintains the anorectal junction at a 90° angle. With defecation the puborectalis relaxes, increasing the anorectal junction angle to about 120°, making it easier for stool to enter the anal canal.

Age-Related Changes

With age, anatomical changes involving the sphincter apparatus may predispose to AI. Aging is associated with thickening of the internal anal sphincter, thinning of the external anal sphincter, and increased pelvic floor descent [9]. Excessive pelvic floor descent can cause a stretch-induced pudendal neuropathy leading to an abnormally relaxed puborectalis muscle [10]. Other changes include decreased anal squeeze pressures, reduced rectal capacity, decreased mucosal electrosensitivity, decreased sensation to rectal distention, decreased density of nerve fibers supplying the external anal sphincter, and increased pudendal nerve terminal motor latency (PNTML) [11–13]. Additionally, comorbidities such as stroke and dementia predispose to AI.

Etiology

AI occurs secondary to obstetric trauma, anorectal surgery, pelvic trauma, anatomic abnormalities, and disease-related changes (Table 56.2). The most common cause is traumatic obstetric injury due to forceps delivery, large head circumference, birth weight over 4 kg combined with abnormal fetal presentation, and delay in second stage of labor [14–16]. About a third of primiparous women will experience an anal sphincter defect after delivery as opposed to 5–10% in multiparous women [17, 18]. Midline episiotomies have a high

association with anal sphincter injury, although this may simply reflect the rate of sphincter injury after vaginal delivery in general. Proponents of postero-lateral episiotomies believe it is less associated with sphincter injury; however, the injuries exhibited here are more complex. Unfortunately, immediate repair of the sphincter by obstetricians or midwives does not seem helpful [16, 19]. In summary, obstetric trauma in earlier life may predispose to AI in the later years. An important association with AI is urinary incontinence, also termed double incontinence, with a prevalence of about 7.5% [20].

Iatrogenic causes of AI include fistulotomy, lateral sphincterotomy, and hemorrhoidectomy although the risks are low. Fistula treatment is associated with incontinence about 6.9% of the time [21] with no procedure-based difference [22]. A chronic anal fissure, historically requiring a posterior midline fissurectomy and sphincterotomy with higher risks of true and pseudoincontinence [23–25], is now treated with a lateral internal sphincterotomy with 2–8% incontinence rate [24]. The historical Lord's procedure, or manual dilatation of the anal canal, was a treatment for hemorrhoidal disease [26] with high rates of sphincter injury [27]. Current treatments for hemorrhoids confer an AI risk of 0.3–8.7% without significant difference between types of procedure [28–33].

History and Physical Examination

Since AI is multifactorial, a thorough history and physical examination are important. Patients may not volunteer information for fear of embarrassment. One must determine if the incontinence is to flatus, liquid stool, and/or solid stool; it is also essential to exclude pseudoincontinence. Physicians must identify duration of symptoms, frequency, urgency, time of day, dietary relationships, relation to exertional activities, and other modifiers. One must elicit information regarding dyschezia, time to evacuation, frequency of bowel movements, and rectal bleeding.

Past history captures possible associated comorbidities including urinary incontinence, congenital anomalies, psychiatric history, diabetic neuropathy, recent illness such as infectious colitis, and medication adverse effect presenting as constipation with overflow incontinence or diarrhea. Prior history must evaluate pregnancies and deliveries, perineal injuries and/or trauma, and perineal or colorectal procedures.

One must determine the impact of incontinence on the patient's quality of life. Is the patient able to engage in activities of daily living and social activities with minimal disturbance? Does the patient require pads?

The physical examination includes inspection with the patient usually in the prone jackknife position or the left lateral decubitus position. Inspection helps differentiate true incontinence from pseudoincontinence, the latter manifest as leakage or drainage from mucosa, hemorrhoids, fistulae, or poor hygiene, leading to pruritis ani and excoriations. Inspection may reveal scars from previous anorectal surgery. Sensory deficits are determined by eliciting the anal wink reflex. A rectal digital examination is crucial, as is a vaginal examination in females. Examination may reveal impacted stool, laxity of the perineal body, a rectovaginal fistula, masses, or palpable defects. During rectal examination, the patient is asked to bear down, or perform a Valsalva maneuver, to get a sense of the resting and squeeze pressures. Administration of 100 mL water enema will grossly evaluate continence to thin liquid.

Incontinence Scoring System

While completing the clinical evaluation, it is important to document the level of severity of the incontinence and its consequences. The Wexner Fecal Incontinence Scoring System is a widely used tool to grade the level of incontinence, accounting for the frequency of type of incontinence, necessity for a pad, and lifestyle alteration [1]. A score of 0 indicates full anal continence, whereas a score of 20 signifies complete AI. The quality of life of a patient affected by AI is assessed by questionnaires, one being the Fecal Incontinence Quality of Life Scale [34].

Diagnostic Testing

The history and physical examination findings help choose diagnostic tests to determine the etiology of incontinence. Anorectal physiology testing, endoanal ultrasound, and defecography are three important adjuncts for assessment. A simple anoscopy will reveal hemorrhoids, fistulae, or mucosal inflammation. Colonoscopy helps evaluate the entire colon if evaluation reveals a palpable mass or signs suggesting neoplasm or irritable bowel disease.

Anorectal Physiology

The anorectal physiology laboratory includes anorectal manometry, electromyography (EMG), and PNTML testing. The tests provide information about the neurologic and sensory components of anorectal function.

Anorectal Monometry

Anorectal monometry (ARM) assesses several components of anorectal function including resting pressure, squeeze pressure, rectal sensation and compliance, and RAIR.

A transducer inserted into the rectum measures the resting and squeeze pressures at 1 cm intervals from the rectum to the anal verge. Resting pressures reflect internal anal sphincter function, whereas squeeze pressures reflect external anal sphincter function. Measures of rectal sensation and compliance help in biofeedback therapy. Anorectal sensation is delineated by placing a latex or polyethylene balloon in the distal rectum. The balloon is slowly distended and the points at which a patient notes detectable sensation, desire to defecate, and severe discomfort are recorded. These three time points are known as the time of first sensation, first urge, and maximum tolerated volume, respectively. These measurements may be used along with biofeedback therapy.

Electromyography

EMG of the external anal canal analyzes summated motor unit potentials of the external anal sphincter and identifies defects that are myopathic or neurogenic in etiology. Needle EMG is a painful test and is replaced by the surface EMG. Surface EMG is recorded by either skin surface gel pads or by a small cigar-shaped anal foam, both noninvasive and well tolerated.

Pudendal Nerve Terminal Motor Latency

PNTML helps determine whether pudendal nerve injury is the basis for incontinence. The pudendal nerve is stimulated at Alcock's canal at the level of the ischial spine, and the time to contraction of the external anal sphincter is measured. Normal conduction time is 2.0 ms. Longer latencies imply injury to the pudendal nerve. Pudendal nerve injury may arise from obstetric trauma, surgery, pelvic floor descent, old age, diabetes, and advanced age.

Endoanal Ultrasound

Endoanal ultrasound helps visualize the anal sphincter and sphincter defects; it is performed by a colorectal surgeon with appropriate training in its use and interpretation. The ultrasound image shows the internal anal sphincter as a "dark" circular band while the external anal sphincter is seen as a reflective, echogenic layer. The main limitation is that it is operator-dependent. A skilled operator may detect sphincter thinning, perineal body length, muscle separation, and the presence of rectovaginal fistulas [35].

Defecography

Defecography, also known as dynamic proctography or fluoroscopic proctography, and magnetic resonance defecography may rarely provide additional information about the pelvic floor musculature [36]. Defecography is reserved for the rare patient whose subjective symptoms do not correlate with objective parameters.

Medical Management

AI is initially treated conservatively. Beyond the initial dietary modification, pharmacologic agents, and bowel management regimen, therapies such as pelvic floor exercises and biofeedback may be beneficial. Figure 56.1 depicts a flow diagram for the medical and surgical management of true AI.

Dietary Modification

Identifying and addressing the cause of loose stools is key to management of AI. Keeping a food diary helps identify possible triggers of fecal incontinence. Lactose intolerance is a frequent problem in many ethnic groups. Celiac disease is a markedly under-diagnosed entity. Colonic transit time is decreased by caffeine, alcohol, fruit juices, and certain vegetables (beans, broccoli, cauliflower). Dietary fiber should be gradually increased over weeks to months (see Chap. 21).

Pharmacologic Agents

If increasing stool bulk does not help attain full continence, pharmacotherapy is needed. Anti-motility agents will increase colon transit time and help solidify stool by allowing for increased absorption of water. Loperamide, diphenoxylate, and codeine are opioid receptor agonists that decrease peristalsis.

Bowel Management Regimen

For the few who experience overflow incontinence from stool impaction or constipation, a bowel management regimen may help. The aim is to have a daily complete bowel movement at a scheduled time and by avoiding constipating foods. Pharmacologic therapy to stimulate peristalsis with bisacodyl and senna may help.

Pelvic Floor Exercises

Pelvic floor exercises, or Kegel exercises, represent one approach to attain continence by strengthening the pelvic floor [37]. The practice involves tightening the pelvic floor muscles as performed when attempting to stop micturition midstream. The exercises need to be performed in sets of

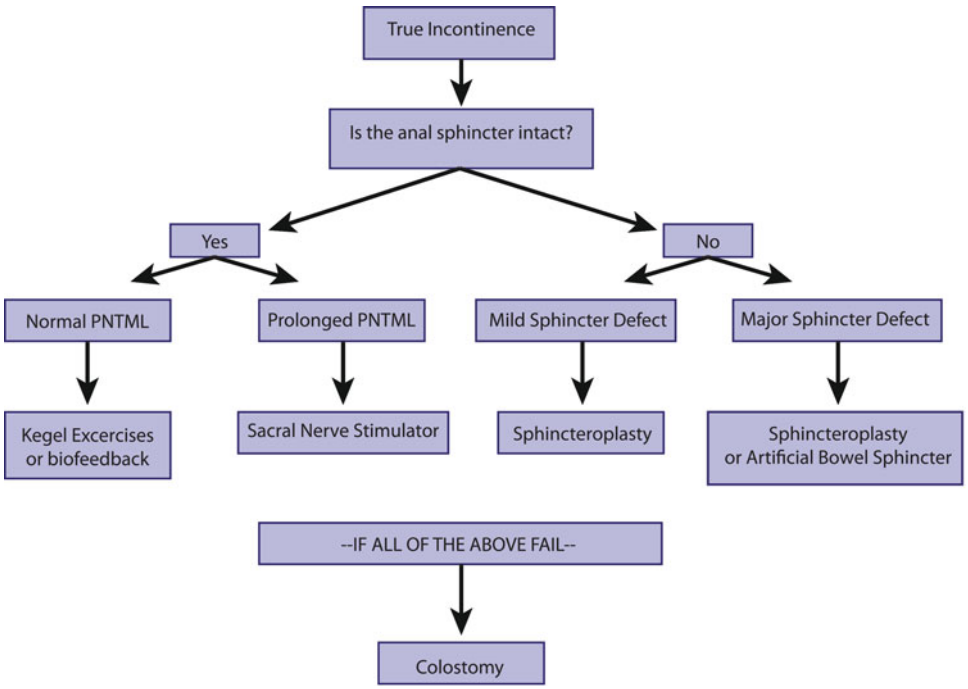

Fig. 56.1 Management of true anal incontinence. A flow diagram showing the medical and surgical treatment options available to patients with true anal incontinence

contractions several times daily in upright, sitting and lying positions. Unfortunately, the exercises are not particularly beneficial in improving continence.

Biofeedback Training

Biofeedback therapy is based on the principle of operant conditioning, which deals with the modification of "voluntary or operant behavior;" the latter refers to "operating" on the environment to produce desirable results. During weekly sessions, a biofeedback therapist helps the patient understand the condition and as to how it could be improved. Topics pertinent to AI are discussed. Pelvic floor exercises are combined with manometry readings and a balloon placed in the anal canal helps patients sense and respond to progressively smaller rectal volumes. EMG-based biofeedback uses surface EMG tracing of anal sphincter contractions. Biofeedback therapy appears more beneficial than pelvic floor exercises alone; treatment protocols vary and it is possible that improvement is based more on patient education and coping strategies than improved squeeze pressures and sensory thresholds.

Miscellaneous Approaches

Conservative treatments are a consideration prior to surgical intervention. Topical estrogens are not beneficial [38], while acupuncture is associated with improvement in continence [39].

Anal Hygiene

Anal hygiene is an important aspect of the medical management of AI. When the anal dermis is in continuous contact with liquid or solid stool as happens with AI, the anal perineum becomes irritated and inflamed, leading to symptoms such as itching. Anal secretions in contact with the skin promote inflammation and itching; seepage should prompt self-cleaning. Depending on culture, some may wash the anal area with water and pat dry with toilet paper whereas others use toilet paper moistened with water. Toilet paper can irritate the skin. An option is the use of moist wipes, which are also transportable. They contain mild skin cleansers and emollients. Wipes containing alcohol or witch hazel are best avoided as they cause dryness and facilitate skin irritation. Moist wipes do not need to be antibacterial. The bidet provides another mechanism for cleansing the perineum. For excoriated and sensitive perianal skin, a gentle stream of water is the most atraumatic and effective method to maintain hygiene.

Surgical Treatment

Not every patient requires surgery for AI, even if conservative management fails. A competent colorectal surgeon must understand the disability incurred from AI. For minor fecal leakage with no impact on quality of life, it would not be appropriate to undergo surgical treatment for incontinence. For those who require surgery, it is essential to undergo appropriate diagnostic testing as described earlier.

Sphincteroplasty

For patients with a disrupted anal sphincter, sphincter repair may be recommended. A young female with a disrupted internal anal sphincter after childbirth would be a candidate for sphincteroplasty; the patient will benefit even with bilateral pudendal neuropathy. In a study of patients with combined internal and external anal sphincter defects, 60% had improvements in AI, with 6% experiencing complete anal continence, after an average follow-up of 9 years [40]. On the contrary, continence may decline years after repair [41].

Artificial Bowel Sphincter

For patients with significant disruption of their sphincter or severe pudendal neuropathy who are not candidates for sphincteroplasty, implanting an artificial bowel sphincter may be beneficial. The Acticon™ Neosphincter (American Medical Systems, Minnetonka, MN, USA) has been used since 1996, receiving FDA approval in the United States in 2001. This device includes a cuff around the anal canal, a balloon implanted in the abdomen, and a pump in either the labium (females) or scrotum (males), all connected to one another with tubing. The fluid-filled cuff fills the circumference of the anal canal to keep it closed. Prior to evacuation of the rectum, the patient squeezes the pump several times causing the fluid to drain out of the cuff and opening the anal canal. After defecation, the fluid automatically drains back into the cuff to close the anal canal and maintain continence.

Complications following artificial bowel sphincter implantation include infections, erosions, ulcerations, device malfunction, balloon and pump leaks, device migration, and constipation [42–44]. A history of perineal infection and decreased time to first bowel movement prior to activation of the device may relate to delayed failure [45]. Over half the devices required explantation at 5 years secondary to long-term complications. Additionally, the patient needs to be cognitively intact and able to operate the pump mechanism. Although the technology is available, it is recommended when conventional methods are less feasible.

Sacral Nerve Stimulation

Sacral nerve stimulation (SNS) is FDA-approved for the treatment of urinary incontinence and works through unknown mechanisms, currently awaiting FDA approval in the United States for anal incontinence. We believe this treatment will especially benefit patients with an intact sphincter and weak pudendal nerves. Patients first undergo a 2-week test period in which a temporary stimulator electrode is placed in the S3 position. Patients achieving greater than 50% improvement in incontinence as recorded in a diary may be candidates for implantation of the permanent stimulator. Representatives from various sacral nerve stimulator implant centers in France have developed a position statement regarding SNS including indications, peripheral nerve evaluation, and follow-up [46]. Indications include fecal incontinence secondary to less than 30% damage to the external sphincter, rectal resection for cancer, scleroderma, peripheral or central, incomplete and nonprogressive neurologic disease. Negative predictors of successful peripheral nerve evaluation include age over 70 years, previous failure of peripheral nerve evaluation, and presence of an external anal sphincter defect [47]; although, other studies also show benefit in patients with sphincter defects [48, 49].

Long-term data on SNS are now available and indicate that SNS significantly improves AI, both short- and long-term. Patients up to 14 years postimplantation show significant improvement in their incontinence scores and quality of life measures [49, 50].

There appears to be greater improvement in symptoms with the Acticon™ Neosphincter than the sacral nerve stimulator [51]; however, placement of the artificial bowel sphincter is more invasive and has higher rates of constipation postimplantation. This highlights the importance of discussing the risks, benefits, and options to individualize treatment.

Radiofrequency Energy

The SECCA procedure is another attempt at treating AI [52–56]. This method applies temperature-controlled radiofrequency energy to the anal canal via needles that penetrate the tissue of the anal canal. The needles act as electrodes, raising the temperature of the tissue and creating injury and subsequent collagen deposition through the processes of wound healing, remodeling, scar formation, and contraction. The base of the needle is cooled with water on the mucosal surface to prevent thermal injury. There is controversy about the effectiveness of the SECCA procedure [57].

Anal Canal Bulking Agents

A less invasive method with unclear benefit for AI involves the submucosal injection of bulking agents such as polytetrafluoroethylene, autologous fat, glutaraldehyde cross-linked collagen, carbon beads, silicone biomaterial, and stabilized nonanimal hyaluronic acid with dextranomer [58–64].

Colostomy

For very severe AI without effective treatment or where radical surgery is either not desired or involves high risk, a colostomy may be performed. The colostomy will allow stool to

be collected via a stoma bag in a relatively controlled fashion and does not require sphincter control. However, stoma care is needed to prevent skin excoriations. This may be difficult in the cognitively impaired and those unable to care for themselves.

Future Research

There may be a role in the future for human umbilical cord matrix and bone marrow-derived mesenchymal stem cells to treat anal sphincter defects [65, 66]. Heterotopic and orthotopic autotransplantation of the anorectal segment has been studied in rats [67] but yet to be studied in humans.

Key Points

- AI is a socially disabling condition among the elderly that impairs the quality of life of the individual.
- Physicians must ask their patients about the symptoms of incontinence, its severity, and its impact on quality of life and function.
- The history and physical examination are relevant in assessment. With adequate evaluation and diagnostic testing, patients are categorized to either conservative or surgical management.
- Overcoming embarrassment regarding AI is key to diagnosis and appropriate treatment.
- Current medical and surgical options have improved the quality of life for patients with AI. The best approach must be individualized.

References

1. Jorge JM, Wexner SD. Etiology and management of fecal incontinence. Dis Colon Rectum. 1993;36:77–97.
2. Whitehead WE, Borrud L, Goode PS, et al. Fecal incontinence in US adults: epidemiology and risk factors. Gastroenterology. 2009;137:512–7.
3. MacLennan AH, Taylor AW, Wilson DH, et al. The prevalence of pelvic floor disorders and their relationship to gender, age, parity and mode of delivery. BJOG. 2000;107:1460–70.
4. Nelson R, Norton N, Cautley E, et al. Community-based prevalence of anal incontinence. JAMA. 1995;274:559–61.
5. Teunissen TA, van den Bosch WJ, van den Hoogen HJ, et al. Prevalence of urinary, fecal and double incontinence in the elderly living at home. Int Urogynecol J Pelvic Floor Dysfunct. 2004;15:10–3; discussion 13.
6. Whitehead WE. Diagnosing and managing fecal incontinence: if you don't ask, they won't tell. Gastroenterology. 2005;129:6.
7. Jorge JMN. Anorectal anatomy and physiology. In: Beck DE, Wexner SD, editors. Fundamentals of anorectal surgery. 2nd ed. London: W.B. Saunders; 1998. p. 557.
8. Miller R, Bartolo DC, Cervero F, et al. Anorectal sampling: a comparison of normal and incontinent patients. Br J Surg. 1988;75:44–7.
9. Papachrysostomou M, Pye SD, Wild SR, et al. Significance of the thickness of the anal sphincters with age and its relevance in faecal incontinence. Scand J Gastroenterol. 1994;29:710–4.
10. Bartolo DC, Read NW, Jarratt JA, et al. Differences in anal sphincter function and clinical presentation in patients with pelvic floor descent. Gastroenterology. 1983;85:68–75.
11. Laurberg S, Swash M. Effects of aging on the anorectal sphincters and their innervation. Dis Colon Rectum. 1989;32:737–42.
12. Ryhammer AM, Laurberg S, Sorensen FH. Effects of age on anal function in normal women. Int J Colorectal Dis. 1997;12:225–9.
13. Schiller LR. Constipation and fecal incontinence in the elderly. Gastroenterol Clin North Am. 2001;30:497–515.
14. Bartolo DC, Paterson HM. Anal incontinence. Best Pract Res Clin Gastroenterol. 2009;23:505–15.
15. Samarasekera DN, Bekhit MT, Preston JP, et al. Risk factors for anal sphincter disruption during child birth. Langenbecks Arch Surg. 2009;394:535–8.
16. Sultan AH, Kamm MA, Hudson CN, et al. Third degree obstetric anal sphincter tears: risk factors and outcome of primary repair. BMJ. 1994;308:887–91.
17. Oberwalder M, Connor J, Wexner SD. Meta-analysis to determine the incidence of obstetric anal sphincter damage. Br J Surg. 2003;90:1333–7.
18. Sultan AH, Kamm MA, Hudson CN, et al. Anal-sphincter disruption during vaginal delivery. N Engl J Med. 1993;329:1905–11.
19. Starck M, Bohe M, Valentin L. Results of endosonographic imaging of the anal sphincter 2–7 days after primary repair of third- or fourth-degree obstetric sphincter tears. Ultrasound Obstet Gynecol. 2003;22:609–15.
20. Ekin M, Kupelioglu LC, Yasar L, et al. The coexistence of anal incontinence in women with urinary incontinence. Arch Gynecol Obstet. 2009;280:971–4.
21. Rosa G, Lolli P, Piccinelli D, et al. Fistula in ano: anatomoclinical aspects, surgical therapy and results in 844 patients. Tech Coloproctol. 2006;10:215–21.
22. Hyman N, O'Brien S, Osler T. Outcomes after fistulotomy: results of a prospective, multicenter regional study. Dis Colon Rectum. 2009;52:2022–7.
23. Bode WE, Culp CE, Spencer RJ, et al. Fissurectomy with superficial midline sphincterotomy. A viable alternative for the surgical correction of chronic fissure/ulcer-in-ano. Dis Colon Rectum. 1984;27:93–5.
24. Mousavi SR, Sharifi M, Mehdikhah Z. A comparison between the results of fissurectomy and lateral internal sphincterotomy in the surgical management of chronic anal fissure. J Gastrointest Surg. 2009;13:1279–82.
25. Nelson RL. Operative procedures for fissure in ano. Cochrane Database Syst Rev. 2010:CD002199.
26. Sames P. Experiences of Lord's procedure for the treatment of hemorrhoids. Proc R Soc Med. 1972;65:782–3.
27. Creve U, Hubens A. The effect of Lord's procedure on anal pressure. Dis Colon Rectum. 1979;22:483–5.
28. Senagore AJ, Singer M, Abcarian H, et al. A prospective, randomized, controlled multicenter trial comparing stapled hemorrhoidopexy and Ferguson hemorrhoidectomy: perioperative and one-year results. Dis Colon Rectum. 2004;47:1824–36.
29. Gravie JF, Lehur PA, Huten N, et al. Stapled hemorrhoidopexy versus milligan-morgan hemorrhoidectomy: a prospective, randomized, multicenter trial with 2-year postoperative follow up. Ann Surg. 2005;242:29–35.
30. Ho YH, Cheong WK, Tsang C, et al. Stapled hemorrhoidectomy—cost and effectiveness. Randomized, controlled trial including incontinence scoring, anorectal manometry, and endoanal ultrasound assessments at up to three months. Dis Colon Rectum. 2000;43:1666–75.

31. Arbman G, Krook H, Haapaniemi S. Closed vs. open hemorrhoidectomy—is there any difference? Dis Colon Rectum. 2000;43:31–4.
32. Brusciano L, Ayabaca SM, Pescatori M, et al. Reinterventions after complicated or failed stapled hemorrhoidopexy. Dis Colon Rectum. 2004;47:1846–51.
33. Oughriss M, Yver R, Faucheron JL. Complications of stapled hemorrhoidectomy: a French multicentric study. Gastroenterol Clin Biol. 2005;29:429–33.
34. Rockwood TH, Church JM, Fleshman JW, et al. Fecal incontinence quality of life scale: quality of life instrument for patients with fecal incontinence. Dis Colon Rectum. 2000;43:9–16; discussion 16–7.
35. Bartram CI, Sultan AH. Anal endosonography in faecal incontinence. Gut. 1995;37:4–6.
36. Taylor SA. Imaging pelvic floor dysfunction. Best Pract Res Clin Gastroenterol. 2009;23:487–503.
37. Tan JJ, Chan M, Tjandra JJ. Evolving therapy for fecal incontinence. Dis Colon Rectum. 2007;50:1950–67.
38. Pinedo G, Garcia E, Zarate AJ, et al. Are topical oestrogens useful in faecal incontinence? Double-blind randomized trial. Colorectal Dis. 2009;11:390–3.
39. Scaglia M, Delaini G, Destefano I, et al. Fecal incontinence treated with acupuncture—a pilot study. Auton Neurosci. 2009;145:89–92.
40. Oom DM, Gosselink MP, Schouten WR. Anterior sphincteroplasty for fecal incontinence: a single center experience in the era of sacral neuromodulation. Dis Colon Rectum. 2009;52:1681–7.
41. Zutshi M, Tracey TH, Bast J, et al. Ten-year outcome after anal sphincter repair for fecal incontinence. Dis Colon Rectum. 2009;52:1089–94.
42. Wong WD, Congliosi SM, Spencer MP, et al. The safety and efficacy of the artificial bowel sphincter for fecal incontinence: results from a multicenter cohort study. Dis Colon Rectum. 2002;45:1139–53.
43. Altomare DF, Binda GA, Dodi G, et al. Disappointing long-term results of the artificial anal sphincter for faecal incontinence. Br J Surg. 2004;91:1352–3.
44. Gallas S, Leroi AM, Bridoux V, et al. Constipation in 44 patients implanted with an artificial bowel sphincter. Int J Colorectal Dis. 2009;24:969–74.
45. Wexner SD, Jin HY, Weiss EG, et al. Factors associated with failure of the artificial bowel sphincter: a study of over 50 cases from Cleveland Clinic Florida. Dis Colon Rectum. 2009;52:1550–7.
46. Leroi AM, Damon H, Faucheron JL, et al. Sacral nerve stimulation in faecal incontinence: position statement based on a collective experience. Colorectal Dis. 2009;11:572–83.
47. Govaert B, Melenhorst J, Nieman FH, et al. Factors associated with percutaneous nerve evaluation and permanent sacral nerve modulation outcome in patients with fecal incontinence. Dis Colon Rectum. 2009;52:1688–94.
48. Boyle DJ, Knowles CH, Lunniss PJ, et al. Efficacy of sacral nerve stimulation for fecal incontinence in patients with anal sphincter defects. Dis Colon Rectum. 2009;52:1234–9.
49. Matzel KE, Lux P, Heuer S, et al. Sacral nerve stimulation for faecal incontinence: long-term outcome. Colorectal Dis. 2009;11:636–41.
50. Altomare DF, Ratto C, Ganio E, et al. Long-term outcome of sacral nerve stimulation for fecal incontinence. Dis Colon Rectum. 2009;52:11–7.
51. Meurette G, La Torre M, Regenet N, et al. Value of sacral nerve stimulation in the treatment of severe faecal incontinence: a comparison to the artificial bowel sphincter. Colorectal Dis. 2009;11:631–5.
52. Efron JE. The SECCA procedure: a new therapy for treatment of fecal incontinence. Surg Technol Int. 2004;13:107–10.
53. Efron JE, Corman ML, Fleshman J, et al. Safety and effectiveness of temperature-controlled radio-frequency energy delivery to the anal canal (Secca procedure) for the treatment of fecal incontinence. Dis Colon Rectum. 2003;46:1606–16; discussion 1616–8.
54. Lefebure B, Tuech JJ, Bridoux V, et al. Temperature-controlled radio frequency energy delivery (Secca procedure) for the treatment of fecal incontinence: results of a prospective study. Int J Colorectal Dis. 2008;23:993–7.
55. Parisien CJ, Corman ML. The Secca procedure for the treatment of fecal incontinence: definitive therapy or short-term solution. Clin Colon Rectal Surg. 2005;18:42–5.
56. Takahashi T, Garcia-Osogobio S, Valdovinos MA, et al. Extended two-year results of radio-frequency energy delivery for the treatment of fecal incontinence (the Secca procedure). Dis Colon Rectum. 2003;46:711–5.
57. Kim DW, Yoon HM, Park JS, et al. Radiofrequency energy delivery to the anal canal: is it a promising new approach to the treatment of fecal incontinence? Am J Surg. 2009;197:14–8.
58. Shafik A. Polytetrafluoroethylene injection for the treatment of partial fecal incontinence. Int Surg. 1993;78:159–61.
59. Danielson J, Karlbom U, Sonesson AC, et al. Submucosal injection of stabilized nonanimal hyaluronic acid with dextranomer: a new treatment option for fecal incontinence. Dis Colon Rectum. 2009;52:1101–6.
60. Davis K, Kumar D, Poloniecki J. Preliminary evaluation of an injectable anal sphincter bulking agent (Durasphere) in the management of faecal incontinence. Aliment Pharmacol Ther. 2003;18:237–43.
61. de la Portilla F, Vega J, Rada R, et al. Evaluation by three-dimensional anal endosonography of injectable silicone biomaterial (PTQ) implants to treat fecal incontinence: long-term localization and relation with the deterioration of the continence. Tech Coloproctol. 2009;13:195–9.
62. Shafik A. Perianal injection of autologous fat for treatment of sphincteric incontinence. Dis Colon Rectum. 1995;38:583–7.
63. Soerensen MM, Lundby L, Buntzen S, et al. Intersphincteric injected silicone biomaterial implants: a treatment for faecal incontinence. Colorectal Dis. 2009;11:73–6.
64. Tjandra JJ, Chan MK, Yeh HC. Injectable silicone biomaterial (PTQ) is more effective than carbon-coated beads (Durasphere) in treating passive faecal incontinence—a randomized trial. Colorectal Dis. 2009;11:382–9.
65. Aghaee-Afshar M, Rezazadehkermani M, Asadi A, et al. Potential of human umbilical cord matrix and rabbit bone marrow-derived mesenchymal stem cells in repair of surgically incised rabbit external anal sphincter. Dis Colon Rectum. 2009;52:1753–61.
66. Lorenzi B, Pessina F, Lorenzoni P, et al. Treatment of experimental injury of anal sphincters with primary surgical repair and injection of bone marrow-derived mesenchymal stem cells. Dis Colon Rectum. 2008;51:411–20.
67. Ferreira Galvao FH, Seid VE, Santos RM Nunes dos, et al. Anorectal transplantation. Tech Coloproctol. 2009;13:55–9.

Rectal Prolapse

57

Sanjiv K. Patankar and Rodolfo Pigalarga

Introduction

Rectal prolapse or procidentia is defined as protrusion of a full-thickness portion of the rectal wall through the anal sphincter (Fig. 57.1). This condition was recognized as long ago as 1500 BC by Ebers Papyrus, as proved by a finding of rectal prolapse in a male mummy. It is likely that at that time, prolapse was common due to an association with malnutrition and intestinal parasites [1, 2]. Initial theories speculated that rectal prolapse was a result of inadequate support to the rectum from surrounding structures [3]. Mikulicz in 1888 described a perineal amputation of a rectal prolapse, a crude version of today's perineal proctosigmoidectomy [4]. Subsequent knowledge on rectal physiology has expanded the horizon of possible surgical procedures, utilizing the perineal approach and abdominal access to the pelvis.

Definition

The definition of rectal prolapse is a full- or partial-thickness protrusion of the rectal wall through the anal orifice. Despite the apparent simplicity, attempts at classification of rectal prolapse have not gained general acceptance.

Altemeier et al. proposed a classification based on purely *anatomic features* [5, 6], with the belief that rectal prolapse was a manifestation of either a sliding hernia or an intussusception in different patients. They proposed three types of prolapse: Type 1: a protrusion of the redundant mucosal layer (so-called "false prolapse," usually associated with hemorrhoids); Type 2: intussusception with an associated cul-de-sac sliding hernia; Type 3: sliding hernia of the cul-de-sac.

Beahrs et al. proposed a *clinical* classification, believing the basis to be intussusception [7, 8] and relied on the completeness of the prolapse:

Type 1: Incomplete (mucosal prolapse).

Type 2: Complete (full-thickness wall prolapse).

- First degree (high or "early," "concealed," "invisible")
- Second degree (externally visible during straining, sulcus evident between rectal wall and anal canal)
- Third degree (externally visible)

This classification provides clinical utility in planning evaluation and management and is the accepted classification today. Lack of a universally accepted classification reflects the difficulty in identifying a single explanation for rectal prolapse. To date, no single common theory can explain the diverse occurrence of rectal prolapse in newborn infants, paraplegic middle-aged men, and older women [3].

Etiology

Three theories explain the onset of rectal prolapse. The first, proposed in 1912 by Moschcowitz, was based on anatomical findings. Patients with rectal prolapse were noted to have a redundant sigmoid colon, pelvic laxity, and a deep cul-de-sac (pouch of Douglas); a redundant sigmoid colon in a deep pelvic pouch produces an acute recto-sigmoid junction and a need to strain during defecation, promoting herniation of the rectum through a weakened pelvic floor and a deep cul-de-sac [9].

The second theory (Broden and Snellman) views rectal prolapse as the endpoint of a pathologic spectrum, beginning as internal intussusception starting approximately 3 in. proximal to the anal verge and progressing to complete prolapse [10]. This theory was elaborated through review of multiple cineradiographic imaging studies. Unfortunately, multiple subsequent studies that followed patients with defecographic signs of intussusception failed to observe a direct progression

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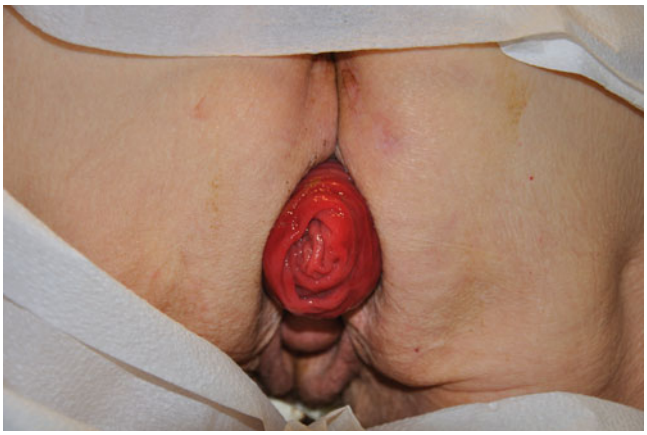

Fig. 57.1 Procidentia or complete rectal prolapse. The entire rectum has protruded through the anal canal. Please note the circular folds of the prolapsed rectum

to complete prolapse, suggesting that intussusception and rectal prolapse are two distinct entities, with a small overlapping subset rather than stages of the same process.

The third theory (Park) suggested that rectal prolapse was in part due to injury to the pudendal nerves from repeated stretching on the pelvic floor [11]. Even though this view is supported by the frequent association between neurogenic fecal incontinence and rectal prolapse, there is no doubt that many patients with rectal prolapse have normal innervations and that incontinence often improves after surgical correction of rectal prolapse, an event that should not occur if the nerves were permanently damaged.

Relevant Anatomy and Physiology

A review of relevant rectal anatomy and physiology is helpful in understanding the clinical picture of rectal prolapse.

The rectum is not a linear and longitudinal structure within the pelvis, but follows a serpentine course from the level of the lumbar–sacral junction to the pelvic floor. Three major muscular groups contribute to the stability and the function of the rectum: the levator ani, the puborectalis sling, and the external anal sphincter muscle [12, 13].

The levator ani contributes to the stability of the rectum and is intimately interconnected to the longitudinal fibers of the rectum to provide structural support that prevents the rectum from slipping through the pelvic floor during defecation. The puborectalis sling contributes to decreasing the opening of the pelvic floor during its contraction; it embraces the lower end of the rectum and connects it to the pubic bone. When under tension, it tilts the rectum forward toward the pubis, creating an acute angle and compressing the structure in front of the rectum; conversely, when the sling relaxes, it "flattens" the acute angle and makes the rectum more vertical. The external anal sphincter muscle is a functional part of the puborectalis sling and contributes to both continence as well as defection, depending on its state of contraction or relaxation [12].

Presentation

The onset of rectal prolapse is gradual, with manifestations reflecting the stage of progression. In early stage, symptoms relate to difficulty in bowel regulation with discomfort and tenesmus (sensation of incomplete evacuation); in later stages, there is a permanently extruded rectum, which becomes excoriated and ulcerated, followed by mucous discharge and bleeding, with soiling of the underclothes. Fecal incontinence and constipation are frequently present, as well as impaired anorectal sensation [13, 14].

The female-to-male prevalence ratio is 6:1. Parity is not a contributing factor. Peak incidence is between 50 and 60 years in women, increasing with age, while in men rectal prolapse is evenly distributed throughout the age ranges. Higher prevalence is noted in institutionalized patients [7, 13].

Associated Conditions

Associated disorders include bladder stones and other common urologic problems, including phimosis, urethral stricture and prostatic enlargement or obstruction [13, 14].

Gastrointestinal associations include constipation, diarrhea, pinworm infestation, and polyps. Multiple psychiatric and neurologic conditions associated with rectal prolapse include bulimia nervosa, anorexia, obsessive–compulsive disorders, and Parkinson's disease [15–17]. An association with progressive systemic sclerosis has been described [18].

Evaluation

History and Physical Examination

History and physical examination are most important in identifying the patient with rectal prolapse and, most importantly, decide the nature of surgery that is appropriate for that individual. The main complaint is usually the prolapse itself; in severe cases, the rectum prolapses with minimal increase of intra-abdominal pressure (e.g., with cough or lifting objects), impairing the quality of life.

Incontinence is frequently related to the prolapse, but may also be a secondary problem in an older adult. Patients may report mucus drainage from the anus, tenesmus, and constipation; bright red bleeding per rectum may be spotty in quantity as observed on wiping. If the prolapse becomes incarcerated (nonreducible) and manual reduction fails, a

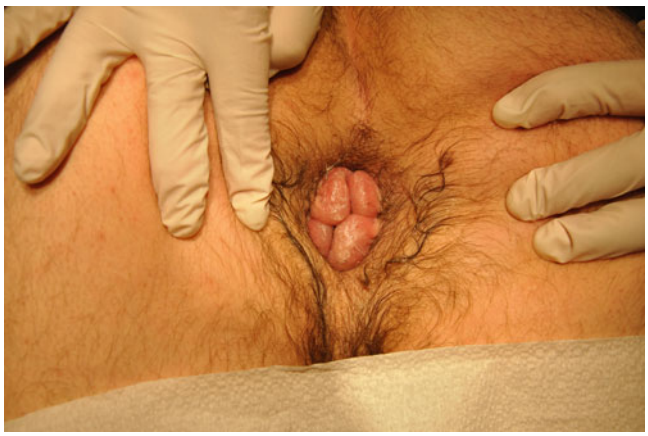

Fig. 57.2 Mucosal prolapse with edema in prolapsed strangulated internal hemorrhoids. Please note the mucosal folds are radial

surgical emergency is recommended. Risk of gangrene of the rectum, a life-threatening complication, might ensue [13, 19].

Physical examination is straightforward in demonstrating the prolapse; but in many, the patient must be examined in a squatting position or be asked to forcibly strain to reveal the prolapse. Mucosal vs. full-thickness rectal wall prolapse is easy to differentiate; the two clinical entities are corrected by entirely different surgical approaches.

The diagnostic feature of complete prolapse is the observation of *concentric* mucosal furrows on the prolapsed rectum. The sulcus between rectal wall and anal canal is easily identified. Additional features are length of prolapse >5 cm and appreciation of double wall thickness on digital rectal examination (Fig. 57.1). In females, cystocele and/or uterine prolapse are present in severe cases. Patulous anus is a constant finding, as well a feeling of a straight rectal canal and weak sphincters on digital examination. A vaginal examination in females helps detect the often associated cystocele or rectocele, as also a thinned and scarred recto-vaginal septum is often noted.

Mucosal prolapse, on the other hand, presents with *radial grooves* of prolapsing internal hemorrhoids, rarely protruding for more than 5 cm. A double mucosal layer is palpated. The sulcus is not visible and an associated prolapse of other pelvic organs is rarely appreciated (Fig. 57.2).

Imaging Studies

In the elderly, sigmoidoscopy is usually sufficient to rule out a rectal polyp or neoplasm functioning as the leading point for rectal prolapse. A more aggressive work-up is questionable in the very old, while in the young a full colonoscopy might be indicated if there is suspicion of underlying inflammatory bowel disease, malignancy, or polyps.

Moreover, in the young, specialized testing helps choose the most appropriate surgical plan when a primary functional abnormality is associated with the rectal prolapse. Videoproctography and anorectal physiologic studies can predict whether continence will be restored after abdominal rectopexy [20, 21]. Colonic transit studies, on the other end, can indicate the need for sigmoidectomy or subtotal colectomy in addition to the rectopexy in case of very prolonged colonic transit time. These are usually performed in specialized centers where a multidisciplinary approach encompasses dedicated radiologic and colorectal surgical expertise.

Nonoperative Treatment

Nonoperative treatment of rectal prolapse is relevant in the geriatric age group who manifest comorbidities that significantly increase the operative risks. Reduction of incarcerated rectal prolapse with use of table sugar or magnesium sulfate compresses have been reported [22]. If the prolapse becomes incarcerated (non-reducible) and manual reduction fails, then an emergent surgical procedure is recommended. The theme might be a reduction of tissue edema that allows manual reduction of prolapse, with temporary relief. Injection of sclerosing agents in rectal mucosa may be successful in children, but not in adults. Perioperative biofeedback and pelvic floor exercises have been used to improve the external sphincter function and decrease postoperative incontinence, but may only truly be an adjunct to surgical repair [23]. Essentially, there is no effective nonoperative treatment for rectal prolapse. Hence if the decision is not to offer surgical correction for an older patient with rectal prolapse, the patient may live a poor quality of life with no relief of symptoms.

Operative Treatment

Multiple surgical procedures describe different approaches to repair of rectal prolapse; the range of choices denotes a lack of single "best" surgical procedure, with each recommendation tailored to an individual's needs, functional status and age, and nature of prolapse requiring correction.

With mucosal prolapse, the initial approach is usually not invasive, as the problem relates to prolapsing rectal mucosa, the rectal wall remaining anatomically in place. Interventions range from a simple band ligation or injection sclerotherapy during multiple office visits to a more invasive PPH procedure (Procedure for Prolapsed Hemorrhoids), which requires a short hospitalization, with the advantage of requiring a single session. The decision-making algorithm is complex for complete rectal prolapse and involves an understanding of patient's expectations, functional status, life expectancy and underlying abnormalities, especially in the younger patients, as these are addressed along with the control of the

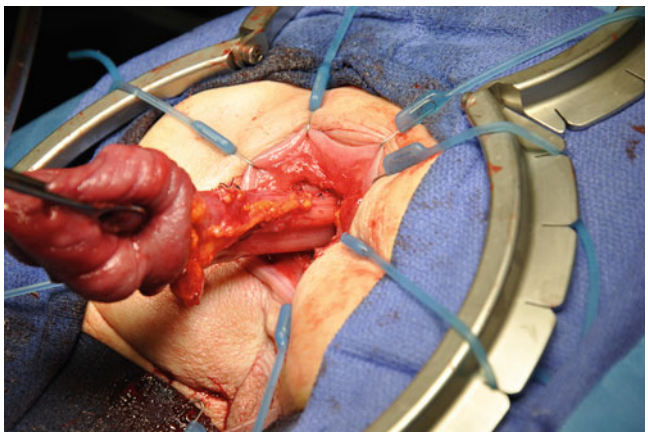

Fig. 57.3 Perineal proctosigmoidectomy (Altemeier operation). The rectal wall forming the outer tube of the prolapse has been incised by transanal approach. Mesorectal vessels have been divided. The sigmoid colon prolapsing as the inner tube of the prolapse is clearly visible

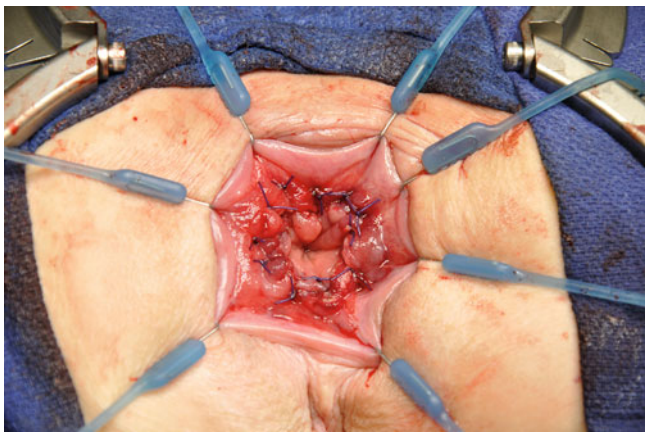

Fig. 57.4 The prolapsed redundant segment has been divided and the sigmoid colon is anastomosed to the anal canal

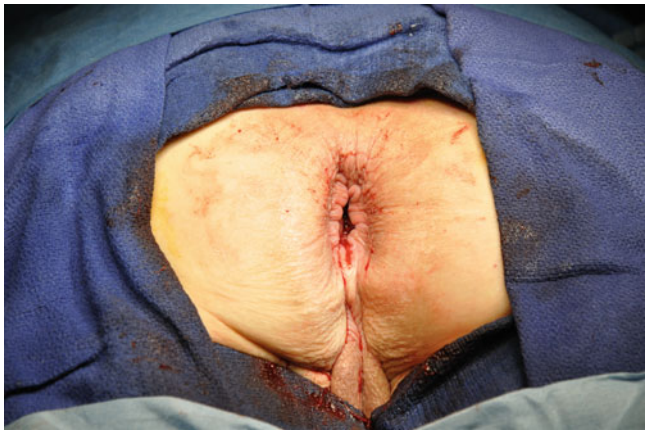

Fig. 57.5 The final result on the operating table. There is no visible incision as the entire surgery is accomplished through the anal canal above the dentate line

Table 57.1 Recurrence, morbidity, and mortality rates of perineal proctosigmoidectomy

Authors	Patient number	Recurrence (%)	Mortality (%)	Morbidity (%)
Kim et al. [40]	183	16	0	14
Williams et al. [26]	114	11	0	12
Friedman et al. [27]	27	50	0	12
Johansen et al. [41]	20	0	5	5

Table 57.2 Results of Delorme procedure

Authors	No. of patients	Recurrence (%)	Mortality (%)	Morbidity (%)
Watkins et al. [42]	52	10	0	4
Senapati et al. [43]	32	12.5	0	6
Tsunoda et al. [44]	31	13	0	13
Oliver et al. [45]	41	22	2.5	25

rectal prolapse. An initial distinction is made between perineal vs. trans-abdominal access to the rectum.

The perineal approach is usually preferred in the older adults with comorbidities and short life expectancy; this is better tolerated by the frail elderly. The procedure is performed under spinal or epidural anesthesia and sometimes under local anesthesia with sedation. The most popular perineal procedures are the Altemeir procedure and the Delorme procedure.

The Altemeier procedure (perineal proctosigmoidectomy or perineal pull-through procedure) consists of delivering the rectum and sigmoid colon outside the pelvis through the patulous anus and weak pelvic floor. The sigmoid colon is then divided and anastomosed to the anal canal either with a hand-sewn or stapled technique (Figs. 57.3, 57.4, and 57.5). The procedure is easily combined with pelvic floor repair (levator plication) through the same access, to improve postoperative fecal incontinence [24–26]. Altemeier himself had a recurrence rate of only 3% (3/106 patients), but higher recurrence rates are described by others [5], with as much as 50% in a small series [27], and 5.5 to 10% in large series [25, 26]. In series with over 100 patients, the mortality rate is 0% and the morbidity 12–24% (Table 57.1). With the low mortality and morbidity rates, the technique is recommended in the frail elderly who may not tolerate an abdominal approach.

The Delorme procedure is a mucosal reduction procedure performed as a perineal plication of the rectal prolapse, with an intent to provide symptomatic relief. This operation is recommended to the elderly with short life expectancy. The advantages are similar to the Altemeier procedure, but additionally, the procedure can be performed under local anesthesia and safely repeated for recurrence, which is common (Table 57.2). Common complications are secondary to bleeding and occasionally late stenosis. Pelvic floor repair (levatorplasty) can be combined with this procedure as well.

The trans-abdominal approach offers the surgeon opportunity to intervene for anatomical abnormalities believed to be causative in rectal prolapse. This approach allows full mobilization of a poorly supported rectum and fixation of the latter to prevent further intussusception through the perineum. At the same time, this approach allows the reduction and obliteration of any sliding hernia and repair of associated pelvic floor defects or other anatomical abnormalities (i.e., vaginal or uterine descent). Abdominal operations offer not only lower recurrence rates but also opportunity for greater likelihood of functional improvement [28]. The frail elderly may not tolerate this surgical approach. Careful analysis of risk vs. benefit ratio is vital in patient selection. Thus, abdominal repair of rectal prolapse is reserved for patients with good cardiorespiratory functional status and ability to tolerate prolonged, aggressive operations. The principal technique is rectopexy or fixation of the rectum to the presacral fascia, accomplished by either suture alone or use of artificial mesh. Suture and mesh rectopexy produce comparable results; the selection depends on the individual surgeon's experience and choice [28, 29]. Polyvinyl alcohol (Ivalon) sponge rectopexy is associated with risk of infectious complications and is largely been abandoned.

One must consider the patient's preexisting bowel function as well as colonic motility. Rectopexy alone and especially with division of the lateral ligaments can increase risk of postoperative constipation [29, 30]. Those with preexisting constipation do better with the addition of segmental bowel resection (sigmoid and recto-sigmoid colon). The advantage of lower rates of constipation is observed with resection rectopexy compared to rectopexy alone [28, 29].

Role of Laparoscopy and Minimally Invasive Surgery

Since the advent of laparoscopic resections of the colon, every type of open abdominal surgical repair of rectal prolapse has been accomplished by laparoscopic means [31].

Studies comparing laparoscopic and open surgical approach for rectal prolapse suggest the two approaches to be equally efficacious in correcting rectal prolapse, with recurrence rates, morbidity and mortality comparable [32]. An additional benefit of laparoscopy is reduced postoperative pain, earlier return of bowel function, better cosmesis, and reduced length of hospital stay [28, 31, 32].

Laparoscopic rectal prolapse repair is safe and effective. Although there is a paucity of large randomized controlled trials, a study of 12 randomized controlled trials with 380 patients concluded that laparoscopic approach was associated with fewer postoperative complications and shorter hospital stay than open surgical technique [29, 33].

Using robotic assistance for laparoscopic rectopexy has been reported as well; robotically assisted laparoscopic surgery is feasible and safe [34–37]. In a small case–control study, robotic rectopexy showed significantly higher recurrence rates (20%) when controlled for age and follow-up time compared to open rectopexy (2%) [36].

A systematic review compared the safety and efficacy of the robotic (Da Vinci Surgical System™) and conventional laparoscopic surgical approaches. In colorectal surgery, longer surgical times were confirmed, and no benefit of any nature was shown [38].

Clearly, further studies to compare perioperative outcomes of robotic-assisted and conventional laparoscopic techniques are needed to determine the utility and efficacy of robotic surgery in the field of colorectal surgery [39].

A learning curve clearly exists for complex laparoscopic procedures. At this time the selection of laparoscopic vs. open approach is predicated upon the individual surgeon's training and experience.

Key Points

- Rectal prolapse is a full-thickness protrusion of the rectum through the anal sphincter, believed to be related to a concentric intussusception of the rectum secondary to weakness of the surrounding structures and exacerbated by constipation.
- Although uncommon in the general population, it is more frequent in older women with long-standing history of constipation and decreased mobility.
- This condition is disruptive to social and quality of life, especially in the later stages, when the rectum prolapses and becomes excoriated and ulcerated. Constipation, incontinence, and anorectal discomfort are common symptoms.
- Other than surgery, no effective treatment option exists, with no single optimal surgical procedure; the choice is influenced by age, comorbidities, extent of prolapse, and preexisting constipation.
- Significant improvement in the quality of life of even a frail elderly patient can be achieved with low mortality and morbidity by perineal operative procedures.
- Abdominal rectopexy and resection rectopexy are chosen for relatively healthy patients and give excellent long-term relief with good functional outcome.
- Laparoscopic repair techniques are effective and offer significant benefits over open abdominal surgical approach.

References

1. Wu JS. Rectal prolapse: a historical perspective. Curr Probl Surg. 2009;46:602–716.
2. Moodie R. Paleopathology. An introduction to the study of ancient evidences of disease. Urbana: University of Illinois Press; 1923. p. 400–1.

3. Karulf RE, Madoff RD, Goldberg SM. Rectal prolapse. Curr Probl Surg. 2001;38:771–832.
4. Mikulicz J. Untitled. Arch Klin Chir. 1888;38:74.
5. Altemeier WA, Culbertson WR, Schowengerdt C, et al. Nineteen years' experience with the one-stage perineal repair of rectal prolapse. Ann Surg. 1971;73:993–1006.
6. Altemeier WA, Culbertson WR, Alexander JW. One-stage perineal repair of rectal prolapse. Twelve years' experience. Arch Surg. 1964;89:6–16.
7. Theuerkauf FJ, Beahrs OH, Hill JR. Rectal prolapse. Causation and surgical treatment. Ann Surg. 1970;171:819–35.
8. Beahrs OH, Vandertoll DJ, Baker NH. Complete rectal prolapse: an evaluation of surgical treatment. Ann Surg. 1965;161:221–4.
9. Moschcowitz A. The pathogenesis, anatomy and cure of prolapse of the rectum. Surg Gynecol Obstet. 1912;15:7–21.
10. Broden B, Snellman B. Procidentia of the rectum studied with cineradiography. A contribution to the discussion of causative mechanism. Dis Colon Rectum. 1968;11:330–47.
11. Parks AG, Swash M, Urich H. Sphincter denervation in anorectal incontinence and rectal prolapse. Gut. 1977;18:656–65.
12. Corman M. Rectal prolapse, solitary rectal ulcer, syndrome of descending perineum, and rectocele. In: Corman ML, editor. Colon and rectal surgery. 4th ed. Philadelphia: Lippincott, Williams & Wilkins; 2005. p. 401–48.
13. Gordon PH. Rectal procidentia. In: Gordon PH, Nivatvongs S, editors. Principles and practice of surgery for the colon, rectum and anus. 2nd ed. St Louis: Quality Medical Publishing; 1999. p. 503–40.
14. Farouk R, Duthie GS. The evaluation and treatment of patients with rectal prolapse. Ann Chir Gynaecol. 1997;86:279–84.
15. Henry JB, Drummond LM, Kolb P. Obsessive-compulsive disorder and rectal prolapse. Eur J Gastroenterol Hepatol. 2006;18:797–8.
16. Malik M, Stratton J, Sweeney WB. Rectal prolapse associated with bulimia nervosa: report of seven cases. Dis Colon Rectum. 1997;40:1382–5.
17. Dreznik Z, Vishne TH, Kristt D, et al. Rectal prolapse: a possibly underrecognized complication of anorexia nervosa amenable to surgical correction. Int J Psychiatry Med. 2001;31:347–52.
18. Leighton JA, Valdovinos MA, Pemberton JH, et al. Anorectal dysfunction and rectal prolapse in progressive systemic sclerosis. Dis Colon Rectum. 1993;36:182–5.
19. Hovey MA, Metcalf AM. Incarcerated rectal prolapse—rupture and ileal evisceration after failed reduction: report of a case. Dis Colon Rectum. 1997;40:1254–7.
20. Birnbaum EH, Stamm L, Rafferty JF, et al. Pudendal nerve terminal motor latency influences surgical outcome in treatment of rectal prolapse. Dis Colon Rectum. 1996;39:1215–21.
21. Neill ME, Parks AG, Swash M. Physiological studies of the anal sphincter musculature in faecal incontinence and rectal prolapse. Br J Surg. 1981;68:531–6.
22. Myers JO, Rothenberger DA. Sugar in the reduction of incarcerated prolapsed bowel. Report of two cases. Dis Colon Rectum. 1991;34:416–8.
23. Hamalainen KJ, Raivio P, Antila S, et al. Biofeedback therapy in rectal prolapse patients. Dis Colon Rectum. 1996;39:262–5.
24. Agachan F, Pfeifer J, Joo JS, et al. Results of perineal procedures for the treatment of rectal prolapse. Am Surg. 1997;63:9–12.
25. Ramanujam PS, Venkatesh KS, Fietz MJ. Perineal excision of rectal procidentia in elderly high-risk patients. A ten-year experience. Dis Colon Rectum. 1994;37:1027–30.
26. Williams JG, Rothenberger DA, Madoff RD, et al. Treatment of rectal prolapse in the elderly by perineal rectosigmoidectomy. Dis Colon Rectum. 1992;35:830–4.
27. Friedman R, Muggia-Sulam M, Freund HR. Experience with the one-stage perineal repair of rectal prolapse. Dis Colon Rectum. 1983;26:789–91.
28. Madiba TE, Baig MK, Wexner SD. Surgical management of rectal prolapse. Arch Surg. 2005;140:63–73.
29. Tou S, Brown SR, Malik AI, et al. Surgery for complete rectal prolapse in adults. Cochrane Database Syst Rev. 2008:CD001758.
30. Speakman CT, Madden MV, Nicholls RJ, et al. Lateral ligament division during rectopexy causes constipation but prevents recurrence: results of a prospective randomized study. Br J Surg. 1991;78:1431–3.
31. Senagore AJ. Management of rectal prolapse: the role of laparoscopic approaches. Semin Laparosc Surg. 2003;10:197–202.
32. Lechaux D, Trebuchet G, Siproudhis L, et al. Laparoscopic rectopexy for full-thickness rectal prolapse: a single-institution retrospective study evaluating surgical outcome. Surg Endosc. 2005;19:514–8.
33. Sajid MS, Siddiqui MR, Baig MK. Open vs laparoscopic repair of full-thickness rectal prolapse: a re-meta-analysis. Colorectal Dis. 2010;12:515–25.
34. Delaney CP, Lynch AC, Senagore AJ, et al. Comparison of robotically performed and traditional laparoscopic colorectal surgery. Dis Colon Rectum. 2003;46:1633–9.
35. Munz Y, Moorthy K, Kudchadkar R, et al. Robotic assisted rectopexy. Am J Surg. 2004;187:88–92.
36. de Hoog DE, Heemskerk J, Nieman FH, et al. Recurrence and functional results after open versus conventional laparoscopic versus robot-assisted laparoscopic rectopexy for rectal prolapse: a case-control study. Int J Colorectal Dis. 2009;24:1201–6.
37. Ayav A, Bresler L, Hubert J, et al. Robotic-assisted pelvic organ prolapse surgery. Surg Endosc. 2005;19:1200–3.
38. Maeso S, Reza M, Majol JA, et al. Efficacy of the da vinci surgical system in abdominal surgery compared with that of laparoscopy: a systematic review and meta-analysis. Ann Surg. 2010;252:254–62.
39. Zimmern A, Prasad L, Desouza A, et al. Robotic colon and rectal surgery: a series of 131 cases. World J Surg. 2010;34:1954–8.
40. Kim DS, Tsang CB, Wong WD, et al. Complete rectal prolapse: evolution of management and results. Dis Colon Rectum. 1999;42:460–6;discussion 466–9.
41. Johansen OB, Wexner SD, Daniel N, et al. Perineal rectosigmoidectomy in the elderly. Dis Colon Rectum. 1993;36:767–72.
42. Watkins BP, Landercasper J, Belzer GE, et al. Long-term follow-up of the modified Delorme procedure for rectal prolapse. Arch Surg. 2003;138:498–502; discussion 502–3.
43. Senapati A, Nicholls RJ, Thomson JP, et al. Results of Delorme's procedure for rectal prolapse. Dis Colon Rectum. 1994;37:456–60.
44. Tsunoda A, Yasuda N, Yokoyama N, et al. Delorme's procedure for rectal prolapse: clinical and physiological analysis. Dis Colon Rectum. 2003;46:1260–5.
45. Oliver GC, Vachon D, Eisenstat TE, et al. Delorme's procedure for complete rectal prolapse in severely debilitated patients. An analysis of 41 cases. Dis Colon Rectum. 1994;37:461–7.

Part XI

Neoplasms

Colorectal Cancer Screening in the Older Adult: A Case-Based Approach

58

Brijen J. Shah and Sita Chokhavatia

Introduction

Among the many targets for screening, colorectal cancer (CRC) screening has received claims for being a successful measure. Randomized controlled studies suggest that CRC screening with earlier recognition of polyps and cancer has reduced mortality. However, the observations are not specific to the older adult, with patient selection and age for cessation of screening being controversial. The standard guidelines [1–11] are presented in Table 58.1 [9]. This chapter discusses CRC screening using a case-based approach.

Case

A.G. is a 79-year-old man with diabetes type II, hypertension, history of deep vein thrombosis, alcohol use, and right hip osteoarthritis status post hip replacement, who comes to you to discuss colon cancer screening. He has never been screened with any modality. Would you recommend colon cancer screening?

Current Recommendations Specifically for Older Adults

As life expectancy has increased, gastroenterologists and primary care physicians will struggle with the application of standard guidelines in the geriatric age group, as these guidelines are generally based on a younger population.

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Major societies agree that CRC screening should be offered to adults between 50 and 74 years at average risk. The US Preventive Services Task Force (USPSTF) currently advises that continued screening for adults, 75–84 years old who have previously been screened, should be individualized as benefit for screening beyond age 74 is small. In those who have never been screened, recommendations should be made with respect to individual health status, comorbidities, and other competing risks [1]. Screening for those over 85 years is currently not recommended by the USPSTF.

Although guidelines are helpful, their application in the geriatric population should be individualized. For example, the USPSTF guidelines are disease-specific recommendations and do not take into account the multiple comorbidities of an older patient. The recommendations are generally based on trials that exclude older patients [2].

Table 58.2 highlights professional society statements on when to stop screening average risk adults. Generally, the recommendation is to begin screening at age 50, but controversy exists in the approach to those 75 and older. Most groups have not made a recommendation for those over 75. The USPSTF and Kaiser Permanent Care Management Institute (KPCMI) agree with cessation of screening in previously screened adults at age 75 years. However, KPCMI allows for screening of those not previously screened up to age 80, based on physician judgment, patient preferences, comorbidities, and procedure risk. The American Cancer Society/US Multi-society Task Force and American College of Radiology (ACS/USMSTF/ACR) use comorbidity and life expectancy to guide decisions, with no specific age cutoffs. If a patient is unlikely to benefit from screening for these reasons, there is no indication for any screening procedure, including CT colonography [9].

As more data pertinent to the geriatric population become available, guidelines and recommendations may change. Clinicians should anticipate updates in guidelines as the population ages, along with advances in technology (e.g., wireless capsule colonoscopy).

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Table 58.1 Guidelines for screening and surveillance for the early detection of colorectal adenomas and cancer in individuals at increased risk or at high risk (table reproduced with permission from ref. [9])

Risk category	Age to begin	Recommendation	Comment
Increased risk—patients with history of polyps at prior colonoscopy			
Patients with small rectal hyperplastic polyps	–	Colonoscopy or other screening options at intervals recommended for average—risk individuals	An exception is patients with a hyperplastic polyposis syndrome. They are at increased risk for adenomas and colorectal cancer (CRC) and need to be identified for more intensive follow-up
Patients with one or two small tubular adenomas with low-grade dysplasia	5–10 years after the initial polypectomy	Colonoscopy	The precise timing within this interval should be based on other clinical factors (such as prior colonoscopy findings, family history, and the preferences of the patient and judgment of the physician)
Patients with three to ten adenomas or one adenoma >1 cm or any adenoma with villous features or high-grade dysplasia	3 years after the initial polypectomy	Colonoscopy	Adenomas must have been completely removed. If the follow-up colonoscopy is normal or shows only one or two small, tubular adenomas with low-grade dysplasia, then the interval for the subsequent examination should be 5 years
Patients with >10 adenomas on a single examination	<3 years after the initial polypectomy	Colonoscopy	Consider the possibility of an underlying familial syndrome
Patients with sessile adenomas that are removed piecemeal	2–6 months to verify complete removal	Colonoscopy	Once complete removal has been established, subsequent surveillance needs to be individualized based on the endoscopist's judgment. Completeness of removal should be based on both endoscopic and pathologic assessments
Increased risk—patients with CRC			
Patients with colon and rectal cancer should undergo high-quality perioperative cleaning	3–6 months after cancer resection, if no unresectable metastases are found during surgery; alternatively, colonoscopy can be performed intra-operatively	Colonoscopy	In the case of nonobstructing tumors, this can be done by preoperative colonoscopy. In the case of obstructing colon cancers, CTC with intravenous contrast or DCBE can be used to detect neoplasms in the proximal colon
Patients that undergo curative resection for colon or rectal cancer	1 year after resection (or 1 year following the performance of the colonoscopy that was performed to clear the colon of synchronous disease)	Colonoscopy	The colonoscopy at 1 year is in addition to the perioperative colonoscopy for synchronous tumors. If the examination performed at 1 year is normal, then the interval before the next subsequent examination should be 3 years. If that colonoscopy is normal, then the interval before the next subsequent examination should be 5 years. Following the examination at 1 year, the intervals before subsequent examinations may be shortened if there is evidence of HNPCC or if adenoma findings warrant earlier colonoscopy. Periodic examination of the rectum for the purpose of identifying local recurrence, usually performed at 3- to 6- month intervals for the first 2 or 3 years, may be considered after low—anterior resection of rectal cancer
Increased risk—patients with a family history			
Either CRC or adenomatous polyps in a first-degree relative before age 60 years or in two or more first-degree relatives at any age	Age 40 or 10 years before the youngest case in the immediate family	Colonoscopy	Every 5 years
Either CRC or adenomatous polyps in a first-degree relative ≥ age 60 years or in two second-degree relatives with CRC	40 years	Screening options at intervals recommended for average—risk individuals	Screening should begin at an earlier age, but individuals may choose to be screened with any recommended form of testing

(continued)

Table 58.1 (continued)

Risk category	Age to begin	Recommendation	Comment
High risk			
Genetic diagnosis of FAP or suspected FAP without genetic testing evidence	Aged 10–12 years	Annual FSIG to determine if the individual is expressing the genetic abnormality and counseling to consider genetic testing	If the genetic test is positive, colectomy should be considered
Genetic or clinical diagnosis of HNPCC or individuals at increased risk of HNPCC	Aged 20–25 or 10 years before the youngest case in the immediate family	Colonoscopy every 1–2 years and counseling to consider genetic testing	Genetic testing for HNPCC should be offered to first-degree relatives of persons with a known inherited MMR gene mutation. It should also be offered when the family mutation is not already known, but one of the first three of the modified Bethesda criteria is present
Inflammatory bowel disease, chronic ulcerative colitis and Crohn's colitis	Cancer risk begins to be significant 8 years after the onset of pancolitis or 12–15 years after the onset of left-sided colitis	Colonoscopy with biopsies for dysplasia	Every 1–2 years, these patients are best referred to a center with experience in the surveillance and management of inflammatory bowel disease

Table 58.2 Guidelines and comments on cessation of CRC screening

Society	Recommendation
US Preventive Services Task Force (USPSTF) [1]	Continued screening in adults 75–84 years of age should be individualized Not recommended in adults over 85 years
Kaiser Permanent Care Management Institute (KPCMI) [3]	Discontinuation of screening is generally recommended at age 75, provided that there is a history of routine screening Discontinuation is recommended at age 80 for those with no history of routine screening The decision to discontinue screening should be based on physician judgment, patient preference, the increased risk of complications in older adults, and existing comorbidities (consensus-based)
World Gastro Organization (WGO) [4]	No comment on age to stop screening
American Society for Gastrointestinal Endoscopy (ASGE) [5]	No comment on when to stop screening
American College of Colon and Rectal Surgeons [6]	No comment on when to stop screening
US Multi-Society Task Force and the American Cancer Society (USMSTF/ACS) [7]	In those with a prior polyp: discontinuation of surveillance colonoscopy should be considered in persons with serious comorbidities and with less than 10 years of life expectancy
British Society of Gastroenterology [8]	FOBT every 2 years offered to all persons 50–69 years of age (depending on location) with current plans to extend to age 75 in most areas
American Cancer Society/US Multi-Society Task Force and American College of Radiology (ACS/USMSTF/ACR) [9]	No specific age cutoff, comorbidity and life expectancy to guide decisions
American College of Gastroenterology (ACG) [10]	No comment on when to stop screening
American Gastroenterological Association (AGA) [11]	No comment on when to stop screening Comment on need for shared decision-making and individualized approach

Prevalence of CRC

Overall, there is a 5% per year incidence of colon cancer in the over 75 year group (40–50 cases/100,000 persons). The median age for diagnosis is age 70 (24.1% are 65–74 years old, 26.2% are 75–84 years old, and 12.2% over 85 years) [12]. Right-sided lesions, which are often asymptomatic, accounted for 35% of all colon cancers in the over 75 year age group [13, 14]. In a registry of over 65,000 patients, a greater proportion of right-sided cancers were detected with increasing age [14]. The increasing prevalence of right-sided lesions and the increasing prevalence of colon cancer in the geriatric population argue for further screening where appropriate, especially if prior screening in the individual did not include evaluation of the right colon.

Approach to CRC Screening in the Elderly

Most clinicians use an instinctive approach for decision-making; a shared approach to decision-making is just as important in geriatrics as in other populations. A clinician should consult with family/caregiver to corroborate history, examination, logistics, and ultimately decision-making for screening.

Two elements in evaluation can guide the clinician: functional assessment and cognitive status. A functional assessment should be part of every screening decision and includes activities of daily living (ability to feed, bathe, transfer, groom, and perform self-hygiene) and instrumental activities of daily living (managing finances, appropriate intake of medications, use a telephone, shopping, housework), and ambulation. Ambulation and ability to follow instructions with regards to adherence to the medication regimen are key components of colonoscopy preparation. Dementia is common in older age; cognitive assessment is helpful not only to determine appropriateness of screening but also to know if the patient is capable of providing informed consent.

Geriatric patients are more likely to be subject to polypharmacy with medications for diabetes, hypertension, and anticoagulation, with several comorbid processes requiring to be managed before and after the procedure. Hypoglycemic agents may need to be held prior to the procedure to avoid risk of hypoglycemia. Antihypertensives are generally continued on the day of the examination to avoid elevation of the blood pressure before or during the procedure; one must prevent dehydration in those on diuretics. Management of anticoagulation is a key part of preprocedure counseling in the elderly (and detailed in Chap. 23). Most procedures can safely be done on aspirin with the use of warfarin and clopidogrel use best individualized to patient and procedure [15].

Case

A.G. would like to undergo colonoscopy for cancer screening if it is appropriate. He lives alone, walks with a cane, and is independent in his activities of daily living. He has come with his son for today's appointment.

A conceptual framework to approach screening decisions weighs four factors: risk of death from CRC, benefits of screening, harms of screening, and patient's personal preferences and desires [16].

In geriatric medicine, prognosticating is a concept that incorporates calculating the *life expectancy* of the individual and the *age-specific mortality*. Life expectancy is the population-based, expected mortality of a person. To account for the heterogeneity in the health status of the geriatric population, life expectancy can be divided into "health percentiles" with the healthiest (fewest comorbidities) in the top 25th percentile (upper quartile) and the sickest in the bottom 25th percentile (lower quartile).

Age-specific morality, originating from SEER (Surveillance Epidemiology and End Results) data, refers to the risk of dying of colon cancer in that particular age group. By multiplying the age-specific mortality and the life expectancy, the *risk of dying from colon cancer* can be calculated (Table 58.3). This number is useful in weighing the benefits and burdens of screening and quantifies the clinical impression of life expectancy.

Case

A.G. is in the middle quartile given his comorbidities. His life expectancy is 9.3 years (Table 58.3). His risk of dying from colon cancer is 1.9%.

Colon cancer is a slow-growing cancer and progression from dysplasia to metaplasia takes several years. The slow biology of this tumor allows provision for a morbidity and mortality benefit through a number of screening tests. Additionally, colon cancer does not always present with obstructive symptoms, weight loss, or bleeding. Thus, without CRC screening, silent cancers or advanced precancerous lesions would go undetected.

Although several tests are available for CRC screening, this chapter will focus on three widely used tests: fecal occult blood test (FOBT), flexible sigmoidoscopy, and colonoscopy. Double-contrast barium enema (DCBE) may be indicated in certain patients; however, local expertise limits a high-quality examination. Currently, this procedure is less commonly used and may be difficult in the elderly. Although FOBT is noninvasive, the other two examinations have the feasibility for biopsy and polypectomy. Flexible sigmoidoscopy allows only for examination of the lower third of the colon.

FOBT may be guaiac testing (g-FOBT) or immunochemical FOBT (i-FOBT). A number of commercially available i-FOBTs are available in the market. Some have been compared to g-FOBT while others have only been tested on the ability to detect blood in the sample. When selecting a test for use, clinicians should see how the test characteristics were developed based on the manufacturer's information [9]. A study revealed that NSAIDs, aspirin and anticoagulants increased the sensitivity of i-FOBT but not the specificity, an important finding as many older patients are on anticoagulants [17].

Stool-based testing is safe and effective in older patients. Stool tests are noninvasive but may be less acceptable to patients as seen by the nonadherence to screening FOBT [9]. In a meta-analysis, FOBT had a sensitivity of 36% and specificity of 96%, after adjusting for verification bias [18]. In general, the quality of the development, reading of the test, and dehydration of the sample limit g-FOBT test results or characteristics.

Table 58.3 Risk of dying from colon cancer

Age group (years and quartiles)	Life expectancy per quartile (years)	Risk of CRC death (%) per quartile	Number needed to screen (NNS)		
			FOBT	Flex sigmoidoscopy	Colonoscopy
Men					
75–79					
Upper	14.2	3.5	207	93	50
Middle	9.3	1.9	525	236	126
Lower	4.9	0.9	–	–	–
80–84					
Upper	10.8	3.2	277	125	66
Middle	6.7	1.8	945	425	227
Lower	3.3	0.8	–	–	–
85–90					
Upper	7.9	2.7	554	249	133
Middle	4.7	1.6	–	–	–
Lower	2.2	0.8	–	–	–
90 or older					
Upper	5.8	2.0	2,008	903	482
Middle	3.2	1.1	–	–	–
Lower	1.5	0.5	–	–	–
Women					
75–79					
Upper	17	3.3	204	92	49
Middle	11.9	2.0	408	182	98
Lower	6.8	0.9	1,797	808	431
80–84					
Upper	13	3.0	262	118	63
Middle	8.6	1.8	581	262	140
Lower	4.6	0.8	–	–	–
85–90					
Upper	9.6	2.5	455	205	109
Middle	5.9	1.6	2,326	1,047	558
Lower	2.9	0.8	–	–	–
90 or older					
Upper	6.8	1.8	1,163	523	279
Middle	3.9	1.0	–	–	–
Lower	1.5	0.4	–	–	–

Adapted from Walter and Covinsky [16] and Ko and Sonnenber [26]

i-FOBT is more sensitive than guaiac-based FOBT and if negative, should be tested annually. A positive test requires a colonoscopic evaluation [9]. A comparison of six qualitative iFOBTs revealed performance differences and better sensitivity in aspirin users [19–21]. Rozen et al. examined i-FOBT in individuals over 75 who also underwent colonoscopy, and calculated sensitivity and specificity for a variety of fecal occult blood concentration. They found that at a stool hemoglobin concentration threshold level of 50 ng/mL for positivity, the test resulted in a sensitivity of 85.7% and a specificity of 79.5% [22]. A positive i-FOBT or g-FOBT should prompt colonoscopic examination.

Fecal DNA tests primarily detect cancer, require a follow-up colonoscopy and are more expensive than i-FOBT. A multitarget DNA panel detected 16 of 31 cancers and improved assays which included new markers improved its sensitivity [19, 23]. Stool DNA is included in ACS/USMSTF/ACR guidelines as an option for CRC screening but no recommendations are made regarding the interval for a repeat test if the initial test is negative [9].

Blood assays are being evaluated as a noninvasive test that would have wider patient acceptance [19, 24, 25] but are not yet available in clinical practice.

Colonoscopy and flexible sigmoidoscopy are more invasive, but provide the benefit of diagnosis and cure. Health economic analysis of CRC screening focuses on cost analysis; a more meaningful approach is the number needed to screen (NNS). A quantitative analysis in older patients, using NNS for men and women with varying levels of health, can help providers and patients make appropriate decisions [26]. In general, the

NNS and benefit is better in the younger and healthiest patients, while this falls with advancing age. Table 58.3 provides estimates for men and women with varying life expectancy.

Case
For A.G., the NNS in order to prevent one colon cancer death is 227 as presented in Table 58.3.

The potential harm from screening is an important consideration. For FOBT, there is little health risk to the patient; however there is a risk of a false positive test result, which could lead to unnecessary evaluation and procedures. FOBT also has a false negative rate of 4% and a false positive rate of 64% [18]. An abnormal test result may cause psychological stress to the patient and family. In addition to harms, there is an added cost incurred by society for unnecessary or unwarranted testing and screening. There is a false negative rate with any procedure, and this concept should be explained to patients and families and must be weighted with the risk of the screening procedure. On the contrary, there is little to no health risk associated with FOBT.

Periprocedural Complications

In a meta-analysis of 265,171 Medicare beneficiaries who underwent colonoscopy, the authors found the incident rates for total adverse events (AE) was 51.4/1,000 cases for those 80 and over, almost sevenfold higher than those age 65 and over; the findings suggest a higher incidence of colonoscopy AEs as the patient ages. AEs, from most frequent to least frequent, were cardiopulmonary complications, postpolypectomy bleeding, and perforation. There was only a slight increase in mortality for those over 80 years of age [27].

The most important piece of this framework is the patient preference. The physician should initiate an unhurried and thorough conversation to elicit the patient's and family's attitudes and beliefs about health screening. This conversation takes time, a barrier in a busy practice. A conversation about colon cancer screening in those over 75 years should convey that there is no universal guideline for CRC screening in the older adult and that a variety of factors have to be considered towards making an informed decision.

Additional Issues Pertinent to Colonoscopy in the Elderly

For CRC screening examination to be complete, it must be thorough, with complete visualization of the colon and performed in reasonable time. Optimal colonoscopy performance relies on a well-cleansed bowel. Decreased social support, limited mobility, comorbidity (e.g., cognitive impairment), and polypharmacy influence colonic motility and contribute to suboptimal bowel preparation. Age, male gender, and diabetes have been cited in the literature as additional factors for poor bowel preparation [28, 29]. Clinicians should anticipate these factors and consider 2-day preps, split-dose prep, bedside commode, collaborating with home health services and bilingual prep information, where appropriate.

Older patients are at increased risk for incomplete examination [30, 31]. A regression analysis showed functional status (OR 4.2) and cognitive status (OR 5.2) to be predictors of an incomplete examination compared to age alone (OR 0.9) [32].

Case
A.G. underwent a screening colonoscopy and was found to have a small 2 mm cecal polyp and a larger 2 cm tubulovillous adenoma which was removed endoscopically and found to have a focus of carcinoma. Since clear margins were not seen, the patient was referred to surgery and underwent a segmental sigmoid resection with primary anastamosis. He will need a surveillance examination in 1 year.

Emerging Techniques for Colorectal Cancer Screening

Efforts are ongoing for development of safe and effective methods for CRC screening which patients would readily accept and not incur substantial costs to society. Colonoscopy remains the gold standard despite reports of missed lesions, barriers to patient adherence, and direct and indirect costs of the procedure. Newer screening technologies include enhanced endoscopic interventions, less invasive radiographic tests, and noninvasive stool and blood tests [19, 33]. Recommendations for incorporation into practice await further studies for most of these modalities.

Endoscopic advances include improved methods for bowel cleansing for colonoscopy and more tolerable and safer preparations that are dosed for optimal efficacy [9, 34–36]. Polyethylene glycol solution may be safer in the older patient, with fewer electrolyte disturbances compared to sodium phosphate or magnesium containing preparations in this age group [35].

New endoscopic techniques are high magnification chromoscopic colonoscopy, confocal spectroscopy, and optical coherence tomography [33]. The potential increased sensitivity and specificity for detecting neoplastic mucosal changes is yet to be validated in clinical studies.

On the other hand, noninvasive endoscopy via the colon capsule endoscopy is an emerging new modality, already tested in the over 80 year age group and ready for incorporation into a colon cancer screening algorithm [9, 23, 37, 38]. The PillCam Colon is well tolerated and detection of clinically significant colon polyps could select out those patients requiring colonoscopy [39]. A second-generation colon capsule has been found to be safe, with sensitivities of 84% and 88% for the detection of polyps >6 and >10 mm, respectively, in patients aged 60–69 years [23].

Computed tomographic colonography (CTC) and magnetic resonance colonography (MRC) are the two minimally invasive radiographic techniques studied in screening for CRC [19, 33, 40–43]. CTC is also known as virtual colonoscopy (VC), requires bowel preparation, although stool tagging techniques have enhanced polyp detection, and air insufflation may cause patient discomfort. A major benefit of CTC is that it is noninvasive and time-efficient, with 10 min of procedure time but none for sedation or recovery. The limitations include the need for bowel preparation for CTC and same day or subsequent referral for colonoscopy if polypectomy is required and if not performed the same day, entails yet another bowel cleansing. Reimbursement for CTC is limited and may be only for the clinical indication of an incomplete colonoscopy. As with colonoscopy, CTC is operator-dependent, with minimal risk for radiation exposure. Finally, in the elderly, there may be increased detection of extracolonic lesions of questionable clinical significance.

The American College of Radiology Imaging Network (ACRIN) trial reported a sensitivity of 90% and specificity of 86% for polyps >10 mm and low detection rates for smaller polyps with CTC [41]. If the initial examination is negative, CTC is recommended every 5 years in the joint guidelines published by the ACS/USMSTF/ACR [9]. A recent observational study found CTC to be a safe and effective screening tool for older patients [42]. MRC can be performed without bowel preparation and air insufflations but is more expensive and contraindicated in patients with pacemakers, metal implants, and claustrophobia. Further studies will determine if it will be a cost-effective screening option.

In summary, today we have several options for CRC screening in the geriatric patient; each option has unique advantages and disadvantages that are listed in Table 58.4 [9]. On the other hand, the options provide opportunity to tailor screening to every geriatric subject.

Table 58.4 Test options for CRC screening

Test	Retest interval	Advantage	Disadvantage
Cancer prevention			
Colonoscopy	10 years	Entire colon is visualized Polypectomy and biopsy feasible	Expensive-direct/indirect costs Poor patient compliance Bowel preparation required Perforation, bleeding, sedation risks Missed lesions
Flexible sigmoidoscopy	5 years	Low cost No sedation Shown to reduce disease/death from left-sided cancers Biopsy/polypectomy is feasible	Bowel preparation required Proximal lesions are missed No sedation—not ideal for polypectomy, uncomfortable Colonoscopy if lesions detected
Double contrast barium enema (DCBE)	5 years	Moderate cost No sedation Detects polyps >1 cm Low complications	Bowel preparation required, uncomfortable Low sensitivity Biopsy not feasible Colonoscopy is indicated if a lesion is detected No study has shown reduction in mortality
Computed tomographic colonography (CTC)/virtual colonoscopy	5 years	Noninvasive, no sedation, time-efficient Good sensitivity for polyps >1 cm Low risk of perforation Can be followed by traditional colonoscopy if positive Detection of extra colonic findings	Expensive Poor results for small polyps Requires bowel preparation Discomfort due to air insufflation Colonoscopy indicated if lesion detected Detection of incidental extra colonic findings, often of no clinical significance
PillCam colonoscopy	NA	Appears to be better accepted Good sensitivity/specificity in early studies	Requires bowel preparation No therapeutic option

(continued)

Table 58.4 (continued)

Test	Retest interval	Advantage	Disadvantage
Cancer detection			
Fecal occult blood test guaiac-based	1 year	Inexpensive	Low sensitivity/specificity
Immunochemical (FIT)	1 year	Good compliance Noted to reduce mortality from CRC Detects lesions in the entire colon FIT is preferred test for CRC detection	Positive test if bleeding from upper GI tract Require two to three stool samples—single sample inadequate Colonoscopy indicated for positive test
Stool DNA	3 years	Noninvasive High sensitivity for CRC	Expensive, colonoscopy for positive test Shipping issues: adequate sample, required preservative and package

Adapted from Levin et al. [9]

Key Points

- The incidence of colon cancer increases with age. Frequency of right-sided lesions increases as age advances.
- Current guidelines support individualization of screening recommendations for those adults over 75 years of age who have not been previously screened.
- Several screening methods are available; one or more may be applicable and requires discussion with the patient and/or caregiver.
- Decisions on when to begin screening, frequency of screening, and cessation of screening are best individualized in older subjects.
- Shared decision-making must factor life expectancy, risk of death from colon cancer, benefits and burdens of the examination, and patient preference.
- Obstacles to suboptimal bowel preparation and incomplete examination should be identified and addressed early.

References

1. US Preventive Services Task Force (USPSTF). Screening for colorectal cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2008;149(9):627–37.
2. Leipzig RM, Whitlock EP, Wolff TA, et al., US Preventive Services Task Force Geriatric Workgroup. Reconsidering the approach to prevention recommendations for older adults. Ann Intern Med. 2010;153(12):809–14.
3. Kaiser Permanente Care Management Institute. Colorectal cancer screening clinical practice guideline. Oakland: Kaiser Permanente Care Management Institute; 2008. p. 190.
4. World Gastroenterology Organisation (WGO). Practice guidelines: colorectal cancer screening. Paris: World Gastroenterology Organisation (WGO); 2007.
5. Davila RE, Rajan E, Baron TH, et al., Standards of Practice Committee, American Society for Gastrointestinal Endoscopy. ASGE guideline: colorectal cancer screening and surveillance. Gastrointest Endosc. 2006;63(4):546–57.
6. Ko C, Hyman NH, Standards Committee of The American Society of Colon and Rectal Surgeons. Practice parameter for the detection of colorectal neoplasms: an interim report (revised). Dis Colon Rectum. 2006;49(3):299–301.
7. Winawer SJ, Zauber AG, Fletcher RH, et al. Guidelines for colonoscopy surveillance after polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer and the American Cancer Society. CA Cancer J Clin. 2006;56(3):143–59.
8. Taylor BA, Ramakrishnan S, Gopal K. The NHS bowel cancer screening programme. Colorectal Dis. 2009;11(3):327–8.
9. Levin B, Lieberman DA, McFarland B, et al., American Cancer Society/US Multi-Society Task Force on Colorectal Cancer/American College of Radiology (ACS/USMSTF/ACR). Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. CA Cancer J Clin. 2008;58(3):130–60.
10. Rex D, Johnson D, Anderson J, et al. American college of gastroenterology guidelines for colorectal cancer screening 2008. Am J Gastroenterol. 2009;104:739–50.
11. Winawer S, Fletcher R, Rex D, et al. AGA Colorectal Cancer screening and surveillance: clinical guidelines and rationale—update based on new evidence. Gastroenterology. 2003;124:544–60.
12. Howlader N, Noone AM, Krapcho M, et al., editors. SEER cancer statistics review, 1975–2008. Bethesda: National Cancer Institute; 2011. http://seer.cancer.gov/csr/1975_2008/, based on November 2010 SEER data submission, posted to the SEER web site.
13. Wilson JA. Colon cancer screening in the elderly: when do we stop? Trans Am Clin Climatol Assoc. 2010;121:94–103.
14. Rozen P, Liphshitz I, Barchana M. The changing epidemiology of colorectal cancer and its relevance for adapting screening guidelines and methods. Eur J Cancer Prev. 2011;20(1):46–53.
15. Kwok A, Faigel D. Management of anticoagulation before and after gastrointestinal endoscopy. Am J Gastroenterol. 2009;104:3085–97.
16. Walter LC, Covinsky KE. Cancer screening in elderly patients: a framework for individualized decision making. JAMA. 2001;285(21):2750–6.
17. Levi Z, Rozen P, Hazazi R, et al. Sensitivity, but not specificity, of a quantitative immunochemical fecal occult blood test for neoplasia is slightly increased by the use of low-dose aspirin, NSAIDs, and anticoagulants. Am J Gastroenterol. 2009;104(4):933–8.
18. Rosman AS, Korsten MA. Effect of verification bias on the sensitivity of fecal occult blood testing: a meta-analysis. J Gen Intern Med. 2010;25(11):1211–21.
19. Kahi CJ, Rex DK, Imperial TF. Screening, surveillance, and primary prevention for colon cancer: a review of the recent literature. Gastroenterology. 2008;135:380–99.

20. Hundt S, Haug U, Brenner H. Comparative evaluation of immunochemical fecal occult blood tests for colorectal adenoma detection. Ann Intern Med. 2009;150:162–9.
21. Brenner H, Tao S, Haug U. Low-dose aspirin use and performance of immunochemical fecal occult blood tests. JAMA. 2010;304:2513–20.
22. Rozen P, Shabtai EI, Liphshitz I, Barchana M. Risk for colorectal cancer in elderly persons and possible methodologies for their screening. Eur J Gastroenterol Hepatol. 2011;23(5):431–7.
23. Imperiale TF, Ransohoff DF, Itzkowitz SH, et al. Fecal DNA versus fecal occult blood for colorectal-cancer screening in an average-risk population. NEJM. 2004;351:2704–14.
24. Habermann JK, Roblick UJ, Luke BT, et al. Increased serum levels of complement C3a anaphylatoxin indicate the presence of colorectal tumors. Gastroenterology. 2006;131:1020–9.
25. Leman ES, Schoen RE, Weissfeld JL, et al. Initial analyses of colon cancer-specific antigen (CCSA)-3 and CCSA-4 as colorectal cancer associated serum markers. Cancer Res. 2007;67:5600–5.
26. Ko CW, Sonnenberg A. Comparing risks and benefits of colorectal cancer screening in elderly patients. Gastroenterology. 2005;129(4):1163–70.
27. Day LW, Inadmoi JM, Somsouk M. Adverse events in elderly patients undergoing colonoscopy: a meta-analysis. Gastroenterology. 2010;138(5 Suppl 1):S-126.
28. Lebwohl B, Wang TC, Neugut AI. Socioeconomic and other predictors of colonoscopy preparation quality. Dig Dis Sci. 2010;55(7):2014–20.
29. Chung YW, Han DS, Park KH, et al. Patient factors predictive of inadequate bowel preparation using polyethylene glycol: a prospective study in Korea. J Clin Gastroenterol. 2009;43(5):448–52.
30. Singhal S, Basi P, Mathur S, et al. Outcome analysis of colonoscopy in elderly African American, Hispanic and Asian Americans above age 85. Gastroenterology. 2010;138(5 Suppl 1):S-126.
31. Neerincx M, Terhaar sive Droste JS, Mulder CJ, et al. Colonic work-up after incomplete colonoscopy: significant new findings during follow-up. Endoscopy. 2010;42(9):730–5.
32. Schmilovitz-Weiss H, Weiss A, Boaz M, et al. Predictors of failed colonoscopy in nonagenarians: a single-center experience. J Clin Gastroenterol. 2007;41(4):388–93.
33. Reguerio CR. AGA Future Trends Committee Report: colorectal cancer: a qualitative review of emerging screening and diagnostic technologies. Gastroenterology. 2005;129:1082–103.
34. Seinela L, Pehkonen E, Laasanen T, et al. Bowel preparation for colonoscopy in very old patients. A randomized prospective trial comparing oral sodium phosphate and polyethylene glycol electrolyte lavage solution. Scand J Gastroenterol. 2003;38:216–20.
35. Cohen L. Split dosing of bowel preparations for colonoscopy: an analysis of its efficacy, safety, and tolerability. Gastrointest Endosc. 2010;72:406–12.
36. Belsey J, Epstein O, Heresbach D. Systematic review: adverse event reports for oral sodium phosphate and polyethylene glycol. Aliment Pharmacol Ther. 2008;29:15–28.
37. Sieg A, Friedrich K, Sieg U. Is PillCam COLON capsule endoscopy ready for colorectal cancer screening? A prospective feasibility study in a community gastroenterology practice. Am J Gastroenterol. 2009;104:848–54.
38. Gay G, Delvaux M, Frederic M, et al. Could the colonic capsule PillCam Colon be clinically useful for selecting patients who deserve a complete colonoscopy?: results of clinical comparison with colonoscopy in the perspective of colorectal cancer screening. Am J Gastroenterol. 2010;105:1076–86.
39. Spada C, Hassan C, Munoz-Navas M, et al. Second-generation colon capsule endoscopy compared with colonoscopy. Gastrointest Endosc. 2011;74(3):581–9.e1.
40. Fenlon HM, Nunes DP, Schroy PC, et al. A comparison of virtual and conventional colonoscopy for the detection of colorectal polyps. NEJM. 1999;341:1496–503.
41. Johnson CD, Chen MH, Toledano AY, et al. Accuracy of CT colonography for detection of large adenomas and cancer. NEJM. 2008;359:1207–17.
42. Kim DH, Pickhardt PJ, Hanson ME, et al. CT colonography: performance and program outcome measures in an older screening population. Radiology. 2010;254:493–500.
43. Lauenstein T, Holtman G, Schoenfelder D, et al. MR colonography without colonic cleansing: a new strategy to improve patient acceptance. AJR. 2001;177:823–7.

Gastrointestinal Polyps

59

Tamir Ben-Menachem

A polyp refers to a growth, mass, or protuberance arising from the normally flat mucosal surface of the gastrointestinal tract. Polyps can be categorized as neoplastic or nonneoplastic. Their endoscopic appearance may be sessile, pedunculated, or intermediate. True polyps or epithelial polyps derive from cells of the mucosal layer, but a multitude of other lesions sometimes called polyps during endoscopic examination actually arise from the deeper submucosal or muscle layers (Table 59.1). The majority of gastrointestinal polyps are discovered incidentally during endoscopy. However, large polyps may present with luminal obstruction, overt bleeding, or iron deficiency anemia. This chapter will discuss the most common epithelial gastrointestinal polyps and certain other lesions that occur at higher frequency in the elderly.

The incidence and prevalence of most malignancies increases with age. Data from international repositories and the Surveillance Epidemiology and End Results (SEER) database in the United States show a gradual rise of all gastrointestinal malignancies over time (Fig. 59.1) [1]. The prevalence of most gastric and colorectal polyps increases with age [2–4]. Exceptions to this rule include the juvenile polyps and syndromic polyps such as familial adenomatous polyposis (FAP) and others. Several factors are thought to contribute to the increasing incidence of neoplasia in the elderly. The progressive decline of the immune system [5], increasing exposure to carcinogens [6], accumulation of abnormal chromatin [7], and an inability to repair DNA abnormalities [8] have all been implicated in age-related DNA damage and carcinogenesis [9]. Several chronic conditions of the gastrointestinal tract such as atrophic gastritis, inflammatory bowel disease, and Barrett's esophagus are known to increase the risk of neoplasia over time.

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Adenomas

Adenomas are defined as epithelial dysplasia and are a precursor lesion for adenocarcinoma [10]. They occur in the entire gastrointestinal tract with varying degrees of frequency. They are most common in the colon and rectum, where about 60% of polyps detected endoscopically are adenomas. The prevalence of colonic adenomas at age 50 is about 25–30% [2], while the prevalence at age 70 in autopsy series approaches 50% [11]. Adenomas detected in the elderly are more frequently right-sided, and more often display advanced histology.

Gastric adenoma prevalence ranges from 0.5 to 3% in countries in the Western Hemisphere, but may be as high as 20% in nations where high risk of gastric cancer is reported [3, 12]. In western countries, 3–7% of gastric polyps are adenomas, and two-thirds occur in patients older than 60 years of age [13]. The increased age-related incidence of adenomas can be attributed in part to the higher incidence of atrophic gastritis in the elderly. Complete or partial atrophy of the antrum and lesser curvature is strongly associated with the development of gastric adenomas [14]. Progression to cancer is higher in polyps greater than 2 cm, villous histology, and with high-grade dysplasia [15]. Management of gastric adenomas is similar to other dysplastic lesions in the GI tract. The American Society of Gastrointestinal Endoscopy (ASGE) and the British Society of Gastroenterology (BSG) recommend complete removal of gastric adenomas. Endoscopic snare polypectomy or advanced techniques such as Endoscopic Mucosal Resection (EMR) or Endoscopic Submucosal Dissection usually are successful. Given the high incidence of synchronous lesions, careful examination of the entire stomach with representative biopsies should be performed. Repeat endoscopy is indicated within 6–12 months, depending on completeness of resection and presence of high-grade dysplasia. Lifetime endoscopic surveillance is indicated once an adenoma has been detected [16, 17].

Small bowel adenomas are rare, but appear to be increasing in frequency in the past decade possibly due to advanced

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Table 59.1 Polyps of the gastrointestinal tract categorized by location

	Organ				
Lesion	Esophagus	Stomach	Duodenum	Small bowel	Colon
Epithelial					
Adenoma	√	√	√	√	√
Fundic gland polyp	–	√	–	–	–
Hamartoma	√	√	√	√	√
Hyperplastic polyp	√	√	√	√	√
Inflammatory pseudopolyp	√	√	√	√	√
Papilloma	√	–	–	–	–
Nonepithelial					
Brunner gland hyperplasia	–	–	√	–	–
Carcinoid	√	√	√	√	√
Cyst	√	√	√	√	√
Desmoid	√	√	√	√	√
Ectopic pancreas	√	√	√	√	–
Fibrovascular polyp	√	–	–	–	–
Granular cell tumor	√	√	√	√	√
Glycogenic acanthosis	√	–	–	–	–
Hemangioma	√	√	√	√	√
Inflammatory fibroid polyp	√	√	√	√	√
Lipoma	√	√	√	√	√
Lymphangioma	√	√	√	√	√
Lymphoma	√	√	√	√	√
Metastases	√	√	√	√	√
Neuroendocrine neoplasm	√	√	√	√	√
Spindle cell neoplasm	√	√	√	√	√
Xanthoma	√	√	√	√	√

"Checked" boxes indicate at least one report of a particular polyp in a particular portion of the GI tract

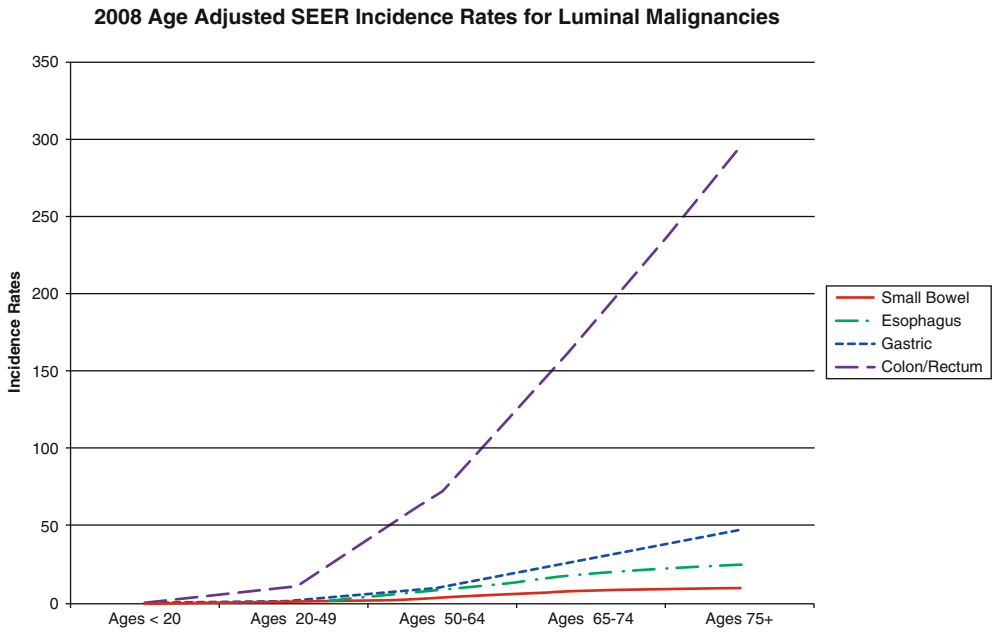

Fig. 59.1 2008 age-adjusted SEER incidence rates for luminal malignancies

detection techniques such as capsule endoscopy, double-balloon enteroscopy and enterography [18, 19]. They are more common in the proximal bowel, and in patients older than 65 years of age [20]. Duodenal adenomas are seen in 80% of patients with FAP, and in 4% of patients with hereditary nonpolyposis colon cancer [20]. Small bowel adenomas should be resected either endoscopically or surgically. A large proportion of duodenal adenomas will involve the ampulla of Vater, making resection more complicated. Moreover, although one-third of duodenal adenomas will become an adenocarcinoma, the decision to perform significant resections such as a pancreaticoduodenectomy for adenomas needs to be weighed carefully against the age and comorbidities of the patient.

Esophageal adenomas arise mostly from Barrett's epithelium, but reports of adenomas arising from gastric heterotopia of the proximal esophagus have been described. Barrett's esophagus with dysplasia is reviewed elsewhere.

Hyperplastic Polyps

Hyperplastic polyps are generally considered nonneoplastic and are fairly common in the stomach and colon. Notable exceptions to the nonneoplastic status of hyperplastic polyps are a small proportion of serrated dysplastic polyps of the colorectum [10] and adenocarcinoma arising from large gastric hyperplastic polyps [21]. Hyperplastic polyps of the esophagus and small bowel are uncommon and will not be discussed further.

Hyperplastic polyps of the stomach represent 30–90% of gastric polyps [3, 12, 22]. Higher rates are seen in countries where the incidence of *H. pylori* is high. The median age is 65 years [3, 23]. They are found mostly in the antrum, but may develop at any site in the stomach or at anastomoses. The most common symptoms due to hyperplastic polyps are acute or chronic blood loss, and rarely intermittent gastric outlet obstruction when prolapsing through the pylorus [24]. In contrast to colorectal hyperplastic polyps, gastric hyperplastic polyps are strongly associated with an underlying mucosal inflammatory process. Abraham and associates found that 61% of 160 patients with hyperplastic polyps had some type of chronic gastritis, including active *H. pylori* infection, atrophic gastritis, chemical gastropathy, or autoimmune metaplasia [23]. Eradication of *H. pylori* is associated with regression of up to 80% of gastric hyperplastic polyps [25]. Although considered nonneoplastic, the incidence of dysplasia arising from hyperplastic polyps ranges from 1.5 to 19%, and the incidence of malignancy ranges from 0.5 to 7% [26–28]. Malignant transformation is seen most often in polyps greater than 2 cm. However, some authors believe that the dysplastic changes are actually a reflection of the background atrophic gastritis, which in itself is a risk factor for malignancy [29]. In support of these assumptions is the observation that when dysplasia or malignancy is found in gastric hyperplastic polyps, the incidence of synchronous malignancy in other parts of the stomach may be as high as 12% [26].

Endoscopic biopsy is accurate for diagnosing gastric hyperplastic polyps, but biopsies without complete resection may miss a region of dysplasia or malignancy in a polyp [30]. Confocal laser endomicroscopy has been shown to improve the in vivo differentiation of adenomas vs. hyperplastic polyps of the stomach [31], but resection of polyps greater than 0.5–1 cm is recommended by the ASGE [16]. In addition, a careful examination of the entire stomach should be performed, along with representative biopsies of different gastric regions and of any visible abnormalities. *H. pylori* should be sought and eradicated. If polyps larger than 1 cm are removed, or if dysplasia was present in any polyp, repeat the EGD in 1 year [16, 17].

Hyperplastic polyps of the colon are seen frequently during screening colonoscopy. They are part of the serrated polyp family and have a variable association with dysplasia and malignancy. Small hyperplastic polyps in the sigmoid and rectum are typically benign, and require no further workup [32]. Large or proximal hyperplastic polyps have been classified as "proximal nondysplastic-serrated polyps" (NDSP) or sessile-serrated polyps [33]. The serrated adenoma or dysplastic-serrated polyp is considered another step in the evolution of the malignant transformation of hyperplastic polyps. The molecular pathway to carcinogenesis for serrated polyps appears to involve the BRAF oncogene and microsatellite instability [34], as opposed to the typical APC pathway described in the adenoma-to-carcinoma sequence [35]. The presence of large NDSP has been associated with an increased risk of synchronous advanced neoplasia [36]. Sessile-serrated adenomas are uncommon, but have a high incidence of dysplastic change, ranging from 4 to 37% [37–40]. Definitive guidelines for management of serrated dysplastic polyps are lacking. However, it is recommended that polyps 1 cm or larger in the colon be removed, regardless of their location [32]. Because the time interval from dysplasia to cancer may be shorter than that of the standard adenoma, some authors recommend surveillance intervals of 1–3 years for patients with serrated neoplasia [41].

Fundic Gland Polyps

Fundic gland polyps (FGP) are found exclusively in the stomach corpus and are one of the most common types of gastric polyp [42]. FGP occur in two settings: sporadic polyps and FGP associated with FAP. Sporadic polyps are usually thought to be less than 1 cm in size and on average

number ten or less [4]. They are associated with a very low prevalence of *H. pylori* infection [43] and have been reported to be more frequent with chronic PPI use [44]. Sporadic FGP are not generally thought to be precancerous, but many FGP will have B-catenin gene mutations [45]. However, the risk of dysplasia in sporadic FGP is less than 1%. In contrast, FGP associated with FAP (syndromic FAP) harbor somatic APC mutations and 40% will have dysplasia at the time of biopsy or polypectomy [46, 47]. Patients with FAP often have FGP, but syndromic FGP are typically younger than those with sporadic FGP. Numerous polyps are usually seen with syndromic FAP, sometime described as a "carpet of polyps." The BSG and several authors recommend considering colonoscopy for patients with multiple FGP or with FGP that have dysplasia [17, 42]. Most authors recommend resection of polyps greater than 1 cm in size, but specific follow-up for sporadic FGP is not necessary.

Neuroendocrine Tumors

Neuroendocrine tumors (NETs) of the digestive system account for about 2% of all GI malignancies. Approximately half of GI NETs are carcinoid tumors. The overwhelming majority of noncarcinoid NETs are located in the pancreas [48], and will not be discussed in this chapter. This section will focus on luminal GI NETs, which are almost always carcinoid tumors. Carcinoids are well differentiated endocrine neoplasms that arise from enterochromaffin cells of the GI tract [49]. They can be classified based on their embryologic origin (foregut, midgut, or hindgut), histologic appearance, and on their biologic behavior (benign vs. malignant). The incidence of carcinoid tumors in the United States and Europe is increasing. Rising rates are documented for all GI carcinoids, but the largest relative increase is for gastric carcinoids [50, 51]. The increasing incidence may be a result of increasing detection with advanced imaging and endoscopic techniques, rather than a true increase in the disease. Carcinoid tumors of the GI tract are found mostly in the sixth decade of life, except for appendiceal carcinoids which are most prevalent at a median age of 47 years [50, 51]. Possible risk factors for developing carcinoid tumors are a family history of malignancy; and specifically for gastric carcinoids, a long-term history of diabetes [52].

Most patients with carcinoid tumors are asymptomatic. The neoplasm is often detected incidentally at the time of endoscopy or surgery for other indications. Carcinoids of the small bowel tend to cause symptoms more often than at other locations. Reported symptoms include abdominal pain in 60%, bowel obstruction in 25%, and the carcinoid syndrome in about 7% of patients [53, 54]. The tumors arise from neuroendocrine cells in the deep mucosa or submucosa and often produce sessile polyps early-on. Diagnosis with standard endoscopic biopsy forceps is usually successful, although polypectomy is sometimes necessary if the tumor is completely subepithelial. Given the deep location of the progenitor cells, standard polypectomy techniques are seldom adequate to completely remove a gastrointestinal carcinoid. The management of carcinoid tumors depends on their location and likelihood of aggressive biologic behavior.

Three types of gastric carcinoids have been described [54, 55]. Type I is related to atrophic gastritis with hypergastrinemia, and accounts for 80% of gastric carcinoids. They very rarely metastasize. EMR can be performed for larger polyps or polyps that ulcerate. Prior to EMR, endoscopic ultrasound is recommended to measure the lesion precisely and to verify that it does not involve the muscularis propria [56]. If polyps recur or are too numerous to remove, an antrectomy will allow for regression of the carcinoid tumors by eliminating the source of gastrin. Type II carcinoids comprise about 5% of gastric carcinoids and occur in the setting of Zollinger-Ellison syndrome or multiple endocrine neoplasia (MEN) type I. Resection (endoscopic or surgical) of the carcinoids and resection of the gastrinoma are adequate treatment. Type 3 gastric carcinoids are sporadic, account for 20% of gastric carcinoids, and are the most likely to progress to malignancy. Type 3 carcinoids should be treated with partial or total gastrectomy and lymph node dissection [57].

Carcinoids of the small bowel, colon and rectum are treated based on their location, size, presence of spread beyond the gut wall, and whether or not metastases are present. Tumors less than 1 cm in size that can be reached endoscopically can be resected by EMR. Larger lesions or those with loco-regional spread require surgical excision with wide margins in order to optimize survival [58].

Rare Polyps with Preponderance for the Elderly

Inflammatory fibroid polyp (IFP) was first described in 1949 and called "eosinophilic submucosal granuloma" [59]. IFPs arise from the submucosal layer, have been described throughout the GI tract, but are most common in the stomach antrum [42]. Previously thought to be nonneoplastic, both gastric and small bowel IFPs have been shown to harbor mutations in platelet-derived growth factor receptor, similar to benign stromal tumors of the GI tract [60]. IFPs are most common in the sixth decade of life and are often associated with chronic inflammatory activity such as atrophic gastritis [61]. Forceps biopsy is not always adequate for diagnosis because these lesions often have normal overlying epithelium. IFPs are not thought to have malignant potential, but may ulcerate or rarely cause luminal obstruction. Endoscopic resection is usually adequate if the resection extends deep into the submucosa, as with EMR or ESD [17].

Fibrovascular polyps of the esophagus represent a group of large benign stromal polyps that are composed of varying degrees of fibrous, adipose, and muscular components with normal overlying squamous mucosa [62]. They are rare polyps that usually arise from the proximal esophagus and grow sausage-like within the esophageal lumen. They are usually symptomatic later in life when the large polyp size can cause dysphagia, emesis, cough, and even asphyxiation due to prolapse into the larynx [63]. Resection of these large polyps usually requires a surgical approach, but there are reports of successful endoscopic resection [64].

Key Points

- Polyps of the gastrointestinal tract increase in frequency with advancing age and are often found incidentally.
- The most common mucosal polyps are adenomas and hyperplastic polyps.
- Gastric mucosal polyps often arise in a background of inflammation or intestinal metaplasia of the stomach.
- Polyps greater than 1 cm in size should be removed, and small polyps sampled representatively.
- Advances in endoscopic technologies have allowed for improved accuracy of polyp detection and for resection of lesions deep within the gut wall.

References

1. Statistics. http://seer.cancer.gov/statistics/.
2. Rex DK, Lehman GA, Ulbright TM, et al. Colonic neoplasia in asymptomatic persons with negative fecal occult blood tests: influence of age, gender, and family history. Am J Gastroenterol. 1993;88(6):825–31.
3. Morais DJ, Yamanaka A, Zeitune JM, Andreollo NA. Gastric polyps: a retrospective analysis of 26,000 digestive endoscopies. Arq Gastroenterol. 2007;44(1):14–7.
4. Carmack SW, Genta RM, Schuler CM, Saboorian MH. The current spectrum of gastric polyps: a 1-year national study of over 120,000 patients. Am J Gastroenterol. 2009;104(6):1524–32.
5. Malaguarnera L, Cristaldi E, Malaguarnera M. The role of immunity in elderly cancer. Crit Rev Oncol Hematol. 2010;74(1):40–60.
6. Pal SK, Hurria A. Impact of age, sex, and comorbidity on cancer therapy and disease progression. J Clin Oncol. 2010;28(26):4086–93.
7. Anisimov VN. Carcinogenesis and aging 20 years after: escaping horizon. Mech Ageing Dev. 2009;130(1–2):105–21.
8. Seviour EG, Lin SY. The DNA damage response: balancing the scale between cancer and ageing. Aging (Albany NY). 2010;2(12):900–7.
9. Hoeijmakers JH. DNA damage, aging, and cancer. N Engl J Med. 2009;361(15):1475–85.
10. Bosman FT, Carneiro F, Hruban RH, Theise ND, editors. WHO classification of tumours of the digestive system. 4th ed. Lyon: IARC Press; 2010. WHO Classification of Tumours, Vol 3; No. 3.
11. Williams AR, Balasooriya BA, Day DW. Polyps and cancer of the large bowel: a necropsy study in Liverpool. Gut. 1982;23(10):835–42.
12. Stolte M, Sticht T, Eidt S, et al. Frequency, location, and age and sex distribution of various types of gastric polyp. Endoscopy. 1994;26(8):659–65.
13. Archimandritis A, Spiliadis C, Tzivras M, et al. Gastric epithelial polyps: a retrospective endoscopic study of 12974 symptomatic patients. Ital J Gastroenterol. 1996;28(7):387–90.
14. Yoshihara M, Sumii K, Haruma K, et al. Correlation of ratio of serum pepsinogen I and II with prevalence of gastric cancer and adenoma in Japanese subjects. Am J Gastroenterol. 1998;93(7):1090–6.
15. de Vries AC, van Grieken NC, Looman CW, et al. Gastric cancer risk in patients with premalignant gastric lesions: a nationwide cohort study in the Netherlands. Gastroenterology. 2008;134(4):945–52.
16. Hirota WK, Zuckerman MJ, Adler DG, et al. ASGE guideline: the role of endoscopy in the surveillance of premalignant conditions of the upper GI tract. Gastrointest Endosc. 2006;63(4):570–80.
17. Goddard AF, Badreldin R, Pritchard DM, et al. The management of gastric polyps. Gut. 2010;59(9):1270–6.
18. Cobrin GM, Pittman RH, Lewis BS. Increased diagnostic yield of small bowel tumors with capsule endoscopy. Cancer. 2006;107(1):22–7.
19. Pasha SF, Leighton JA, Das A, et al. Double-balloon enteroscopy and capsule endoscopy have comparable diagnostic yield in small-bowel disease: a meta-analysis. Clin Gastroenterol Hepatol. 2008;6(6):671–6.
20. Schottenfeld D, Beebe-Dimmer JL, Vigneau FD. The epidemiology and pathogenesis of neoplasia in the small intestine. Ann Epidemiol. 2009;19(1):58–69.
21. Hizawa K, Fuchigami T, Iida M, et al. Possible neoplastic transformation within gastric hyperplastic polyp. Application of endoscopic polypectomy. Surg Endosc. 1995;9(6):714–8.
22. Borch K, Skarsgard J, Franzen L, et al. Benign gastric polyps: morphological and functional origin. Dig Dis Sci. 2003;48(7):1292–7.
23. Abraham SC, Singh VK, Yardley JH, Wu TT. Hyperplastic polyps of the stomach: associations with histologic patterns of gastritis and gastric atrophy. Am J Surg Pathol. 2001;25(4):500–7.
24. Jain R, Chetty R. Gastric hyperplastic polyps: a review. Dig Dis Sci. 2009;54(9):1839–46.
25. Ohkusa T, Takashimizu I, Fujiki K, et al. Disappearance of hyperplastic polyps in the stomach after eradication of Helicobacter pylori. A randomized, clinical trial. Ann Intern Med. 1998;129(9):712–5.
26. Orlowska J, Pietrow D. Multifocal gastric carcinoma arising from hyperplastic and adenomatous polyps. Am J Gastroenterol. 1990;85(12):1629–34.
27. Antonioli DA. Precursors of gastric carcinoma: a critical review with a brief description of early (curable) gastric cancer. Hum Pathol. 1994;25(10):994–1005.
28. Dijkhuizen SM, Entius MM, Clement MJ, et al. Multiple hyperplastic polyps in the stomach: evidence for clonality and neoplastic potential. Gastroenterology. 1997;112(2):561–6.
29. Dirschmid K, Platz-Baudin C, Stolte M. Why is the hyperplastic polyp a marker for the precancerous condition of the gastric mucosa? Virchows Arch. 2006;448(1):80–4.
30. Sung HY, Cheung DY, Cho SH, et al. Polyps in the gastrointestinal tract: discrepancy between endoscopic forceps biopsies and resected specimens. Eur J Gastroenterol Hepatol. 2009;21(2):190–5.
31. Li WB, Zuo XL, Zuo F, et al. Characterization and identification of gastric hyperplastic polyps and adenomas by confocal laser endomicroscopy. Surg Endosc. 2010;24(3):517–24.
32. Winawer SJ, Zauber AG, Fletcher RH, et al. Guidelines for colonoscopy surveillance after polypectomy: a consensus update by the US

Multi-Society Task Force on Colorectal Cancer and the American Cancer Society. Gastroenterology. 2006;130(6):1872–85.
33. Snover DC, Jass JR, Fenoglio-Preiser C, Batts KP. Serrated polyps of the large intestine: a morphologic and molecular review of an evolving concept. Am J Clin Pathol. 2005;124(3):380–91.
34. Koinuma K, Shitoh K, Miyakura Y, et al. Mutations of BRAF are associated with extensive hMLH1 promoter methylation in sporadic colorectal carcinomas. Int J Cancer. 2004;108(2):237–42.
35. Vogelstein B, Fearon ER, Hamilton SR, et al. Genetic alterations during colorectal-tumor development. N Engl J Med. 1988; 319(9):525–32.
36. Hiraoka S, Kato J, Fujiki S, et al. The presence of large serrated polyps increases risk for colorectal cancer. Gastroenterology. 2010;139(5):1503–10; 1510 e1501–3.
37. Longacre TA, Fenoglio-Preiser CM. Mixed hyperplastic adenomatous polyps/serrated adenomas. A distinct form of colorectal neoplasia. Am J Surg Pathol. 1990;14(6):524–37.
38. Rex DK, Ulbright TM. Step section histology of proximal colon polyps that appear hyperplastic by endoscopy. Am J Gastroenterol. 2002;97(6):1530–4.
39. Goldstein NS, Bhanot P, Odish E, Hunter S. Hyperplastic-like colon polyps that preceded microsatellite-unstable adenocarcinomas. Am J Clin Pathol. 2003;119(6):778–96.
40. Li D, Jin C, McCulloch C, et al. Association of large serrated polyps with synchronous advanced colorectal neoplasia. Am J Gastroenterol. 2009;104(3):695–702.
41. O'Brien MJ. Hyperplastic and serrated polyps of the colorectum. Gastroenterol Clin North Am. 2007;36(4):947–68; viii.
42. Park do Y, Lauwers GY. Gastric polyps: classification and management. Arch Pathol Lab Med. 2008;132(4):633–40.
43. Genta RM, Schuler CM, Robiou CI, Lash RH. No association between gastric fundic gland polyps and gastrointestinal neoplasia in a study of over 100,000 patients. Clin Gastroenterol Hepatol. 2009;7(8):849–54.
44. Declich P, Ambrosiani L, Bellone S, et al. Fundic gland polyps under omeprazole treatment. Am J Clin Pathol. 1999;112(4):576–7.
45. Torbenson M, Lee JH, Cruz-Correa M, et al. Sporadic fundic gland polyposis: a clinical, histological, and molecular analysis. Mod Pathol. 2002;15(7):718–23.
46. Bertoni G, Sassatelli R, Nigrisoli E, et al. Dysplastic changes in gastric fundic gland polyps of patients with familial adenomatous polyposis. Ital J Gastroenterol Hepatol. 1999;31(3):192–7.
47. Jung A, Vieth M, Maier O, Stolte M. Fundic gland polyps (Elster's cysts) of the gastric mucosa. A marker for colorectal epithelial neoplasia? Pathol Res Pract. 2002;198(11):731–4.
48. Warner RR. Enteroendocrine tumors other than carcinoid: a review of clinically significant advances. Gastroenterology. 2005;128(6): 1668–84.
49. Kloppel G, Perren A, Heitz PU. The gastroenteropancreatic neuroendocrine cell system and its tumors: the WHO classification. Ann N Y Acad Sci. 2004;1014:13–27.
50. Ellis L, Shale MJ, Coleman MP. Carcinoid tumors of the gastrointestinal tract: trends in incidence in England since 1971. Am J Gastroenterol. 2010;105(12):2563–9.
51. Yao JC, Hassan M, Phan A, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol. 2008;26(18): 3063–72.
52. Hassan MM, Phan A, Li D, et al. Risk factors associated with neuroendocrine tumors: a U.S.-based case-control study. Int J Cancer. 2008;123(4):867–73.
53. Marshall JB, Bodnarchuk G. Carcinoid tumors of the gut. Our experience over three decades and review of the literature. J Clin Gastroenterol. 1993;16(2):123–9.
54. Modlin IM, Champaneria MC, Chan AK, Kidd M. A three-decade analysis of 3,911 small intestinal neuroendocrine tumors: the rapid pace of no progress. Am J Gastroenterol. 2007;102(7):1464–73.
55. Borch K, Ahren B, Ahlman H, et al. Gastric carcinoids: biologic behavior and prognosis after differentiated treatment in relation to type. Ann Surg. 2005;242(1):64–73.
56. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. Cancer. 2003;97(4):934–59.
57. Schindl M, Kaserer K, Niederle B. Treatment of gastric neuroendocrine tumors: the necessity of a type-adapted treatment. Arch Surg. 2001;136(1):49–54.
58. Soreide JA, van Heerden JA, Thompson GB, et al. Gastrointestinal carcinoid tumors: long-term prognosis for surgically treated patients. World J Surg. 2000;24(11):1431–6.
59. Vanek J. Gastric submucosal granuloma with eosinophilic infiltration. Am J Pathol. 1949;25(3):397–411.
60. Lasota J, Wang ZF, Sobin LH, Miettinen M. Gain-of-function PDGFRA mutations, earlier reported in gastrointestinal stromal tumors, are common in small intestinal inflammatory fibroid polyps. A study of 60 cases. Mod Pathol. 2009;22(8):1049–56.
61. Ozolek JA, Sasatomi E, Swalsky PA. Inflammatory fibroid polyps of the gastrointestinal tract: clinical, pathologic, and molecular characteristics. Appl Immunohistochem Mol Morphol. 2004; 12(1):59–66.
62. Avezzano EA, Fleischer DE, Merida MA, Anderson DL. Giant fibrovascular polyps of the esophagus. Am J Gastroenterol. 1990;85(3):299–302.
63. Carrick C, Collins KA, Lee CJ, Prahlow JA, Barnard JJ. Sudden death due to asphyxia by esophageal polyp: two case reports and review of asphyxial deaths. Am J Forensic Med Pathol. 2005;26(3):275–81.
64. Schmied C, Roedel H, Bernardi M. Fibrovascular polyp of the esophagus. Gastrointest Endosc. 2002;55(1):80.

Gastric Neoplasms

60

Philip Chang and Isidor Segal

Gastric cancer is the second leading cause of death due to cancer; in 2002, an estimated 900,000 new cases were diagnosed, making it the fourth most common cancer worldwide, with approximately 700,000 deaths from this disease [1]. As a group, gastric neoplasms can be classified broadly into gastric adenocarcinomas (GC), gastrointestinal stromal tumours (GISTs) and primary gastric lymphomas (PGLs). Gastric adenocarcinomas are by far the most common form of gastric neoplasm, with rates of PGL accounting for only 5% of all gastric neoplasms and GIST being responsible for only ~1% of all gastrointestinal tumours [2, 3].

Gastric Adenocarcinoma

Gastric adenocarcinoma is the most common form of gastric neoplasm. Incidence of gastric cancer is highest in China, Japan, Korea and Eastern Europe. Early detection is crucial for the management of this condition, with outcomes largely dependent on staging at detection. Unfortunately, in the western world, GC is often diagnosed at an advanced stage, with an overall 5-year survival rate of less than 30% [4], while Japan reports a 5-year survival rate of over 60% [5]. This may be due to the systematic screening programme that Japan has in place [6].

Epidemiology and Aetiology

GCs are of two histological types, based on the Lauren classification: intestinal and diffuse [7]. Diffuse type GC has a greater likelihood of presenting in younger patients, has an association with pernicious anaemia and is more likely to have a genetic basis. The more common intestinal-type GC follows a better defined progression pathway, from metaplasia to dysplasia and to carcinoma. Intestinal-type GC is the most common form of gastric neoplasm in the elderly population. Vascular and lymphatic invasion were found more frequently in the older than in middle aged groups [8]. The incidence of the scirrhous type did not differ between the two groups but the medullary type and intermediate type occurred more frequently in the elderly.

Overall, GC incidence is decreasing worldwide (although cancers specifically at the gastro-oesophageal junction are on the increase for reasons not clear); this is at least partially attributed to the success of *Helicobacter pylori* (*H. pylori*) eradication. The discovery of *H. pylori* in 1983 markedly changed the gastric carcinogenic theory, especially with regards to the more common intestinal-type GC. It is now widely accepted that there is a strong association between *H. pylori* infection and gastric cancer [9, 10]. *H. pylori* infection induces chronic inflammation of the gastric mucosa and atrophic gastritis [11]. The subsequent resulting intestinal metaplasia is regarded as essential in the progression pathway for intestinal-type GC.

An interesting point regarding the relationship between *H. pylori* infection and GC incidence can be observed when analysing GC rates in Sub-Saharan Africa. *H. pylori* is ubiquitous in Africa, with some studies showing up to 86.5% of children being infected [12]; the majority of them with the cytotoxin-associated gene A (cagA) strain which is well recognised as being associated with increased levels of inflammation and thus confers a higher risk of GC [12]. However, GC rates in Soweto were found to be relatively low compared with the rates of *H. pylori* infection [13]. This "African Enigma" has several possible explanations; one of which involves high levels of parasitic co-infection in Sowetan adults and children resulting in high systemic levels of total IgE and IgG [1]. This implies a different immune response to *H. pylori* in this

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Table 60.1 Risk and predisposing factors for gastric cancer

Risk factors	Predisposing factors
Alcohol	Chronic atrophic gastritis, and pernicious anaemia
Cigarette smoking	Gastric polyps especially familial adenomatous polyposis
Helicobacter pylori infection	*H. pylori* infection
Genetic factors	Prior gastric surgery (e.g. post-gastrectomy)
Diet (low fibre, high salt)?	Menetrier's disease
Foods with nitrites and nitrates	Type A blood group
Male gender?	Age over 70 years
Relative (first degree) with gastric cancer	Gastric adenoma

community [14]. Also, in the same vein, *H. pylori* infection with helminth co-infection (which is common in Sub-Saharan Africans) has been shown to result in a T-helper 2 (Th2) rather than a T-helper 1 (Th1) immune response [15]. This is significant, as Th2 immune responses are associated with less gastric corpal atrophy and mucosal metaplasia as compared with Th1 responses, thus resulting in possibly lower rates of GC.

Other chronic mucosal inflammatory states such as chronic atrophic gastritis are also shown to predispose individuals to develop GC. In addition, as in other gastrointestinal sites (such as the colon), mucosal polyps in the stomach may predispose to gastric cancer. However, unlike in the colon, adenomas with a malignant potential are far rarer in the stomach and thus polyp related GCs are far less common than *H. pylori* related diffuse type GCs.

Common Western lifestyle factors such as alcohol and cigarette smoking have been implicated as risk factors for GC, besides certain dietary components such as salt and fried food. There is conjecture as to whether these factors contribute to increased risk of GC in certain ethnic populations around the world, without conclusive data. Risks and predispositions are listed Table 60.1.

The potential carcinogenicity of certain medications in pathogenesis of GC is debated. Use of oral bisphosphonates, known to cause esophagitis, was not significantly associated with incident esophageal or gastric cancer [16]. Anti-inflammatory medications are stated as potentially protective in a variety of gastrointestinal malignancies. Daily aspirin intake reduced deaths in several cancers including esophageal, stomach and colorectal cancer, in an analysis of eight eligible trials with 670 cancer deaths, involving different populations [17], despite the known ulcerogenic effect of aspirin in the stomach. The benefits from aspirin may relate to inhibition of cyclooxygenase, a player in prostaglandin synthesis.

Clinical Features, Diagnosis and Staging

Typical presenting symptoms of GC include abdominal pain, anorexia, early satiety, malena and weight loss. Signs that may be present on examination include a palpable left supraclavicular node (Virchow's node), palpable abdominal mass or palpable ovarian mass (Krukenberg tumour). However, many of these symptoms often occur late in the disease course, and thus the disease is often at an advanced stage by the time the typical patient seeks medical attention.

Upper gastrointestinal endoscopy with biopsy will usually confirm the diagnosis of GC. Usually, a large ulcerated mass lesion will be apparent; nevertheless, it is essential to take deep mucosal biopsies as some forms of GC such as linitis plastica may not be readily evident at endoscopy. Mass lesions are most typically seen at the angularis, lower gastric body and antrum, although increasingly lesions are being seen at the gastro-oesophageal junction (whether these lesions represent true gastric malignancies or are actually spread from oesophageal malignancies is open to debate). In the very elderly in whom endoscopy may be contraindicated on medical grounds, an upper gastrointestinal series may be useful to make a diagnosis, even without a tissue biopsy. Transabdominal ultrasonography is not helpful in the diagnosis of gastric cancer, in contrast to endoscopic ultrasound (EUS).

GC staging relies on the TNM (T-tumour depth, N-presence or absence of nodal involvement, M-presence or absence of metastatic involvement) staging system, recommended by the American Joint Committee on Cancer [18]. Contrast enhanced imaging with chest/abdominal/pelvis CT is considered standard for evaluation of metastatic disease in GC. However, diagnostic laparoscopy for staging should be considered in all possible candidates fit for surgical resection as CT has relatively low sensitivity for detecting peritoneal spread. EUS plays a vital role and is ideal for the evaluation of tumour penetration (T-stage) with sensitivities of not lower than 82% for all T stages (up to 99% for T4) [19]. It can also play a role in evaluating local nodal spread with a reported sensitivity of between 89 and 92% [20]. The role for FDG-PET and serum tumour markers in GC is unclear, and should not be considered as part of routine staging [21]. Despite the fact that serum tumour markers lack data regarding their use in staging, other biochemical studies can be useful in the assessment of GC. For example low albumin concentrations were associated with lower survival in gastric cancer and thus can be used as a prognostic marker; but the strength of the relationship may be really influenced by systemic inflammatory responses evidenced by the presence of elevated C Reactive Protein levels [22, 23].

Treatment

Treatment of GC includes surgery, chemotherapy (in an adjuvant and/or neoadjuvant setting) and endoscopic techniques.

Surgery remains the preferable option in localised GC. The exact extent of surgery and associated lymph node dissection are debated. The current goal is to achieve a resection with a minimum of a D1 lymph node retrieval, with at least 15 lymph nodes needed for staging [24]. Some trials, mainly from Japan, have suggested better mortality data for D2 lymphadenectomy, but the outcomes have not been reproduced in Western populations [25]. Given the relative complexity of the operation, better outcomes are achieved in high-volume centres. Newer modalities such as laparoscopic resections are still lacking in data, and cannot be recommended presently. Chemotherapy remains a mainstay for treatment in both surgical resected patients and those deemed not suitable for surgery (on either staging or medical co-morbidity grounds). It is difficult to advocate a standard of care for adjuvant chemotherapy as treatment regimes vary across countries in terms of the type and dose of chemotherapy. It is now generally regarded that multimodal treatment is the current standard of care, and surgery alone is rarely offered as the sole form of treatment. Radiotherapy has been trialled as an adjunct to chemotherapy, with variable success; however, it plays an important role in treating bleeding from GC (i.e. malena).

Chemotherapy as the modality for treating advanced GC (as is often the case in older adults with GC) poses difficulties, aiming a balance of controlling disease activity vs. maintaining quality of life for the patient. Newer regimes including oral chemotherapeutic agents appear superior to best supportive care [26].

Endoscopic therapy for GC is a relatively new field where endomucosal resection (EMR) and endoscopic submucosal dissection (ESD) are used for early gastric cancers (T1) [27]. These therapies are suitable for the elderly cohort, as the procedures are associated with minimal morbidity compared with surgical resection (subtotal/total gastrectomy); but in reality, most GCs in the geriatric population are discovered late due to the insidious onset of symptoms, presenting with late stage tumours (T3/4). Endoscopic therapy is also useful in the palliative treatment of patients with GC; endoscopic delivered gastric stents help treat complications such as gastric outlet obstruction without resorting to high morbidity procedures such as gastric resections/bypasses.

Gastric Cancer in the Elderly

While the incidence of gastric cancer has been decreasing worldwide, the incidence of GC in older adults appears to be increasing [20]. The distribution of gastric neoplasms in the over 79 year group suggests a greater prevalence of antral localisation whereas in the below 70 year group, there appears a greater localisation at the corpus. Macroscopic appearance of both early and advanced stage GC is influenced by age [28]. In the elderly, irrespective of tumour stage, the tumour is mainly well differentiated [20]. Advanced stage disease GC in older subjects exhibits more aggressive histological characteristics as compared with early stage disease [20]. Also, synchronous cancers are more prevalent among the elderly, with their incidence increasing with age. In the older population, the course of GC is characterised by less metastatic activity and recurrence; when metastases occur, they are mainly confined around the primary tumour site [20]. This pattern of disease distribution with age explains the different surgical approach for GC in the old compared to the general population. Note that the widespread availability of endoscopy with earlier diagnosis of GC combined with improved surgical and anaesthetic techniques have resulted in a significant increase in resection and curative resection rates in the elderly [20]. Thus standard surgical treatment for GC is feasible in the elderly with pre-existing morbidity. However in the frail elderly with significant co-morbidity and poor health, less aggressive surgical therapies may be applied.

In older patients there is a greater incidence of diffuse gastric cancer. Differences also exist in recurrence patterns; the <70 years group have more frequent loco-regional recurrences, while the over 70 year group manifests more peritoneal and haematogenous recurrences [21]. In summary, GC presents age based clinico-pathological differences, a higher male/female ratio in the elderly, and pathologically, more frequent antral localization, with a greater incidence of peritoneal and haematogenous recurrence. In addition as older adults manifest co-morbidities and are on numerous medications, any surgical approach should be modulated on an individual basis, with age itself not a contraindication for curative surgery. As the elderly have a reduced functional reserve, a subtotal gastrectomy may be the best surgical approach [21]. Surgical curability, defined as no residual tumour, was less frequently attained in the older age group, compared to the middle age. Further, the elderly have a lower survival rate, with a higher post-operative death rate [20]. Older age by itself did not influence morbidity and surgical complications, with long-term survival comparable to young patients [29].

Conclusions

Overall, GC has a higher incidence and poorer survival in the elderly, likely as a result of medical co-morbidities and direct tumour related factors. This is demonstrated in a Japanese cohort, where the incidence of GC in the older age group (age>70 years) has increased from 18.4% in the previous decade to 24.4% more recently, despite the overall decrease in incidence in patients of all ages [8]. Multiple gastric cancers

were found in 7.69% of the elderly with GC, significantly higher than that in the middle age patients with GC. The long-term prognosis in the old is poor, because of delays in diagnosis and aggressiveness of the tumour [25]. However on the optimistic side most studies agree that fit elderly patients with operable GC should be candidates for the recommended standard extensive surgical resection accompanied by resection of at least 14 lymph nodes provided that existing co-morbidities and tumour location are considered [20]. Patients with operable locally advanced disease should also be submitted to perioperative chemotherapy or post-operative chemoradiotherapy. With regard to recurrent and metastatic disease palliative systemic chemotherapy should be considered since it offers prolonged survival and preserves quality of life [20].

Gastrointestinal Stromal Tumours

GIST is the most common subepithelial tumour of the stomach, with an estimated prevalence of 129 per million according to European population-based studies [30]. The median incidence is in the fifth decade but they can occur at any age from infancy to old age. The tumours are considered to arise from the interstitial cells of Cajal [31], and are usually localised, although they do have potential to metastasise.

Clinical Features and Diagnosis

The clinical presentation of GIST is not specific, symptoms ranging from vague dyspepsia, including epigastric pain or discomfort centred in the upper abdomen, to alarm symptoms, such as gastrointestinal bleeding or weight loss. There appears an association with Neurofibromatosis type-1 and Carney's Triad [28]. GISTs are most commonly detected on upper endoscopy, appearing typically as a solitary submucosal lesion with normal overlying mucosa. Uncommonly, GISTs may co-exist with other GI and extra-GI tumours. Standard biopsy techniques are usually inadequate, due to shallow mucosal biopsy depth; EUS is the preferred modality for investigation of GISTs, allowing for both visualisation and mucosal depth assessment with the added ability to do deep submucosal biopsies [28].

Staging and Treatment

GISTs less than 20 mm in diameter are considered low risk, with no consensus data on treatment modalities or surveillance. Lesions greater than 20 mm upon endoscopic evaluation are evaluated by EUS (if not already done) and PET scan as staging investigations. Apart from size, GISTs with cystic spaces, irregular borders, associated lymphadenopathy or location in the small intestine are all considered high risk. Surgical laparoscopic resection is the recommended treatment for all high risk lesions; some recent reports suggest that even low risk lesions should be considered for surgery given the uncertainty regarding malignant potential in these lesions. Surveillance with EUS has also been proposed for low risk lesions, however, no timeframe for EUS has been validated as definitely beneficial.

Novel treatments such as tyrosine kinase inhibitors demonstrate benefit in metastatic GIST and as adjuvant therapy in surgically resected cases.

Primary Gastric Lymphomas

PGLs are subepithelial gastric tumours thought to arise from mucosal-associated lymphoid tissue in Peyer's patches (MALT) and activated by presence of *H. pylori*. Current thinking is that bacterial antigens from *H. pylori* stimulate lymphoid follicles populated by B-cells leading to lymphoid hyperplasia and formation of a monoclonal B cell population. Hence PGLs are described as extra-nodal lymphomas by haematologists. So-called MALT lymphomas represent the largest group of PGLs; however, follicular and mantle cell lymphomas also fall under the heading of PGL. There remains considerable debate among haematologists regarding classification of PGLs, with some evidence pointing towards all PGLs being derived in essence from some form of MALT lymphoma.

Clinical Features and Diagnosis

Like GISTs, presentation of PGLs is often asymptomatic. However, patients may experience abdominal pain, weight loss and malena. They are diagnosed endoscopically, but are highly variable in appearance, ranging from simple mucosal erythema to a large ulcerated lesion [32]. Lesions are typically located at pyloric antrum, corpus and cardia. Multiple biopsies are usually required for an accurate diagnosis, and may require the use of so-called "jumbo" forceps or mucosal lift biopsies for acquisition of larger samples to better facilitate the polymerase chain reaction to demonstrate B-cell monoclonality that helps makes the diagnosis of MALT lymphoma [33]. Molecular markers can be ascertained from the biopsies and the presence of specific genetic mutations such as the t(11;18) translocation can affect the effectiveness of different treatments [29].

Staging and Treatment

EUS and chest/abdominal/pelvis CT remain the modalities for staging of PGLs. EUS specifically allows the physician to

ascertain presence of metastasis to local lymph nodes and depth of tumour invasion [8]. Lesions that invade deeply into the gastric wall are associated with a greater risk of lymph nodal involvement and lower responsiveness to antibiotic treatment [34]. The most commonly used system for staging is Lugarno's modification to Blackledge's system. The Ann Arbor/TNM system is also utilised.

Low grade MALT lymphomas in patients who are *H. pylori* positive can be cured with effective antibiotic eradication therapy, with remission rates of 60–100% being achieved. More high grade PGLs and patients with molecular mutations such as t(11;18) require multimodal treatment that involves a combination of chemotherapy (standard and monoclonal therapy), radiotherapy and in select cases, surgical resection.

Regardless of the modality of treatment chosen, EUS/endoscopy should be used as surveillance in patients in whom remission is achieved, usually at a 12 month interval.

Key Points

- *Helicobacter pylori* is a major carcinogenic factor in diffuse type GC (the most common form of GC worldwide).
- Gastric cancer incidence is on the increase in the elderly although it is on a decline in other population groups.
- Geriatric patients tend to have poorer survival, stage for stage, compared to the general population; a result of patient factors (co-morbidities, unsuitability for aggressive treatment) and tumour factors (site of lesions and spread).
- Treatment of gastric adenocarcinoma is best individualised based on co-morbidities; age by itself is not a contraindication to surgical or medical intervention.
- Although the incidence of non adenocarcinoma gastric malignancies is low, they are increasing in number in older adults, and should be recognised as potential contributors to morbidity and mortality in this age.

References

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin. 2005;55(2):74–108.
2. Miettinen M, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the stomach: a clinicopathologic, immunohistochemical, and molecular genetic study of 1765 cases with long-term follow-up. Am J Surg Pathol. 2005;29:52–68.
3. Nakamura S, Matsumoto T, Iida M, et al. Primary gastrointestinal lymphoma in Japan. A clinicopathologic analysis of 455 patients with special reference to its time trends. Cancer. 2003;97:2462–73.
4. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. J Clin Oncol. 2006;24(14):2137–50.
5. Tan KT, Fielding JWL. Early diagnosis of early gastric cancer. Eur J Gastroenterol Hepatol. 2006;18:821–9.
6. Tsubono Y, Hisamichi S. Screening for gastric cancer in Japan. Gastric Cancer. 2000;3(1):9–18.
7. Lauren P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma: an attempt at a histo-clinical classification. Acta Pathol Microbiol Scand. 1965;64:31–49.
8. Kitamura K, Yamaguchi T, Taniguchi H, et al. Clinicopathological characteristics of gastric cancer in the elderly. Br J Cancer. 1996;73(6):798–802.
9. Goodman KJ, Cockburn M. The role of epidemiology in understanding the health effects of *Helicobacter pylori*. Epidemiology. 2001;12:266–71.
10. Mizuno S, Mili I, Ishida T, et al. Prescreening of a high-risk group for gastric cancer by serologically determined *Helicobacter pylori* infection atrophic gastritis. Dig Dis Sci. 2010;55(11):3132–7.
11. Correa P. *Helicobacter pylori* and gastric cancer. Cancer Epidemiol Biomarkers Prev. 2003;12:238s–241.
12. Ally R, Mitchell HM, Segal I. Cag A +ve *H. pylori* aplenty in South Africa: the first systematic study of *H. pylori* infection in asymptomatic children in Soweto. Gut. 1999;45 Suppl 111:a97–8.
13. Oliver SL, Hale M, Mohamed AE, Segal I. Low incidence of gastric cancer in Sowetan blacks. S Afr Med J. 1991;80:50 (Abstract).
14. Mitchell HM, Ally R, Ahmed R, Segal I. The host immune response to *H. pylori* infection in Sowetans is significantly different from that in western subjects. S Afr Med J. 2000;90:640.
15. Fox JG, Beck P, Dangler CA, et al. Concurrent enteric helminth infection modulates inflammation and gastric immune responses and reduces *Helicobacter*-infused gastric atrophy. Nat Med. 2000;6:336–42.
16. Cardwell CR, Abnet CC, Cantwell MM, Murray LJ. Exposure to oral bisphosphonates and risk of esophageal cancer. JAMA. 2010;304(6):557–63.
17. Rothwell PM, Fowkes FG, Belch JF, et al. Effect of daily aspirin on long-term risk of death due to cancer: an analysis of individual patient data from randomized trials. Lancet. 2011;377(9759):3–4.
18. Greene FL, Page DL, Fleming ID, et al. AJCC cancer staging manual. 6th ed. New York, NY: Springer; 2002.
19. Puli SR, Batapati Krishna Reddy J, et al. How good is endoscopic ultrasound for TNM staging of gastric cancers? A meta-analysis and systemic review. World J Gastroenterol. 2008;14:4011–9.
20. Vander Noot MR, Eloubeidi MA, Chen VK, et al. Diagnosis of gastrointestinal tract lesions by endoscopic ultrasound-guided fine needle aspiration biopsy. Cancer. 2004;102:157–63.
21. Mukai K, Ishida Y, Okajima K, Isokazi H, Morimoto T, Nishiyama S. Usefulness of pre-operative FDG-PET for detection of gastric cancer. Gastric Cancer. 2006;9(3):192–6.
22. Crumley AB, Stuart RC, McKernan M, McMillan DC. Is hypoalbuminemia an independent prognostic factor in patients with gastric cancer? World J Surg. 2010;34(10):2399–400.
23. Yamashita H, Katai H. Systemic inflammatory response in gastric cancer. World J Surg. 2010;34(10):2393–8.
24. Barbour AP, Rizk NP, Gonen M, et al. Lymphadenectomy for adenocarcinoma of the gastro-oesophageal junction (GEJ): impact of adequate staging on outcome. Ann Surg Oncol. 2007;12(2):306–12.
25. Cuschieri A, Weeden S, Fielding J, et al. Patient survival after D1 and D2 resections for gastric cancer: long-term results of the MRC randomized surgical trial. Surgical Co-operative Group. Br J Cancer. 1999;79(9–10):1522–30.
26. Wagner AD, Grothe W, Haerting J, et al. Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. J Clin Oncol. 2006;24(18):2903–9.
27. Gotoda T. Endoscopic resection for premalignant and malignant lesions of the gastrointestinal tract from the oesophagus to the colon. Gastrointest Endosc Clin N Am. 2008;18:435–50.

28. Saif MW, Makrilia N, Zalonis A, et al. Gastric cancer in the elderly: an overview. Eur J Surg Oncol. 2010;36:709–17.
29. Guida F, Antonino A, Conte P, et al. Gastric cancer in elderly: clinico-pathological features and surgical treatment. BMC Geriatr. 2009;9 Suppl 1:A66.
30. Scarpa M, Bertin M, Ruffolo C, et al. A systematic review on the clinical diagnosis of gastrointestinal stromal tumours. J Surg Oncol. 2008;98:384–92.
31. Shinomura Y, Kinoshita K, Tsutsui S, Hirota S. Pathophysiology, diagnosis, and treatment of gastrointestinal and stromal tumors. J Gastroenterol. 2005;40:775–80.
32. Ahmad A, Govil Y, Frank BB. Gastric mucosal-associated lymphoid tissue associated lymphoma. Am J Gastroenterol. 2003; 98:975–86.
33. Bolondi L, Casanova P, Caletti GC, et al. Primary gastric lymphoma versus gastric carcinoma: endoscopic US evaluation. Radiology. 1987;165:821–6.
34. Sackmann M, Morgner A, Rudolph B, et al. Regression of gastric MALT lymphoma after eradication of *Helicobacter pylori* is predicted by endosonographic staging. MALT Lymphoma Study Group. Gastroenterology. 1997;113:1087–90.

Esophageal Cancer

61

Noah Kornblum

Introduction

Esophageal carcinoma represents a relatively uncommon malignancy, which remains highly lethal [1]. Substantial changes in our understanding of this disease, in particular its epidemiological pattern and histopathology, have developed over the last several decades [2]. Advances in diagnosis, staging, prognostication, and treatment have resulted in small but meaningful improvements in outcomes for some patients.

Epidemiology

Wide global differences exist in the incidence patterns and distribution of specific histological subtypes of esophageal cancer [3]. In the United States, of the 16,640 people (13,130 men and 3,510 women) diagnosed with esophageal cancer in 2010, approximately 14,500 will die [4]. Worldwide, an estimated 482,300 new esophageal cancer cases occurred in 2008 leading to 406,800 deaths (Fig. 61.1) [5].

Squamous cell carcinomas (SCCs), generally located in the middle or upper one-third of the esophagus, represent the predominate subtype (~90%) of the cancers diagnosed in the highest incidence regions. Indeed, a so-called "esophageal cancer belt" exists, stretching from northern Iran to across central Asia to North-Central China [6]. These cancers may be on rise in certain countries including Taiwan and parts of Asia, likely due to increases in cigarette smoking and alcohol use [7]. Conversely, SCCs of the esophagus are on the decline in Western countries, a positive development attributed to reductions in alcohol consumption and tobacco use [8].

Esophageal adenocarcinomas (EACs), cancers which generally arise in the lower one-third of the esophagus and gastroesophageal junction, are increasing in incidence in several Western countries, including England and the United States [9]. This trend has been noted for several decades. In fact, while in the 1960s 90% of the esophageal tumors seen in the United States were SCCs, currently adenocarcinomas predominate [10].

Some of these notable differences in histological type and geographic distribution can be attributed to differences in identifiable risk factors, for example disparities in diet, trends in obesity, and rates of chronic gastroesophageal reflux disease (GERD) leading to Barrett's esophagus (see section "Risk Factors") [11].

Interestingly, the frequency of this cancer varies widely even within the United States, with much higher rates noted in urban rather than rural areas. In a report from Washington, DC, the rates among African American males reached 28.6 per 100,000, compared to the overall rates of 3–4 per 100,000 in the nation [12]. Esophageal cancer trends reveal a distinct male predominance. The lifetime risk for American men and women is 0.8% and 0.3%, respectively, with African American men at particular [4]. The epidemiologic pattern of esophageal carcinoma is not different in older adults. Most studies report similar clinical symptoms at presentation, as well as similar distribution of histology, stage, and location of tumors for patients older and younger than 70 years of age [13].

Risk Factors

Advances in basic science across multiple disciplines, including genetics, molecular biology, infectious disease, and immunology, have yielded new insights into the pathobiology, etiology, and understanding of specific risk factors in the development of esophageal cancer.

Known risks for esophageal cancer are listed in Table 61.1, and include, age, gender, GERD, Barrett's esophagus, tobacco and alcohol use, obesity, diet, workplace exposure, injury to the esophagus, achalasia, tyelosis, esophageal webs, *Helicobacter pylori*, and other cancers.

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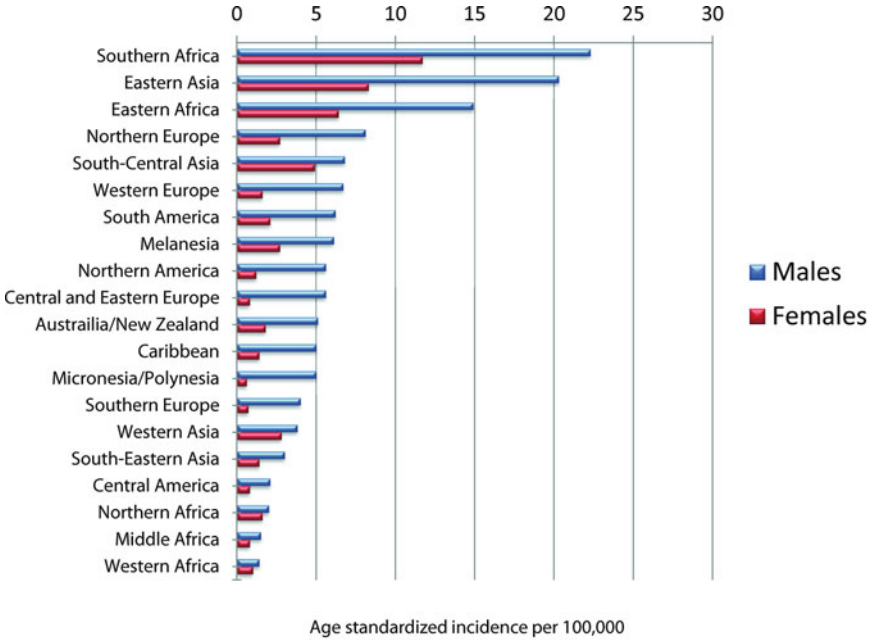

Fig. 61.1 Age-standardized esophageal cancer incidence rates by sex and world area. *Source*: GLOBOCAN 2008 [1], figure 12, p. 81; obtained permission for reprint

Table 61.1 Esophageal cancer risk factors

Modifiable risks
Tobacco use
Alcohol use
GERD
Barrett's esophagus
Diet
Obesity
Workplace exposure
Nonmodifiable risks
Age
Gender
Race
Achalasia
Injury
Tyelosis
Esophageal webs

Age/Gender

The chance of developing esophageal cancer increases with age, with fewer than 15% of cases in those younger than age 55, and most cases seen in individuals 65 and older.

The highest sex ratios were seen in EAC in the age group 50–59, perhaps relating to female sex hormone exposure playing a protective role, though this theory is not clearly established [14].

Gastroesophageal Reflux Disease

Chronic GERD has been identified as an important risk factor for the development of Barrett's esophagus, a precursor to EAC. Primary care providers must maintain a high index of suspicion and identify patients with significant risks of developing Barrett's esophagus for referral to a gastroenterologist for appropriate endoscopic screening [15]. Older patients represent challenges as many are asymptomatic or present atypically.

Barrett's Esophagitis

The esophagus has four histological layers: mucosa, submucosa, muscularis, and adventitia. The esophageal lumen is normally lined by stratified squamous epithelium. Barrett's esophagus is defined as a change in the esophageal epithelium of any length that can be recognized at endoscopy and is confirmed to have intestinal metaplasia of the tubular esophagus and excludes intestinal metaplasia of the cardia [16].

Metaplasia is the physiological process whereby one fully differentiated (adult) cell type replaces another fully differentiated type. In Barrett's esophagus, this metaplastic change is thought to occur as a result of chronic acid peptic esophagitis. With continued inflammatory injury, over time, dysplasia develops in this lower esophageal region. Cancers in Barrett's esophagus develop through a sequence of DNA alterations and morphological changes recognized as dysplasia. Dysplasia is not a single abnormality, but rather, represents a constellation of histological aberrations whereby one or more clones of cells have acquired genetic damage rendering them neoplastic and predisposed to malignancy [17]. Table 61.2 outlines the diagnosis, surveillance, and goals of therapy of Barrett's esophagus (BE) [16].

Screening of patients with GERD helps identify those at risk of EAC; both observational and computer models support

Table 61.2 Diagnosis, surveillance, and goals of therapy of Barrett's esophagus (BE) [16]

Screening
Patients with chronic GERD symptoms are most likely to have BE and should undergo endoscopy
Diagnosis
Requires systematic biopsy of abnormal-appearing mucosa to document intestinal metaplasia and detect dysplasia
Surveillance
Grade of dysplasia determines endoscopy interval and abnormalities on the epithelial surface need sampling
Grade of dysplasia and development of adenocarcinoma: dysplasia grade (none to low or high grade) correlates with greater likelihood of cancer
Frequency of follow-up endoscopy 3 years for no dysplasia to every 3 months for high-grade dysplasia
Goals of therapy
The goals of therapy for BE are same as for GERD: to control symptoms from GERD and maintenance of healed mucosa

the benefit of screening and surveillance, with the benefit of endoscopic screening comparable to mammography for breast cancer [18].

Considerable controversies and difficulties exist among experts regarding several components of this diagnosis. For example, there exist significant differences in the endoscopic definition of the esophagogastric junction (EGJ), the original or background mucosa of Barrett's adenocarcinoma (BA), the definition of Barrett's esophagus (BE), and the histologic criteria for high-grade dysplasia or well-differentiated adenocarcinoma with early invasion in the esophagus and stomach [19].

Adenocarcinomas arising in the gastroesophageal junction (GEJ) often stretch proximally into the lower esophagus, and distally to the superior upper region of the gastric cardia. This presents a classification challenge, as it is essentially impossible to determine if these cancers arose in the lower esophagus as a result of intestinal type metaplasia, or in the proximal stomach. The tumors are not distinct from one another morphologically, and epidemiologically both GEJ and gastric adenocarcinomas appear to be on the rise in Caucasian males [20].

Patients with Barrett's esophagus face an approximately 30-fold increase in the relative risk of developing esophageal cancer, though their absolute risk remains low [21]. Annual cancer incidence estimates in BE have ranged from 0.2 to 2.0%, with differences in risks between endoscopically found metaplasia alone and true BE [22, 23].

Smoking

Smoking increases the risk of both SCC and EAC, the latter particularly true with BE [24]. In a large pooled data analysis from the International BEACON (Barrett's Esophagus and Esophageal Adenocarcinoma Consortium), smoking was associated with a more than twofold increased risk of adenocarcinoma compared to controls [25].

Cigarette smoking is an established risk factor for SCC particularly in those who also abuse alcohol. Unfortunately, cigarette smoking appears to be on the rise in Asian countries, and likely, in part, explains the trends in increased aerodigestive cancer incidence, particularly in China [26]. Cigar and pipe smoking are linked to increased esophageal cancer incidence, though not to the extent seen with cigarette smoking [27, 28].

Alcohol

Alcoholism although not clearly linked to the development of EAC has a relationship with SCC, an injury augmented by concomitant tobacco use [29].

Diet

Foods containing *N*-nitrosamines have long been implicated in the development of GI malignancies especially in China and parts of Asia where vegetables are frequently pickled using this form of food preservative [30]. These carcinogens directly damage DNA through alkylation [31]. Similar substances are produced by certain fungi, particularly within corn crops in certain regions of China and elsewhere [32]. Betel nut chewing, which is extensive across regions of Asia, has been linked to the development of esophageal SCC, and may involve the release of copper with resulting induction of collagen synthesis by fibroblasts [33, 34].

Foods and beverages consumed at high temperatures may increase the risk of esophageal cancer from thermal mucosal injury [35]. Weaker dietary associates have been reported with red meat, low selenium, zinc and folate intake, but need substantiation [36–39]. A study comparing five major dietary patterns suggested that diet rich in foods of animal origin and poor in vitamins and fiber content increased esophageal cancer risk [40].

Structural Esophageal Disease

Underlying anatomical abnormalities to the esophagus including achalasia and strictures (from caustic damage, lye, etc.) are linked to the development of esophageal cancer [41].

Tyelosis

Tylosis is a rare disease associated with hyperkeratosis of the palms of the hands and soles of the feet; these patients demonstrate high rates of esophageal SCC [42].

Obesity

Obesity has been linked to the development of EACs, but not squamous cell cancer in at least one pooled meta-analysis [43]. The increased risk is ascribed to the high incidence of GERD and erosive esophagitis [44].

Occupational Risk

Occupational exposure may represent a potential risk for the development of certain cancers. Sulfuric acid and carbon black exposures are the most implicated substances [45].

Other Factors

The role for bisphosphonates, a class of drugs used in osteoporosis, and known to be linked to the development of pill esophagitis, has been raised recently, with opposing views presented on the relationship [46]. The role for esophageal webs (Paterson Jelly and Plummer Vinson) has been raised, although the iron deficiency anemia is unrelated to esophageal cancer.

Clinical Presentation

EAC and SCC generally present similarly, though EAC more frequently involves the lower portion of the esophagus and the GEJ.

Early symptoms include dysphasia, initially primarily to solids, later progressing to liquids. Patients may complain of retro-sternal pain, "heartburn," or atypical chest pain. As the disease progresses, weight loss may develop, which can be severe, leading to cachexia. Dysphagia is the most common manifestation (seen in 90% of patients), followed by odynophagia. Significant bleeding associated with the primary lesion may lead to symptomatic iron deficiency anemia characterized by fatigue and malaise. Severe bleeding may present as hematemesis or melena. The development of hoarseness or voice quality changes should raise the suspicion of local compression of the recurrent laryngeal nerve. Sympathetic nerve compression may lead to Horner's syndrome, spinal pain, hiccups, or diaphragmatic paralysis.

Chronic and persistent, severe cough would raise concerns for aspiration or a tracheoesophageal fistula, a particularly ominous and dreaded complication associated with very short life expectancy [47–49].

Common manifestations are summarized in Table 61.3.

Table 61.3 Common clinical manifestations

Symptoms from local tumor effects
Dysphagia (solids, progressing to liquids)
Odynophagia
Weight loss
Regurgitation
Upper GI bleeding (hematemesis/melena)
Anemia (iron deficiency)
Heartburn
Symptoms from invasion of surrounding structures
Hoarseness (recurrent laryngeal nerve)
Tracheoesophageal fistulae
Hiccups (phrenic nerve)
Atypical chest pain
Symptoms of distant disease
Cachexia
Fatigue/malaise
Hypercalcemia
Metastatic disease (lungs, liver, bones, CNS)

Diagnosis

When the diagnosis of esophageal cancer is suspected, initial evaluation includes a comprehensive history and physical examination, with specific attention paid to an evaluation of lymph nodes. While barium contrast-enhanced radiography may prove useful, ultimately the diagnosis is established through endoscopic biopsy [50]. Upper endoscopy detects early esophageal cancers, which may appear as superficial plaques, nodules, or ulcerations.

More advanced lesions appear as strictures, ulcerated, circumferential, or large masses [51].

Once a biopsy histopathology report confirms cancer, comprehensive staging is required.

Formal staging requires a careful evaluation of both the local-regional tumor area, with particular attention to determining the depth of spread through the esophageal wall or into adjacent structures (T-stage), and the regional lymph nodes (N-stage).

Endoscopic ultrasound (EUS) has emerged as the most accurate and best method for determining local-regional disease extent and evaluation of the regional lymph nodes. In experienced hands this technology yields extremely precise information regarding depth of tumor penetration through the esophageal wall, as well as an opportunity for image-guided biopsies of local-regional lymph nodes (including mediastinal nodes) allowing pathological confirmation of nodal disease involvement [52, 53].

Full-body imaging, generally with contrast-enhanced CT, MRI, or PET/CT, is required to assess for possible distant disease spread (M-stage). While not routinely required, the use of more invasive techniques including laparoscopy and thorocoscopy may be appropriate, especially when biopsy confirmation of metastatic disease spread would prevent an unjustified major surgery [54].

TNM Staging

The tumor-node-metastasis (TNM) staging system of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) for esophageal cancer is generally universally accepted and utilized [55].

Most recent changes as of 2010 include the creation of two distinct stage groupings based on histology (adenocarcinoma vs. squamous), refinements in the definitions of carcinoma in-situ, simplification of tumor locations, and subclassifications based on the T and N stages, in part to better reflect potential resectability [56, 57].

Prognosis

The prognosis of patients diagnosed with esophageal cancer is directly linked to the stage of the disease. However, the overall 5-year survival rates remain poor for patients with both locally advanced and metastatic disease. For those with advanced stage disease, the overall rates of long-term survival is poor (5-year survival: <5%) [58]. Treatment with surgical resection alone for locally advanced disease results in 5-year survival of approximately 20–25% [59, 60]. Combined modality therapy, employing chemotherapy or chemoradiotherapy with surgery, increases the 5-year survival rate to 30–35% [61–63]. The median overall survival time for patients with metastatic disease is approximately 8–10 months [2].

Management

Treatment planning for patients with esophageal cancer requires the multidisciplinary collaboration between experts across multiple fields including surgery, medical oncology, radiation oncology, nutrition, and supportive care teams.

Options for management include local therapies, such as endoscopic resection, surgical resection, chemotherapy (both neoadjuvant and adjuvant), radiotherapy, and chemoradiotherapy. Combinations of bi- and trimodality therapy are not uncommon, and are associated with some of the best outcome data for those patients fit enough to receive complex and aggressive care plans. Management options are summarized in Table 61.4.

Early Stage Disease

The optimal management for localized carcinomas of the esophagus and EGJ is intensely controversial [64]. Surgical resection alone has been the standard and predominant therapy traditionally, but has been challenged by detractors based on the low rates of long-term survival and infrequency of early diagnosis [62, 65].

Very early stage cancers (T1a), those involving only the superficial mucosa, may be treated with endoscopic mucosal resection. Adding chemotherapy, radiation, or concurrent chemoradiation to surgical resection has shown mixed results.

Tumors arising in the middle to lower one-third of the thoracic esophagus generally require total esophagectomy, in part due to the presence of submucosal longitudinal lymphatic vessels which connect to the superior mediastinal and the paracardial lymphatics and can lead to skip metastasis [66–69]. A number of surgical procedures may be used in esophageal resection, most commonly the transthoracic or transhiatal approach. Differences include extent of lymphadenectomy and morbidity and mortality rates, however neither approach has been proven to be superior [70].

Table 61.4 Management options: esophageal cancer

Disease extent	Treatment	Options	Comments
Early			
T1a tumors (mucosal involvement)	Endoscopic mucosal resection	Neoadjuvant chemotherapy	Improved rates of complete resection without clear OS benefit
Mid to lower one-third of esophagus	Total esophagectomy	Transhiatal esophagectomy with gastric pull-up	Lower surgical morbidity and mortality
		Transthoracic esophagectomy	Better lymphadenectomy
Locally advanced			
T1-4N0M0 TanyN+M0	Definitive concurrent chemoradiotherapy	Induction chemotherapy followed by chemoradiotherapy	Higher toxicity and no clear survival advantage
Metastatic disease			
M+ disease	Systemic chemotherapy	Single agents (cisplatin; 5-FU; doxorubicin; methotrexate; etoposide)	Improved OS compared to best supportive care
	Combination chemotherapy—standard approach for fit patients	Newer agents (taxanes; irinotecan)	
		Cisplatin and 5-FU	Higher toxicities without increased duration of response
		Three drug regimens (ECF or DCF)	Superior response rates (~35%), but higher toxicities
		Capecitabine containing regimens	Not inferior to infusional 5-FU containing regimens

Locally Advanced Disease

Management of patients diagnosed with locally advanced cancers of the esophagus and GEJ is complicated by the heterogeneous nature of this group. Patients may be considered potentially resectable or unresectable based on characteristics of their disease, or deemed to be nonsurgical candidates based on poor performance status.

In general, a multimodality approach is required. Long-term survival is uncommon, and palliation and quality of life improvements are important goals. Available management options include systemic chemotherapy, radiotherapy (including brachytherapy), and concurrent chemoradiotherapy. Many local control modalities exist including esophageal dilatation, stenting, laser ablation, photodynamic therapy, chemical ablation, and palliative surgery.

At present, definitive concurrent chemoradiotherapy represents the standard of care for fit patients with locoregional esophageal cancer, which may be followed by surgical resection. Historically, there have been many randomized controlled trials comparing chemoradiotherapy to radiotherapy alone for the definitive management of esophageal cancer [71–73]. The results have been mixed. Some studies seem to indicate a clear survival advantage with combined therapy, while others do not, perhaps in part due to suboptimal radiation dosing. Sequential treatment is inferior to concurrent therapy.

Metastatic Disease

Systemic chemotherapy is the mainstay treatment for advanced metastatic esophageal and GEJ cancers. The goals of treatment include symptom palliation and prolonged survival.

Single-Agent Chemotherapy

Multiple older single-agent chemotherapeutic agents have been tested and used in advanced esophageal cancers. These include traditional alkylators and antimetabolite drugs such as cisplatin, 5-FU, doxorubicin, methotrexate and etoposide, to name a few [74–76]. Most demonstrate modest response rates and only small improvements in overall survival. Complete responses are infrequent, and response duration rarely exceeds 6 months.

Newer single agents, such as taxanes and irinotecan, may offer slightly higher response rates, but are associated with serious toxicities [77–79].

Combination Chemotherapy

Studies comparing single agents vs. combination therapy generally demonstrate superior response rates in favor of combination therapy, but this has not translated into meaningful survival differences. Cisplatin and 5-FU, a commonly employed regimen, has an established and manageable toxicity profile, with response rates in the range of 35% [75, 80]. At present, most fit patients with good performance status are managed with three drug combination regimens, which are favored and considered standard first-line treatment. These are ECF (epirubicin, cisplatin, infusional 5-FU) and DCF (docetaxel, cisplatin, infusional 5-FU) [81, 82]. Capecitabine (Xeloda®), a newer oral fluoropyrimidine, has been successfully substituted for infusional 5-FU with good results.

How Do Older Adults Respond to Treatment?

In general, older patients with esophageal cancer can benefit from cancer treatment (curative intent or best supportive care, including palliative care); weight loss, WHO performance status, and Charlson score help select appropriate treatment in the older age group [13]. While increasing age was a risk factor for mortality and survival after esophageal resection, the mortality is particularly high with perioperative cardiac or respiratory morbidity [83]. Esophageal surgery in those over 75 years has an acceptable morbidity and mortality; but when a severe complication occurs, half the patients die [84]. Esophagectomy can even be performed successfully in octogenarians with good cardiac and pulmonary function [85].

Recent Advances and Novel Agents

Approximately 7–34% of human gastric and esophagogastric cancers have been shown to overexpress HER2, an oncogene important for cancer growth and development [86]. Trastuzumab, a monoclonal antibody targeted against HER2 currently used for breast cancer treatment, has recently shown benefit in gastric and GE junction cancers which overexpress HER2 [87].

Lapatinib is an orally active small molecule inhibitor of both EGFR I and II (HER2) which is currently being investigated for the treatment of patient with advanced gastric cancer (in combination with paclitaxel), and may hold promise for the treatment of advanced HER2-positive esophageal cancer [88].

Additional agents targeting EGFR include cetuximab, a monoclonal antibody, as well as the small molecule tyrosine kinase inhibitors gefitinib and erlotinib. Early testing results with these agents have been mixed, and full conclusions regarding their clinical utility will require data form randomized phase III trials [89–94].

Another important biological target which has recently emerged in the treatment of advanced cancers is the vascular endothelial growth factor receptor (VEGF) pathway, as well as other targets implicated in tumor angiogenesis [95–97].

Bevacizumab (Avastin®), a monoclonal antibody against the VEGF-A molecule, is the most well-known and established agent targeting angiogenesis and the VEGF pathway, with an established beneficial role in several tumor types [98]. Unfortunately, chemotherapy in combination with Avastin tested in locally advanced unresectable or metastatic gastric or GE-junction cancers in a recent phase III study (AVAGAST trial) failed to demonstrate a statistically significant improvement in median overall survival [99].

Multiple signaling pathways that are in operation in esophageal cancer are the focus of current and future research and drug development. Promising targets include ERK MAP kinase inhibition, PI3 kinase, NF-κB, mTOR, VEGF, and EGFR [100].

Key Points

- Esophageal carcinoma represents a relatively uncommon malignancy which remains highly lethal.
- Squamous cell carcinomas (SCCs) are generally located in the middle or upper one-third of the esophagus while adenocarcinomas (EAC) present in the lower one-third of the GE junction.
- Major risk factors for adenocarcinoma include long-standing gastroesophageal reflux disease (GERD), Barrett's metaplasia, obesity, and possibly ethnicity in view of the observation that it affects predominantly Caucasian men.
- Risk factors for squamous carcinoma include alcoholism and smoking.
- Manifestations include dysphagia to solids and liquids, weight loss, and aspiration.
- Diagnosis requires upper endoscopy and target biopsies. Staging requires endoscopic ultrasound (EUS) and CT imaging of chest and abdomen.
- Management includes surgery, chemotherapy, and chemoradiation, based on location, stage and type of cancer, in addition to age and comorbidity.

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011;61:69–90.
2. Enzinger PC, Mayer RJ. Esophageal cancer. N Engl J Med. 2003;349:2241–52.
3. Jemal A, Center MM, DeSantis C, Ward EM. Global patterns of cancer incidence and mortality rates and trends. Cancer Epidemiol Biomarkers Prev. 2010;19:1893–907.
4. American Cancer Society. Cancer facts & figures 2010. Atlanta: American Cancer Society; 2010.
5. Ferlay JSH, Bray F, Forman D, Mathers C, Parkin DM. GLOBOCAN 2008, cancer incidence and mortality worldwide: IARC CancerBase No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer; 2010. http://globocan.iarc.fr. Accessed 26 July 2011.
6. Gholipour C, Shalchi RA, Abbasi M. A histopathological study of esophageal cancer on the western side of the Caspian littoral from 1994 to 2003. Dis Esophagus. 2008;21:322–7.
7. Lu CL, Lang HC, Luo JC, et al. Increasing trend of the incidence of esophageal squamous cell carcinoma, but not adenocarcinoma, in Taiwan. Cancer Causes Control. 2010;21:269–74.
8. Cook MB, Chow WH, Devesa SS. Oesophageal cancer incidence in the United States by race, sex, and histologic type, 1977–2005. Br J Cancer. 2009;101:855–9.
9. Lepage C, Rachet B, Jooste V, Faivre J, Coleman MP. Continuing rapid increase in esophageal adenocarcinoma in England and Wales. Am J Gastroenterol. 2008;103:2694–9.
10. Brown LM, Devesa SS. Epidemiologic trends in esophageal and gastric cancer in the United States. Surg Oncol Clin N Am. 2002;11:235–56.
11. Kamangar F, Chow WH, Abnet CC, Dawsey SM. Environmental causes of esophageal cancer. Gastroenterol Clin North Am. 2009;38:27–57, vii.
12. Pottern LM, Morris LE, Blot WJ, Ziegler RG, Fraumeni Jr JF. Esophageal cancer among black men in Washington, D.C. I. Alcohol, tobacco, and other risk factors. J Natl Cancer Inst. 1981;67:777–83.
13. Tougeron D, Hamidou H, Scotte M, et al. Esophageal cancer in the elderly: an analysis of the factors associated with treatment decisions and outcomes. BMC Cancer. 2010;10:510.
14. Nordenstedt H, El-Serag H. The influence of age, sex, and race on the incidence of esophageal cancer in the United States (1992–2006). Scand J Gastroenterol. 2011;46:597–602.
15. Morganstern B, Anandasabapathy S. GERD and Barrett's esophagus: diagnostic and management strategies in the geriatric population. Geriatrics. 2009;64:9–12.
16. Sampliner RE. Updated guidelines for the diagnosis, surveillance, and therapy of Barrett's esophagus. Am J Gastroenterol. 2002;97:1888–95.
17. Goldblum JR. Barrett's esophagus and Barrett's-related dysplasia. Mod Pathol. 2003;16:316–24.
18. Spechler SJ, Barr H. Review article: screening and surveillance of Barrett's oesophagus: what is a cost-effective framework? Aliment Pharmacol Ther. 2004;19 Suppl 1:49–53.
19. Takubo K, Vieth M, Aida J, et al. Differences in the definitions used for esophageal and gastric diseases in different countries: endoscopic definition of the esophagogastric junction, the precursor of Barrett's adenocarcinoma, the definition of Barrett's esophagus, and histologic criteria for mucosal adenocarcinoma or high-grade dysplasia. Digestion. 2009;80:248–57.
20. Cameron AJ, Lomboy CT, Pera M, Carpenter HA. Adenocarcinoma of the esophagogastric junction and Barrett's esophagus. Gastroenterology. 1995;109:1541–6.
21. Van der Veen AH, Dees J, Blankensteijn JD, Van Blankenstein M. Adenocarcinoma in Barrett's oesophagus: an overrated risk. Gut. 1989;30:14–8.
22. Rastogi A, Puli S, El-Serag HB, Bansal A, Wani S, Sharma P. Incidence of esophageal adenocarcinoma in patients with Barrett's esophagus and high-grade dysplasia: a meta-analysis. Gastrointest Endosc. 2008;67:394–8.
23. Jung KW, Talley NJ, Romero Y, et al. Epidemiology and natural history of intestinal metaplasia of the gastroesophageal junction and Barrett's esophagus: a population-based study. Am J Gastroenterol. 2011;106(8):1447–55.
24. Pandeya N, Williams GM, Sadhegi S, Green AC, Webb PM, Whiteman DC. Associations of duration, intensity, and quantity of smoking with adenocarcinoma and squamous cell carcinoma of the esophagus. Am J Epidemiol. 2008;168:105–14.

25. Cook MB, Kamangar F, Whiteman DC, et al. Cigarette smoking and adenocarcinomas of the esophagus and esophagogastric junction: a pooled analysis from the international BEACON consortium. J Natl Cancer Inst. 2010;102(17):1344–53.
26. Chen ZM, Xu Z, Collins R, Li WX, Peto R. Early health effects of the emerging tobacco epidemic in China. A 16-year prospective study. JAMA. 1997;278:1500–4.
27. Randi G, Scotti L, Bosetti C, et al. Pipe smoking and cancers of the upper digestive tract. Int J Cancer. 2007;121:2049–51.
28. Iribarren C, Tekawa IS, Sidney S, Friedman GD. Effect of cigar smoking on the risk of cardiovascular disease, chronic obstructive pulmonary disease, and cancer in men. N Engl J Med. 1999;340:1773–80.
29. Druesne-Pecollo N, Tehard B, Mallet Y, et al. Alcohol and genetic polymorphisms: effect on risk of alcohol-related cancer. Lancet Oncol. 2009;10:173–80.
30. Islami F, Ren JS, Taylor PR, Kamangar F. Pickled vegetables and the risk of oesophageal cancer: a meta-analysis. Br J Cancer. 2009;101:1641–7.
31. Wang L, Zhu D, Zhang C, et al. Mutations of O6-methylguanine-DNA methyltransferase gene in esophageal cancer tissues from Northern China. Int J Cancer. 1997;71:719–23.
32. Chu FS, Li GY. Simultaneous occurrence of fumonisin B1 and other mycotoxins in moldy corn collected from the People's Republic of China in regions with high incidences of esophageal cancer. Appl Environ Microbiol. 1994;60:847–52.
33. Pickwell SM, Schimelpfening S, Palinkas LA. 'Betelmania'. Betel quid chewing by Cambodian women in the United States and its potential health effects. West J Med. 1994;160:326–30.
34. Trivedy C, Baldwin D, Warnakulasuriya S, Johnson N, Peters T. Copper content in *Areca catechu* (betel nut) products and oral submucous fibrosis. Lancet. 1997;349:1447.
35. Islami F, Boffetta P, Ren JS, Pedoeim L, Khatib D, Kamangar F. High-temperature beverages and foods and esophageal cancer risk—a systematic review. Int J Cancer. 2009;125:491–524.
36. Cross AJ, Freedman ND, Ren J, et al. Meat consumption and risk of esophageal and gastric cancer in a large prospective study. Am J Gastroenterol. 2011;106:432–42.
37. Steevens J, van den Brandt PA, Goldbohm RA, Schouten LJ. Selenium status and the risk of esophageal and gastric cancer subtypes: the Netherlands cohort study. Gastroenterology. 2010; 138:1704–13.
38. Abnet CC, Lai B, Qiao YL, et al. Zinc concentration in esophageal biopsy specimens measured by x-ray fluorescence and esophageal cancer risk. J Natl Cancer Inst. 2005;97:301–6.
39. Larsson SC, Giovannucci E, Wolk A. Folate intake, MTHFR polymorphisms, and risk of esophageal, gastric, and pancreatic cancer: a meta-analysis. Gastroenterology. 2006;131:1271–83.
40. Bravi F, Edefonti V, Randi G, et al. Dietary patterns and the risk of esophageal cancer. Ann Oncol. 2012;23(3):765–70.
41. Sandler RS, Nyren O, Ekbom A, Eisen GM, Yuen J, Josefsson S. The risk of esophageal cancer in patients with achalasia. A population-based study. JAMA. 1995;274:1359–62.
42. Stevens HP, Kelsell DP, Bryant SP, et al. Linkage of an American pedigree with palmoplantar keratoderma and malignancy (palmoplantar ectodermal dysplasia type III) to 17q24. Literature survey and proposed updated classification of the keratodermas. Arch Dermatol. 1996;132:640–51.
43. Hampel H, Abraham NS, El-Serag HB. Meta-analysis: obesity and the risk for gastroesophageal reflux disease and its complications. Ann Intern Med. 2005;143:199–211.
44. Cook MB, Greenwood DC, Hardie LJ, Wild CP, Forman D. A systematic review and meta-analysis of the risk of increasing adiposity on Barrett's esophagus. Am J Gastroenterol. 2008;103: 292–300.
45. Parent ME, Siemiatycki J, Fritschi L. Workplace exposures and oesophageal cancer. Occup Environ Med. 2000;57:325–34.
46. Dixon WG, Solomon DH. Bisphosphonates and esophageal cancer—a pathway through the confusion. Nat Rev Rheumatol. 2011;7:369–72.
47. Daly JM, Fry WA, Little AG, et al. Esophageal cancer: results of an American College of Surgeons Patient Care Evaluation Study. J Am Coll Surg. 2000;190:562–72; discussion 72–3.
48. Coia LR, Sauter ER. Esophageal cancer. Curr Probl Cancer. 1994;18:189–247.
49. Lagergren J, Lagergren P. Oesophageal cancer. BMJ. 2010;341:c6280.
50. Gross SA, Raimondo M, Conio M. Upper gastrointestinal tumors. Endoscopy. 2007;39:110–2.
51. Kuipers EJ, Haringsma J. Diagnostic and therapeutic endoscopy. J Surg Oncol. 2005;92:203–9.
52. van Vliet EP, Heijenbrok-Kal MH, Hunink MG, Kuipers EJ, Siersema PD. Staging investigations for oesophageal cancer: a meta-analysis. Br J Cancer. 2008;98:547–57.
53. Lightdale CJ, Kulkarni KG. Role of endoscopic ultrasonography in the staging and follow-up of esophageal cancer. J Clin Oncol. 2005;23:4483–9.
54. Yau KK, Siu WT, Cheung HY, Li AC, Yang GP, Li MK. Immediate preoperative laparoscopic staging for squamous cell carcinoma of the esophagus. Surg Endosc. 2006;20:307–10.
55. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti III A, editors. AJCC staging manual. 7th ed. New York: Springer; 2009.
56. Rizk NP, Venkatraman E, Bains MS, et al. American Joint Committee on Cancer staging system does not accurately predict survival in patients receiving multimodality therapy for esophageal adenocarcinoma. J Clin Oncol. 2007;25:507–12.
57. Barbour AP, Jones M, Gonen M, et al. Refining esophageal cancer staging after neoadjuvant therapy: importance of treatment response. Ann Surg Oncol. 2008;15:2894–902.
58. Daly JM, Karnell LH, Menck HR. National cancer data base report on esophageal carcinoma. Cancer. 1996;78:1820–8.
59. Orringer MB, Marshall B, Iannettoni MD. Transhiatal esophagectomy: clinical experience and refinements. Ann Surg. 1999;230:392–400; discussion 400–3.
60. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006;355:11–20.
61. Tepper J, Krasna MJ, Niedzwiecki D, et al. Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. J Clin Oncol. 2008;26:1086–92.
62. Walsh TN, Noonan N, Hollywood D, Kelly A, Keeling N, Hennessy TP. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. N Engl J Med. 1996;335: 462–7.
63. Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med. 2001;345:725–30.
64. O'Reilly S, Forastiere AA. Is surgery necessary with multimodality treatment of oesophageal cancer. Ann Oncol. 1995;6:519–21.
65. Urba SG, Orringer MB, Turrisi A, Iannettoni M, Forastiere A, Strawderman M. Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. J Clin Oncol. 2001;19:305–13.
66. Hosch SB, Stoecklein NH, Pichlmeier U, et al. Esophageal cancer: the mode of lymphatic tumor cell spread and its prognostic significance. J Clin Oncol. 2001;19:1970–5.
67. Nigro JJ, Hagen JA, DeMeester TR, et al. Prevalence and location of nodal metastases in distal esophageal adenocarcinoma confined

to the wall: implications for therapy. J Thorac Cardiovasc Surg. 1999;117:16–23; discussion 23–5.
68. Kato H, Tachimori Y, Watanabe H, et al. Intramural metastasis of thoracic esophageal carcinoma. Int J Cancer. 1992;50:49–52.
69. Tachimori Y, Nagai Y, Kanamori N, Hokamura N, Igaki H. Pattern of lymph node metastases of esophageal squamous cell carcinoma based on the anatomical lymphatic drainage system. Dis Esophagus. 2011;24:33–8.
70. Barreto JC, Posner MC. Transhiatal versus transthoracic esophagectomy for esophageal cancer. World J Gastroenterol. 2010;16:3804–10.
71. Herskovic A, Martz K, al-Sarraf M. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. N Engl J Med. 1992;326:1593–8.
72. al-Sarraf M, Martz K, Herskovic A, et al. Progress report of combined chemoradiotherapy versus radiotherapy alone in patients with esophageal cancer: an intergroup study. J Clin Oncol. 1997; 15:277–84.
73. Wobbes T, Baron B, Paillot B, et al. Prospective randomised study of split-course radiotherapy versus cisplatin plus split-course radiotherapy in inoperable squamous cell carcinoma of the oesophagus. Eur J Cancer. 2001;37:470–7.
74. Ezdinli EZ, Gelber R, Desai DV, Falkson G, Moertel CG, Hahn RG. Chemotherapy of advanced esophageal carcinoma: Eastern Cooperative Oncology Group experience. Cancer. 1980;46:2149–53.
75. Bleiberg H, Conroy T, Paillot B, et al. Randomised phase II study of cisplatin and 5-fluorouracil (5-FU) versus cisplatin alone in advanced squamous cell oesophageal cancer. Eur J Cancer. 1997;33:1216–20.
76. Kok TC, van der Gaast A, Splinter TA. 5-Fluorouracil and folinic acid in advanced adenocarcinoma of the esophagus or esophagogastric junction area. Rotterdam Esophageal Tumor Study Group. Ann Oncol. 1996;7:533–4.
77. Ilson DH, Wadleigh RG, Leichman LP, Kelsen DP. Paclitaxel given by a weekly 1-h infusion in advanced esophageal cancer. Ann Oncol. 2007;18:898–902.
78. Muro K, Hamaguchi T, Ohtsu A, et al. A phase II study of single-agent docetaxel in patients with metastatic esophageal cancer. Ann Oncol. 2004;15:955–9.
79. Einzig AI, Neuberg D, Remick SC, et al. Phase II trial of docetaxel (taxotere) in patients with adenocarcinoma of the upper gastrointestinal tract previously untreated with cytotoxic chemotherapy: the Eastern Cooperative Oncology Group (ECOG) results of protocol E1293. Med Oncol. 1996;13:87–93.
80. Warner E, Jensen JL, Cripps C, et al. Outpatient 5-fluorouracil, folinic acid and cisplatin in patients with advanced esophageal carcinoma. Acta Oncol. 1999;38:255–9.
81. Findlay M, Cunningham D, Norman A, et al. A phase II study in advanced gastro-esophageal cancer using epirubicin and cisplatin in combination with continuous infusion 5-fluorouracil (ECF). Ann Oncol. 1994;5:609–16.
82. Ajani JA, Moiseyenko VM, Tjulandin S, et al. Clinical benefit with docetaxel plus fluorouracil and cisplatin compared with cisplatin and fluorouracil in a phase III trial of advanced gastric or gastroesophageal cancer adenocarcinoma: the V-325 Study Group. J Clin Oncol. 2007;25:3205–9.
83. Elsayed H, Whittle I, McShane J, et al. The influence of age on mortality and survival in patients undergoing oesophagogastrectomies. A seven-year experience in a tertiary centre. Interact Cardiovasc Thorac Surg. 2010;11:65–9.
84. Honore C, Al-Azzeh A, Gilson N, et al. Esophageal cancer surgery in patients older than 75: long term results. Acta Chir Belg. 2011;111:12–7.
85. Zehetner J, Lipham JC, Ayazi S, et al. Esophagectomy for cancer in octogenarians. Dis Esophagus. 2010;23:666–9.
86. Gravalos C, Jimeno A. HER2 in gastric cancer: a new prognostic factor and a novel therapeutic target. Ann Oncol. 2008; 19:1523–9.
87. Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet. 2010;376:687–97.
88. De Vita F, Giuliani F, Silvestris N, Catalano G, Ciardiello F, Orditura M. Human epidermal growth factor receptor 2 (HER2) in gastric cancer: a new therapeutic target. Cancer Treat Rev. 2010;36 Suppl 3:S11–5.
89. Pinto C, Di Fabio F, Barone C, et al. Phase II study of cetuximab in combination with cisplatin and docetaxel in patients with untreated advanced gastric or gastro-oesophageal junction adenocarcinoma (DOCETUX study). Br J Cancer. 2009;101: 1261–8.
90. Pinto C, Di Fabio F, Siena S, et al. Phase II study of cetuximab in combination with FOLFIRI in patients with untreated advanced gastric or gastroesophageal junction adenocarcinoma (FOLCETUX study). Ann Oncol. 2007;18:510–7.
91. Lorenzen S, Schuster T, Porschen R, et al. Cetuximab plus cisplatin-5-fluorouracil versus cisplatin-5-fluorouracil alone in first-line metastatic squamous cell carcinoma of the esophagus: a randomized phase II study of the Arbeitsgemeinschaft Internistische Onkologie. Ann Oncol. 2009;20:1667–73.
92. Janmaat ML, Gallegos-Ruiz MI, Rodriguez JA, et al. Predictive factors for outcome in a phase II study of gefitinib in second-line treatment of advanced esophageal cancer patients. J Clin Oncol. 2006;24:1612–9.
93. Ferry DR, Anderson M, Beddard K, et al. A phase II study of gefitinib monotherapy in advanced esophageal adenocarcinoma: evidence of gene expression, cellular, and clinical response. Clin Cancer Res. 2007;13:5869–75.
94. Dragovich T, McCoy S, Fenoglio-Preiser CM, et al. Phase II trial of erlotinib in gastroesophageal junction and gastric adenocarcinomas: SWOG 0127. J Clin Oncol. 2006;24:4922–7.
95. Gerger A, LaBonte M, Lenz HJ. Molecular predictors of response to antiangiogenesis therapies. Cancer J. 2011;17(2):134–41.
96. Dvorak HF, Weaver VM, Tlsty TD, Bergers G. Tumor microenvironment and progression. J Surg Oncol. 2011;103:468–74.
97. Janjigian YY, Shah MA. Molecularly targeted therapies in advanced gastric cancer. Minerva Gastroenterol Dietol. 2011;57:75–88.
98. Damasceno M. Bevacizumab for the first-line treatment of human epidermal growth factor receptor 2-negative advanced breast cancer. Curr Opin Oncol. 2011;23(Suppl):S3–9.
99. Kang Y, Ohtsu A, Van Cutsem E, et al. AVAGAST: a randomized, double-blind, placebo-controlled, phase III study of first-line capecitabine and cisplatin plus bevacizumab or placebo in patients with advanced gastric cancer (AGC). ASCO Meeting Abstracts. 28:LBA4007.
100. Keld RR, Ang YS. Targeting key signalling pathways in oesophageal adenocarcinoma: a reality for personalised medicine? World J Gastroenterol. 2011;17:2781–90.

Pancreatic Cancer

62

Gaurav Aggarwal and Suresh T. Chari

Introduction

Pancreatic cancer is the second most common gastrointestinal malignancy in the United States, with an estimated 42,470 cases in 2009 [1]. Despite being the tenth most common malignancy overall, pancreatic cancer is the fourth most common cause of cancer deaths contributing to 35,240 deaths in 2009 [1]. The 5-year relative survival rate over the last 3 decades has increased infinitesimally in absolute terms from 2.5 to 5% [2]. This dismal survival rate is attributable to the lack of an early detection strategy and limited therapeutic options.

Epidemiology

Pancreatic cancer is rare before age 45 but the incidence rises thereafter, being a significant problem in the geriatric population. The disease is more common in men than women (1.3:1) and in African-Americans as compared to the general population [2]. In Canada, the overall incidence has remained stable between 1992 and 2005, but has decreased in men, perhaps due to changes in smoking behavior [3].

Risk Factors

Genetic/Hereditary Factors

Various studies have reported that 4–16% patients with pancreatic cancer either have a family history of pancreatic cancer or a known genetic syndrome (Table 62.1) with a predisposition to pancreatic cancer [4]. Besides familial syndromes, patients with non-O (i.e., A, B, AB) ABO blood groups have increased susceptibility to pancreatic cancer as compared to their blood group O counterparts [5].

Environmental and Dietary Factors

An increased risk (relative risk 1.5–3) of pancreatic cancer exists in smokers, likely related to aromatic amines. The risk increases with greater intensity (≥30 cigarettes/day), duration (≥50 years) and cumulative smoking dose (≥40 pack-years), and diminishes to baseline after 15 years of smoking cessation [6]. Dietary factors incriminated include diets rich in fat and meat, while fruits and vegetables have a protective effect against the cancer [7]. The association between pancreatic cancer and alcohol, caffeine, and NSAID use remain inconclusive. Besides diet, other life style factors that influence insulin resistance (such as physical activity) also affect pancreatic cancer risk [8].

Host Factors

The association between diabetes and pancreatic cancer is well recognized. While long-standing diabetes is an etiologic factor, new-onset diabetes is a manifestation of the cancer. Though most studies suggest an elevated risk of pancreatic cancer among long-standing diabetics, the strength of this association is modest at best. In a meta-analysis of 20 epidemiologic studies, the pooled relative risk of pancreatic cancer in diabetics diagnosed at least 1 year prior to either diagnosis of pancreatic cancer or to pancreatic cancer death was 2.1 (95% CI, 1.6–2.8) [9]. Many, but not all, cohort studies reveal that the risk of pancreatic cancer associated with diabetes decreases with increasing duration of follow-up [10]. As many as 47% patients with pancreatic cancer are reported to have diabetes mellitus (DM) [10]. In 74% of these patients, diabetes is of recent onset (<2 years) [10]. Furthermore, the diabetes resolves in 57% patients after

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Table 62.1 Genetic syndromes associated with increased risk of pancreatic cancer [29–31]

Syndrome	Mutated gene	Risk of pancreatic cancer at age 70 (%)
Hereditary pancreatitis	Trypsinogen	25–40
Peutz–Jeghers syndrome	STK11	30–60
HNPCC syndrome	Mismatch repair	<5
Breast cancer	BRCA2	5

HNPCC Hereditary nonpolyposis colorectal cancer syndrome

tumor resection [10]. These characteristics suggest that DM in pancreatic cancer may result from tumor secreted products. Despite the well described association, data does not support screening new onset diabetics for pancreatic cancer.

Various premalignant lesions in the pancreas are associated with an increased risk of pancreatic cancer. Chronic (nonhereditary) pancreatitis is associated with a 9–16-fold increased risk of pancreatic cancer [11], an association reflective of a direct causal relationship or shared risk factors (such as smoking) between the two entities. Intraductal papillary mucinous neoplasm (IPMN) and mucinous cystic neoplasm (MCN) are precursor lesions in the pancreas that warrant surveillance or surgical resection based on the clinical context [12].

Other Factors

Female hormone use has been implicated; use of estrogen during reproductive years may contribute to the development of pancreatic cancer later in life, but this finding needs to be confirmed [13]. While obesity in early adulthood might lead to an increased risk of pancreatic cancer, obesity in older patients with pancreatic cancer has been associated with reduced survival [14].

Pathology

Up to 90% of pancreatic cancers are ductal adenocarcinomas [15]. The tumors arise from precursor lesions called pancreatic intraepithelial neoplasia (PanIN), the pancreatic head being the most common location (70%). Typically, tumors in the head are smaller at presentation than more distal tumors, reflective of the delay in development of symptoms in the latter based on location. Ductal adenocarcinomas are typically associated with a prominent desmoplastic reaction giving them a firm consistency on macroscopic examination. The tumor typically invades the perineural space and lymphatics. Metastatic disease involves the liver, lungs, kidneys, adrenals, bone, and peritoneum. The remaining 10% of pancreatic tumors are acinar cell carcinomas, islet cell tumors, and rare non-epithelial malignancies. In this chapter, the term pancreatic cancer is used to describe pancreatic adenocarcinoma.

Clinical Presentation

Symptoms

Most patients with pancreatic cancer remain asymptomatic until late in the course, leading to a delayed diagnosis. Hence, fewer than 20% tumors are resectable at the time of diagnosis [16]. Abdominal pain resulting from involvement of the celiac or superior mesenteric arterial plexus is the most common presenting symptom, occurring in up to 80% of patients [17]. The pain is typically a dull ache in the upper abdomen that might radiate to the back and may be relieved by lying in a curled position. Jaundice due to obstruction of the common bile duct, is present in greater than 50% patients. Acute pancreatitis due to pancreatic duct obstruction can be the initial presentation of the cancer in 5% patients [18]. This is a relevant consideration in the older adult who presents with acute pancreatitis of unclear etiology. Pancreatic duct obstruction may cause steatorrhea, malabsorption, and weight loss. New onset DM heralds the diagnosis of pancreatic cancer in several patients. Besides local symptoms caused by the tumor, patients can present with symptoms resulting from local spread or distant metastases; these may include gastric outlet obstruction, gastrointestinal bleeding, and colonic obstruction.

Signs

Jaundice and evidence of recent weight loss are the most common; palpable abdominal mass or ascites are rare findings and reflect advanced disease. Approximately one-third of patients presenting with jaundice also have a palpable gall bladder (Courvoisier's sign). A left supraclavicular lymph node (Virchow's node) or a rectal shelf may be evident in metastatic disease. Pancreatic cancer is associated with a hypercoagulable state leading to arterial and venous thromboses (Trousseau's syndrome) and associated complications.

Asymptomatic pancreatic lesions (APLs) are being discovered with increasing frequency, likely due to an increase in the use of imaging modalities such as computed tomography and magnetic resonance imaging [19]. While the identification of these lesions often results in fear of malignancy and anxiety on the part of patients and treating physicians, the differential for these lesions is broad and ranges from benign to premalignant and malignant. A majority of

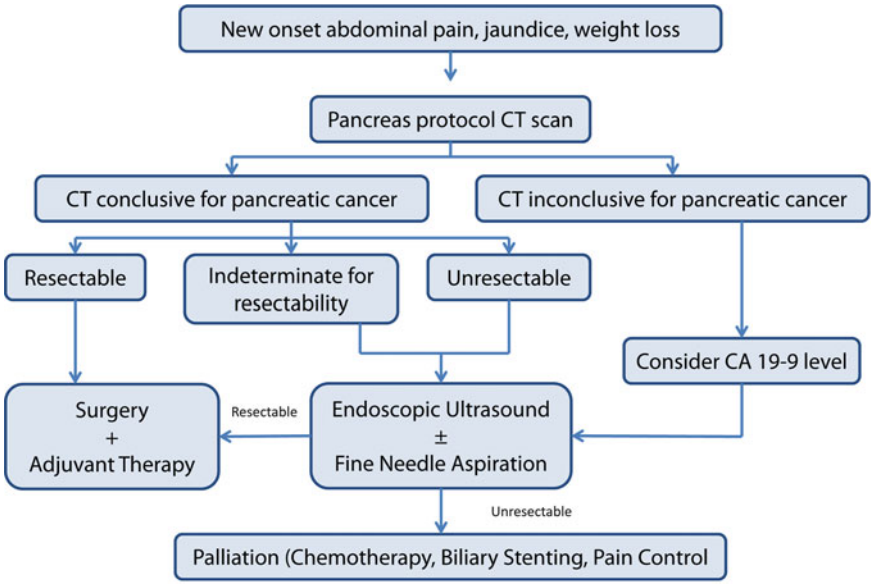

Fig. 62.1 Our approach to a patient with suspected pancreatic cancer

these patients thus undergo periodic surveillance as dictated by established guidelines (Sendai criteria) [12]. In a series of 110 patients operated for APLs, the overall malignancy rate was 24% [19]. In this study, patients with malignancy were substantially older than the remaining cohort [19].

Management

The diagnostic and therapeutic approach to a patient with pancreatic cancer is described in Fig. 62.1. A discussion of each element follows.

Diagnosis

Tumor Markers

Although several tumor markers are elevated in pancreatic cancer, CA19-9 is the only one with clinical utility as an adjunct in diagnosis. Its utility in prognosis and following response to therapy is controversial.

The sensitivity and specificity of CA19-9 varies with the threshold value used. A systematic review of literature on using CA 19-9 in the diagnosis of pancreatic cancer yielded a median sensitivity of 79% (70–90%) and a median specificity of 82% (68–91%) [20]. Furthermore, the sensitivity of CA19-9 in detecting early stage pancreatic cancer is lower than advanced disease. The test has other pitfalls. Patients with jaundice (even due to benign biliary tract obstruction), renal failure, autoimmune disease, and hypothyroidism may have elevated CA19-9 levels resulting in false positive results. Further, 5–10% of the population does not express Lewis antigens, accounting for false negative results in this group.

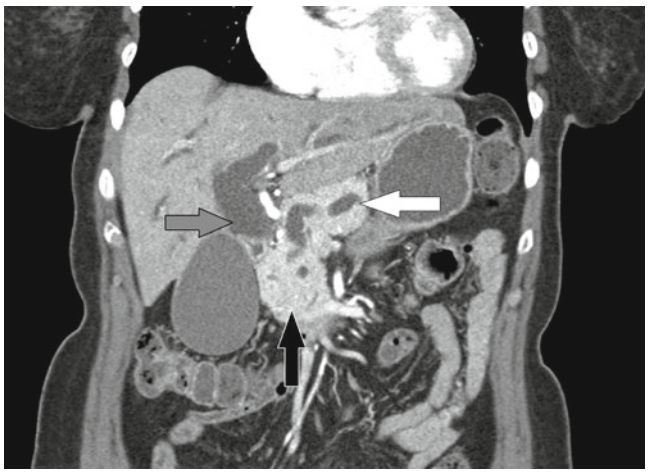

Fig. 62.2 Pancreas protocol CT scan showing a hypo-attenuating mass (*black arrow*) in the pancreatic head, a dilated pancreatic duct (*white arrow*), and a dilated bile duct (*gray arrow*)

Imaging

Contrast enhanced multidetector computed tomography with an arterial and a venous phase remains the cornerstone for diagnosis and staging of pancreatic cancer. The sensitivity of the "pancreas protocol CT" for diagnosis, is approximately 85% [21]. Pancreatic cancer typically appears as a hypoattenuating mass in the pancreas (Fig. 62.2). In patients with biliary obstruction, the "double duct sign" with a dilated pancreatic and common bile duct may be seen (Fig. 62.2).

Table 62.2 Criteria for resectability of pancreatic cancer (All three must be absent for the cancer to be considered resectable)

Distant metastasis (e.g., liver, peritoneum, other)
Arterial involvement (celiac axis, superior mesenteric artery, hepatic artery, or aorta)
Occlusion of the portal vein or superior mesenteric vein

Information from Callery et al. [32].

CT is almost 100% sensitive in predicting unresectability. The criteria for resectability of pancreatic cancer are listed in Table 62.2.

Alternative imaging modalities including ultrasound, magnetic resonance cholangio pancreatography (MRCP) and PET scan are of limited utility in the absence of a contraindication to a pancreas protocol CT scan. PET scan is utilized for assessing response to chemotherapy and to differentiate tumor recurrence from postoperative changes following resection.

Endoscopic Ultrasound

Endoscopic ultrasound (EUS) is the most accurate test for diagnosis and detection of vascular involvement from pancreatic cancer (higher sensitivity and specificity than CT) [22]. In addition, EUS has the advantage of the ability to perform fine needle aspiration (FNA) of the tumor for cytology. Despite these advantages, the problems with EUS include operator dependence, cost, and the inability to detect distant metastases. Thus, utility of EUS is primarily in making a tissue diagnosis (by FNA) for those with unresectable disease, since patients with resectable disease rarely need a tissue diagnosis preoperatively.

Treatment

Surgery

Surgical resection is the only potentially curative treatment for pancreatic cancer. Despite this, surgery is still underutilized in the United States for treatment of pancreatic cancer, especially for patients over 65 years [23]. The standard surgical procedure is a pancreaticoduodenectomy or Whipple procedure. With advances in surgical techniques, mortality rates for the procedure are less than 3% in centers with experience [24].

Chemotherapy and Radiotherapy

Gemcitabine and 5-Fluorouracil are the only agents associated with greater than 5 month survival. Adjuvant chemoradiation is typically administered following resection; however, the data on benefit are controversial at best [25]. Patients with metastatic disease at presentation or following resection are considered candidates for chemotherapy, primarily for palliation of disease related signs and symptoms. Gemcitabine supersedes 5-FU in this group in 1 year survival (18% vs. 2%) and palliation (23.8% vs. 4.8%) [26].

Palliation

Pain is a clinically significant symptom in pancreatic cancer. Chemical neurolysis with alcohol (surgical, percutaneous, or endoscopic) or celiac plexus block can help reduce pain. Oral analgesia, including opioids are necessary in conjunction. Radiation therapy may help pain management.

Patients with jaundice often require palliative endoscopic stenting (via Endoscopic Retrograde Cholangio Pancreatography), if the cancer is unresectable. Duodenal obstruction is relieved with a gastrojejunostomy or endoscopic stent placement. Those who manifest pancreatic insufficiency (e.g., steatorrhea) might benefit from pancreatic enzyme replacement. Referral to a hospice program should be considered when appropriate.

Prognosis

The prognosis for pancreatic cancer remains poor with an overall 5 year survival of 5%. Even after resection, median survival is about 18 months with only 10% surviving 5 years [27]. Standards for pancreatic resection in the elderly should be similar to those applied to younger patients [31]. Complications in the elderly can be reduced by providing quality care including attention to age-related needs, geriatric consultation, nutrition, and rehabilitation [28].

Screening

Currently, there are no recommendations for routine screening of asymptomatic patients for pancreatic cancer.

Key Points

- Pancreatic cancer is a common gastrointestinal malignancy in the geriatric population.
- Contrast enhanced CT is generally sufficient to diagnose and determine resectability.
- Surgery is the mainstay of treatment but only 20% are resectable at diagnosis.
- Overall prognosis is poor even in candidates suitable for resection.
- Routine screening for pancreatic cancer is not recommended.

References

1. American Cancer Society. Cancer facts & figures 2009. Atlanta: American Cancer Society; 2009.
2. Altekruse SF, Kosary CL, Krapcho M, Neyman N, Aminou R, Waldron W, Ruhl J, Howlader N, Tatalovich Z, Cho H, Mariotto A, Eisner MP, Lewis DR, Cronin K, Chen HS, Feuer EJ, Stinchcomb DG, Edwards BK. SEER cancer statistics review, 1975-2007. Bethesda, MD: National Cancer Institute; 2009.
3. Flook R, van Zanten SV. Pancreatic cancer in Canada: incidence and mortality trends from 1992-2005. Can J Gastroenterol. 2009; 23(8):546–50.
4. Klein AP, Hruban RH, Brune KA, et al. Familial pancreatic cancer. Cancer J. 2001;7:266–73.
5. Amundadottir L, Kraft P, Stolzenberg-Solomon RZ, et al. Genome-wide association study identifies variants in the ABO locus associated with susceptibility to pancreatic cancer. Nat Genet. 2009;41: 986–90.
6. Lynch SM, Vrieling A, Lubin JH, et al. Cigarette smoking and pancreatic cancer: a pooled analysis from the pancreatic cancer cohort consortium. Am J Epidemiol. 2009;170:403–13.
7. Nothlings U, Wilkens LR, Murphy SP, et al. Meat and fat intake as risk factors for pancreatic cancer: the multiethnic cohort study. J Natl Cancer Inst. 2005;97:1458–65.
8. Zhang J, Dhakal IB, Gross MD, et al. Physical activity, diet and pancreatic cancer: a population based, case control study in Minnesota. Nutr Cancer. 2009;61(4):457–65.
9. Everhart J, Wright D. Diabetes mellitus as a risk factor for pancreatic cancer. A meta-analysis. JAMA. 1995;273(20):1605–9.
10. Pannala R, Leirness JB, Bamlet WR, et al. Prevalence and clinical profile of pancreatic cancer-associated diabetes mellitus. Gastroenterology. 2008;134:981–7.
11. Raimondi S, Maisonneuve P, Lowenfels AB. Epidemiology of pancreatic cancer: an overview. Nat Rev Gastroenterol Hepatol. 2009;6(12):699–708.
12. Tanaka M, Chari S, Adsay V, et al. International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. Pancreatology. 2006;6:17–32.
13. Zhang Y, Coogan PF, Palmer JR, et al. A case-control study of reproductive factors, female hormone use and risk of pancreatic cancer. Cancer Causes Control. 2010;21(3):473–8.
14. Li D, Morris JS, Liu J, Hassan MM, et al. Body mass index and risk, age of onset and survival in patients with pancreatic cancer. JAMA. 2009;301(24):2553–62.
15. Hruban RH, Pitman MB, Klimstra DS, editors. Ductal adenocarcinoma. In: AFIP atlas of tumor pathology. Tumors of the pancreas, Washington, DC: American Registry of Pathology; 2007. pp 111–64.
16. Li D, Xie K, Wolff R, et al. Pancreatic cancer. Lancet. 2004; 363:1049–57.
17. Holly EA, Chaliha I, Bracci PM, Gautam M. Signs and symptoms of pancreatic cancer: a population-based case-control study in the San Francisco Bay area. Clin Gastroenterol Hepatol. 2004;2: 510–7.
18. Mujica VR, Barkin JS, Go VL. Acute pancreatitis secondary to pancreatic carcinoma. Study group participants. Pancreas. 2000;21: 329–32.
19. Sachs T, Pratt WB, Callery MP, Vollmer Jr CM. The incidental asymptomatic pancreatic lesion: nuisance or threat? J Gastrointest Surg. 2009;13(3):405–15.
20. Goonetilleke KS, Siriwardena AK. Systematic review of carbohydrate antigen (CA 19-9) as a biochemical marker in the diagnosis of pancreatic cancer. Eur J Surg Oncol. 2007;33(3):266–70.
21. Soriano A, Castells A, Ayuso C, et al. Preoperative staging and tumor resectability assessment of pancreatic cancer: prospective study comparing endoscopic ultrasonography, helical computed tomography, magnetic resonance imaging, and angiography. Am J Gastroenterol. 2004;99:492–501.
22. DeWitt J, Devereaux B, Chriswell M, et al. Comparison of endoscopic ultrasonography and multidetector computed tomography for detecting and staging pancreatic cancer. Ann Intern Med. 2004; 141:753–63.
23. Bilimoria KY, Bentrem DJ, Ko CY, et al. National failure to operate on early stage pancreatic cancer. Ann Surg. 2007;246:173–80.
24. Yeo CJ, Cameron JL, Lillemoe KD, et al. Pancreaticoduodenectomy with or without distal gastrectomy and extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma, part 2: randomized controlled trial evaluating survival, morbidity, and mortality. Ann Surg. 2002;236:355–66.
25. Neoptolemos JP, Stocken DD, Friess H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. N Engl J Med. 2004;350:1200–10.
26. Small Jr W, Berlin J, Freedman GM, et al. Full-dose gemcitabine with concurrent radiation therapy in patients with nonmetastatic pancreatic cancer: a multicenter phase II trial. J Clin Oncol. 2008;26:942–7.
27. Schmidt CM, Powell ES, Yiannoutsos CT, et al. Pancreaticoduodenectomy: a 20-year experience in 516 patients. Arch Surg. 2004;139: 718–25.
28. Pratt WB, Gangavati A, Agarwal K, et al. Establishing standards of quality for elderly patients undergoing pancreatic resection. Arch Surg. 2009;144(10):950–6.
29. Joergensen MT, Brusgaard K, Crüger DG, Gerdes AM, Schaffalitzky de Muckadell OB. Genetic, epidemiological, and clinical aspects of hereditary pancreatitis: a population-based cohort study in Denmark. Am J Gastroenterol. 2010;105(8):1876–83.
30. Giardiello FM, Brensinger JD, Tersmette AC, et al. Very high risk of cancer in familial Peutz-Jeghers syndrome. Gastroenterology. 2000;119:1447–53.
31. Hahn SA, Greenhalf B, Ellis I, et al. BRCA2 germline mutations in familial pancreatic carcinoma. J Natl Cancer Inst. 2003;95: 214.
32. Callery MP, Chang KJ, Fishman EK, et al. Pretreatment assessment of resectable and borderline resectable pancreatic cancer: expert consensus statement. Ann Surg Oncol. 2009;16:1727.

Colorectal Cancer

63

Giridhar U. Adiga and Janice P. Dutcher

Introduction

Older patients currently comprise the largest group of oncology patients, with the numbers predicted to expand. The over 65 group will constitute about 20% of the population by 2040 [1]. With a median age of 70 years at diagnosis, colorectal cancer (CRC) is a neoplasm predominantly of the old. Significant differences exist in the behavior and management of CRC in the older group as compared to the young.

Epidemiology

CRC is the third most frequently diagnosed and second leading cause of cancer death for men and women combined in the U.S. In 2010, an estimated 142,570 new cases with 51,370 deaths occurred due to CRC [2] (Table 63.1). Over 90% of newly diagnosed cases occur among the ≥50-year age group. Other relevant statistical data are presented in Table 63.1. Recent data suggest a decline in the incidence and mortality for CRC associated with an increase in the utilization of CRC screening options in the past decade [3]. This declining trend was observed only among people ≥50 years of age. The decline in mortality may reflect better screening, improvements in therapy, and alterations in environmental factors. Age-adjusted incidence of CRC is highest in African Americans in the U.S. and lowest in Asian countries; while this may reflect the benefits of screening, other factors may be causative.

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Risk Factors

Environmental and Lifestyle Factors

CRC is linked to environmental and genetic risk factors. Most CRC (about 70%) is sporadic, associated with environmental and patient-related risk factors (Table 63.2). Defined hereditary syndromes account for 5% of CRC, but up to 25% of those affected have a family history of CRC with a pattern that does not meet criteria for known inherited syndromes [4].

Disease Associations

Individuals with colonic adenomas and inflammatory bowel diseases (Crohn's and ulcerative colitis) are associated with the highest risk. Obesity is associated with 1.5-fold increased risk of CRC as well as a higher likelihood of dying from CRC. Weak associations for increased risk exist with long-standing diabetes and postcholecystectomy states.

Familial/Genetic Syndromes

Two major inherited forms of CRC include polyposis syndromes and hereditary nonpolyposis colorectal cancer (HNPCC). Polyposis syndromes include familial adenomatous polyposis (FAP), Peutz-Jeghers syndrome, juvenile polyposis, and Cowden disease. HNPCC (or Lynch syndrome) is an autosomal dominant disease accounting for 2–3% of all CRC. Major features and gene defects for these syndromes are noted in Table 63.3. The noninherited polyposis syndromes include Cronkhite-Canada syndrome and miscellaneous nonfamilial polyposis. In older adults, with the exception of HNPCC, other familial syndromes are uncommon.

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Table 63.1 Colorectal cancer-related US statistics at a glance [2, 3]

Parameter	Numbers of colorectal cancer (CRC)
Incidence (2010 estimated)	142,570
Men	72,090
Women	70,480
Age group distribution	
35–44 years	3.8%
45–54 years	12.4%
55–64 years	19.2%
65–74 years	24.4%
75–84 years	26.8%
≥85 years	12.2%
Incidence rate[a] (all races)	
Males	55.8
Females	41.7
Death rates[a] (all races)	
Males	21.2
Females	14.9
Prevalence (January 1, 2007)	
Total	1,112,493
Men	540,636
Women	571,857
Median age at diagnosis	70 years
Median age at death	75 years

http://seer.cancer.gov/csr/1975_2005/results_single/sect_01_table.01.pdf
Colon and rectum section (http://seer.cancer.gov/csr/1975_2005/results_merged/sect_06_colon_rectum.pdf)
[a]Per 100,000 population

Protective Factors

CRC is multifactorial in etiology. Although controversial, protective factors include grains, fruits and vegetables, and calcium supplementation, with perhaps questionable benefit with fish, garlic, folic acid, Vitamin B6, and magnesium. Among medications, NSAIDs, postmenopausal hormone replacement therapy, and statins are associated with decreased risk. Physical activity may have a protective role.

Chemoprevention

Chemoprevention trials have chosen adenoma formation rather than CRC incidence or mortality as the primary outcome. Cyclooxygenase-2 is overexpressed in the majority of CRCs, a partial explanation for studies suggesting reduction in risk of adenomas with ASA and NSAIDs. This risk reduction with ASA is related to both dose and duration of therapy and is associated with risks of bleeding. Considering benefits and risks, the United States Preventive Service Task Force (USPSTF) does not recommend use of aspirin in average-risk individuals.

Table 63.2 Risk factors linked to CRC [2–5]

Lifestyle-related factors
Diet high in red meats and processed meats
Cooking meats at very high temperatures (Ex. frying)
Physical inactivity
Obesity
Smoking
Heavy alcohol use
Night shift work
Comorbidities associated with variable risk
History of colorectal polyps or CRC
Inflammatory bowel disease
Prior history of breast cancer
Type 2 diabetes
Cholecystectomy
Genetic, familial, and racial factors
Family history of CRC
African Americans
Familial syndromes (see Table 63.3)

http://seer.cancer.gov/csr/1975_2005/results_single/sect_01_table.11_2pgs.pdf

Pathogenesis and Pathology

The Adenoma-Carcinoma Sequence

Colon cancer usually begins as a benign adenomatous polyp that develops dysplasia and progresses to an invasive cancer in 10–15 years. The prevalence of adenomatous polyps in the 50–75 year group was 27% in 671 asymptomatic individuals with negative fecal occult blood tests in the U.S [5] (see chapter on polyps and CRC screening). Colorectal carcinogenesis is a multifactorial and multistep process involving interaction of gene expression and environmental influences [6]. Progressive accumulation of genetic alterations occur resulting in malignant transformation (Table 63.4). This stepwise evolution to cancer provides the opportunity to screen, detect, and potentially remove precancerous lesions.

Histopathology

Most CRCs are adenocarcinomas. Mucinous carcinoma that produce extracellular mucin have a predilection for the rectosigmoid site and respond less favorably to chemotherapy. Signet ring cell carcinoma whose cellular shape is due to intracellular mucin displacing nuclei has a propensity for intramural and peritoneal spread. Medullary carcinoma, a distinctive type with tumor-infiltrating lymphocytes, is associated with microsatellite instability and the HNPCC syndrome. These are treated similarly to adenocarcinoma. Other pathologic types seen in the colon include squamous, adenosquamous, lymphomas, carcinoid tumors, neuroendocrine tumors, and Kaposi's sarcoma. Treatment is, of course, based on tumor histology.

Table 63.3 Familial syndromes associated with increased risk of CRC

Familial syndrome	Major features
Familial adenomatous polyposis (FAP)	Caused by germline mutation in the APC[a] gene Accounts for 2–3% of all CRC Characterized by presence of 100–1,000 s of benign polyps Polyps occur early in life; 95% develop polyps by age 35, often detected in teens, 50% develop polyps by age 15 100% chance that some polyps will develop cancer
Variants of FAP (Turcot's syndrome, Gardner's syndrome, attenuated FAP)	All variants are associated with mutation in the APC gene Turcot's syndrome is associated with medulloblastoma Gardner's syndrome is associated with extraintestinal manifestations including osteomas of the skull, fibromas, desmoids tumor, and thyroid malignancy Attenuated FAP is a milder variant with fewer adenomas and later onset of disease
Peutz-Jeghers syndrome	Inherited mutation of the STK11/LKB1 gene in majority of cases with variable penetrance Intestinal hamartomatous polyps in association with mucocutaneous melanocytic macules Numerous pigmented spots on lips and buccal mucosa; with tendency to develop multiple hamartomatous polyps throughout the GI tract
Juvenile polyposis syndrome	The term "juvenile" refers to histologic type of polyp Associated with mutations in *BMPR1A* and *SMAD4* genes Characterized by predisposition to hamartomatous polyps in the gastrointestinal tract
Cowden disease	Caused by germline mutations in the PTEN gene Characterized by multiple hamartomatous lesions Breast and thyroid cancers more common than CRC
MYH-associated polyposis	Autosomal recessive inheritance unlike other inherited polyposis, which are autosomal dominant Caused by germline mutation of MYH gene, an excision repair protein The clinical syndrome is similar to attenuated FAP with no detected germline APC mutation
Hereditary nonpolyposis colorectal cancer (HNPCC or Lynch syndrome)	Germline mutations in DNA mismatch repair genes autosomal dominant, accounts for 2–3% of CRC Early onset of adenomas and CRC in absence of polyposis Average age at onset of cancer is about 45 years Other cancers associated with HNPCC: endometrial, ovarian, gastric, urogenital, small intestinal cancers

http://seer.cancer.gov/csr/1975_2005/results_single/sect_01_table.13_2pgs.pdf
[a]The APC is significantly different from zero ($p<0.05$)

The degree of tumor differentiation is assessed in tumor grading. Poorly differentiated or undifferentiated tumors (high grade) have poorer prognosis compared to moderately and well-differentiated tumors (low grade). Irregular infiltrating pattern of growth as opposed to a smooth pushing (expanding) border is an independent adverse prognostic factor

Clinical Features

Screening for CRC has resulted in disease identification increasingly at early asymptomatic stages [3, 7]. Common clinical manifestations with late diagnosis include abdominal pain, hematochezia, altered bowel habits, and iron deficiency anemia.

CRC spreads by contiguous lymphatic and hematogenous spread. About 20% of patients have metastatic disease at time of diagnosis, with symptoms and signs referable to sites of metastases and degree of spread. The liver is the most common initial site of hematogenous spread, although tumors arising in the distal rectum may metastasize initially to the lungs due to differences in venous drainage. Unusual presentations include malignant fistula, fever of unknown origin, abscesses, *Streptococcus bovis* bacteremia, *Clostridium septicum* sepsis, and adenocarcinomas of unknown primary.

Symptomatic patients, including those who present with obstruction or perforation, have poorer prognosis. Rectosigmoid cancers arising at or below the peritoneal reflection have poorer prognosis as well.

Table 63.4 Adenoma-carcinoma sequence correlated with some of the known major molecular mechanisms [4, 6]

Stages of carcinogenesis	Major associated molecular abnormalities	
	Genes	Chromosome
Normal colon	Not applicable	Not applicable
Small adenoma	MMR genes, *APC, CTNNB1*	5q loss
Large adenoma	*KRAS, BRAF*	18q loss
Carcinoma	*PTEN, TP53*	17q loss, 8q loss

MMR genes—mismatch repair genes. Major MMR genes involved are *MLH1, MLH3, MSH2, MSH6, PMS1,* and *PMS2*. Germline (inherited) mutations result in HNPCC. Somatic mutations occur in about 15% of sporadic cases. These mutations result in microsatellite instability, measured as microsatellite high or low depending on the degree of instability

APC—adenomatous polyposis coli gene. *APC* is a tumor suppressor gene. *APC* gene encodes APC protein, which is a component of β-catenin degradation complex. Inactivating mutations in the *APC* or activating mutations of β-catenin gene *(CTNNB1)* result in activation of Wnt pathway. Germline mutation in the *APC* gene results in FAP or related syndromes. Somatic inactivation of *APC* occurs in about 85% of sporadic CRCs

KRAS gene (v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog)—encodes K-Ras protein, a GTPase which relay mitogenic signals from receptor tyrosine kinases and activates MAP kinase and PI3K pathway. *BRAF* gene (v-raf murine sarcoma viral oncogene homolog)—encodes B-Raf protein, a downstream mediator of MAP kinase pathway. Hence, biologic consequences of BRAF mutations mimic *KRAS* mutations. These mutations are acquired during later part of adenoma progression. *KRAS* mutations are seen in about 50% of CRCs and BRAF mutations in about 15%

PTEN gene (phosphatase and tensin homolog), a tumor suppressor gene, encodes PTEN protein. PTEN protein is a phosphatase which dephosphorylate phosphatidylinositol 3-kinases (PI3K). Inactivating mutations of *PTEN* result in activation of PI3K pathway signaling

TP53 gene (tumor protein p53) encodes p53 protein which plays a role in cell cycle regulation, DNA repair, and apoptosis. It is a tumor suppressor gene located on the short arm of chromosome 17 (17p). Loss of heterozygosity in the 17p locus, a relatively late event in the progression is seen in up to 75% of CRCs. Germ line mutation results in Li-Fraumeni syndrome

Prognostic Factors

Besides the clinical and pathologic factors mentioned, prognosis is progressively worse with increasing TNM stage (Table 63.5). Other established adverse prognostic factors include local extent of disease, lymph node involvement including nodal micrometastases, venous and angiolymphatic invasion, residual tumor after definitive therapy, and preoperative CEA values ≥5.0 ng/mL. The presence of tumor-infiltrating lymphocytes has been cited as a favorable prognostic factor in many but not all studies.

Among various molecular markers that are still being evaluated, testing for microsatellite instability may be clinically useful. Microsatellite instability-High (MSI-H), reflecting loss of DNA mismatch repair, is associated with longer survival (Table 63.4); adjuvant 5-fluorouracil (5FU)-based chemotherapy may be less beneficial for MSI-positive tumors, especially with stage II disease. In a small Japanese study, the presence of *KRAS* mutation although higher among the older age group, was associated with poor prognosis only in the younger group [8].

Evaluation

Staging evaluations include complete clinical examination, laboratory studies including complete blood counts, chemistry, liver function tests, CEA level, in addition to colonoscopy and CT scans of chest, abdomen, and pelvis with contrast. Thorough preoperative assessment must include comorbidity, functional, and socioeconomic status, and where possible, comprehensive geriatric assessment.

Additional evaluation for rectal cancer include proctoscopy and endorectal ultrasound and pelvic MRI to assess depth of tumor penetration and lymph nodal metastases. Though not routinely indicated, positron emission tomography scan may be useful in the evaluation of a suspicious abnormality on a CT scan or in resectable metastatic disease to identify unrecognized metastatic foci.

Final staging utilizes the TNM classification (Table 63.5). The Duke's classification is no longer widely used. Pathologic examination should include grade, depth of penetration, extension, margins, involvement of lymph node, and peritoneum. Testing for *KRAS* mutation status on archived specimens is recommended at the time of diagnosis of stage IV disease. *KRAS* mutation predicts lack of response to cetuximab or panitumumab to help guide therapy.

Management of Colon Cancer

General Aspects

There are limitations in applying available scientific data to the elderly population. Older individuals are typically underrepresented or excluded from clinical trials and pharmacokinetic studies. Data on the elderly are generally obtained from retrospective subset analysis or studies mainly involving fit elderly with fewer comorbidities, which may not be represented by the typical patient. Prospective clinical data need to better focus on the older age group.

With the available information, it is considered that the elderly derive benefit from CRC chemotherapy, both in the adjuvant and metastatic settings with outcomes comparable to the young. Relevant management concerns for older adults include medication reconciliation, identifying

Table 63.5 Staging of CRC

Stage	Description	TNM category	Dukes
0	Carcinoma in situ	Tis N0 M0	
I	Tumor invades submucosa (T1)	T1 N0 M0	Dukes A
	Tumor invades muscularis propria (T2)	T2 N0 M0	
II	Tumor invades into pericolorectal tissues (T3)	T3 N0 M0	Dukes B
	Tumor penetrates the visceral peritoneum (T4a) or directly invades other organs or structures (T4b)	T4a N0 M0 T4b N0 M0	
III	With regional lymph node metastasis		Dukes C
	N1: metastasis in 1–3 regional lymph nodes	Any T N1 M0	
	N2: metastasis in ≥4 regional lymph nodes	Any T N2 M0	
IV	With evidence of distant metastasis		
	M1a: metastasis confined to one organ or site	Any T Any N M1a	
	M1b: more than one organ or site or involvement of peritoneum	Any T Any N M1b	

inappropriate medications, assessment of adequate organ function, consideration for drug interactions, adverse drug reactions, dose modification for renal function when required, and evaluation for compliance.

In addition to estimating cancer-related morbidity and mortality risks, assessments should include other factors that may interfere with or affect treatment tolerance and life expectancy. These include cognitive status, mood disorders, swallowing difficulty, falls risk, social support, patient values, and treatment goals. Advance directives (living will or healthcare proxy) must be encouraged and implemented where possible. Frequent revisions of plans may be necessary.

Comorbidity and Functional Status

Aging is a highly individualized process; defining age cut off is arbitrary. Biologic aging is increasingly recognized as the more relevant factor; risk stratification should include functional status, comorbidities, and attributes of biologic aging.

The importance of performance status on outcomes of chemotherapy is well known for variety of tumors. Commonly used measures of functional status such as Eastern Cooperative Oncology Group (ECOG) performance status and Karnofsky score do not incorporate comorbid conditions. Comprehensive geriatric assessment is useful, but is time-consuming and not specifically studied in reference to chemotherapy and colon cancer outcomes. Other available tools include Charlson comorbidity index and Cumulative Illness Rating Scale for Geriatrics. A short self-administered geriatric assessment as a tool to predict outcomes is currently being evaluated [9]. Computer-based comprehensive geriatric assessment for individuals 70 or older with gastrointestinal malignancies is currently undergoing trial (NCI Protocol ID 09-035 NCT00973440).

Locoregional Disease

Surgery

Surgical resection is the mainstay in the management of locoregional (stages I, II and III) and subsets of stage IV colon cancer. European data suggest that older patients are less likely to receive curative surgery and more likely to undergo emergency surgery [10]. Although reports are conflicting, operative complications and mortality may increase with age. Comprehensive preoperative assessment, careful patient selection, avoidance of urgent surgery, and optimizing medical status are important. Laproscopic surgery may be associated with lower morbidity and mortality [11]. Resection of solitary hepatic metastases is safe in selected older patients [12].

Adjuvant Chemotherapy

Adjuvant chemotherapy helps prevent disease recurrence and prolongs survival in patients with at least 5 years of life expectancy [13]. The benefits in lymph node positive disease (Stage III) are established, with improved disease-free and overall survival. The proportion of patients with stage III colon cancer receiving adjuvant chemotherapy is considered a quality care measure [14]. The role of adjuvant chemotherapy in stage II colon cancer is unclear; current evidence does not support its routine use. In a recent study of stage III community older patients, only 50% of those over 75 received adjuvant treatment. Older individuals received less toxic and shorter duration of chemotherapy and did not experience more ADRs than younger patients [13].

Based on a survey of 123 patients including 30% older than 70 years and 74% with stage III cancer, the majority of patients believed that even small survival benefits were sufficient to consider adjuvant chemotherapy as worthwhile, with the younger group hoping for greater benefits [15]

Table 63.6 Considerations for commonly used chemotherapeutic agents in elderly [29]

Chemotherapeutic agent	Comments
5-Fluorouracil (5-FU)	Hematologic toxicity more common in elderly and with bolus 5-FU
	Other toxicity may be higher in elderly though studies are not conclusive (cardiac, neurotoxicity)
	Weekly regimens are better tolerated than monthly regimens
Capacitabine	Age alone does not affect pharmacokinetics
	Dose should be adjusted to creatinine clearance; starting dose to be no more than 1,000 mg/m^2
Oxaliplatin	No increase in toxicity with mild-to-moderate renal impairment
	Neurotoxicity is common but does not increase with age
	No data to support reduction in dose based on age alone
	Best avoided in the presence of preexisting neuropathy
Irinotecan	Pharmacokinetics similar to younger individuals
	Both early and delayed diarrhea are more common in elderly
	Q 3 weekly regimen may be associated with lower rate of diarrhea
	Reduced starting dose recommended for patients over age 70
Bevacizumab	Limited data on pharmacokinetics with age
	Increased risk of arterial thromboembolic events, GI side effects, fatigue, and proteinuria
Cetuximab/panitumumab	Limited data. Tolerated, with efficacy similar to younger patients

The major chemotherapeutic agents used and specific concerns with the elderly are presented in Table 63.6. Adjuvant therapy for over 6 months does not have a favorable risk benefit ratio, while chemotherapy for 3 months may provide meaningful benefit where longer duration (up to 6 months) is not feasible [16]. Older patients may experience more ADRs especially myelosupression and fatigue. Common adjuvant regimens used in the elderly include infusional 5-FU with leucovorin (LV), single agent capecitabine, or oxaliplatin in combination with either 5FU/LV (FOLFOX) or capecitabine and leucovorin (XELOX) [17]. In an analysis of 10,499 patients <70 years compared to 2,170 patients >70 years from the ACCENT (Adjuvant Colon Cancer End Points) database, the authors compared combination and oral chemotherapy to IV 5FU alone. Patients >70 years did not obtain more clinically meaningful benefit from combination chemotherapy or oral chemotherapy, compared to IV 5FU [18]. The implications for routine practice are unclear. Age by itself is not a barrier for chemotherapy. Pooled analyses support the use of adjuvant therapy for otherwise fit elderly.

Approximately 75% of stage II patients are cured by surgery alone [19]. Studies suggest a decreasing disease-specific survival with increasing risk factors, and only a small subset of stage II patients with high-risk features may benefit with adjuvant chemotherapy. Online tools are available to estimate recurrence risk [20]. MSH-H tumors may be a marker of more favorable outcome and decreased benefit from adjuvant fluoropyrimidine alone [21].

Adjuvant radiotherapy (RT) may be used in highly select cases of locally advanced disease (T4) involving ascending or descending colon (considered anatomically immobile structures) or positive resection margin.

Metastatic Disease

Most patients with metastatic disease cannot be cured except for a subset with surgically resectable disease. Median survival with supportive care alone is about 6 months. With combination regimens, the median overall survival ranges from 18 to 24 months [22]. Combination chemotherapy has similar efficacy in older individuals compared to the young and is standard therapy in fit elderly. Commonly used regimens include FOLFOX and FOLFIRI (irinotecan with 5FU/LV), with or without bevacizumab. Staged excision is possible for resectable liver or lung metastases after combination chemotherapy for 2–3 months.

Among targeted agents, the efficacy of bevacizumab in the elderly is similar to that in the young with similar toxicity except for increased risk of thromboembolism. Cetuximab may have acceptable toxicity and has similar efficacy compared to younger patients. Panitumumab significantly improved PFS with manageable toxicity in chemorefractory disease compared to best supportive care [23]. Tumors with mutated *KRAS* do not respond to anti EGFR therapies; hence, testing is essential prior to such therapies.

Risks of therapy may be considerable in the frail elderly with limited life expectancy. However, when poor functional status is caused by cancer, treatment may improve the general condition. Techniques to decrease toxicity include stepwise addition of agents with multiagent chemotherapy, avoidance of bolus 5FU component in combination regimens, use of single agent rather than combinations, dose reduction, use of growth factors, and chemotherapy holidays [24], as well as periodic reassessment. In addition to chemotherapy, other palliative measures include palliative colon resection, RT for uncontrolled bleeding, stents for obstruction, laser ablation, and other supportive measures (Fig. 63.1).

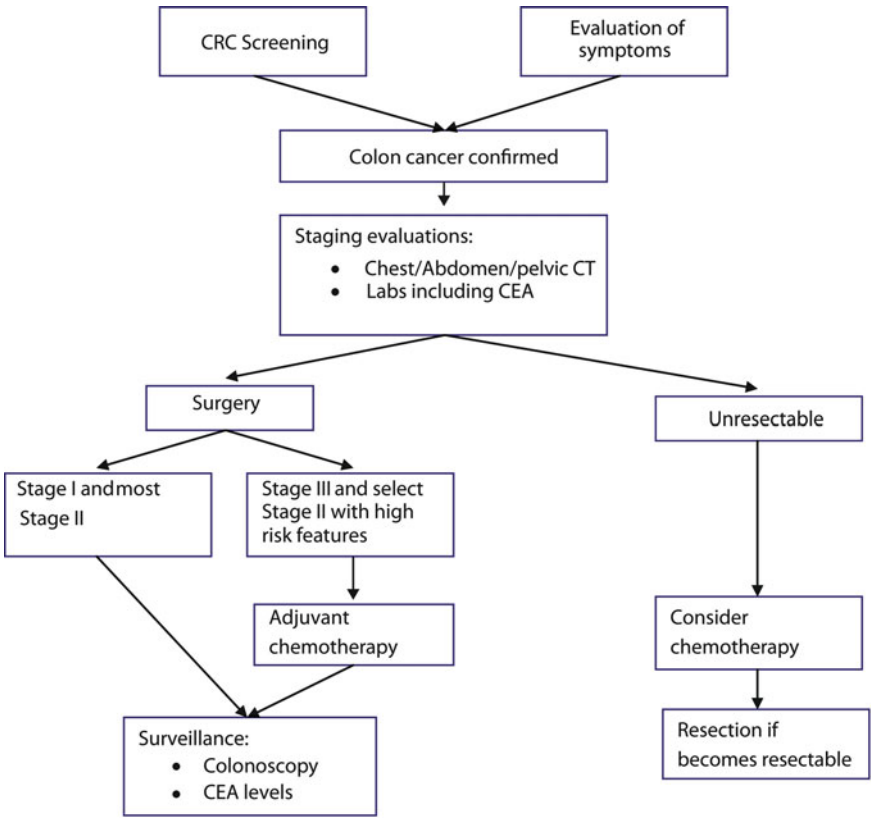

Fig. 63.1 General management of colon cancer [10, 11, 13, 18, 19]

Management of Rectal Cancers

Rectal cancers are large bowel cancers found within 12 cm of the anal verge by rigid proctoscopy. In those >85 years, rectal cancer constitutes one-third of all neoplasms [25]. Rectal cancer differs from colon cancer in its pattern of spread and pelvic recurrence.

Surgery is associated with potential bowel and bladder disturbances. In a study based on the SEER database (1991–2002), age >70 was associated with less aggressive treatment and increased cancer-related mortality [26]. Major rectal resection can be performed with similar rates of local recurrence, distant metastasis, and relative survival, irrespective of age in selected patients [27]. In patients over 70 years with locally advanced rectal cancer, those with mild comorbidities can receive the same treatment as the fit elderly, since tolerability was similar [25]. Evidence suggests that management of rectal cancer in the old should be similar to that in the young, individualized by frailty-associated factors and patient preferences.

General treatment modalities include surgical resection, chemotherapy, and radiation. Chemotherapy for rectal cancer is similar to that of colon cancer. Early-stage disease may be managed by surgery alone. In contrast to colon cancer, neoadjuvant and adjuvant therapies often include locoregional radiation in view of high risk for local recurrence.

Neoadjuvant chemoradiotherapy is indicated for locally advanced T3/T4 tumors and for other subgroups where tumor shrinkage might allow sphincter sparing surgery. Continuous infusion 5FU with RT is a commonly used neoadjuvant regimen. Other regimens include capecitabine + RT and bolus 5FU with leucovorin + RT.

Adjuvant chemoRT is used for those at higher risk for pelvic failure (pT3-4, or N1-2) who have not received neoadjuvant chemoRT. Adjuvant chemoRT regimens commonly employ a sandwich approach where chemoRT (similar to neoadjuvant regimen) is sandwiched between periods of chemotherapy alone. Adjuvant 5FU-based chemotherapy without RT is used for all patients who received neoadjuvant chemoradiation. Metastatic cancer is treated similarly to colon cancer (Fig. 63.2).

Surveillance

Posttreatment monitoring after adjuvant therapy provides the opportunity to assess complications of treatment, identify recurrence at an early stage, and counsel for risk factor reduction and health promotion. Recommended surveillance includes clinical examination every 3–6 months for 2 years, and thereafter every 6 months until 5 years. CEA is measured every 3–6 months for 2 years and every 6 months up to 5 years.

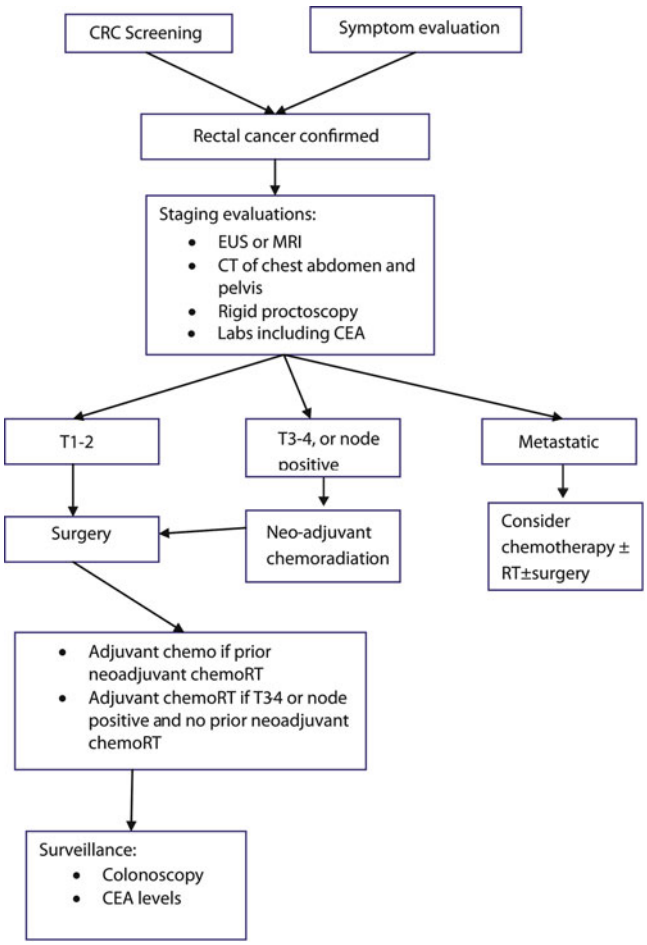

Fig. 63.2 General management of rectal cancer [25–28]

Colonoscopy is recommended at 1 year, 3 year, and every 5 years following resection unless indicated more often for abnormal interval findings or for HNPCC. If colonoscopy was not performed preoperatively due to obstructing lesion, it should be performed 3–6 months postresection. For stage II and III patients who are candidates for potentially curative resection of liver or lung metastases, annual CT scans are recommended for 3–5 years [28]. Elevation of CEA following surgery warrants complete evaluation for disease recurrence. Frequency and intensity of surveillance should consider individual goals and feasibility of surgery for early recurrence of disease.

Key Points

- Colorectal cancer (CRC) predominantly affects older individuals with a median age of 71 years at diagnosis.
- CRC is linked to environmental and genetic factors; familial syndromes with defined genetic abnormalities account for 5% of cases.
- Nonsteroidal anti-inflammatory drugs and aspirin use are associated with reduced risk of colonic adenomas; chemoprevention is not indicated for average-risk individuals at this time.
- Multidisciplinary approach and incorporation of appropriate geriatric assessment are helpful in the management of CRC.
- Older adults derive comparable benefits with chemotherapy in both adjuvant and metastatic settings.
- Molecular information is increasingly useful in both diagnosis and management of CRC. Testing for *KRAS*, *BRAF* mutations, and microsatellite instability in select patients helps select appropriate therapy.

Definitions

Annual percent change (APC) The average annual percent change over several years. The APC is used to measure trends or the change in rates over time. For information on how this is calculated, go to Trend Algortihms in the SEER*Stat Help system. The calculation involves fitting a straight line to the natural logarithm of the data when it is displayed by calendar year.

Joinpoint analyses A statistical model for characterizing cancer trends which uses statistical criteria to determine how many times and when the trends in incidence or mortality rates have changed. The results of joinpoint are given as calendar year ranges and the annual percent change (APC) in the rates over each period.

Survival rates Survival examines how long after diagnosis people live. Cancer survival is measured in a number of different ways depending on the intended purpose.

Relative survival rate A measure of net survival that is calculated by comparing observed (overall) survival with expected survival from a comparable set of people who do not have cancer to measure the excess mortality that is associated with a cancer diagnosis.

Stage distribution Stage provides a measure of disease progression, detailing the degree to which the cancer has advanced. Two methods commonly used to determine stage are AJCC and SEER Summary Stage. The AJCC method (see Collaborative Staging Method) is more commonly used in the clinical settings, while SEER has strived to provide consistent definitions over time with their Local/Regional/Distant staging.

Lifetime risk The probability of developing cancer in the course of one's lifespan. Lifetime risk may also be discussed in terms of the probability of developing or of dying from cancer. Based on cancer rates from 2004 to 2006, it was estimated that men had about a 44% chance

of developing cancer in their lifetimes, while women had about a 38% chance.

Probability of developing cancer The chance that a person will develop cancer in his/her lifetime.

Prevalence The number of people who have received a diagnosis of cancer during a defined time period, and who are alive on the last day of that period. Most prevalence data in SEER is for limited duration because information on cases diagnosed before 1973 is not generally available. (http://seer.cancer.gov/statfacts/html/colorect.html) (Accessed May 23, 2011).

References

1. http://www.census.gov/population/www/projections/files/nation/summary/np2008-t2.xls. Accessed 23 May 2011.
2. Altekruse SF, Kosary CL, Krapcho M, et al. (eds). SEER Cancer Statistics Review, 1975–2007. Bethesda, MD: National Cancer Institute. http://seer.cancer.gov/csr/1975_2007/, based on November 2009 SEER data submission, posted to the SEER web site; 2010.
3. Edwards BK, Ward E, Kohler BA, et al. Annual report to the nation on the status of cancer, 1975–2006, featuring colorectal cancer trends and impact of interventions (risk factors, screening, and treatment) to reduce future rates. Cancer. 2010;116(3):544–73.
4. Souglakos J. Genetic alterations in sporadic and hereditary colorectal cancer: implementations for screening and follow-up. Dig Dis. 2007;25(1):9–19.
5. Rex DK, Lehman GA, Ulbright TM, et al. Colonic neoplasia in asymptomatic persons with negative fecal occult blood tests: influence of age, gender, and family history. Am J Gastroenterol. 1993;88(6):825.
6. Markowitz SD, Bertagnolli MM. Molecular basis of colorectal cancer. N Engl J Med. 2009;361:2449–60.
7. Lines LM, Lang K, Lee DW, et al. Trends in stage distribution and survival among elderly colorectal cancer patients in the U.S. J Clin Oncol (Meeting Abstracts). 2008;26(15S):4043.
8. Onozato W, Yamashita K, Yamashita K, et al. Genetic alterations of K-ras may reflect prognosis in stage III colon cancer patients below 60 years of age. J Surg Oncol. 2011;103(1):25–33.
9. Hurria A, Gupta S, Zauderer M, et al. Developing a cancer-specific geriatric assessment: a feasibility study. Cancer. 2005;104(9):1998–2005.
10. Simmonds PD, Best L, George S, et al., Colorectal Cancer Collaborative Group. Surgery for colorectal cancer in elderly patients: a systematic review. Lancet. 2000;356(9234):956.
11. Faiz O, Haji A, Bottle A, et al. Elective colonic surgery for cancer in the elderly: an investigation into postoperative mortality in English NHS hospitals between 1996 and 2007. Colorectal Dis. 2011;13(7):779–85.
12. Pallis AG, Papamichael D, Audisio R, et al. EORTC Elderly Task Force experts' opinion for the treatment of colon cancer in older patients. Cancer Treat Rev. 2010;36(1):83–90. Epub 2009 Nov 26.
13. Kahn KL, Adams JL, Weeks JC, et al. Adjuvant chemotherapy use and adverse events among older patients with stage III colon cancer. JAMA. 2010;303(11):1037–45.
14. Patwardhan MB, Samsa GP, McCrory DC, et al. Cancer Care Quality Measures: Diagnosis and Treatment of Colorectal Cancer. Evidence Report/Technology Assessment No. 138. Prepared by the Duke Evidence-based Practice Center under Contract No. 290-02-0025. AHRQ Publication No. 06-E002. Rockville, MD: Agency for Healthcare Research and Quality; May 2006.
15. Blinman P, Duric V, Nowak AK, et al. Adjuvant chemotherapy for early colon cancer: what survival benefits make it worthwhile? Eur J Cancer. 2010;46(10):1800–7.
16. Des Guetz G, Uzzan B, Morere JF, Perret G, Nicolas P. Duration of adjuvant chemotherapy for patients with non-metastatic colorectal cancer. Cochrane Database Syst Rev. 2010;(1):CD007046. doi:10.1002/14651858.CD007046.pub2.
17. Ades S. Adjuvant chemotherapy for colon cancer in the elderly: moving from evidence to practice. Oncology (Williston Park). 2009;23(2):162–7.
18. McCleary J, Meyerhardt E, Green G, et al. Impact of older age on the efficacy of newer adjuvant therapies in > 12,500 patients (pts) with stage II/III colon cancer: findings from the accent database. J Clin Oncol. 2009;27(Suppl):15s (Abstract 4010).
19. Marshall JL. Risk assessment in stage II colorectal cancer. Oncology. 2010;24 Suppl 1:9–13.
20. https://www.adjuvantonline.com/index.jsp. Accessed 23 May 2011.
21. Sargent DJ, Marsoni S, Monges G, et al. Defective mismatch repair as a predictive marker for lack of efficacy of fluorouracil-based adjuvant therapy in colon cancer. J Clin Oncol. 2010;28(20):3219–26. Epub 2010 May 24.
22. Kopetz S, Chang GJ, Overman MJ, et al. Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy. J Clin Oncol. 2009;27(22):3677–83. Epub 2009 May 26.
23. Van Cutsem E, Peeters M, Siena S, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. J Clin Oncol. 2007;25(13):1658–64.
24. Raftery L, Sanoff HK, Goldberg R. Colon cancer in older adults. Semin Oncol. 2008;35(6):561–8.
25. Pasetto LM, Basso U, Friso ML, et al. Determining therapeutic approaches in the elderly with rectal cancer. Drugs Aging. 2007;24(9):781–90.
26. Chang GJ, Skibber JM, Feig BW, et al. Are we undertreating rectal cancer in the elderly? An epidemiologic study. Ann Surg. 2007;246(2):215–21.
27. Endreseth BH, Romundstad P, Myrvold HE, et al. Rectal cancer treatment of the elderly. Colorectal Dis. 2006;8(6):471–9.
28. National Comprehensive Cancer Network. (2011). http://www.nccn.org/professionals/physician_gls/PDF/colon.pdf. Accessed 23 May 2011.
29. Lichtman SM, Boparai MK. Anticancer drug therapy in the older cancer patient: pharmacology and polypharmacy. Curr Treat Options Oncol. 2008;9:191–203.

Part XII

Palliative Care

Palliative Care of GI Issues at the End of Life

64

John M. Heath and Elizabeth Poplin

What Is Palliative Care?

The practice of palliative care is derived from the definition of the root word *Palliate: to reduce the violence of a disease; to ease symptoms with curing the underlying disease* [1]. Palliative care is the aggregate of treatments provided to patients with serious or life-threatening illnesses focused on alleviating pain and other symptoms. Such care is not necessarily provided only at the end of life, but can be utilized throughout the trajectory of a serious illness, in conjunction with curative-focused medical care. Figure 64.1 illustrates the current perspective of how palliative care is viewed over time of treatment.

The application of palliative care within gastroenterology (GI) has been described as a "promising philosophical framework for gastroenterology" [2]. This is because of the wide range of symptoms of many chronic GI conditions in the elderly that require careful attention to symptom management, for which palliative care is uniquely well suited. Palliative care is especially helpful when there are concurrent multiple medical comorbidities such as cancer, heart failure, or dementia that conspire to weaken an older adult with a predominant GI problem.

Palliative care is most often delivered by a team consisting of physicians and nurses, with the support of social workers, pharmacists, nutritionists, physical therapists, and chaplains, and may include others such as anesthesiologists, neurologists, and psychiatrists. While the services are usually hospital-based, formal palliative care teams can serve community patients and long-term care residents.

Ideally, palliative care is included alongside treatment of the serious or life-threatening illness, broadening its intervention as the patient's illness progresses. The focus of palliative care efforts with the primary disease-centered care will change over time with course of the illness. For a patient with rectal cancer, for instance, initial efforts might focus on restoration of normal eating or bowel function or helping the adjustment to a colostomy. Subsequent efforts, should the patient have disease progression, might focus on optimizing function in the presence of metastatic cancer, pain management, control of chemotherapy-related nausea, narcotic-related constipation, or malignant bowel obstruction.

Palliative Care Versus Hospice Care

Palliative care and hospice care can often be confused or, incorrectly, considered synonymous with each other. While both share many techniques and interventions, Table 64.1 presents key distinctive elements of each.

In presenting such distinctions to patients and their family caregivers, it is useful to point out that palliative care can be given alongside curative or "aggressive" interventions. In contrast, the hospice Medicare insurance benefit is limited to patients with life-terminating disease when survival is estimated to be less than 6 months. Often this hospice prognostic assessment can be phrased to the provider as: "Would you be surprised if this patient would die within the next 6 months from their current conditions?" If the answer is "no," hospice referral should be considered. While patients can be recertified to remain on hospice for additional 6-month periods, the formal prognosis determination is a key distinction between palliative care and hospice.

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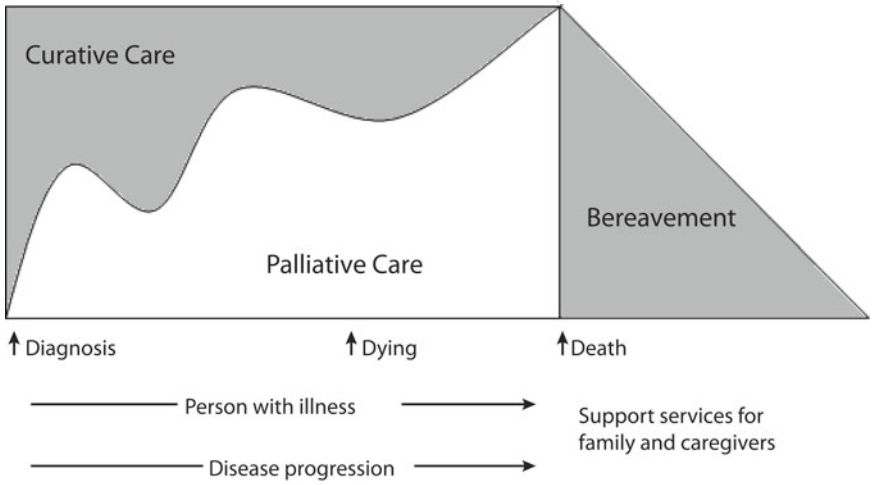

Fig. 64.1 The integration of palliative care with curative care over the course of a patient's chronic *Illness* (adapted from: Murray et al. [18]. Used with permission)

Table 64.1 Distinctions between hospice and palliative care

Palliative care characteristics	Hospice characteristics
Independent of prognosis	Requires formal prognosis estimation from physician
Appropriate throughout illness course, including terminal phase	Appropriate for terminal phase of illness, especially when "actively dying"
Focus on optimizing function through symptom relief	Focus on terminal symptom management
Funded through existing payment mechanisms	Funded through Medicare part A benefit
Interventions often adjunctive to curative treatment/interventions	May exclude interventions focused solely on longevity

Table 64.2 The hierarchal domains of functional measures

Integrative activities of daily living	Driving and transportation Home safety
Instrumental activities of daily living	Cooking Cleaning Shopping Communicating Handling finances Administering medications
Basic activities of daily living	Bathing Dressing Toileting and continence Transferring and mobility Feeding

Palliative Care Measures and Outcomes

The goals of palliative care treatments for older adults with GI issues focus more on suppressing morbidity and enhancing quality of life aspects. Such goals are best expressed in terms of functional abilities. Table 64.2 reviews the terminology of function expressed as activities of daily living (ADLs).

The highest level of function, integrative or executive, brings together multiple aspects of health and wellness requiring intact cognitive functions of judgment, awareness, and insight to make the most of the other two functional domains. Instrumental ADLs reflect tasks that, when impaired, prompt the need for in-home supplemental services such as meal delivery, home maker, cooking, cleaning, finances, or medication monitoring. Impairment of multiple basic ADLs will often require consideration of institutional placement—e.g., an assisting living residence, skilled nursing facility—or 24 h care in the home if feasible. The hierarchical nature of ADLs is important in both assessing the interaction between diseases common in older adults and arranging for supplemental services. For example, the progressive nature of many dementing illnesses such as Alzheimer's disease will cause integrative and instrumental ADL impairments long before basic ADLs become impaired; basic ADLs are the last function to be lost. A demented patient who abruptly develops bowel incontinence but retains independence in many higher level function areas would not be expected to have the incontinence attributed to the dementia but rather due to some other intervening and potentially correctable condition.

Palliative care interventions are effective in optimizing function and quality of life. In a study of patients with cancer receiving regular oncology care and a palliative care-focused intervention addressing physical, psychosocial, and care coordination, outcomes included better quality of life and mood despite similar symptom intensity and reduced days in the hospital, intensive care unit utilization, and emergency department visits [3]. Another study assessed the impact of an inpatient palliative care team in a randomized trial; patients with a wide variety of life-limiting diseases were assigned to receive usual care or usual care plus palliative care services which consisted of discussion of medical issues, end-of-life issues, management of physical symptoms, psychological and spiritual issues,

Table 64.3 Overcoming common barriers during end-of-life geriatric care

Common barriers	Specific issues	Strategies
Sensory impairments	Hearing loss	Assistive listening device (e.g., PocketTalker©)
	Visual impairment	Access to concise large print patient instruction materials
	Taste loss	Consider mineral and vitamin deficiencies
		Saliva replacement
In-office functional mobility	Poor standing balance for weight	Seated chair scale
	Inability to climb onto exam table	Electric tilt tables
		Grab bars/hand rails for toilets and care settings
Provider–patient communication	Limited English proficiency	Access to medical translation services
	Limited health literacy	Confirm mutual understanding between patient, caregiver, and provider during encounters
Cognitive impairment	Dementias	Facilitate office staff—family caregiver interactions
	Fluctuating alertness	Communicate written plans with involved care providers

practical needs, and assistance with discharge planning. There was no difference in the initial hospital stay duration, though patients receiving palliative care had better implementation of advance directives. There was no difference in quality of life between the groups but higher satisfaction with the hospital care among the recipients of palliative care consults. However, the patients who received palliative care consults had fewer ICU stays on readmission, decreasing significantly the overall cost of care for these patients [4]. A study limited to patients with metastatic lung cancer randomly assigned to have a palliative care team assist the primary oncologic team in the treatment of patients or to no additional assistance found that those who received additional input of palliative care had fewer symptoms, less depression, and less frequent aggressive end-of-life care, and lived approximately 2.5 months longer [5].

To achieve positive outcomes through palliative care integration into care of geriatric GI patients, common communication and geriatric care delivery barriers need to be addressed, as reviewed in Table 64.3.

Palliative Care Techniques Targeting Specific End-of-Life Gastrointestinal Symptom Management

Gastrointestinal symptoms are prominent throughout a variety of elder life-threatening or life-terminating illnesses, i.e., cancer, heart failure, dementia, and terminal frailty. Table 64.4 outlines common palliative care concerns that geriatricians or gastroenterologists may need to address, for which palliative care offers a specific agenda.

Anorexia, Inadequate Oral Intake, and Enteral/Parental Feeding

Decreased intake may be from multiple etiologies, some remediable once identified. The problems may relate to poor state of teeth, poor denture fit, or an oral yeast infection that may respond to local therapy. A medication review may identify medications that decrease appetite such as amiodarone, digoxin, aminophylline, levodopa, fluoxetine, lithium, metronidazole, and several chemotherapy agents [6]. Concurrent chronic illnesses, such as COPD or congestive heart failure, may sap energy, as may progressive neurologic conditions with associated oropharyngeal muscle impairment such as dysphasia of Parkinson's disease and Alzheimer's dementia [7]. Narcotics may cause both nausea and constipation; slow titration may limit nausea which is generally a time-limited side effect. A bowel regimen must be initiated at the same time narcotics are begun.

Palliative care includes pharmacologic approaches to anorexia. Megesterol, as oral suspension, 400–800 mg/day is sometimes effective, though it does not increase lean body mass. A limiting concern with this agent is the increased likelihood of deep vein thrombosis in this often sedentary population. Dronabinol, 2.5–5 mg, is less commonly used in older subjects compared to the young; it may be associated with delirium or nausea. Methylphenidate, 2.5–5 mg given in the morning and early afternoon, may increase appetite and activity level but can increase heart rate and agitation. The antidepressant agent mirtazapine, 7.5 mg, at bedtime has variable efficacy but is a first choice for older adults with depression and insomnia accompany anorexia. Prednisone10–20 mg, in the morning, may also be used short term for treatment of anorexia, with appropriate concern for glucose intolerance, gastritis, and muscle weakness.

Providers should acknowledge the emotional impact of reduced food intake common among terminally ill older adults and their family caregivers. Relatives and friends who witness the decline of their loved one within health care settings may feel powerless to influence the course of the illness and resort to prior interventions in an effort to "do something." When these interventions are perceived as ineffective, their distress can be imparted to the patient, worsening the situation. A useful concept in such situations is that of comfort or recreational feeding [8]. Rather than focus on quantitative calorie intake, the sensory aspects of taste, smell, texture, and any associated

Table 64.4 The palliative care agenda in common geriatric GI issues

Common geriatric gastroenterology issues	Disease contexts	Palliative care intervention
Abdominal pain	Advanced GI malignancies Chronic pancreatitis Constipation	Analgesia delivery and monitoring Proactive management of narcotic-related adverse effects
Dysphagia	Advanced dementias (e.g., Alzheimer's disease) Stroke	Defining goals of care for enteral feeding technology Comfort feeding when appropriate
Ascites	End-stage liver disease Metastatic disease	Therapeutic paracentesis Drainage procedures
Constipation	Advanced neurologic diseases (e.g., parkinsonism) Metabolic diseases (e.g., diabetes) Narcotic use	Stool motility medications Ensuring skin hygiene and integrity Fluid intake
Obstructive jaundice	Pancreatic cancer Metastatic disease	Surgical bypass procedures Biliary stenting Treatment for associated pruritus
Intestinal obstruction	GI malignancies	Decompression Antinausea interventions
Anorexia	Depression Malignancies	Appetite stimulants

memories with highly evocative foods may be stressed. Small amounts of pleasing foods and beverages presented by hand allow caregiver and patient to interact in a mutually beneficial way to complement the health care provider's interventions.

In addressing the anorexia of terminal care of the elderly with chronic GI issues, total parental nutritional (TPN) becomes a consideration. In a patient with significant likelihood of recovery, the implementation of nutritional support using parenteral nutrition may be an appropriate intervention [9]. However, for a patient with a life-limiting illness, artificial parenteral nutrition should only be considered as a short-term intervention to allow a person to attain realizable near-term improvement in function or quality of life. Cancer patients most likely to benefit from TPN are those for whom less invasive methods have failed, those who able to participate in their own care, and who have an estimated survival of greater than 1.5–2 month with good social and financial support, with a home provider of care [10].

The use of enteral tube feeding (e.g., pericutaneous enteral gastrostomy; PEG) is a major concern and requires careful consideration before being placed in patients with inability to eat and substantial weight loss at end of life. In patients with advanced dementia, there is no evidence of increased survival; reduced pressure ulcers; or improved quality of life, nutritional status, function, behavior, or psychiatric symptoms in patients fed via gastrostomy tubes [11, 12]. Further, this modality of feeding may bypass the personal interaction that is part of nurturing care.

Families frequently suggest end-of-life parenteral nutrition, tube feeding, or intravenous hydration interventions because of their understandable concerns of symptomatic thirst, hunger, or dehydration [13]. These discussions may be difficult or uncomfortable, but do allow the medical providers to explore patient's and families' fears, concerns, and goals of care for the patient. It is always helpful to ascertain any prior expressed wishes by the patient about such treatments, as well as ensuring that caregivers understand that TPN and intravenous hydration have risks including need for venous access, edema, and infection, and may merely prolong the dying process rather than restore their loved ones to health [14]. Some data exists that terminally ill patients do not suffer from thirst or hunger as death approaches [15]. The outcomes from such discussions can be put into a revised advanced directive document such as "Physician Orders for Life-Sustaining Treatments" (POLST) or "Medical Orders for Life-Sustaining Treatment" (MOSLT) that are becoming recognized in many states as a means to address out-of-hospital directives [16].

Ascites

Ascites in the palliative care setting is treated by conventional methods that include diuretics, paracentesis, and possibly portal decompression. Unfortunately, patients with malignant ascites rarely improve through the use of diuretics or portal decompression so that repeated paracentesis can become necessary on an increasingly frequent basis. The discomfort of refractory, symptomatic malignant ascites may be relieved with the use of an indwelling peritoneal catheter (Pleurx®) which can be drained at home. The proactive involvement of a multidisciplinary team to assist family caregivers in the

education and management of such catheters helps reduce anxiety of patient and caregiver while minimizing unnecessary hospital visits after the patient is transferred out of hospital to home with such a device in place.

Constipation

Constipation is a common occurrence in the elderly requiring palliative care. In planning interventions that often require multiple bowel agents, one must ensure that the volume of fluids and number of pills does not excessively burden patients' routine or compromise the ability for adequate nutritional intake. Stool softeners such as docusate may be combined with a stimulant laxative, such as bisacodyl or senna, but only after fecal impaction is addressed through topical anesthetic gel-accompanied manual disimpaction. Proactive attention to the predicable reduced mobility effects of narcotic analgesics is essential, with the need to initiate a routine stimulant laxative when narcotics are started [17]. Multiple daily doses of the laxative are commonly required with a gradual increase of the stimulant dose with concurrent increases in the amount of narcotic analgesics. Methylnaltrexone is helpful for patients with severe opioid-induced constipation, but parenteral administration is required. Lubiprostone is under study for the treatment of opioid-induced constipation.

Cancers with Intestinal Obstruction

Cancers of GI origin may cause obstruction at any site from the esophagus to the rectum, and sometimes at multiple levels. Palliative interventions "to buy time" can be considered while definitive treatment is awaited, or as comfort measures near the end of life. Surgical interventions may be considered for a single, localized bowel obstruction whereas endoscopically placed stents are useful for palliation of esophageal, duodenal obstruction, and some colonic/rectal obstructions. For a patient with bowel obstruction not amenable to surgery or stenting, a venting gastrostomy is relatively easily placed, and allows patients to be free of emesis and nasogastric tube. Octreotide, given subcutaneously twice or thrice daily, can decrease GI secretions and lessen emesis.

Summary

Ultimately, the aim of palliation of GI symptoms is to focus on the "big-picture" of the patient's disease, the overall prognosis, and the realistic functional goals that are identified for this phase of illness. Through careful application of integrating palliative care principles and techniques into the ongoing GI care delivery, patients can be made more comfortable and functional through their terminal illness.

Key Points

- Palliative care and hospice care share many symptom-directed therapeutic strategies, though palliative care can be utilized earlier in the course of a patient's illness, before the terminal 6 months of life expectancy required for activating Medicare hospice benefit.
- The goals of therapy during end-of-life care to decrease morbidity while enhancing quality of life can be assessed in terms of function abilities and measured in "units" of activities of daily living (ADLs).
- Proactively addressing symptoms like narcotic-related constipation, terminal-phase anorexia, and caregiver concerns about parental or enteral feedings are best addressed through a palliative multidisciplinary care team integrated with the geriatrician, primary physician, and gastroenterologist.

References

1. Merriam-Webster Collegiate Dictionary. 10th ed. Springfield: Merriam-Webster; 2001.
2. Dunn GP. Palliative care: a promising philosophical framework for gastroenterology. Gastroenterol Clin North Am. 2006;35:1–21.
3. Bakitas M, Doyle Lyons K, Hegel M, et al. Effects of a palliative care intervention on clinical outcomes in patients with advanced cancer. JAMA. 2009;302(7):741–9.
4. Gade G, Venohr I, Conner D, et al. Impact of an inpatient palliative care team, a randomized controlled trial. J Palliat Med. 2008;11:80–90.
5. Temel J, Greer J, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med. 2010;363:733–42.
6. DiFrancesco V, Fantin F, Omizzolo F, et al. The anorexia of aging. Dig Dis. 2007;25:129–37.
7. Mitchell L. Clinical crossroads: a 93-year-old man with advanced dementia and eating problems. JAMA. 2007;298:2527–36.
8. Palecek EJ, Teno JM, Cararett DJ, et al. Comfort feeding only: a proposal to bring clarity to decision-making regarding difficulty with eating for persons with advanced dementia. J Am Geriatr Soc. 2010;58(3):580–4.
9. August D, Huhmann M. A.S.P.E.N. clinical guidelines: nutrition support therapy during adult anticancer treatment and in hematopoietic cell transplantation. J Parenter Enteral Nutr. 2009;33:472.
10. Casarett D, Kapo J, Caplan A. Appropriate use of artificial nutrition and hydration-fundamental principles and recommendations. N Engl J Med. 2005;353:2607–15.
11. Sampson E, Candy B, Jones L. Enteral tube feeding for older people with advanced dementia. Cochrane Database Syst Rev. 2009:CD007209.

12. Kurien M, McAlindon M, Westaby D, Sanders D. Percutaneous endoscopic gastrostomy (PEG) feeding. Br Med J. 2010; 340:c2414.
13. Gillick M, Volandes A. The standard of caring: why do we still use feeding tubes in patients with advanced dementia. J Am Med Dir Assoc. 2008;9:364–7.
14. Fordyce M. American geriatric society foundation for health and aging patient education forum: end of life care—a guide for patients and caregivers. 2011. http://www.healthinaging.org/public_education/pef/end_of_life_care.php. Accessed 12 Jan 2011.
15. McCann R, Hall W, Groth-Junker A. Comfort care for the terminally ill patient: the appropriate use of nutrition and hydration. JAMA. 1992;272:1263–6.
16. New York Department of Health. Medical Orders for Life-Sustaining Treatments. 2011. http://www.health.state.ny.us/professionals/patients/patient_rights/molst. Accessed 12 Jan 2011.
17. Morrison RS, Meier DE. Palliative Care. N Engl J Med. 2004; 350:2582–90.
18. Murray SA, Kendall M, Boyd K, Sheikh A. Illness trajectories and palliative care. Br Med J. 2005;330(7498):1007–11.

Part XIII

Surgery

The Surgical Abdomen

65

Carlos A. Pelaez and Nanakram Agarwal

Introduction

Surgery has an essential role in the care of the geriatric patient. Patients 65 years of age and older are two to three times more likely to undergo surgical procedures, e.g., 1,327 procedures/10,000 persons aged 65–84 years vs. 626 procedures/10,000 persons aged 45–64 years [1]. Older adults account for approximately 50% of all emergent operations but 75% of operative mortality [2].

Improvements in anesthesia techniques, perioperative monitoring, endoscopic and minimal access techniques have added to the ease and safety of operative therapy resulting in reduced mortality, increased ambulatory surgery, and shorter stay hospitalizations. The lack of physiologic reserve is the single most important factor that decreases the older adult's ability to tolerate surgery. Physiologic age more than chronological age, in addition to comorbidity, more accurately predicts surgical outcomes in the elderly [3]. Attention to details is critical. It is imperative that the surgeon identifies those at increased risk and tailor treatment accordingly.

Abdominal Pain

Abdominal pain is a challenging complaint as it commonly represents a benign condition, but could also stage serious pathology. While arbitrary, acute abdomen or "surgical abdomen" are terms denoting sudden severe abdominal pain of less than a day's duration that rapidly worsens in the absence of early intervention. However, the term "acute abdomen" should never be equated with the invariable need for surgery [4].

The elderly account for 20% of all emergency department visits, of which 3–4% are for abdominal pain. Though most causes of abdominal pain are not true emergencies, the older patient always represents a concern due to delayed presentation, often coupled with nonspecific symptoms. They may delay seeking care due to fear of losing independence, lack of health insurance, lack of transportation, diminished caregiver support, and fear of hospitalization or death [5]. Half the older patients presenting to the emergency department with abdominal pain require hospital admission, and 20–33% will require immediate surgery [6]. About 40% are initially misdiagnosed and carry an associated mortality as high as 34% [5].

Older adults often present atypically, in part due to associated comorbidity and impaired cognitive status which makes it difficult to obtain an accurate history. The presence of dementia or delirium from adverse drug effect, infection, and fluid or electrolyte imbalance contributes frequently to misdiagnoses. With gastrointestinal events such as acute appendicitis, cholecystitis, or bowel obstruction, a third may not manifest fever, elevated white blood cell count, or physical findings of peritonitis [1]. Failure to adequately evaluate the older adult at time of initial presentation may reflect in increased morbidity and mortality [4].

Thorough focused history taking and physical examination are essential to correct diagnosis and timely treatment. History should include: time and course of pain, location (Table 65.1), type (Table 65.2), radiation, exacerbating and relieving factors, associated manifestations, past medical and surgical history, and current medications [4]. Patient can be given narcotics without obscuring the clinical findings [7]. Frequent reassessment, preferably by the same examiner, is important. Differential diagnosis should include a wide spectrum of disease for abdominal pain; exclude several before contemplating surgical intervention.

Routine laboratory tests, although essential, are not diagnostic. Upright chest X-ray is crucial to evaluate for free intraperitoneal air (Fig. 65.1) and rule out pulmonary disease. Abdominal plain films have a role while abdominal CT and ultrasound have higher yields.

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Table 65.1 Diagnosis based on location of abdominal pain

Right upper quadrant	Epigastrium	Left upper quadrant
Biliary colic	Peptic ulcer	Peptic ulcer
Acute cholecystitis	Acute cholecystitis	Diverticulitis
Duodenal ulcer	Esophageal perforation	Ruptured spleen
Appendicitis	Pancreatitis	
Diverticulitis		
Right lumbar	**Periumbilical**	**Left lumbar**
Duodenal ulcer	Early appendicitis	Ureteric colic
Diverticulitis	Small bowel obstruction	Diverticulitis
Ureteric colic	Perforated peptic ulcer	Sigmoid volvulus
Appendicitis	Pancreatitis	
	Ruptured aortic aneurysm	
	Mesenteric ischemia	
	Meckel's diverticulitis	
Right lower quadrant	**Hypogastrium**	**Left lower quadrant**
Appendicitis	Large bowel obstruction	Diverticulitis
Diverticulitis	Diverticulitis	Sigmoid volvulus
Ureteric colic	Cystitis	Ureteric colic
Inguinal or femoral hernia		Colon carcinoma
Meckel's diverticulitis		Inguinal or femoral hernia
Cecal volvulus or bascule		

Table 65.2 Types of abdominal pain

Onset	Sudden (instant)	Perforated ulcer
		Ruptured aneurysm
	Rapid (minutes)	Perforated viscus
		Biliary colic
		Renal colic
		Volvulus
		Mesenteric ischemia/ infarction
	Gradual (hours)	Appendicitis
		Intestinal obstruction
		Strangulated hernia
		Cholecystitis
		Pancreatitis
Type	Visceral	Dull, vague, poorly localized
		Upper abdomen: stomach, gallbladder
		Midabdomen: small bowel, appendix, colon
		Lower abdomen: colon, bladder, uterus, ovaries
	Parietal	Sharp and localized
		McBurney's point: acute appendicitis
		Tearing: dissecting/rupture aneurysm
	Referred	Right scapula: gallbladder
		Left scapula: spleen
		Groin: renal colic
		Back: pancreas, aortic aneurysm
Colic	Renal	Highest intensity with shortest intervals
	Biliary	Acute and persistent
	Small intestine	Acute and paroxysmal
	Large intestine	Low intensity with longest intervals

The most common causes of acute abdomen in the geriatric population include acute cholecystitis, appendicitis, perforated peptic ulcer disease (PUD), acute pancreatitis, intestinal obstruction, ischemic bowel disease, diverticulitis, and obstructed hernias. Several are discussed elsewhere in the text.

Biliary Tract Disease

Biliary tract disease accounts for a third to half the patients over age 55 who present to the emergency department with acute abdominal pain [5]. Once the diagnosis of cholecystitis is made, supportive care including hydration, antibiotics, and analgesia is initiated. The selection of treatment and timing of definitive therapy (i.e., cholecystectomy) depends upon the severity of the symptoms and patient's risk for surgery. Laparoscopic cholecystectomy is the procedure of choice over open removal of the gallbladder. Generally, early cholecystectomy, within 48–72 h of admission is preferred, but many surgeons advocate a "cool-down" period, when patients received antibiotics for 1 week and surgery is delayed for 6–10 weeks; this approach was considered associated with lower risk of morbidity and mortally and lower conversion

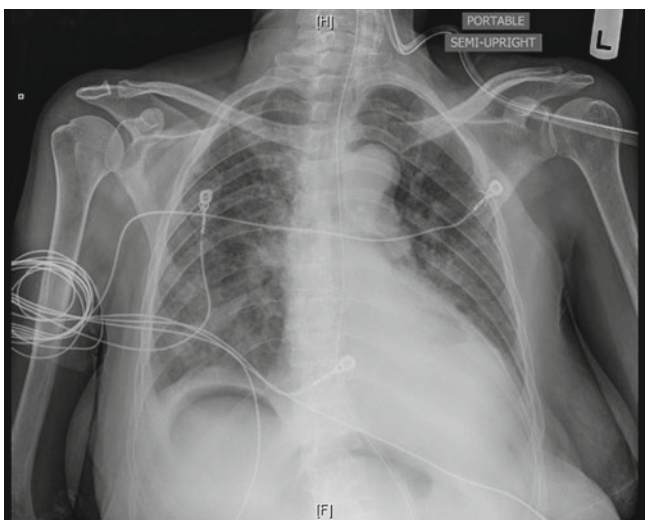

Fig. 65.1 Perforated viscus. Chest X-ray demonstrates subdiaphragmatic free air above the dome of the liver

rates, but multiple studies, including a meta-analysis of ten prospective randomized trials found no difference in morbidity and mortality between early and delayed cholecystectomy [8]. An intraoperative cholangiogram performed selectively when the anatomy is uncertain, better delineates the cystic and common bile duct, and addresses the concern of common bile duct stones; however, normal preoperative bilirubin levels generally indicate that the clinically insignificant stones will pass spontaneously with no sequelae. If the patient is unfit for surgery, or comorbidity increases surgery risk, a percutaneous catheter decompression of the gallbladder can be easily performed, typically by an interventional radiologist.

Older adults, diabetics, and those who delay seeking care have progressive acute inflammation that can lead to gangrene, empyema, or perforation of the gallbladder (Fig. 65.2). Gangrenous cholecystitis is a common complication in older adults, diabetics, and in those who delay getting evaluation. Perforation often occurs in gangrenous cholecystitis and leads to abscess formation or perforation into the peritoneum, with consequent tenfold increase in mortality [9]. Evidence of emphysematous cholecystitis, sepsis, or rapidly deteriorating status warrants prompt attention and cholecystectomy. Similarly, other complications including cholecysto-enteric fistulas, gallstone ileus, and gallstone pancreatitis are more common in the elderly.

Prophylactic cholecystectomy is not indicated in most patients with asymptomatic gallstones. Possible exceptions include ethnic groups with high risk for gallbladder carcinoma, gallbladder polyp, porcelain gallbladder, and gallstones larger than 3 cm in diameter; here prophylactic cholecystectomy or incidental cholecystectomy may be offered at the time of another abdominal operation.

Choledocholithiasis is the presence of stones within the common bile duct and are present in 5–10% of the patients who require surgery for symptomatic cholelithiasis. Endoscopic Retrograde Cholangiopancreatography (ERCP) and sphincterotomy with removal of common bile duct stones followed by laparoscopic cholecystectomy is the preferred treatment option. Laparoscopic common bile duct exploration during cholecystectomy is another option, dependent on the expertise of the surgeon.

Appendicitis

The presentation of appendicitis differs in the old compared to the young. With the old, the history is frequently incomplete and confusing, and "classic" symptoms rarely occur making the diagnosis of acute appendicitis a challenge. The likely presentation is generalized abdominal pain, longer duration of symptoms, less impressive fever, and leukocytosis [5], with the incidence of perforation five times higher than in younger people. Even though only 5–10% of all appendicitis occurs in the geriatric age group, older adults account for the majority of deaths associated with appendicitis [10].

Delayed and atypical presentations, delayed diagnosis and treatment while awaiting test results eventually lead to higher morbidity and mortality rates [11]. CT is the diagnostic test of choice (Fig. 65.3) with an accuracy of 100% as compared to 81% for ultrasound.

Antibiotics as the primary treatment of nonperforated appendicitis are suggested in select patients, as reported in multiple studies. In a large meta-analysis, significant selection bias and crossover to surgery was found, concluding that antibiotics only are unlikely to supersede appendectomy [12]; at present, appendectomy is still the gold standard therapy for acute appendicitis. It is possible that the

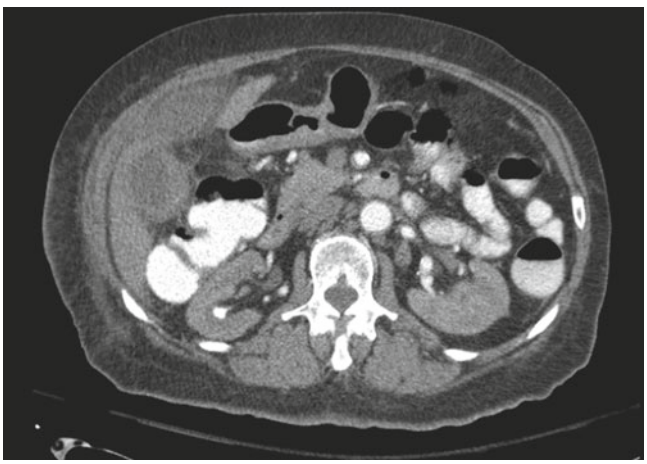

Fig. 65.2 Acute cholecystitis. CT abdomen demonstrating an inflamed gallbladder

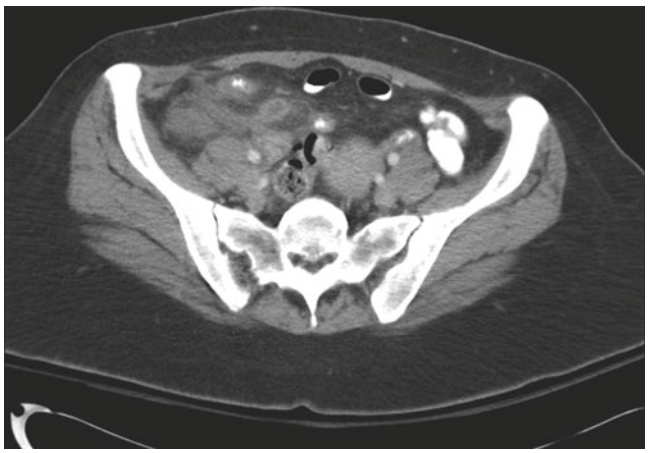

Fig. 65.3 Acute appendicitis. CT abdomen and pelvis demonstrates a dilated fluid filled appendix with enhancing wall and adjacent fat stranding

diagnosis of significant pathology such as carcinoid or carcinoma may be delayed if appendectomy is not performed.

Peptic Ulcer Disease

PUD accounts for 16% of the older patients with abdominal pain [13]. Although the frequency of need for surgical therapy has declined, the indications have remained the same, and include nonhealing ulcers, uncontrolled bleeding by endoscopy, perforation, and obstruction. Recent reports indicate an increased risk in peptic ulcer perforation in the old, especially in woman [14]. If an ulcer fails to heal after 12 weeks of appropriate medical therapy, it is termed "intractable" with cancer a consideration.

Bleeding ulcers have an overall mortality of approximately 10%. Endoscopic evaluation and treatment is the initial strategy of choice. If unsuccessful, distal gastrectomy including the ulcer is ideal for bleeding gastric ulcers. For duodenal bleeding ulcers or gastric ulcers in the unstable patient, biopsy and oversewing of the ulcer may be performed.

For perforated ulcer, surgery is almost always indicated, but at times the perforation seals without operation; this approach is associated with prohibitive morbidity and mortality. For a perforated gastric ulcer, which may be malignant, the preferred approach is partial gastrectomy. If the patient is unstable or high risk for surgery, patch closure may be performed with a biopsy to rule out malignancy.

Surgery in PUD is currently infrequent in an era of *Helicobacter pylori*. For perforated duodenal ulcers while definitive ulcer surgery with an acid-reducing procedure is desirable, simple patch closure only has become the preferred option in presence of effective medical treatment with proton-pump inhibitors and therapy for *H. pylori* [15]. NSAID-related perforation can be treated with simple closure if the medication can be discontinued postoperatively.

Complications and mortality with peptic ulcer are higher in the geriatric age group and relate to atypical presentations, delayed diagnosis, and comorbidity. In a study of 269 patients operated for perforated peptic ulcer, multivariate analysis suggested that only age, delayed surgery, ASA score, presence of shock, and definitive operation were independent predictors of mortality. Patients older than 65 had a 37.7% mortality compared to 1.4% in younger patients. A delay of over 24 h after onset of symptoms increased mortality 6.5-fold and complications 3.4-fold. The main modifiable factor that could improve prognosis in perforated peptic ulcer is delay in diagnosis [14].

Diverticulitis

Diverticulitis, the most common complication of diverticular disease, occurs in the sigmoid colon in over 90% of patients. The spectrum of disease ranges from mild uncomplicated diverticulitis to free perforation and diffuse peritonitis that requires emergency laparotomy.

Complicated diverticulitis includes abscess, obstruction, diffuse peritonitis, or fistulas between the colon and adjacent structures. Most patients require surgery in addition to bowel rest, intravenous broad-spectrum antibiotics, and fluids. Small abscesses (less than 3 cm diameter) can be treated just with parenteral antibiotics. Larger abscesses are best treated with CT-guided percutaneous drainage. The majority with complications will ultimately require resection of the diseased segment of colon with end colostomy (Hartmann's procedure), but percutaneous drainage may allow a one-stage elective procedure and may obviate the need for colostomy if full recovery follows the drainage [3].

The indications for surgery in recurrent diverticulitis are controversial, with trends favoring nonoperative therapy and individualizing surgery to patients. The number of attacks of uncomplicated diverticulitis is not necessarily an overriding factor in defining appropriateness of surgery. CT-graded severity of a first attack, or subsequent attacks, is a better predictor of adverse natural history and helps determine need for surgery [16]. Immunosuppressed patients may require surgery after the first episode of diverticulitis. Colon carcinoma may be identical in presentation to complicated or uncomplicated diverticulitis; all patients must be evaluated for malignancy after resolution of symptoms, with colonoscopy 4–6 weeks postrecovery [3].

Intestinal Obstruction

Intestinal obstruction of the bowel lumen may be total or partial, resulting in failure of the intestinal contents to pass distally beyond the obstruction. The cause of bowel obstruction may be within its lumen (e.g., foreign bodies or gallstones), in the wall of the bowel (e.g., tumors or strictures), or outside the bowel (e.g., adhesions, hernias, or carcinomatosis). Adhesions cause about two-thirds of the episodes of small bowel obstruction, followed by hernia (about 20%) and tumors [5]. Adhesions are the result of prior abdominal surgery and usually do not cause obstruction of the colon due to its large lumen. Malignancy is the most common cause of large bowel obstruction in the elderly.

The clinical presentation is pain, vomiting, constipation, and abdominal distention. Pain is colicky in nature, usually in the mid-abdominal region. Vomiting occurs early in proximal small bowel obstruction, but is late and feculent in distal small bowel and colonic obstruction. Similarly, distention is pronounced if the lesion is located more distally.

Bowel ischemia and gangrene can complicate any type of intestinal obstruction warranting prompt intervention. Unrelenting abdominal pain disproportionate to the degree

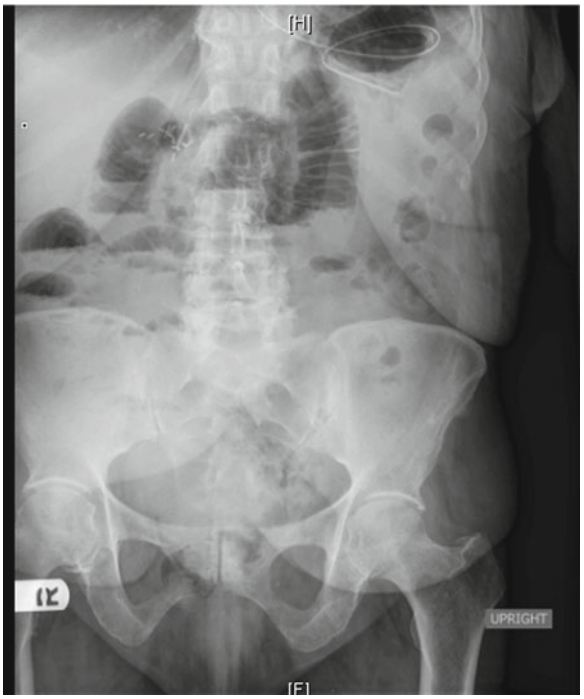

Fig. 65.4 Small bowel obstruction. Upright abdominal X'ray demonstrates air-fluid levels, dilated small bowel loops, and paucity of gas in the colon

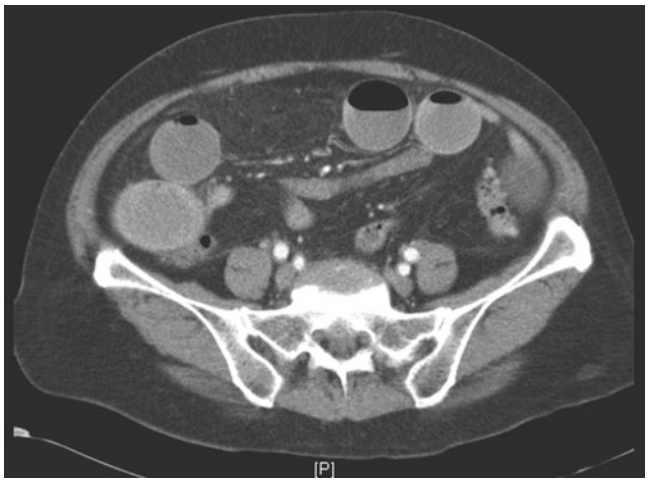

Fig. 65.5 Small bowel obstruction. CT abdomen demonstrates dilated small bowel loops with air-fluid levels, collapsed distal small bowel, and collapsed colon

of abdominal findings suggests intestinal ischemia and is an indication for surgical intervention. Tachycardia, fever, marked leukocytosis, acidosis, and localized abdominal tenderness are signs of possible strangulation requiring early surgical intervention [4].

A plain radiograph of the abdomen shows characteristic findings confirming the diagnosis in less than half of the patients. The finding most specific for small bowel obstruction is the triad of dilated small bowel loops (>3 cm in diameter), air fluid levels, and paucity of air in the colon (Fig. 65.4). CT scan with contrast is the preferred diagnostic test, with a sensitivity of 80–90% and specificity of 70–90%. It outlines the obstructing site of the bowel, type of obstruction (e.g., closed loop or strangulation), as well as the etiology (e.g., sigmoid or cecal volvulus, intussusception or tumor). The findings of small bowel obstruction include a discrete transition zone with dilatation of bowel proximally, collapsed loop distally, nonpassage of contrast beyond the transition zone, and a colon containing little gas or fluid (Fig. 65.5). Thickening of the bowel wall, pneumatosis intestinalis, portal venous gas, mesenteric haziness, and ascitic fluid suggest strangulation [17]. In prospective studies, the water-soluble contrast, gastrografin, used during CT was of diagnostic and therapeutic value. The appearance of contrast in the colon 4–24 h after administration predicted resolution of the adhesive small bowel obstruction with a sensitivity and specificity of 96 and 98%, respectively. Furthermore, patients assigned to water-soluble contrast agent had a significant reduction in the need for surgical intervention and had a significant shorter hospital stay by almost 2 days [18].

Management of bowel obstruction may be entirely nonsurgical, particularly when adhesions are the basis. Treatment includes intravenous fluids, replacement of electrolytes, and nasogastric tube decompression of stomach. A Foley catheter monitors urine output. Failure to resolve the obstruction on this regimen in 24–48 h or development of signs of ischemia is indication for surgery [3]. The threshold for operation in older adults should be low with early rather than late intervention. Mortality for patients with gangrenous strangulated obstruction is substantially higher than for nonstrangulated small bowel obstruction (4.5–31% vs. approximately 1%) [19].

Early Postoperative Obstruction

Obstruction in the early postoperative period (within 30 days of initial surgery) is seen in approximately 1% of the patients after laparotomy [20]. It is highest after pelvic surgery, especially colorectal procedures. Most patients present with symptoms of bowel obstruction after an initial period of return of bowel function. In some patients, bowel function fails to return within 3–5 days of surgery; this represents paralytic or adynamic ileus and needs to be distinguished from bowel obstruction. CT scan is diagnostic.

Management is conservative, as the obstruction is rarely associated with strangulation and resolves in 90% of patients. In contrast, early postoperative obstruction after laparoscopic surgery usually needs early surgical intervention.

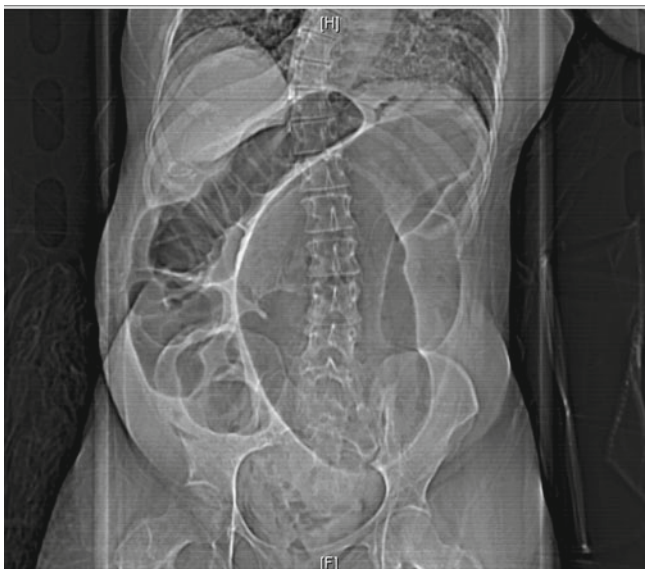

Fig. 65.6 Sigmoid volvulus. CT topogram outlines dilated sigmoid colon with "coffee bean" appearance

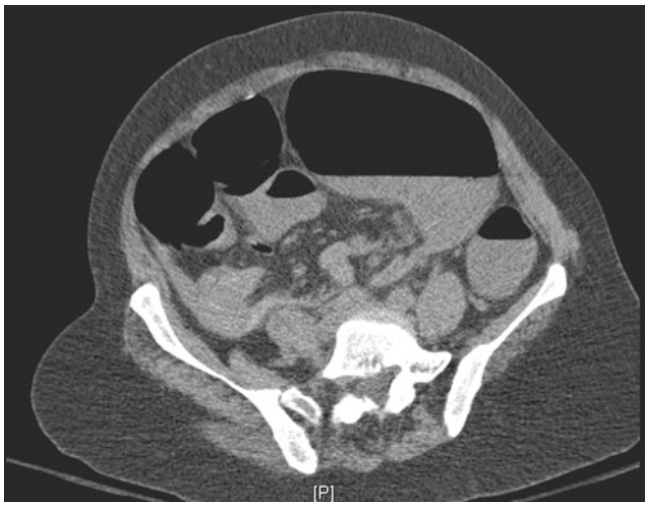

Fig. 65.7 Sigmoid volvulus: CT abdomen and pelvis demonstrates "birds beak" narrowing at the site of the volvulus with proximally dilated colon

Volvulus

Volvulus or twisting of the bowel is more likely to occur when the bowel is redundant and attached to the posterior abdominal wall with a short-based mesentery. The twist of loop at its base occludes blood supply to the bowel with resultant early ischemia. Volvulus can occur in the small intestine but in older adults, the colon is the most common site [21]. It involves the sigmoid colon in up to 90% of cases and the cecum in 20–50% of patients. The prevalence of sigmoid volvulus varies geographically; it is the leading cause (as high as 50%) of acute colonic obstruction in South America, Africa, Eastern Europe, and Asia, but is rare (less than 5%) in developed countries such as USA, UK, Japan, and Australia [22]. The typical patient is institutionalized and debilitated elderly with neurologic or psychiatric illness. Abdominal pain, nausea, abdominal distention, and constipation are the presenting symptoms, while vomiting is infrequent. Plain X-ray of the abdomen (Fig. 65.6) reveals the characteristic "bent inner tube or coffee bean" appearance in 65% of the cases [23]. CT or gastrografin enema shows the pathognomonic "birds beak" narrowing at the site of the volvulus (Fig. 65.7).

Most patients, up to 90%, present prior to development of gangrene [24]. The initial management is resuscitation followed by endoscopic detorsion using a flexible or rigid sigmoidoscope maneuver that is successful in 95% of the cases. A sudden expulsion of gas indicates successful reduction of the volvulus. A rectal tube is left in place to maintain decompression. The risk of recurrence is as high as 50%; therefore, elective sigmoid resection with primary anastomosis should be performed after stabilization and bowel preparation, except in those with a prohibitive surgical risk.

Clinical signs of gangrene or perforation (sepsis, fever, peritonitis) require immediate surgical exploration; sigmoidoscopy should not be performed. Similarly, the presence of gangrenous mucosa on sigmoidoscopy is an indication for surgery. For gangrenous bowel, resection of sigmoid colon with end colostomy (Hartmann's procedure) is the safest approach. Mortality of sigmoid volvulus is primarily related to presence of gangrene, being as high as 60% in those with gangrene vs. less than 10% without gangrene.

Cecal Volvulus

Cecal volvulus results from incomplete fixation of the cecum to the parietal peritoneum. While most patients have full axial rotation involving the ilio-colic vessels, approximately 10% of the patients will have the cecum and ascending colon fold in an anterior cephalic direction (cecal bascule). CT is the preferred diagnostic test. Endoscopic reduction is usually not successful and risks colonic perforation [25]. As gangrene sets in early, immediate exploration with right hemicolectomy and primary ileo-colic anastomosis is the procedure of choice.

Hernia

A hernia occurs when the contents of a body cavity bulge out of the area where they are normally contained. These contents, usually portions of intestine or abdominal fatty tissue, are enclosed in the thin membrane that naturally lines the inside of the cavity. Most hernias are asymptomatic, but for a swelling; however nearly all carry a risk of becoming

irreducible (incarceration) or having their blood supply cut off (strangulation) leading to gangrene of the trapped tissues resulting in a surgical emergency.

Of all hernias, 70% are inguinal, 10% ventral, 6% femoral, 3% umbilical, and 1% esophageal hiatal, and about 10% of abdominal operations result in incisional hernias. Although 85% of all inguinal hernias occur in men, 84% of femoral hernias occur in females [26]. Obturator hernia, also known as "little old lady's hernia," is a rare hernia seen in thin older woman. They can present as pain or paresthesia radiating from the groin or hip to the medial aspect of the thigh due to compression of the obturator nerve (Howship–Romberg sign). In older males, it may be worth verifying the presence of conditions that cause straining such as benign prostatic hyperplasia.

Inguinal herniorrhaphy with mesh placement under local anesthesia is a safe procedure with a high success rate in the elderly. In a study of over 2,000 herniorrhaphies, older patients with significant comorbidities did not have higher incidence of complications compared to the young (7% vs. 6%) nor recurrences (3% vs. 2%) [27]. Elective repair of inguinal hernia is advisable soon after the diagnosis is made as mortality risks are far higher for emergency repair. Mortality increases 7-fold after emergency surgery and 20-fold if bowel resection is undertaken, in contrast to nearly 0% for elective repair [28].

Key Points

- Geriatric patients with abdominal pain account for 3–4% of all emergency department visits, with 50% requiring hospital admission, and 20–30% needing immediate surgery with an associated mortality as high as 34%.
- Symptoms and physical findings are unreliable in the elderly; delayed presentation, assessment, diagnosis, consultation, and surgical intervention account for adverse outcomes.
- Upright chest X-ray and CT scans of the abdomen are the diagnostic tests of choice.
- Early diagnosis, aggressive resuscitation, and timely surgical intervention, individualized to the patient, help improve survival.

References

1. Elinhouser A, Andrews RM. Profile of inpatient operating room procedures in U.S. hospitals in 2007. Arch Surg. 2010;145:1201–8.
2. Richardson J, Cocanour C, Kern J, et al. Perioperative risk assessment in the elderly and high risk patients. J Am Coll Surg. 2004;199:133.
3. Brunicardi FC, Andersen DK, Billiar TR, et al., editors. Schwartz's principles of surgery. 9th ed. New York: McGraw-Hill; 2009.
4. Silen W, editor. Cope's early diagnosis of the acute abdomen. 20th ed. New York: Oxford University Press; 2001.
5. Lyon C, Clark DC. Diagnosis of acute abdominal pain in older patients. Am Fam Phys. 2006;74(9):1537–44.
6. Hendrickson M, Naparst TR. Abdominal surgical emergencies in the elderly. Emerg Med Clinic North Am. 2003;21:937–69.
7. Thomas SH, Silen W, Cheama F, et al. Effects of morphine analgesia in the diagnostic accuracy in the emergency department in patients with abdominal pain. A prospective randomized trial. J Am Coll Surg. 2003;196:18.
8. Shikata S, Noguchi Y, Fukui T. Early versus delayed cholecystectomy: a meta-analysis of randomized control trials. Surg Today. 2005;35(7):553–60.
9. Tsai MJ, Chen JD, Tiu CM, et al. Can acute cholecytitis with gallbladder perforation be detected preoperatively by computed tomography in ED? Correlation with clinical data and computed tomography features. Am J Emerg Med. 2009;27(5):574–81.
10. Goldacre MJ, Duncan ME, Griffith M, Davidson M. Trends in mortality from appendicitis and from gallstone disease in English populations, 1979–2006: study of multiple-cause coding of deaths. Postgrad Med J. 2011;87:245–50.
11. Hui TT, Major KM, Avital I, et al. Outcome of elderly patients with appendicitis. Effect of computed tomography and laparoscopy. Arch Surg. 2002;137:995–8.
12. Varadhan KK, Humes DJ, Neal KR, Lobo DN. Antibiotic therapy versus appendectomy for acute appendicitis: a meta-analysis. World J Surg. 2010;34(2):199–209.
13. McCarthy DM. Acid peptic disease in the elderly. Clin Geriatr Med. 1991;137:995–8.
14. Kocer B, Surmeli S, Solak C, et al. Factors affecting mortality and morbidity in patients with peptic ulcer perforation. J Gastroenterol Hepatol. 2007;22(4):565–70.
15. Datsis AC, Rogdakis A, Kekelos S, et al. Simple closure of chronic duodenal ulcer perforation in the era of Helicobacter pylori: an old procedure, today's solution. Hepatogastroenterology. 2003;50(53):1396–8.
16. Rafferty J, Shellito P, Hyman NH. Practice parameters for sigmoid diverticulitis. Dis Colon Rectum. 2006;49(7):939–44.
17. Maginte DD, Heitkamp DE, Howard TJ. Current concepts in imaging of small bowel obstruction. Radiol Clin Am. 2003;41:263.
18. Branco BC, Barnporas G, Schnuriger B, et al. Systemic review and meta-analysis of the diagnostic and therapeutic role of water-soluble contrast agent in adhesive small bowel obstruction. Br J Surg. 2010;97:470.
19. Stewardson RH, Bombech CT, Nyhus LM. Critical operative management of small bowel obstruction. Ann Surg. 1987;206:126.
20. Steward RH, Page CP, Brendon J, et al. The incidence and risk of early postoperative small bowel obstruction. A cohort study. Am J Surg. 1987;154:643.
21. Avots-Avotins KV, Waugh DE. Colon volvulus and the geriatric patient. Surg Clin North Am. 1982;62:249.
22. Raveenthiran V, Madiba TE, Atamanalp SS, De U. Volvulus of the sigmoid colon. Colorectal Dis. 2010;12(7):1–17.
23. Atamanalp S, Yildirgan M, Bosuglu M, et al. Retraction. Clinical presentation and diagnosis of sigmoid volvulus: outcomes of 40-year and 859-patient experience. J Gastroenterol Hepatol. 2009;24:1154–9.
24. Peoples J, McCafferty J, Scher K. Operative therapy for sigmoid volvulus. Identification of risk factors affecting outcome. Dis Colon Rectum. 1990;33:643.
25. Friedman J, Odland M, Bubrick M. Experience with colon volvulus. Dis Colon Rectum. 1989;32:409.
26. Nyhus LM, Bombeck CT, Klein MS. Hernias. In: Sabiston DC, editor. Textbook of surgery. 14th ed. Philadelphia: WB Saunders; 1991.
27. Rogers FB, Guzman EA. Inguinal hernia repair in a community setting: implications for the elderly. Hernia. 2011;15(1):37–42.
28. Nilsson H, Stylianidis G, Haapamäki M, Nilsson E, Nordin P. Mortality after groin hernia surgery. Ann Surg. 2007;245(4):656–60.

Colostomy and Ileostomy Care

66

Juan J. Omana and Nanakram Agarwal

Introduction

Fecal diversion is among the most revolutionary and progressive accomplishments of modern surgery. The word *stoma* is derived from ancient Greece to describe an "opening." The earliest stomas were not created by surgeons but by pure forces of "Mother Nature," usually from a spontaneous enterocutaneous fistula resulting from distal obstruction or following penetrating abdominal trauma.

The first colostomy was performed in 1776 and the first ileostomy over 100 years later in 1879 [1]. These initial proximal stomas carried high morbidity associated with skin complications. With introduction of "Brooke ileostomy" in 1952, by everting the ileal mucosa, local skin complications were dramatically reduced [1]. The first disposable ostomy bag was created by a nurse for her sister with colon cancer in 1955.

Currently fecal diversion is performed as a temporary or permanent measure to manage several conditions. Based on anatomical location, ostomies may be ileostomies or colostomies; the surgical design classifies them as loop or end.

Ostomy Classification

Colostomies

A colostomy is created to provide fecal diversion or to resect the distal colon or rectum. If the recto-anal sphincter mechanism is intact there is potential to revert the colostomy.

Decompressive colostomy: There are clinical instances where a temporary colostomy is created to decompress an obstructed distal colon [2]; this is usually a transverse loop colostomy or cecostomy. The advantage of a decompressive colostomy is that it can be created quickly with low morbidity or surgical risk and allows for evaluation and definitive treatment on an elective basis.

Diverting colostomy: Created with the intent to allow healing of a fistulous tract, minimize fecal contamination of an injured segment of colon or to protect distal anastomosis when delayed healing is anticipated. However, routine diversion is no longer recommended [3, 4].

Loop colostomy: There are several techniques to construct a loop colostomy. Most frequently a loop of transverse colon is brought to the anterior abdominal wall in the right upper quadrant and a plastic rod is placed to support the colostomy and prevent this loop of colon from retracting back into the abdomen. The colon is then opened at the apex and the edges of the opening are sutured to skin (Fig. 66.1). Loop colostomies tend to be bulky, hard to conceal, more likely to prolapse and difficult to deal with by patients.

End colostomy: The proximal colon is brought up as an end colostomy paired with the distal segment, which is also brought to the anterior abdominal wall as a mucous fistula.

The Hartman's procedure popularized for obstructive sigmoid tumors, involves resection of the diseased segment and closure of distal colon which is left intraabdominally and creation of an end colostomy using the proximal segment. The procedure is also used to treat complicated diverticulitis. The end colostomy is temporary or permanent as part of the abdominoperineal resection for low rectal and anal tumors. Usually end colostomies are created on the left side of the abdomen (Fig. 66.2).

Ileostomies

Ileostomies are performed when the colon and rectum are bypassed or removed. If the anal sphincter complex is removed, as in a total proctocolectomy, the ileostomy is permanent. A permanent ileostomy is usually an end ileostomy called Brook ileostomy. The Brooke ileostomy is performed by everting the ileal end to create a protruding nipple that

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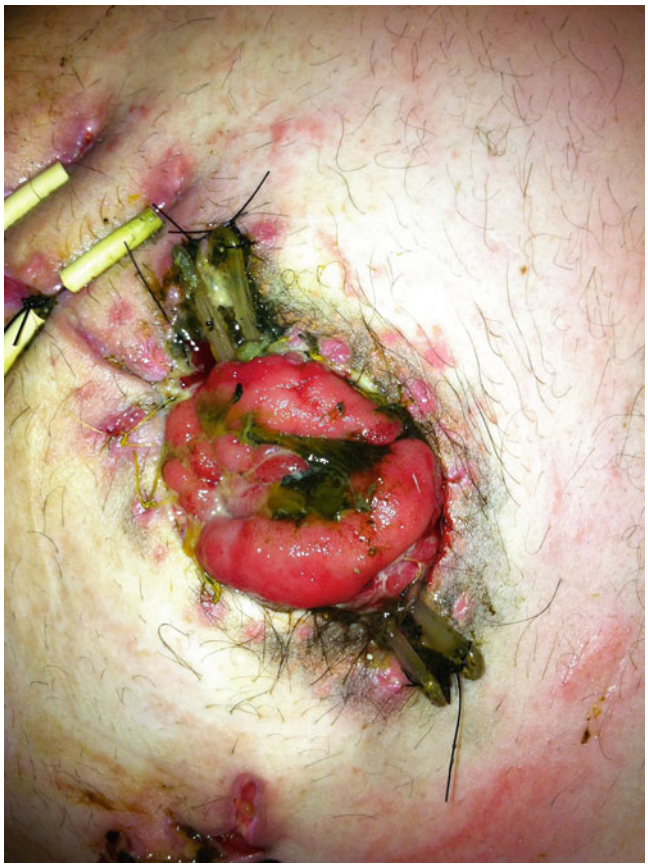

Fig. 66.1 Transverse colon loop colostomy

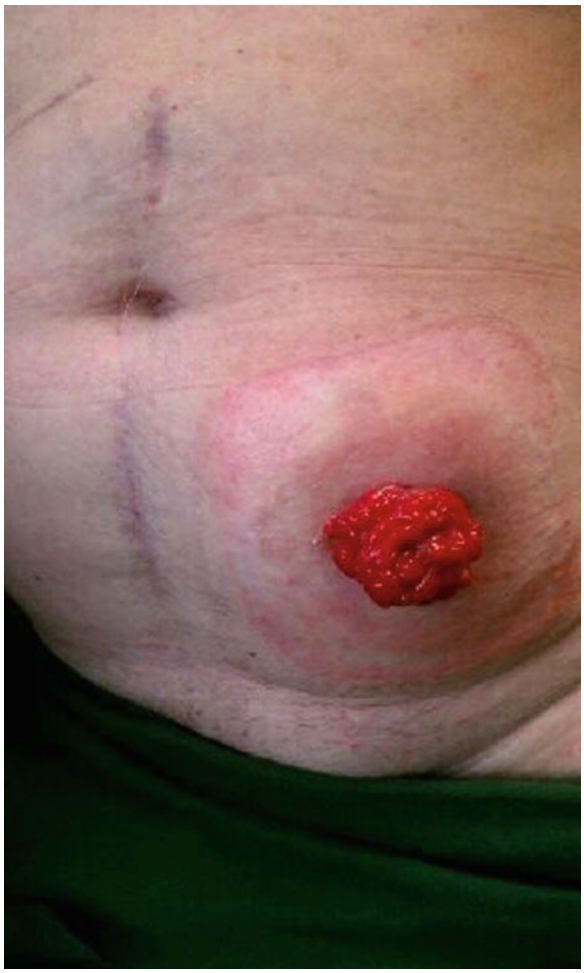

Fig. 66.2 Descending colon end colostomy

prevents development of skin erosions and is easier to manage. Ileostomies are also created to protect a distal anastomosis and manage conditions like complicated ulcerative colitis and *C. difficile* colitis [5]. Ileostomies are usually created on the right side of the anterior abdominal wall. The liquid ileostomy output of 500–1,000 mL/day is rich in electrolyte output; appropriate pouching and adequate appliance fit to maintain peristomal skin integrity, fluid, and electrolyte balance is needed.

Lifestyle Considerations

Patients in all walks of life are able to continue a full "normal" life and enjoy good health despite the stoma. It is necessary to reassure and provide useful and pertinent information about lifestyle modifications necessary to accept and enjoy life after fecal diversion.

Psychological adaptation: This term refers to the process requiring patients to adapt to new fecal elimination patterns and accept the new body image. It usually consists of four phases. The average person naturally revolts at the thought of wearing a colostomy bag. This initial phase of shock or panic may last days or weeks. The second phase of defense, retreat, and denial lasts weeks to months. It is only after several months that the patient finally acknowledges the need for an ostomy, constituting the third phase. The final phase called adaptation and resolution can take several years; here the patient is able to master and get familiarized with the new and necessary skills to continue a normal and productive life with the stoma [6].

Many interventions promote an easy psychological adaptation; these include:

- Listen and ally patient's fears and misconceptions by encouraging dialogue with other patients with stomas and involve the ostomy nurse specialist preoperatively.
- Preoperative stoma site selection by a surgeon or by a stoma nurse at a location easily accessible and in the patient's visual field, away from skin creases and scars and bony prominences that can make pouching difficult.
- The stoma should be brought up through the *rectus abdominis* muscle situated below the belt line and at the apex of the infraumbilical abdominal bulge [7].
- A strong focus on individual education tailored to the unique circumstances afflicting the patient.

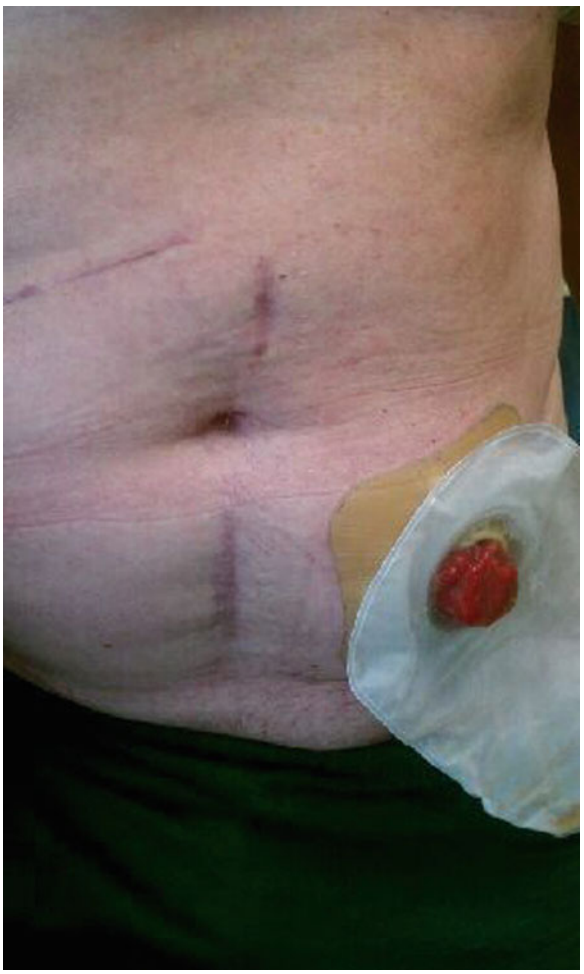

Fig. 66.3 Descending end colostomy with a two-piece appliance

Disposable adherent stoma appliances: The selection of an appropriate appliance system or pouch for containment of stool and gas is important and provides an effective barrier to protect the skin. One- and two-piece systems are available. The one-piece system consist of an adhesive barrier ring attached to an odor proof pouch, while the two-piece system include a barrier ring with a flange or adhesive landing zone to which the patient attaches a separate odor proof pouch (Fig. 66.3). The pouches can be open or close ended. The open ended enables the bottom of the pouch to be opened to drain contents, usually used for ileostomies, with large liquid output. The closed ended pouch is removed and disposed when it is full and is usually recommended for descending colon or sigmoid colostomies which have more firm stool consistency. The one-piece system provides simplicity and flexibility, paramount for the patient whose stoma is located in a deep crease. The two-piece system has the benefit of allowing patients to change the pouch without having to remove the flange, but occasionally leakage occurs between the bag and the flange [8, 9].

Several strategies promote pouch adherence and minimize stool leakage including:

- Selection of a system well suited to patient's abdominal contours.
- Instructing the patient on cutting the appropriate size opening on the flange so as to cover the area of exposed skin. This should be slightly bigger than the stoma by 2–3 mm.
- Recommend emptying the pouch when one-third or half full to prevent breakdown of the seal caused by excessive weight.
- Teaching the patient to change the appliance or pouch once or twice a week to prevent potential leakage. The appliance should be removed gently and the skin is cleansed thoroughly and made dry before application of a new system.
- Patients are educated to recognize signs of leakage (itching or burning of the peristomal skin) and use of various stoma accessories [8].

Products available to improve pouching and prevent damage to the peristomal skin include: skin "sealants" (e.g., Skin Prep), skin paste, adhesive agents, and skin barrier powder [8]. Skin films are helpful for dry sensitive or excessively oily skin, while powder-based pastes, strips, or rings protect the skin from damage caused by digestive enzymes in the output.

Dietary modification: Patients with stomas can eat a regular diet. Odor, excessive gas, and stool consistency are common concerns. Several dietary changes can decrease gas production and result in firmer consistency of output. The first is to avoid common foods that contain poorly digested carbohydrates that lead to excessive gas production by the intestinal bacteria; e.g., beans, cabbage, cauliflower, Brussels sprouts, broccoli, and asparagus. Carbohydrates that promote gas formation include starch and soluble fiber contained in potatoes, corn, noodles, and wheat. On the hand, rice, fresh parsley, yogurt, and buttermilk do not produce gas and their consumption is encouraged. Similarly large quantities of fruit, vegetables, cereals, beer, and some wines may cause diarrhea. The patient should become knowledgeable of foods that can cause diarrhea and minimize their use. Lack of fiber consumption can result in constipation and fecal impaction; it is important to consume reasonable amount of fruits and vegetables [8, 9]. The concept of "lag time" term refers to the amount of time from the ingestion of gas producing foods and the actual flatulence. This period can vary from 2 to 4 h for patients with ileostomies and 6–8 h with colostomies. The colostomy activity can be regulated to one or two times and made predictable, while this state is never reached in some resulting in a continuously active stoma that is hard to predict and manage. Other modifications especially for ileostomies is to avoid sipping through a straw, and minimize chewing gum, smoking, and chewing with an open mouth as these activities increase gas production. For those with large volumes of gas, pouching systems with filters can vent and deodorize flatus [10].

Effect of drugs: Simethicone containing products can decrease gas production. For loose or frequent bowel movements methyl-

cellulose preparation or kaolin powder can be effective. In severe intractable cases. preparations containing diphenoxylate or codeine phosphate are helpful. For constipation, stool softeners, senna, lactulose, or sorbitol can help.

Daily activities: Most daily activities are not affected by the stoma. Bathing and showering can be performed with or without the pouch. Other activities like dancing, exercise, and sports like golf, baseball, tennis, and even swimming can be resumed without any particular concern with the exception of contact sports that can potentially traumatize the stoma or the peristomal skin. Generally clothing modification is unnecessary but the addition of an abdominal belt or binder can provide a more natural appearance and improve stoma concealment [11].

Sexual activity: The presence of a stoma does not impair sexual function, however low rectal resections can disrupt pelvic nerves responsible for the sexual function. Men can experience erectile dysfunction and or retrograde ejaculation. Women can experience vaginal dryness leading to dyspareunia. Patients are recommended to empty the pouch and assure an intact pouch seal before engaging in sexual activity [12, 13].

Traveling: Patients who travel are advised to carry supplies in a carry-on bag instead of checked in luggage. They should avoid extreme temperatures and perspiration that can affect adherence of skin appliances and take precautions to prevent enteral infections and diarrhea. While driving, supplies are kept in the coolest part of the vehicle [13].

Complications

Complications occur early in the postoperative period or years later [7]. These may be anatomical (i.e., retraction, parastomal hernia, prolapse, peristomal skin conditions, and necrosis); functional (i.e., odor, poor dexterity, visualization, clothing, and dietary) and psychological (depression, anxiety, sexual concerns, and failure to return to work) [14]. Overall management becomes more difficult with increasing age and decreased manual dexterity. Fortunately most complications are preventable by proper stoma site selection and adequate instructions and education (Tables 66.1 and 66.2).

Peristomal skin problems are the most frequent complications as a result of direct trauma, chemical dermatitis from stoma output or allergic reaction to the pouching system [15, 16]. Skin abrasion from repeated trauma usually presents as patchy areas of irritated denuded skin around the stoma and typically results from frequent appliance changes or too aggressive cleansing. Patients should be educated on appropriate use of skin sealants and gentle cleaning techniques. Hair surrounding the stoma is best clipped to prevent follicle trauma and potential nidus for infection. Allergic dermatitis can present as pruritus, erythema, and blistering and usually involves the skin in direct contact with the causative agent giving a distinct pattern. Treatment involves eliminating triggering factors and occasional use of topical steroids. Chemical dermatitis from stoma effluent presents as areas of skin damage in the inferior or dependent portion of the stoma. This complication is more frequent with ileostomies or stomas with poor pouching or retraction. For the affected areas, skin barrier powder or films are recommended [16].

Parastomal hernia is a common complication of colostomies. Factors predisposing to parastomal hernia formation include obesity, poor abdominal wall tone, and placement of the stoma outside the rectus muscle or through an excessively large fascial opening. Most hernias are asymptomatic and rarely progress to incarceration. They can be managed effectively with

Table 66.1 Management of functional stomal complications

Odor	Dietary modification, lower consumption of complex carbohydrates, asparagus, eggs, garlic, fish, onions, and alcoholic beverages Pharmacological agents: bismuth subgallate, chlorophyllin copper complex
Excessive gas	Dietary modification: minimize use of beans, cabbage, cauliflower, potatoes, corn, noodles, and wheat Increase intake of rice, fresh parsley, yogurt, and buttermilk Pharmacological agents: simethicone Pouches with filters
Increase stool output (diarrhea)	Dietary modification: decrease fruits, beans, spicy foods, prunes, milk, caffeinated beverages, and beer Increase intake of applesauce, banana, rice, and yogurt Pharmacological agents: methylcellulose, kaolin, diphenoxylate, and codeine
Constipation	Increase fiber intake, green beans, spinach, vegetables, and prunes Increase fluid intake: eight 8-oz glasses of fluids per day Pharmacological agents: fiber, stool softeners, laxatives

Table 66.2 Management of anatomical stomal complications

Complication	Management
Peristomal skin problems	
Abrasion	Gentle appliance removal/use of adhesive removers
Chemical dermatitis	Use of barrier creams, films, sprays, or wipes
Allergic dermatitis	Protective powder paste, topical steroids
Retraction	Convex appliance
Leakage or poor pouching	Proper stomal placement, filler paste/seal or skin films
Stenosis	Dietary modifications, increase fiber and water intake, digital dilation or surgical revision
Parastomal hernia	Abdominal binder and possible surgical revision

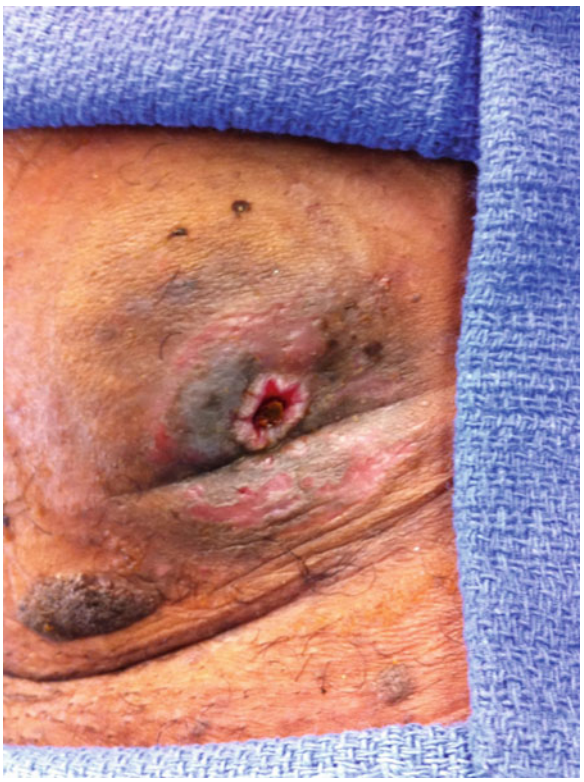

Fig. 66.4 Stenosis of colostomy with peristomal chemical dermatitis

an abdominal stoma hernia support belt [7]. Surgical intervention is indicated for pain, obstruction, acute incarceration and when the hernia results in poor pouching [17].

Retraction occurs from tension due to inadequate mobilization and is more often seen in obese patients. The major problem is achieving an adequate seal resulting in leakage and skin breakdown. Management consists of using a convex pouching system or surgical correction [7].

Stomal stenosis refers to narrowing occurring as a consequence of ischemia, infection or inadequate opening in the skin or fascia. Mild stenosis is usually asymptomatic; severe stenosis can present clinically as crampy abdominal pain followed by explosive output. Mild stenosis is managed by gentle dilatation of the stoma, but severe cases require surgical revision (Fig. 66.4) [7, 14].

Stomal prolapse occurs as a result of too large a fascial opening, elevated intraabdominal pressure, or poor fixation to the anterior abdominal wall. It is more common in transverse loop colostomy and ileostomy than descending end colostomy. Prolapse poses a management problem but is only significant if it impairs function or leads to bowel ischemia. Management usually involves pouching modification and application of an abdominal belt or binder; surgical intervention is warranted if the prolapse is severe enough to produce ischemic changes in the bowel [7].

Minor bleeding usually occurs after excessively vigorous stomal cleaning. Major bleeding from the stoma is rare and results from a stoma ulcer secondary to poorly fitting appliances or stomal varices from portal hypertension. Initial treatment involves direct pressure, cautery, or suturing [18].

Peristomal varices occur with ileostomy after colectomy for ulcerative colitis, in those with primary sclerosing cholangitis with cirrhosis and portal hypertension. Management includes direct pressure, epinephrine compresses, and sclerotherapy; although recurrence is frequent. Transjugular intrahepatic portosystemic shunt (TIPS) and surgical portocaval shunt are recommended for selected candidates [18].

Diversion colitis is an iatrogenic nutritional complication of fecal diversion that manifests in the diverted colon within weeks and resolves after continuity is reestablished. Lack of short chain fatty acids have been proposed as a causative factor, administration of short chain fatty acid enemas is beneficial.

Although the majority of patients can manage colostomies and ileostomies, the frail and cognitively impaired elderly will need help from the caregiver to manage their ostomies. This will add to the caregiver burden.

Key Points

- Fecal diversion might be a temporary or permanent measure.
- Based on anatomic location ostomies are ileostomy or colostomy; based on surgical construction, they are loop or end.
- Patients with a stoma must adapt to lifestyle changes relating to fecal diversion. Adequate support and education are necessary to ensure successful adaptation, prevention, and treatment of complications.
- Stoma related complications can occur in the early postoperative period or years later and include peristomal skin breakdown, stenosis, retraction, parastomal hernia, stomal prolapse, bleeding, and diversion colitis.
- Most complications are preventable by preoperative stoma site marking, appropriate surgical technique, selection of an appropriate pouching system, dietary modifications and use of various stoma accessories.

References

1. Cataldo PA. Intestinal stomas: 200 years of digging. Dis Colon Rectum. 1999;42(2):137–42.
2. Guenaga KF, Lustosa SA, Saad SS, et al. Ileostomy or colostomy for temporary decompression of colorectal anastomosis. Systematic review and meta-analysis. Acta Cir Bras. 2008;23(3):294–303.
3. Bowley DM, Boffard KD, Goosen J, et al. Evolving concepts in the management of colonic injury. Injury. 2001;32(6):435–9.
4. Demetriades D, Murray JA, Chan L, et al. Penetrating colon injuries requiring resection: diversion or primary anastomosis?

An AAST prospective multicenter study. J Trauma. 2001;50(5):765–75.
5. Olivas AD, Umanskiy K, Zuckerbraun B, Alverdy JC. Avoiding colectomy during surgical management of fulminant *Clostridium difficile* colitis. Surg Infect (Larchmt). 2010;11(3):299–305.
6. Simmons KL, Smith JA, Bobb KA, Liles LL. Adjustment to colostomy: stoma acceptance, stoma care self-efficacy and interpersonal relationships. J Adv Nurs. 2007;60(6):627–35.
7. Kann BR. Early stomal complications. Clin Colon Rectal Surg. 2008;21(1):23–30.
8. Burch J. Peristomal skin care and the use of accessories to promote skin health. Br J Nurs. 2011;20(7):S4, S6, S8.
9. Burch J. Nutrition for people with stomas. 2: an overview of dietary advice. Nurs Times. 2008;104(49):26–7.
10. Slater RC. Managing quality of life in the older person with a stoma. Br J Community Nurs 2010; 15(10):480–2, 484.
11. Jones T, Springfield T, Brudwick M, Ladd A. Fecal ostomies: practical management for the home health clinician. Home Healthc Nurse. 2011;29(5):306–17.
12. Li CC. Sexuality among patients with a colostomy: an exploration of the influences of gender, sexual orientation, and Asian heritage. J Wound Ostomy Continence Nurs. 2009;36(3):288–96.
13. Dabirian A, Yaghmaei F, Rassouli M, Tafreshi MZ. Quality of life in ostomy patients: a qualitative study. Patient Prefer Adherence. 2010;5:1–5.
14. Salvadalena G. Incidence of complications of the stoma and peristomal skin among individuals with colostomy, ileostomy, and urostomy: a systematic review. J Wound Ostomy Continence Nurs. 2008;35(6):596–607.
15. Burch J, Sica J. Common peristomal skin problems and potential treatment options. Br J Nurs 2008; 17(17):S4, S6, S8.
16. Black P. Peristomal skin care: an overview of available products. Br J Nurs. 2007;16(17):1048–56.
17. Wara P. Parastomal hernia repair. An update. Minerva Chir. 2011;66(2):123–8.
18. Spier BJ, Fayyad AA, Lucey MR, et al. Bleeding stomal varices: case series and systematic review of the literature. Clin Gastroenterol Hepatol. 2008;6(3):346–52.

Part XIV

Systems Disorders

Gastrointestinal and Hepatic Manifestations of Systemic Diseases

67

Ellen C. Ebert

Introduction

The gastrointestinal (GI) manifestations of systemic diseases are important for several reasons. For one, the prevalence of certain systemic diseases is increasing, such as diabetes mellitus (DM) with the obesity epidemic and chronic kidney disease (CKD) with increased longevity. Changes in the function of GI organs can affect treatment of systemic diseases, such as glycemic control in a patient with DM and gastroparesis or treatment of diabetic ketoacidosis (DKA) in the presence of pancreatitis. GI procedures may be affected by systemic diseases such as the risk of certain enemas in end-stage renal disease (ESRD) and the possibility of perforation during colonoscopy in the presence of vasculitis. Finally, GI diseases may affect morbidity and mortality, such as aspiration in scleroderma or mesenteric ischemia in ESRD.

Diabetes Mellitus

Type 1 DM is caused by autoimmune-mediated destruction of the β-cells in the pancreatic islets early in life with loss of insulin (Table 67.1). Type 2 DM is a multifactorial disorder commonly affecting older individuals. With increasing life expectancy, DM is common in the aged; with longstanding history of diabetes, complications of the disease occur. The prevalence of celiac disease in type 1 DM ranges from 1 to 7% [1]. Some favor screening diabetics for celiac disease as a gluten-free diet would prevent complications such as osteopenia and growth retardation [2]. Others screen only those with symptoms as the asymptomatic patient tends not to adhere to dietary restrictions for both diseases. Parietal cell antibodies are found in 15–21% of type 1 diabetics [3]. Antibody inhibition of the H^+/K^+ ATPase pump results in hypo- or achlorhydria with atrophic gastritis from autoimmune mucosal damage, hypergastrinemia from lack of acid inhibition of gastrin production, and iron-deficiency anemia from lack of hydrochloric acid, a requirement for optimal iron absorption.

Diabetics may have abnormal esophageal motility, including multipeaked or spontaneous contractions, failed peristalsis, and decreased lower esophageal sphincter (LES) pressure [4]. Pyrosis, a burning chest sensation, is common with obesity, decreased motility, and hyperglycemia.

Cross-sectional studies suggest that gastric emptying of solids and liquids is slower in 30–50% of diabetics [5] although rapid emptying may occur early in the disease. Gastric emptying studies correlate poorly with symptoms of abdominal fullness and bloating. Poor glycemic control delays gastric emptying, which in turn, hinders glycemic control.

A low-fat, low-residue diet with small, frequent meals is advocated. Prokinetic drugs include metoclopramide, erythromycin, and domperidone. New modalities include gastric electrical stimulation and botulinum toxin injection of the pylorus.

Diarrhea tends to occur with long-standing, poorly controlled diabetes and must be differentiated from fecal incontinence, also frequent in diabetics. Alternatively, constipation tends to be a major problem in diabetics with impaired myoelectric response of the colon [6]. Gallstones do not correlate with the presence of diabetes, but rather with increasing age and BMI [7].

Patients with chronic pancreatitis acquire the same complications as other diabetics, indicating that strict glycemic control is always a goal. However, strict control may be difficult to achieve in the elderly, with their comorbid problems including cognitive impairment, visual and musculoskeletal disorders. DKA, due to an extreme deficiency of insulin with elevated glucagon levels, can be complicated by acute pancreatitis in 11% of cases [8]. The identification of acute

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Table 67.1 Gastrointestinal manifestations of diabetes and management

Manifestations
Pyrosis, early satiety, bloating, diarrhea, constipation, fecal incontinence
Diagnostic findings
General: elevated blood sugar and HbA1c
Esophagus: abnormal esophageal motility
Stomach: rapid or delayed gastric emptying
Small bowel: screen may reveal celiac sprue, thyroid disease, pancreatic insufficiency
Liver: imaging may identify nonalcoholic fatty liver disease
Pancreatic function evaluation may help
Treatment
General: overall control of diabetes
Esophagus: acid-reducing therapy for heartburn
Stomach: consider prokinetic drugs, gastric electrical stimulation, botulinum toxin injection of pylorus for delayed gastric emptying (caution: side effects)
Small bowel motility: address underlying cause of diarrhea (e.g., medications, exclude celiac sprue, pancreatic insufficiency, hyperthyroidism)
Colonic motility: consider bulking agents
Liver: weight control for NAFLD
Pancreatitis in diabetic ketoacidosis (DKA): volume repletion, delay feeding, address complications

pancreatitis may make management in the geriatric age group complex. Volume depletion and hyperglycemia may be exacerbated; feeding may require to be delayed; complications of pancreatitis may occur; and Ranson's criteria may overestimate the severity of disease.

If diarrhea occurs in a diabetic, considerations include: (1) medications particularly metformin; (2) malabsorption due to celiac sprue whose prevalence is high in type 1 diabetics; (3) osmotic diarrhea due to sorbitol used as an artificial sweetener if ingested in large amounts in a diabetic trying to lose weight; (4) maldigestion due to pancreatic insufficiency as a cause or consequence of diabetes; (5) rapid transit from hyperthyroidism which is increased in prevalence in type 1 diabetes; (6) inflammatory bowel disease, increased in prevalence in type 1 DM [9]; and (7) secretory diarrheas due to rare hormonal causes.

Amyloidosis

Amyloidosis is characterized by extracellular deposition of abnormal protein with six types: primary, secondary, hemodialysis-related, hereditary, senile, and localized [10]. The nomenclature consists of the letter A (for amyloid) followed by a description of the precursor protein. Primary AL or light chain (L) amyloidosis is associated with monoclonal light chains in serum and/or urine. Secondary AA amyloidosis with the acute-phase reactant serum amyloid A protein (A) is associated with inflammatory, infectious, and neoplastic diseases. Senile amyloidosis mainly involves the heart but can be associated with amyloid in the subserosal veins of the large and small bowel.

A dilated, atonic esophagus with decreased peristalsis predisposes to aspiration. Gastric and duodenal diseases are usually asymptomatic. Amyloid deposition is greatest in the small intestine, involving the intima or adventitia of vessels causing luminal narrowing with ischemia or infarction. Alternatively, amyloid may deposit between muscle fibers, eventually replacing the muscle layers. Symptoms include diarrhea, steatorrhea, hemorrhage, or pain from mesenteric ischemia. The diarrhea may be due to a sprue-like condition from infiltration of the villous tips with amyloid. Alternatively, diarrhea could be the result of autonomic dysfunction from amyloid infiltrating the Auerbach's and Meissner's plexuses, inducing rapid transit. With delayed orocecal transit, diarrhea may result from bacterial overgrowth. Pseudoobstruction involving small bowel and/or colon carries a particularly grave prognosis, with poor response to promotility agents [11, 12].

Hepatic involvement is common but clinical manifestations are usually mild with hepatomegaly and an elevated alkaline phosphatase being frequent findings. Stigmata of chronic liver disease and portal hypertension are rare. Amyloid deposits usually begin periportally in the space of Disse followed by atrophy of hepatocytes due to compression by amyloid fibrils [13].

Biopsy sites to diagnose amyloidosis include fat, kidney, intestine, or bone marrow. The risk of bleeding with liver biopsies is controversial [10]. Amyloid appears homogeneous and amorphous under light microscopy. With Congo red stain, it is red in normal light and apple-green in polarized light. The routine method to determine the amyloid type is immunohistochemistry.

Amyloidosis must be a consideration in patients with proteinuria, cardiomyopathy, hepatomegaly (with mildly abnormal liver tests), peripheral and autonomic neuropathy, weight loss, and GI symptoms (Table 67.2).

Thyroid Disease

Thyroid disease affects most hollow organs [14]. Hashimoto's disease, the most common cause of hypothyroidism, may be associated with an esophageal motility disorder presenting as dysphagia or heartburn with diminished LES pressure and reduced amplitude of contractions [15]. Dyspepsia, nausea, or vomiting result from delayed gastric emptying. Abdominal discomfort, flatulence, and bloating occur with bacterial overgrowth and improve with antibiotics [16]. Reduced acid production is due to autoimmune gastritis or low gastrin levels [14]. Constipation results from diminished motility, leading to ileus, megacolon, or rarely, pseudoobstruction. Ascites in

Table 67.2 Main characteristics and treatment of amyloidosis

Symptoms
Weakness, weight loss, joint pain, dyspnea, diarrhea
Physical findings
Purpura, macroglossia, joint swelling, congestive heart failure, hepatomegaly, orthostatic hypotension (from autonomic neuropathy)
Diagnostic findings
General: monoclonal light chains, proteinuria, Congo Red-positive biopsy
Esophagus: dilated and atonic, may resemble achalasia
Stomach: polyps, antral narrowing, thickened folds
Small bowel: mesenteric ischemia, pneumatosis intestinalis, obstruction, and pseudo-obstruction
Colon: polyps, ulcerations, strictures, infarction, bleeding, perforation
Liver: elevated serum alkaline phosphatase, hepatomegaly with heterogeneous tracer distribution on liver–spleen scan
Treatment
AL amyloidosis: high-dose chemotherapy and stem cell transplantation
AA amyloidosis: treatment of underlying disease
ATTR amyloidosis: orthotopic liver transplantation

hypothyroidism is of high protein content and occurs with or without heart failure (HF).

Graves' disease accounts for 60–80% of thyrotoxicosis. Hyperthyroidism is accompanied by variable gastric emptying times with low acid production perhaps due to an autoimmune gastritis with hypergastrinemia [17]. Transit time from mouth to cecum is accelerated, resulting in diarrhea. Steatorrhea is due to hyperphagia and to stimulation of the adrenergic system [18]. Rarely, the older adult presents with resolution of constipation, rather than diarrhea; hyperphagia is often absent. Hyperthyroidism is associated with abnormal liver function tests, especially in the presence of HF. Elevated alkaline phosphatase levels have been attributed to osteoblastic activity and may increase temporarily with treatment.

MCT is a calcitonin-producing tumor of the C cells of the thyroid gland. It is associated with watery diarrhea, particularly in those with extensive metastatic disease. Diarrhea may resolve with removal of the tumor and may be due to calcitonin, prostaglandins, 5-hydroxyindoleacetic acid, or to undefined elements.

Liver disease affects thyroid function tests. Low 3,5,3′-L-tri-iodothyronine (T3) syndrome, a low total T3 with normal total L-thyroxine (T4) in the absence of clinical hypothyroidism, is found in chronic liver disease due to impaired liver conversion of T4 to T3 [19]. There is an inverse correlation between T3 concentration and severity of liver disease, suggesting that T3 may be a helpful prognostic indicator.

Patients with hepatitis C probably have a higher rate of thyroid autoimmune disorders than do either patients with hepatitis B or normal individuals [20]. Interferon-alpha (IFN-α) used to treat hepatitis C induces the entire spectrum of autoimmune thyroid diseases from the presence of thyroid antibodies without clinical disease to overt hyper- and hypothyroidism [21]. IFN-α treatment should continue despite hypothyroidism, the most common complication, but its cessation should be considered with Graves' thyrotoxicosis or destructive thyroiditis.

Hepatotoxicity resulting from antithyroid drugs is rare and usually occurs in the first few months of treatment probably due to a hypersensitivity reaction [22]. Propylthiouracil induces a hepatocellular pattern, while carbimazole and methimazole cause a cholestatic picture.

Sarcoidosis

Sarcoidosis is a multisystem disease characterized by noncaseating granulomas in affected organs [23]. Over 90% of patients have lung involvement with restrictive disease [24]. Diagnosis is based on a compatible history, demonstration of granulomas in at least two organs, negative staining and culture for acid fast bacilli, and a lack of occupational or domestic exposure to toxins.

Involvement of the GI tract is extremely rare. Dysphagia and weight loss have been attributed to dysmotility of the esophagus [24]. The stomach, particularly the antrum, is the most frequently affected hollow organ with epigastric pain the most prominent symptom; the small bowel is the least involved. Obstruction can occur at any site in the GI tract due to external compression by lymphadenopathy. While a variety of lesions may contain granulomas, it is unclear whether they are truly due to sarcoidosis or to another process with granulomas an incidental finding [25].

The liver follows the lymph nodes and lung in the frequency of involvement. Symptoms of liver disease, although uncommon, are usually pruritus and abdominal pain. Up to 35% of patients have abnormal liver function tests unrelated to the degree of aggression and extent of disease. A significant fraction (26% in one report) [26] has liver without lung involvement. Alkaline phosphatase is more reliable than γ-glutamyl-transpeptidase in predicting liver involvement [24]. Hyperglobulinemia is common, while jaundice is rare. Hepatomegaly is seen in 21% of patients clinically and in over half the patients with abdominal CT scans. Histology includes noncaseating granulomas, chronic intrahepatic cholestasis, progressive diminution in the number of interlobular bile ducts, periportal fibrosis, and eventually, biliary cirrhosis. Schaumann bodies, while diagnostic of sarcoid granulomas, are rarely seen. Portal hypertension from granulomas in the portal triad is rare and associated with preserved liver function.

Involvement of the spleen causes symptoms in 15% of patients and associated with hypersplenism in 20%, mostly

from giant splenomegaly [27]. Hepatomegaly and abnormal liver function tests occur in 86% of patients with splenomegaly. Splenic nodules, which are more common than hepatic nodules, tend to be discrete but may coalesce with increasing size.

In general, corticosteroids should be instituted when organ function is threatened, usually involving lungs, eyes, and central nervous system. Their role in treatment of GI or hepatic sarcoidosis is unclear. Ursodeoxycholic acid is reported to be beneficial [28].

Scleroderma

GI involvement, occurring in up to 90% of patients with scleroderma, is the third most common manifestation after skin disease and Raynaud phenomenon. In 10% of cases, GI disease occurs before the appearance of cutaneous manifestations [29]. The primary event may be vascular damage with hypoperfusion and ischemia [30]. Neurogenic involvement is due to microvascular changes in the vasa nervorum, nerve compression by collagen, and/or inflammation. This is followed by secondary smooth muscle atrophy, weak muscle contractions, and replacement of muscle with fibrosis.

The esophagus is the most commonly affected site (in 50–90% of cases) [30]. These patients are at particular risk for reflux due to low or absent peristalsis, reduced LES pressure, associated hiatal hernia from shortening of the esophagus, gastroparesis, autonomic nervous system dysfunction, and associated sicca syndrome with loss of salivary bicarbonate. Heartburn, dysphagia, and regurgitation occur in up to 82% of patients [31]. Dysphagia, usually for both liquids and solids, is most often due to dysmotility and reflux [30]. Candida esophagitis occurs due to poor emptying of the esophagus, treatment with immunosuppressive agents, and acid suppression. Stricture formation occurs in 17–29% of patients. It is unclear whether the incidence of Barrett esophagus or esophageal carcinoma is increased in patients with scleroderma compared to other patients with significant reflux.

Esophageal manometry demonstrates decreased amplitude of contractions in the distal two-thirds of the esophagus (containing smooth muscle) followed later by a decline in LES pressure, although these findings are seen in other diseases [31]. The upper one-third containing striated muscle is usually spared. Cine-esophagram provides anatomic data, whereas the scintigraphy is easier to quantitate and documents aspiration.

Gastric emptying, particularly to solids, is delayed in 10–75% of patients depending upon the mode of diagnosis [32]. The gastric emptying study correlates with symptoms, such as early satiety, bloating, and emesis [33]. Metoclopramide and erythromycin can improve gastric emptying [32].

GI hemorrhage is most commonly due to mucosal telangiectasias which occur throughout the GI tract. Gastric antral vascular ectasia or watermelon stomach is typically seen in elderly females with blood loss and anemia. The dilated, ectatic, convoluted vessels travel longitudinally in the antrum converging at the pylorus.

Small bowel involvement occurs in 17–57% of patients depending on the mode of detection [32]. Motility disturbances are common, such as absent or abnormal migrating motor complexes, predisposing to bacterial overgrowth [34]. "Hide-bound" bowel consists of dilatation with closely packed valvulae conniventes from atrophy of the longitudinal fibers of the muscularis propria shortening the bowel [35].

Barium enemas demonstrate pancolonic involvement in 10–50% of cases although the radiologic features do not necessarily correlate with symptoms [32]. The true diverticuli involving all layers of the intestinal wall generally do not lead to diverticulitis due to their wide necks. Pseudoobstruction can be treated with octreotide and erythromycin [36]. Complications from chronic constipation and pseudoobstruction include stercoral ulcers from impaction of hard feces in the rectum, volvulus from dilation and elongation of the colon causing excess mobility, and perforations due to the thin, atrophic bowel [37, 38]. Pneumatosis cystoides intestinalis and benign pneumoperitoneum, without rebound tenderness or the need for urgent surgery, may occur [39].

The internal anal sphincter (IAS), composed mainly of smooth muscle, undergoes atrophy and fibrosis. Since the IAS composes 85% of the resting anal pressure, there is an abnormal descent of rectal air and feces into the anal canal. The resulting incontinence of feces can be treated by solidifying liquid stool, by biofeedback although responses are often unsatisfactory, by sacral nerve stimulation, and by surgical approaches [32, 40].

Heart Disease

Malabsorption, clinical or occult, is present in 56% of patients with chronic heart failure (HF), in part due to bowel wall edema and decreased perfusion with increased bowel wall thickness [41, 42]. Low cardiac output leads to ischemia of intestinal villus tips. Protein-losing enteropathy results from increased intestinal permeability. Constrictive pericarditis even without typical hemodynamic changes but with thickened pericardium (seen in MRI) may cause protein-losing enteropathy and peripheral edema, with normalization after pericardectomy [43]. Colonic angiodysplasia have a controversial association with aortic stenosis and GI bleeding [44].

GI mucosal changes, particularly a mosaic-like pattern, are seen in the majority of patients with HF and correlate with GI symptoms [45]. Congestive hepatopathy is due to hepatic

hypoxia and results in centrilobular damage with reduced forward flow and backward congestion. Modest liver function abnormalities are noticed with a cardiac index less than 1.5 L/min/m^2 [46]. Over time, fibrous tissue bands adjoin centrolobular areas and encircle relatively normal portal tracts. Hepatic function, however, correlates primarily with centrolobular congestion, not with liver fibrosis. Abdominal discomfort, due to stretching of the liver capsule, is a striking manifestation of hepatic congestion. Physical findings include hepatomegaly (95%), ascites (25%), and rarely splenomegaly [47]. HF is associated with a high serum ascites albumin gradient and high ascites protein content due to high systemic venous pressures of the liver and peritoneal cavity. Portal hypertension and hepatic encephalopathy are rare. Serum bilirubin is usually below 5 mg/100 mL, often with unconjugated pigment. Serum transaminases are usually mildly elevated while the international normalized ratio (INR) is often prolonged. CT scan shows lobulated, patchy, inhomogeneous, enlarged liver with distention of the inferior vena cava. These patients should receive treatment for the heart failure and paracentesis for refractory ascites. Albumin does not need to be replaced with paracentesis since synthetic function is preserved. Transjugular portosystemic shunts are contraindicated. Prognosis relates to severity of the underlying cardiac disease. Surgical GI complications after coronary artery bypass grafts greatly increase the mortality [48].

Hypoxic liver injury (HLI) usually occurs in a setting of liver congestion from right-sided heart failure and low cardiac output, precipitated by an acute event, usually arrhythmia or pulmonary edema, often without documented hypotension [49]. Transaminases increase within 48 h after the initiating event and decrease within 72 h if the causative event is eliminated. The incidence of HLI defined as transaminase elevations greater than 20 times normal is 0.16% for inpatients, 0.9% for critical care patients, and 2.6% for cardiac care patients. Symptoms include weakness, shortness of breath, and right upper abdominal pain. Ultrasound reveals hypoechoic areas, while CT scans show hypodense lesions, all of which usually resolve completely. The INR may increase, bilirubin may be mildly elevated, but clinical jaundice is unusual.

Kidney Disease

The prevalence of CKD and ESRD has increased steadily in the US. CKD increases in prevalence in older diabetics and hypertensives. GI manifestations may be evident in 79% of those with CKD [50], most common being nausea, vomiting, abdominal pain, constipation, and diarrhea.

Although upper GI symptoms are common in CKD, there is no clear increase in gastroparesis, abnormal gastric emptying time, ulcer disease, or *Helicobacter pylori* infection. GI bleeding, however, is common, most commonly from angiodysplasias [51] or may be secondary to uremic effects on GI mucosa, platelet function abnormalities, or use of heparin and antiplatelet drugs. Hypergastrinemia results from impaired excretion of gastrin or increased synthesis due to hypochlorhydria and reduced parietal cell sensitivity to gastrin.

Table 67.3 Summary of GI manifestations in kidney and heart disease

System	Manifestations
Chronic kidney disease	Appetite: anorexia, metallic taste
	Nausea, vomiting
	Bleeding from uremia, low platelet effects, use of heparin and antiplatelet drugs
	Hypergastrinemia
	Arterio-venous malformations
	Constipation, autonomic or medication induced
	Pancreatic amylase or lipase elevation
	Nonocclusive mesenteric ischemia
Chronic heart disease	Congestive hepatopathy
	Hypoxic hepatitis
	Malabsorption and protein-losing enteropathy
	Intestinal ischemia (poor perfusion-related)
	Cardiac cirrhosis

Constipation is common in CKD and ESRD due to reduction in physical activity and fiber intake (from potassium-restricted diets); use of iron, calcium supplements, or phosphate binders; and presence of comorbidity such as DM or cerebrovascular disease. Magnesium- and phosphate-containing enemas are best avoided.

While pancreatic abnormalities are observed at autopsy in 56–60% of patients with ESRD, the incidence of pancreatitis is probably not increased [52]. Amylase levels in CKD are due to poor renal clearance. Lipase levels are increased due to heparin-induced lipolytic activity in patients on dialysis. However, a threefold increase in serum amylase levels suggests pancreatitis.

The incidence of nonocclusive mesenteric ischemia particularly of the cecum and right colon is higher in hemodialysis patients [53]. This is due to intradialytic hypotension, excessive use of erythropoietin, and calcification of mesenteric arteries [50]. Patients present with abdominal pain, guarding, fever, and leukocytosis. Early surgical resection is often necessary as the mortality rate is high. Encapsulating peritoneal sclerosis is a rare but lethal complication of peritoneal dialysis characterized by peritoneal thickening and encapsulation of the bowel.

Sodium polystyrene sulfonate (Kayexalate)-sorbitol enemas may cause intestinal necrosis and ulcerations; the complication can be reduced with cleansing enemas administered before and after its use [50]. Acute phosphate nephropathy occurs in 1–4% of patients using a sodium phosphate preparation, such as phosphosoda for laxation or prior to colonoscopy [54]. The use of phosphorus- and magnesium-containing preparations is relatively contraindicated in CKD (Table 67.3).

Key Points

- Gastrointestinal manifestations are common in systemic disease.
- Diabetes affects the esophagus (pyrosis), stomach (bloating), intestine (diarrhea or constipation), pancreas (pancreatitis), and the liver (nonalcoholic fatty liver).
- In amyloidosis, the liver is commonly involved but symptoms are mild and due to intestinal involvement, resulting in diarrhea, steatorrhea, or abdominal pain.
- Thyroid disease usually causes motility disorders or appetite changes.
- Sarcoidosis is associated with hepatomegaly, elevated alkaline phosphatase, intrahepatic cholestasis eventually progressing to biliary cirrhosis, and granulomas, but with few symptoms.
- Scleroderma is associated with esophageal dysmotility, reflux, delayed gastric emptying, intestinal dysmotility, wide-mouthed diverticuli, and pseudoobstruction.
- Heart failure may result in congestive hepatopathy, hypoxic hepatitis, malabsorption, and protein-losing enteropathy.
- Chronic kidney disease (CKD) is associated with bleeding, mild hyperamylasemia, hypergastrinemia, constipation, and nonocclusive mesenteric ischemia.

References

1. Rewers M, Liu E, Simmons J, et al. Celiac disease associated with type 1 diabetes mellitus. Endocrinol Metab Clin North Am. 2004; 33:1197–214.
2. Freemark M, Levitsky LL. Screening for celiac disease in children with type 1 diabetes. Two views of the controversy. Diabetes Care. 2003;26:1932–9.
3. DeBlock CE, DeLeeuw IH, Van Gaal LF. High prevalence of manifestations of gastric autoimmunity in parietal cell antibody-positive type 1 (insulin-dependent) diabetic patients. The Belgian Diabetes Registry. J Clin Endocrinol Metab. 1999;84:4062–7.
4. Loo FD, Dodds WJ, Soergel KH, et al. Multipeaked esophageal peristaltic pressure waves in patients with diabetic neuropathy. Gastroenterology. 1985;88:485–91.
5. Horowitz M, O'Donovan D, Jones KL, et al. Gastric emptying in diabetes: clinical significance and treatment. Diabet Med. 2002;19: 177–94.
6. Battle WM, Snape WR, Alavi A, et al. Colonic dysfunction in diabetes mellitus. Gastroenterology. 1980;79:1217–21.
7. Jorgensen T. Gallstones in a Danish population. Relation to weight, physical activity, smoking, coffee consumption, and diabetes mellitus. Gut. 1989;30:528–34.
8. Nair S, Yadav D, Pitchumoni CS. Association of diabetic ketoacidosis and acute pancreatitis: observations in 100 consecutive episodes of DKA. Am J Gastroenterol. 2000;96:2795–800.
9. Leeds JS, Hopper AD, Hadjivassiliou M, Tesfaye S, Sanders DS. Inflammatory bowel disease is more common in type 1 diabetes mellitus. Gut. 2011;60(1):A208.
10. Ebert EC, Nagar M. Gastrointestinal manifestations of amyloidosis. Am J Gastroenterol. 2008;103:776–87.
11. Hiramatsu K, Kaneko S, Shirota Y, et al. Gastrointestinal amyloidosis secondary to hypersensitivity vasculitis presenting with intestinal pseudoobstruction. Dig Dis Sci. 1998;43:1824–30.
12. Liapis K, Michelis FV, Delimpasi S, Karmiris T. Intestinal pseudoobstruction associated with amyloidosis. Amyloid. 2011;18(2): 76–8.
13. Skinner MS, Kattine AA, Spurlock BO. Electron microscopic observations of early amyloidosis in human liver. Gastroenterology. 1966;50:243–7.
14. Ebert EC. The thyroid and the gut. J Clin Gastroenterol. 2010;44: 402–6.
15. Eastwood GL, Braverman LE, White EM, et al. Reversal of lower esophageal sphincter hypotension and esophageal aperistalsis after treatment for hypothyroidism. J Clin Gastroenterol. 1982;4:307–10.
16. Lauritano EC, Bilotta AL, Gabrielli M, et al. Association between hypothyroidism and small intestinal bacterial overgrowth. J Clin Endocrinol Metab. 2007;92:4180–4.
17. Williams MJ, Blair DW. Gastric secretion in hyperthyroidism. Br Med J. 1964;1:940–4.
18. Thomas FB, Caldwell JH, Greenberger NJ. Steatorrhea in thyrotoxicosis. Relation to hypermotility and excessive dietary fat. Ann Intern Med. 1973;78:669–75.
19. Nomura S, Pittman CS, Chambers JB, et al. Reduced peripheral conversion of thyroxine to triiodothyronine in patients with hepatic cirrhosis. J Clin Invest. 1975;56:643–52.
20. Antonelli A, Ferri C, Fallahi P, et al. Thyroid disorders in chronic hepatitis C virus infection. Thyroid. 2006;16(6):563–72.
21. Mandac JC, Chaudhry S, Sherman KE, et al. The clinical and physiological spectrum of interferon-alpha induced thyroiditis: toward a new classification. Hepatology. 2006;43:661–72.
22. Cooper DS. Antithyroid drugs. N Engl J Med. 2005;352:905–17.
23. Idannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. N Engl J Med. 2007;357:2153–65.
24. Ebert EC, Kierson M, Hagspiel KD. Gastrointestinal and hepatic manifestations of sarcoidosis. Am J Gastroenterol. 2008;103:1–9.
25. Sachar DB, Rochester J. The myth of gastrointestinal sarcoidosis: a case of guilt by association. Inflamm Bowel Dis. 2004;10:441–3.
26. Kennedy PT, Zakaria N, Modawi SB, et al. Natural history of hepatic sarcoidosis and its response to treatment. Eur J Gastroenterol Hepatol. 2006;18:721–6.
27. Kataria YP, Whitcomb ME. Splenomegaly in sarcoidosis. Arch Intern Med. 1980;140:35–7.
28. Baratta L, Cascino A, Delfino M, et al. Ursodeoxycholic acid treatment in abdominal sarcoidosis. Dig Dis Sci. 2000;45:1559–62.
29. Kinder RR, Fleischman R. Systemic scleroderma: a review of organ systems. Int J Dermatol. 1974;13:362–95.
30. Ebert EC. Esophageal disease in scleroderma. J Clin Gastroenterol. 2006;40:769–75.
31. Mukhopadhyay AK, Graham DY. Esophageal motor dysfunction in systemic diseases. Arch Intern Med. 1976;136:583–7.
32. Ebert EC. Gastric and enteric involvement in progressive systemic sclerosis: a review. J Clin Gastroenterol. 2008;42:5–12.
33. Marie I, Levesque H, Ducrotte P, et al. Gastric involvement in systemic sclerosis: a prospective study. Am J Gastroenterol. 2001;96:77–83.
34. Marie I, Levesque H, Ducrotte P, et al. Manometry of the upper intestinal tract in patients with systemic sclerosis. Arthritis Rheum. 1998;41:1874–83.
35. Horowitz AL, Meyers MA. The "hide-bound" small bowel of scleroderma: characteristic mucosal fold pattern. Am J Roentgenol. 1973;119:332–4.
36. Verne GN, Eaker EY, Hardy E, et al. Effect of octreotide and erythromycin on idiopathic and scleroderma-associated intestinal pseudoobstruction. Dig Dis Sci. 1995;40:1892–901.

37. Robinson JC, Teitelbaum SL. Stercoral ulceration and perforation of the sclerodermatous colon. Report of two cases and review of the literature. Dis Colon Rectum. 1974;17:622–32.
38. Budd DC, Nirdlinger EL, Sturtz DL, et al. Transverse colon volvulus associated with scleroderma. Am J Surg. 1977;133: 370–2.
39. Ritchie M, Caravelli J, Shike M. Benign persistent pneumoperitoneum in scleroderma. Dig Dis Sci. 1986;31:552–5.
40. Kenefick NJ, Vaizey CJ, Nicholls RJ, et al. Sacral nerve stimulation for faecal incontinence due to systemic sclerosis. Gut. 2002;51: 881–3.
41. Berkowitz D, Groll MN, LIkoff W. Malabsorption as a complication of congestive heart failure. Am J Cardiol. 1963;11:43–7.
42. Sandek A, Bauditz J, Swidsinski A, et al. Altered intestinal function in patients with chronic heart failure. J Am Coll Cardiol. 2007;50:1561–9.
43. Muller C, Globits S, Glogar D, et al. Constrictive pericarditis without typical haemodynamic changes as a cause of oedema formation due to protein-losing enteropathy. Eur Heart J. 1991;12: 1140–3.
44. Batur P, Stewart WJ, Isaacson JH. Increased prevalence of aortic stenosis in patients with arteriovenous malformations of the gastrointestinal tract in Heyde syndrome. Arch Intern Med. 2003;163:1821–4.
45. Raja K, Kochhar R, Sethy P, et al. An endoscopic study of upper-GI mucosal changes in patients with congestive heart failure. Gastrointest Endosc. 2004;60:887–93.
46. Kubo C, Walter BA, John DHA, et al. Liver function abnormalities in chronic heart failure. Influence of systemic hemodynamics. Arch Intern Med. 1987;147:1227–30.
47. Dunn GD, Hayes P, Breen KJ, et al. The liver in congestive heart failure: a review. Am J Med Sci. 1973;265:174–89.
48. Guler M, Yamak B, Erdogan M, et al. Risk factors for gastrointestinal complications in patients undergoing coronary artery bypass graft surgery. J Cardiothorac Vasc Anesth. 2011;25(4):637–41.
49. Ebert EC. Hypoxic liver injury. Mayo Clin Proc. 2006;81:1232–6.
50. Shirazian S, Radhakrishnan J. Gastrointestinal disorders and renal failure: exploring the connection. Nat Rev Nephrol. 2010;6:480–92.
51. Farsakh A, Roweily NA, Rababaa M, et al. Evaluation of the upper gastrointestinal tract in uraemic patients undergoing haemodialysis. Nephrol Dial Transplant. 1996;11:847–50.
52. Gupta A, Yuan ZY, Balaskas EV, et al. CAPD and pancreatitis: no connection. Perit Dial Int. 1992;12:309–16.
53. Bassilios N, Menoyo V, Berger A, et al. Mesenteric ischaemia in haemodialysis patients: a case/control study. Nephrol Dial Transplant. 2003;18:911–7.
54. Lien YH. Is bowel preparation before colonoscopy a risky business for the kidney? Nat Clin Pract Nephrol. 2008;4:606–14.

Abdominal Aortic Aneurysm

68

T.S. Dharmarajan

Significance

Abdominal aortic aneurysm (AAA) is defined as a focal dilatation of the abdominal aorta. While intact aneurysms are usually asymptomatic, aneurysmal rupture is among the most dramatic vascular abdominal emergencies, often leading to rapid hypovolemic shock and death if not promptly diagnosed and addressed. The lethality following rupture is 80–95%; a high index of suspicion is critical for early diagnosis and prompt management to ensure a favorable outcome [1–5]. While there is lack of uniform agreement on the definition of AAA and this has consequences for practice, most definitions use aortic diameter as the basis [6]. The aortic diameter is influenced by body size, age, and gender [6]. The normal diameter of the aorta is around 2 cm. A generally accepted definition for AAA is an aortic diameter over 3 cm [7].

The size of an aneurysm helps in the follow up assessment. Generally AAAs of 3–3.9 cm are considered small and do not require intervention; size 4–5.4 cm requires surveillance; surgical repair for AAAs at least 5.5 cm may lead to a reduction in AAA-associated mortality [1, 2]. Most AAAs are located at a level between the renal arteries and the aortic bifurcation. Pathological features of AAA include aortic extracellular matrix degradation, inflammation, and neovascularization [8].

AAA affects 5% of the population in developed countries. They are more common in men, whites, and smokers [8]. Aneurysms pose variable risks of rupture based on risk factors, and accordingly pose substantial risk for mortality and a need for elective or emergency surgical intervention. Despite the awareness, the diagnosis of aneurismal rupture is commonly missed or delayed in practice [5].

Risk Factors

The most common risk factors for AAA are age ≥65 years, male sex, and being an "ever smoker" (defined as ≥100 cigarettes in a lifetime). History of AAA in a first degree relative and the presence of vascular disease are also risk factors. Smoking is the most important reversible risk factor and adversely influences the development, expansion, and rupture of an AAA, stressing the importance of counseling for smoking cessation [1, 7]. Weaker associations include hypertension and hyperlipidemia; interestingly, diabetes is not a risk factor. However, the presence of diabetes or chronic kidney disease influences morbidity and mortality in those with AAAs [1].

The prevalence of large AAAs in women is low; data suggests that the ratio of AAAs in men to women is 4–6 to 1 [1, 7]. In a large randomized controlled trial in white women and men 65–80 years, the prevalence in women was a sixth of that in men; the incidence of rupture was the same in both screened and control groups of women [9] justifying the USPSTF recommendation for not screening women. The literature also suggests that the prevalence of AAA might be underestimated in women. Estrogen-mediated reduction in macrophage MMP-9 production may be a mechanism for gender disparities [10]. Women however, are at a greater risk for aneurysmal rupture, especially with smaller AAAs, compared to men [1, 10].

The Society for Vascular Surgery has classified risk factors into three groups: those that impact AAA development (e.g., tobacco use, hypertension, male gender, hypercholesterolemia, and family history of male predominance); AAA expansion (advanced age, cardiac disease, tobacco use, prior stroke, cardiac, or renal transplant); and AAA rupture (female gender, large AAA diameter, high mean blood pressure, current

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tobacco use, cardiac or renal transplant, wall stress/strength factors) [1].

The role of infection has been mentioned as a risk factor, due to detection of antibodies against *Chlamydia pneumonia* and a claim for inflammation as a basis for vascular disease; it is more likely that proteins cross react with chlamydial antibodies, indicating "molecular mimicry" [4]. Data on the role of antibiotics is not conclusive.

Presentation

The vast majority of AAAs are asymptomatic and detected as an incidental finding on ultrasonography or CT imaging for other disorders. The presence of a pulsatile mass on examination is very suggestive of an AAA. Generally large aneurysms (over 5 cm) are detected on physical examination, while smaller ones may be missed. It is generally safe to palpate an aneurysm [5]. The detection of a palpable pulsatile mass calls for further evaluation.

The most dramatic presentation is aneurysmal rupture and hemorrhagic shock from blood loss. Other manifestations include syncope, acute abdominal or back pain, and gastrointestinal dysfunction [5]. Factors that predispose to rupture include size of aneurysm, rate of expansion, and gender [1, 3, 5]. Increasing size of aneurysm is associated with a higher risk [1]. A large number of patients die before they reach a hospital, and many who do, are unable to survive surgery. Clearly, poor control of hypertension may increase likelihood of rupture. Thrombosis and embolization are additional complications.

Rarely upper abdominal pain and bloody vomiting may be a result of an aneurysm compressing the distal duodenum, causing ischemic duodenitis from superior mesenteric artery syndrome [11]. AAAs may be associated with cognitive dysfunction infrequently [12].

There is a high likelihood that patients with popliteal or femoral aneurysm have also an AAA; in contrast, there is a smaller likelihood that a patient with AAA also has a femoral or popliteal artery aneurysm [1]. Hence, a patient with one aneurysm requires scrutiny for another aneurysm elsewhere. AAAs expand more rapidly in smokers [13].

The differential diagnosis includes disorders that manifest with abdominal discomfort or back pain and include gastrointestinal, genitourinary, and spine disease. However, the first priority is to exclude rupture of an AAA than make a diagnosis of less serious conditions [5]. Para-aortic abdominal lymph nodes or other masses and thin habitus may transmit aortic pulsations and mislead the provider on physical examination or imaging [5].

Table 68.1 presents a overview on AAA.

Table 68.1 Abdominal aortic aneurysm (AAA): an overview [1, 3–5, 7]

Risk factors
Older age
Smoking history
Male gender
Family history
White race
Hypertension
Hyperlipidemia
Atherosclerotic occlusive vascular disease
Presentation
Largely asymptomatic; diagnosis often incidental
Abdominal pulsatile mass
Abdominal discomfort (pain or pressure effects)
Chronic back pain
Neuropsychiatric manifestations, rarely
Complications
Rupture and hemorrhagic shock
Syncope
Gastrointestinal or genitourinary dysfunction
Thromboembolic phenomena
Differential diagnosis
Spine disorders with pain
Gastrointestinal or genitourinary disorders
Para-aortic lymph nodes or other mass on imaging, with pressure effects
Abdominal hernia
Screening recommendations and surveillance (Table 68.2)
Management
Watchful waiting, with periodic surveillance for size of aneurysm
Medical management
History for symptoms at each visit
Abdominal examination at each visit
Address lifestyle risk factors: promote smoking cessation
Control hypertension (beta blockers, ACE inhibitors)
Statins for hyperlipidemia
Role for antibiotics unclear
Surgical management
Preoperative testing, including cardiopulmonary status
Elective vs. emergency surgical repair
Choices in surgery: open vs. endovascular
Elective repair indicated when the external diameter is 5.5 cm
Immediate repair is indicated for ruptured AAAs
Open repair: cost high, perioperative mortality 2–5%, perioperative morbidity high
Endovascular repair: cost higher, perioperative mortality 0–2%, perioperative morbidity low
Outcomes between open and endovascular equivalent at 2 years

Screening and Surveillance

The prevalence of AAA is predicted to go up with the anticipated increase in the global aging of people [14, 15]. As an aneurysm causes much morbidity and mortality, screening for aneurysms in the asymptomatic state assumes relevance. Often, a diagnosis of AAA is incidental during imaging for

Table 68.2 Screening recommendations for AAA

United States Preventive Services Task Force [7]
Screening is indicated for AAA in men aged 65–75 years, who ever smoked
No recommendation for or against in men 65–75 years, who never smoked
Benefits of screening in male ever smokers aged 65–75 years outweigh the harm
Abdominal ultrasonography is accurate for screening with high sensitivity and specificity
The USPSTF recommends against routine screening in women; harms of screening outweigh the benefit (Grade D)
Adults below 65 years or any age who never smoked are at low risk and unlikely to benefit from screening
Surgical repair of large AAAs (≥5.5 cm) is associated with decreased AAA-specific mortality
Canadian Society for Vascular Surgery [17]
Recommend screening for men 65–75 years who are potential candidates for surgery.
Screening not indicated in women over 65 years of age in general
Individualize screening for women with multiple risk factors (smoking, family history, and cerebrovascular disease)
Society for Vascular Surgery and Society for Vascular Medicine and Biology [1]
Screening in all men age 65 years and older
Screening for women aged 65 and older if they have smoked or have a family history
Screen all men aged ≥55 years with a family history of AAA
Ultrasonography every 6 months if AAA diameter is 4.5–5.4 cm
Ultrasonography yearly if AAA diameter is 3.5–4.4 cm
If healthy, recommend imaging every 3 years for AAAs 3.0–3.4 cm, and every 5 years for AAAs 2.6–2.9 cm
Rescreening is not recommended if the initial ultrasound at age 65 or older demonstrates an aortic diameter <2.6 cm
In those with AAA and abdominal or back pain, imaging is recommended
Timely referrals to vascular surgery for large or expanding aneurysms

other conditions [7]. National programs have been implemented for screening in the US, UK, and Sweden. While there is general agreement on the need for screening, the recommendations on whom to screen, age at which to screen and frequency of screening are not consistent in all guidelines [16].

Screening recommendations and practice guidelines stress several areas that are significant in the care for patients with AAA [1, 7, 17]. While recommendations are not consistent, there is general agreement in screening men over 65 years [1, 7, 17]. There is consensus on the need for a one-time screening of older men to detect and treat AAAs ≥5.5 cm; for smaller AAA, however, prediction models and a cost analysis are necessary to provide further guidance [15, 16]. Screening and surveillance recommendations are summarized in Table 68.2.

In the UK Multicentre Aneurysm Screening Study (MASS) (2009–2010), of the 6,091 men aged 65 years invited for screening, two-thirds attended; 162 self-referrals were also screened. Aneurysms turned out to be more common in the self-referrals than in the invited group; all detected aneurysms were in white men [18].

AAA screening and surveillance utilize ultrasound imaging to measure the antero-posterior diameter of the infra-renal aorta. The sensitivity and specificity of ultrasonography screening are 95% and 100% respectively [7]. Yet, variations in observer interpretations and reproducibility have been cited, warranting the need for standard training and quality assessment to make the screening program effective [19]. In a study comparing measurements between ultrasound and computerized tomography (CT), significant differences between the two imaging modalities existed, especially in the 5–5.5 cm range; the authors recommended that AAAs measuring ≥5 cm in ultrasound be referred to a vascular service and CT imaging [10]. In general ultrasound is an effective imaging modality but is less precise for measurements than CT [20]. CT also has the ability to evaluate the mesenteric and iliac areas and presence of suprarenal aneurysms better [21]. Magnetic resonance imaging (MRI) is at least as good as CT, but at a higher cost [22], and offers no advantage over CT. Demonstrating blood in the retroperitoneum following rupture of an AAA requires a CT scan or MRI [5]. When rupture is suspected at presentation, a CT or MRI should be requested rather than ultrasound. For unruptured aneurysms, ultrasonography is the imaging of choice for surveillance and initial study [5].

Selective screening at the vascular laboratory is deemed cost-effective [23]. A study of 5,924 patients (mean age 72.8 years) referred to a university hospital vascular lab for arterial examination revealed an AAA by ultrasonography in 181 patients; 21.5% underwent elective repair with a perioperative mortality of 5.1% [23]. An Italian study found that AAA screening with ultrasound was cost-effective compared to non screening scenarios [24]. Age at initial screening has an impact on the cost-utility ratio. Studies including a high proportion of men >75 years failed to show significant reduction in AAA-related deaths [15]. Overall, there is growing consensus on the value of screening, in that a single ultrasound at age 65 can rule out significant disease for life in 95% of men [15].

More recently the value of transthoracic echocardiography has been demonstrated in detecting AAA, as the cardiac ultrasound probes fit perfectly for AAAs; the prevalence of AAAs over 3 cm in a study was up to 19% in men over 70 years [25]. In another study 5.1% of those over 55 years had AAAs; the mean aortic diameter was 3.9 ± 1.22 cm, with the ratio of men to women with aneurysms 7.3 to 1 [26].

Although there is adequate evidence for benefits from ultrasound screening for AAA, application of the principle in practice to offer systematic screening is poor and places much responsibility on family physicians [27]. The benefit of screening is in the reduction of AAA mortality with the opportunity for secondary benefit for cardiovascular mortality, since AAA is a prognostic marker for cardiovascular disease [27].

Management

AAAs are monitored conservatively through the use of medical imaging when they are small; when the size (aortic diameter) approaches 5–5.5 cm, surgical repair may be required [14]. Management strategies can address any of three options or a reasonable combination: life style measures, medical management, and surgery. Watchful waiting combined with medical management is an option whenever surgery is not a consideration.

Life Style Measures

Smoking cessation is perilous in those with vascular disease, with the benefits of cessation of smoking greatly exceeding any risks from pharmacological treatment to achieve the goal. Success is achieved through a systematic approach with a focus on the five As (Ask, Advise, Assess, Assist, and Arrange) [28]. No other life style intervention offers such a tremendous benefit. Dietary recommendations must be consistent and individualized to risk factors present, such as hypertension, vascular disease, and dyslipidemia.

Pharmacological Measures

Drug management must address risk factors such as hypertension and hyperlipidemia. The role of beta blockers in this regard is controversial [5]. Benefits from their use have been cited years ago [29]; beta adrenergic agents and angiotensin converting enzyme inhibitors (ACEIs) have been recommended as beneficial [30], although data is limited. The contrasting view is that propranolol does not inhibit aneurysm expansion, but level B evidence is available suggesting that roxithromycin and doxycycline decrease the rate of aneurysm expansion [31]. Antibiotics have been proposed on the basis of inflammation playing a role in development of AAAs, a view unproven. The same paper also cites Level B and C evidence in favor of statins inhibiting AAA expansion; and animal data in favor of ACEIs and angiotensin receptor blockers in decreasing the rate of expansion [31]. Interestingly, there is also paucity of data on the benefit of beta blockers, statins, and macrolides for thoracic aorta aneurysms, a related vascular disorder [32]. As higher mean blood pressure is associated with risk of rupture, AAAs are enough reason to treat hypertension, a noncontroversial statement [5]. Although the role of beta blockers is not clear in the prevention of growth of AAAs, the level of recommendation and evidence to continue beta blockers in the perioperative period is strong [1].

The role of statins on expansion rate has been raised due to two reasons. First, dyslipidemia is an established risk factor for vascular disease; secondly, statins have nonlipid pleiotropic effects on the arterial wall (addressing cellular components) and on the process of inflammation [33]. Even NSAIDs have been mentioned as having benefit, although not supported by data. After a review of 15 cohort studies and over 12,000 patients, the patterns of drug benefits were not consistent; the conclusion was that properly designed RCTs are required to ascertain the effects of these agents on aneurysm expansion [34].

Surgery

Data from two trials suggest no advantage for early surgery for AAAs in the 4–5.5 cm range [35]. A large study from 2005 to 2009 involved surgical repair of ruptured AAAs and outcomes across nine countries, data was collected from vascular registries in Australia and Europe. Here, 31,427 intact AAA repairs were performed in the old, mean age 72.6 years, including many octogenarians [36]. The perioperative mortality rate was 2.8%; increasing age, open repair, and comorbidities predicted outcome; the same study also identified 7,040 ruptured repairs, with mean age 73.8 years, and a perioperative mortality of 31.6% [36]. The outcomes differed with geographical locations [36].

Endovascular aneurysm repair, is one option, and utilizes an expandable graft introduced into the aorta to protect the AAA from arterial pressure. It is a valid alternative to open repair and offers lower 30 day mortality and morbidity than open repair, but no survival advantage after 1–2 years [5, 37]. Surgical mortality in a recent study of octogenarians was 26.7% and confounded by the presence of cardiac disease and hypovolemic shock, rather than age [38]. The near normal long-term prognosis in this age group following successful repair justifies the surgical correction in well-selected cases even in octogenarians [38]. Treatment mortality appears higher in women for both elective and ruptured repair of AAAs [10]. Ischemic colitis is a rare complication of AAA surgery, requiring the surgeon to be proactive to prevent this occurrence [39].

Ultimately one must take into account the preferences of patients and family members, in addition to the recommendations of vascular surgeons. Advance directives, if present, must always be respected. Preoperative cardiac assessment needs to be efficient and accurate to obtain satisfactory operative results [40]. Cardiopulmonary exercise testing was the only means that predicted both 30 day outcome and 30 month mortality in a UK study [41]. Major complications and re-intervention risk were most influential for responses of patients, family, and surgeon, as also costs, recovery time, and anesthesia in lesser importance [42]. Understanding these facts can help optimize treatment.

Once patients understand the implications of diagnosis, they are more likely to be satisfied with results [43].

Future Directions

There is an expectation that better diagnostic and prognostic markers for AAA will be available in future; molecular markers await identification [1, 14]. Markers may assist diagnosis and monitoring of response to therapy, but thus far markers lack sensitivity and specificity [1]. Recent data suggests that men with AAA and those with aortic diameters 25–29 mm have increased risk of mortality compared to those with aortic diameter <24 mm [44]. Emergency department death is a cause of mortality with AAA rupture, and relates to delay in arrival and delays in providing definitive care, calling for improvement in regional systems of care [45]. In the future, genome-wide screening may identify genetic markers to assist early diagnosis.

Key Points

- Abdominal aortic aneurysm (AAA) is defined as a dilatation of the abdominal aorta, generally accepted as over 3 cm.
- AAAs are usually asymptomatic, rupture is followed by dire consequences.
- Risk factors include older age, smoking, male gender, Caucasian ethnicity, and presence of hypertension and vascular disease.
- The USPSTF guidelines recommend screening through one-time abdominal ultrasonography in men between 65 and 75 years who have ever smoked.
- Ultrasonography screening for AAA is specific and sensitive, but does carry interpreter bias.
- CT imaging although more precise, is not the first choice screening modality; disadvantages include cost, and risks of intravenous contrast and radiation.
- Medical management addresses risk factors such as tobacco use, hypertension, and hyperlipidemia through life style modification and use of medications.
- Surveillance for size of the aneurysm through periodic imaging is part of the strategy in watchful waiting
- Patients with aneurysm size over 5.5 cm are candidates for elective surgery.
- Candidates for surgery must be carefully assessed preoperatively, utilizing cardiopulmonary exercise testing.
- Surgical repair decisions are guided by size of aneurysm, rate of growth, and comorbidity and above all patient preferences; options for surgery include open and endovascular repair.

References

1. Chaikof EL, Brester DC, Dalman RL, et al. The care of patients with an abdominal aortic aneurysm: the Society for Vascular Surgery practice guidelines. J Vasc Surg. 2009;50(4 Suppl):S2–S49.
2. Lewiss RE, Egan DJ, Shreves A. Vascular abdominal emergencies. Emerg Med Clin North Am. 2011;29(2):253–72.
3. Aggarwal S, Qamar A, Sharma V, Sharma A. Abdominal aortic aneurysm: a comprehensive review. Exp Clin Cardiol. 2011;16(1):11–5.
4. Lindholt JS. Abdominal aortic aneurysms. Dan Med Bull. 2010;57(12):B4219.
5. Lane C, Goldmann DR, Sox HC. Abdominal aortic aneurysm. Ann Intern Med. 2009;150:ITC5-1–ITC5-16.
6. Wanhainen A. How to define an abdominal aortic aneurysm—influence on epidemiology and clinical practice. Scand J Surg. 2008;97(2):105–9.
7. Calonge N, Allan JD, Berg AO, et al. Screening for abdominal aortic aneurysm: recommendation statement. US Preventive Services Task Force. 2005;142:198–202.
8. Klink A, Hyafil F, Rudd J, et al. Diagnostic and therapeutic strategies for small abdominal aortic aneurysms. Nat Rev Cardiol. 2011;8(6):338–47.
9. Scott RA, Wilson NM, Ashton HA, Kay DN. Influence of screening on the incidence of ruptured aortic aneurysm: 5 year results of a randomized controlled study. Br J Surg. 1995;82:1066–70.
10. Grootenboer N, Bosch JL, Hendriks JM, van Sambeek MR. Epidemiology, aetiology, risk of rupture and treatment of abdominal aortic aneurysms: does sex matter? Eur J Vasc Endovasc Surg. 2009;38(3):278–84.
11. Okuyama Y, Kawakami T, Ito H, et al. A case of ischemic duodenitis associated with superior mesenteric artery syndrome caused by an abdominal aortic aneurysm. Case Rep Gastroenterol. 2011;5(2):278–82.
12. Baune BT, Unwin SJ, Quirk F, Golledge J. Neuropsychiatric symptoms in patients with aortic aneurysms. PLoS One. 2011;6(7):e22632.
13. Brady AR, Thompson SG, Fowkes FG, et al.; UK Small Aneurysm Trial Participants. Abdominal aortic aneurysm expansion: risk factor and time intervals for surveillance. Circulation. 2004;110:16–21.
14. Moxon JV, Parr A, Emeto TI, et al. Diagnosis and monitoring of abdominal aortic aneurysm: current status and future prospects. Curr Probl Cardiol. 2010;35(10):512–48.
15. Montreull B, Brophy J. Screening for abdominal aortic aneurysms in men: a Canadian Perspective using Monte Carlo-based estimates. Can J Surg. 2008;51(1):23–34.
16. Ferket BS, Grootenboer N, Colkesen EB, et al. Systematic review of guidelines on abdominal aortic aneurysm. J Vasc Surg. 2012;55:1296–1304.
17. Mastracci TM, Cina CS. Canadian Society for Vascular Surgery Screening for abdominal aortic aneurysm in Canada: review and position statement of the Canadian Society for Vascular Surgery. J Vasc Surg. 2007;45:1268–76.
18. Conway AM, Malkawi AH, Hinchliffe RJ, et al. First year results of a national abdominal aortic aneurysm screening programme in a single center. Br J Surg. 2012;99(1):73–7.
19. Beales L, Wolstenhulme S, Evans JA, et al. Reproducibiity of ultrasound measurement of the abdominal aorta. Br J Surg. 2011; 98(11):1517–25.
20. Foo FJ, Hammond CJ, Goldstone AR, et al. Agreement between computed tomography and ultrasound on abdominal aortic aneurysms and implications on clinical decisions. Eur J Vasc Endovasc Surg. 2011;42(5):608–14.

21. Isselbacher EM. Thoracic and abdominal aortic aneurysm. Circulation. 2005;111:816–26.
22. Petersen MJ, Cambria RP, Kaufman JA, et al. Magnetic resonance angiography in the preoperative evaluation of abdominal aortic aneurysms. J Vasc Surg. 1995;21:891–8.
23. Mani K, Alund M, Bjorck M, et al. Screening for abdominal aortic aneurysm among patients referred to the vascular laboratory is cost effective. Eur J Vas Endovasc Surg. 2010;39(2):208–16.
24. Giardina S, Pane B, Spinella G, et al. An economic evaluation of an abdominal aortic aneurysm screening program in Italy. J Vasc Surg. 2011;54(4):938–46.
25. Aboyans V, Kownator S, Lafitte M, et al. Screening abdominal aorta aneurysm during echocardiography: literature review and proposal for a French nationwide study. Arch Cardiovasc Dis. 2010;103(10):552–8.
26. Gentille-Lorente DI, Salvado-Usach T. Screening for abdominal aortic aneurysm by means of transthoracic echocardiography. Rev Esp Cardiol. 2011;64(5):395–400.
27. Aboyans V, Guessous I, Leclerc A, Lacroix P. From guidelines for screening to their (poor) implementation: the case of the abdominal aortic aneurysm. Rev Med Suisse. 2010;6(256):1405–9.
28. Ratchford EV, Black 3rd JH. Approach to smoking cessation in the patient with vascular disease. Curr Treat Options Cardiovasc Med. 2011;13(2):91–102.
29. Gadowski GR, Pitcher DB, Ricci MA. Abdominal aortic aneurysm expansion rate. Effect of size and beta-adrenergic blockade. J Vasc Surg. 1994;19:727–31.
30. Sule S, Aronow WS. Management of abdominal aortic aneurysms. Compr Ther. 2009;35(1):3–8.
31. Baxter BT, Terein MC, Dalman RL. Medical management of small abdominal aortic aneurysms. Circulation. 2008;117(14):1883–9.
32. Liao SL, Elmariah S, van der Zee S, et al. Does medical therapy for thoracic aortic aneurysms really work? Are beta blockers truly indicated? CON. Cardiol Clin. 2010;28(2):261–9.
33. Van Kuijk JP, Flu WJ, Witteveen OP, et al. The influence of statins on the expansion rate and rupture risk of abdominal aortic aneurysms. J Cardiovasc Surg (Torino). 2009;50(5):599–609.
34. Bergqvist D. Pharmacological interventions to attenuate the expansion of abdominal aortic aneurysm (AAA)—a systematic review. Eur J Vasc Endovasc Surg. 2011;41(5):663–7.
35. Ballard DJ, Filardo G, Fowkes G, Powell JT. Surgery for small asymptomatic abdominal aortic aneurysms. Cochrane Data base Syst Rev. 2008;8(4):CD001835.
36. Mani K, Lees T, Beiles B, et al. Treatment of abdominal aortic aneurysm in nine countries 2005–2009: a vascunet report. Eur J Vasc Endovasc Surg. 2011;42(5):598–607.
37. Lederle FA. Abdominal aortic aneurysm—open versus endovascular repair. N Eng J Med. 2004;351:1677–9.
38. Opfermann P, von Allmen R, Diehm N, et al. Repair of ruptured abdominal aortic aneurysm in octogenarians. Eur J Vasc Endovasc Surg. 2011;42(4):475–83.
39. Necpal R, Sefranek V, Slysko R, Tomka J. Ischemic colitis following AAA procedures. Rozhl Chir. 2011;90(1):31–6.
40. Troisi N, Pulli R, Dorigo W, et al. Preoperative cardiac assessment in patients undergoing majour vascular surgery. Vascular. 2011;19(4):178–86.
41. Thompson AR, Peters N, Lovegrove RE, et al. Cardiopulmonary exercise testing provides a predictive tool for early and late outcomes in abdominal aortic aneurysm patients. Ann R Coll Surg Engl. 2011;93(6):474–81.
42. Faggiol G, Scanlone L, Mantovani LG, et al. Preference of patients, their family caregivers and vascular surgeons in the choice of abdominal aortic aneurysms treatment options: the PREFER study. Eur J Vasc Endovasc Surg. 2011;42(1):26–34.
43. Khan JA, Mazcan FA, Abdul Rahman MN, et al. Patients' perspectives of functional outcomes after elective abdominal aortic aneurysm repair: a questionnaire survey. Ann Vasc Surg. 2011; 25(7): 878–86.
44. Duncan JL, Harrild KA, Iversen L, et al. Long term outcomes in men screened for abdominal aortic aneurysm: prospective study. Brit Med J. 2012;344:e2958.
45. Mell MW, Calicut RA, Bech F, et al. Predictors of emergency department death for patients presenting with ruptured abdominal aortic aneurysms. J Vasc. Surg. 2012. Ahead of print.

Rheumatological Manifestations of Gastrointestinal Disease

69

Nayan K. Kothari and Srilatha Kothandaraman

Introduction

The prevalence of rheumatic manifestations in association with colopathies of elderly is impressive. There exists a strong link between the gut and the joint, a relationship emphasized by the fact that musculoskeletal manifestations are well-recognized complications of gastrointestinal (GI) disorders. Many rheumatological diseases also present with GI manifestations. Diagnosis becomes a challenge in the geriatric population as presentations may be atypical in addition to the coexistence of other musculoskeletal problems. As the population ages, there is a need to be aware of the varied presentations and limitations involved in diagnosis and management especially with regard to safe drug regimens. The pathophysiology of rheumatological manifestations may involve increased intestinal permeability in specific GI disorders resulting in a "leaky gut" situation whereby antigenic material may cross the gut wall and produces antibodies that cross-react with host antigens and exhibit systemic symptoms. A description follows on common GI disorders with rheumatological manifestations (Table 69.1).

Reactive Arthritis

Reactive arthritis (ReA) is an asymmetric inflammatory oligoarthritis usually involving lower extremities, axial skeleton accompanied by enthesitis, in about a third of patients with an episode of bacterial gastroenteritis, nongonococcal urethritis or cervicitis, usually resolving in 4–6 months. Progression is noted in 30–50% [1], with antibiotics usually unhelpful [2]. The incidence is between 2 and 33% [3] and varies based on the rate of HLA-B27 positivity in the population and the type of infectious organism. There exists an association between HLA B27 and severity of joint symptoms [4]. Two forms of ReA have been described, postvenereal (*Chlamydia trachomatis* [Ct]) and postdysentery (*Salmonella*, *Shigella*, *Campylobacter*, and *Yersinia*) [1]. Cases of poststreptococcal and urinary *Escherichia coli* ReA have also been reported in older adults [5–7]. A major association between reactive joint pain and HLA-B27 was found for *Salmonella*, *Shigella*, and *Yersinia* but not for *Campylobacter* and *E. coli*. [4]. *C. trachomatis* was detected in the synovial tissue from patients with ReA by electron microscopy recently [8] and is the most common cause of ReA in the US, with *Yersinia* least common though both are in decline [1] (Table 69.2).

Pathogenesis

In genetically vulnerable individuals, peripheral joint inflammation with gut infections such as *Salmonella typhimurium*, *Campylobacter jejuni*, *Yersinia enterocolitica*, and *Shigella* suggested for a possible relationship between inflammation of the gut mucosa and peripheral arthritis [9]. The exact mechanism of ReA is unknown; however an impaired TH1-cytokine response, a low tumor necrosis factor (TNF) alpha status in HLA B27 positive subjects [10], molecular mimicry [11], secretory IgA as a protective factor [12], 60 kD shock protein as a target for response of CD4 and CD8 cells [13], toll-like receptors, and cellular uptake [1] are implicated. Rarely antigenic material and bacterial fragments from gut organisms including *Yersinia*, *Shigella,* and *Salmonella* have been isolated from synovial cells or fluid [1, 14].

Radiologically, sacroiliitis, periostitis, nonmarginal syndesmophytes, periosteal new bone formation, joint erosions, and joint space narrowing with syndesmophytes can be appreciated. Sacroiliitis is seen more commonly with postvenereal ReA rather than postenteric ReA. NSAIDs, corticosteroids,

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Table 69.1 Gastrointestinal disorders associated with rheumatological manifestations

Gastrointestinal	
Acute intestinal-reactive arthritis	*Chlamydia* *Shigella* *Salmonella* *Campylobacter* *Yersinia* *Clostridium difficile* Other organisms—parasites, *Helicobacter pylori*, etc.
Seronegative spondyloarthropathies	Peripheral arthritis Axial arthropathy Others—osteonecrosis, steroid-induced osteoporosis, etc.
Miscellaneous	Celiac disease Whipple's disease Postbypass arthritis
Hepatic	
Viral	Hepatitis B Hepatitis C
Nonviral	Primary biliary cirrhosis Autoimmune hepatitis Liver cirrhosis (viral causes included) Hereditary hemochromatosis Postliver transplant Malignancy
Pancreatic	
Pancreatitis, carcinoma pancreas, pancreatic pseudocysts, pancreatic duct stenosis, vascular pancreatic fistulas	

Table 69.2 Organisms associated with reactive arthritis (ReA) [1, 14]

Organism	Relevant facts and HLAB27 positivity
Chlamydia trachomatis	Most common cause May be etiology for undiagnosed spondyloarthropathy
Shigella dysenteriae, *flexneri*, and *sonnei*	First organism to be described Less common cause for ReA in developed countries HLA B27—36% based on a French study in 2005
Salmonella typhimurium and *enteritidis*	Attack rate 6–30% HLA B27—17–50% Salmonella Saint Paul in USA [1]
Campylobacter	In contrast to other microbial ReA, inflammatory back pain uncommon No significant association with HLA B27
Yersinia enterocolitica and *pseudotuberculosis*	Uncommon cause Denmark study mentions attack rate to be 23%
Clostridium difficile	HLA B27 positivity may mark serious or persistent disease [1] ReA with MTX and CDAD [82]
Strongyloides stercolaris reported [83, 84], Paragonimiasis [85], *Isospora belli* [86] and cryptosporidiosis [87], *Giardia lamblia* [88], *Hafnia alvei*, *Ureaplasma urealyticum*, *Helicobacter pylori*, intravesicular Bacillus Calmette-Guerin	

disease modifying agents (DMARDs) such as sulfasalazine are used in therapy. Sulfasalazine is especially helpful as one study showed that 67% of patients with ReA have histological evidence consistent with inflammatory bowel disease (IBD) on bowel biopsies. Antibiotics are useful for postchlamydial ReA rather than postdysenterial ReA [1].

Spondyloarthropathies and Inflammatory Bowel Disease

IBD including Crohn's disease (CD) and ulcerative colitis (UC) can develop in genetically prone individuals as a result of interaction between gut flora and host immune system. The mean incidence and prevalence of IBD in Western Europe and North America is estimated to be 6–150/100,000, respectively, for CD, and 20–200/100,000, respectively, for UC [15]. Historically, IBD and arthropathies have been described in association time and again. Similar pathogenesis may exist at a molecular level. Mechanisms such as mucosal dysregulation [16], bacterial recognition, endoplasmic reticulum stress, IL23/Th17 axis, response to hypoxia, activation of invariant natural killer T cells, and inhibition of leukocyte homing have been proposed in IBD genetics [17]. The triple combination comprising of a specific collagen or tissue matrix (termed as "soft collagen"), genetic predisposition (HLA B27, PSORS1, NODS2/CARD mutations), and triggering event (trauma or infection) is described as mechanisms for spondyloarthropathies [18]. Three genetic loci have been identified which could explain IBD-associated arthropathy [19] and chr1q32 and *STAT3* as ankylosing spondylitis susceptibility loci [20]. GWAS (Genomic Wide Association Studies) have supported the theory of some similar susceptibility genes between CD and UC [19]. Genes in the innate immune response (NOD2), autophagy (ATG6L1), and regulation of the IL-23 pathway (IL-23R) affect the disease susceptibility [21]. However, the definite mechanism remains unclear yet [19]. A recent study suggests that IL-23R and IL-17 gene polymorphisms affect IL-17A gene expression and are associated with etiology of IBD [22]. The common presentations include peripheral arthritis (7–16%), isolated sacroiliitis, spondylitis (1–10%), enthesitis (5–10%) predominantly in CD [23], dactylitis (2–4%), and arthralgias (8–16%). IBD is bimodal in distribution [24] with the second peak at 60–70 years of age in 10–15% of the population [25]. Overlapping rheumatic inflammatory diseases with IBD,

psoriatic, anterior uveitis, reactive, idiopathic, and undifferentiated arthritis have been reported [19]. Joint hypermobility is more common in CD than UC [26].

Pathogenesis

Histological evidence of ileocolitis without GI symptoms was found in particularly HLA B27 positive unidentified inflammatory arthritis [14]. Sixty to seventy percent of spondyloarthritis (SpA) patients have long-term gut inflammation by ileocolonoscopy wherein IBD manifests in about 7% [19]. In one study, Bactericidal Permeability Increasing Protein (BPI) was identified as a major target antigen of antineutrophil cytoplasmic antibody (ANCA) in IBD and Primary Sclerosing Cholangitis (PSC) [27].

The two major types of arthropathies seen in IBD include peripheral arthropathy and axial arthropathy with similar prevalence in ulcerative colitis (UC) and Crohn's disease (CD) [28, 29]. Ultrasound entheseal abnormalities are present in IBD patients without symptoms of arthropathy and are independent of activity, duration, and type of gut disease [30]. A mild polyarticular arthralgia similar to IBD arthropathy has been observed following restorative proctocolectomy [31] and cases of arthritis following diverticulitis have been reported [32, 33]. Peripheral and axial arthropathy are present in 20–30% of patients with IBD [17, 19] (Table 69.3).

Among patients with Crohn's disease, those with colitis have a greater chance of developing synovitis than small bowel disease. The clinical course of extraintestinal manifestations (EIM) such as axial arthritis and primary sclerosing cholangitis is independent of IBD activity. One Swiss study showed the prevalence of EIM to be: arthritis (CD 33%, UC 21%), aphthous stomatitis (CD 10%, UC 4%), uveitis (CD 6%, UC 4%), erythema nodosum (CD 6%, UC 3%), ankylosing spondylitis (CD 6%, UC 2%), psoriasis (CD 2%, UC 1%), pyoderma gangrenosum (CD and UC each 2%), and PSC (CD 1%, UC 4%) [34] (Fig. 69.1). About 36% of IBD patients have at least one EIM; anti-TNF therapy especially in CD with articular involvement has improved the symptoms [35] and in cases of severe spondylosis and enteropathy, considered first line [36]. Since TNF-alpha blockers are common drugs for joint, gut, eye, and skin disease, TNF-alpha is proposed to be a common mediator [17]. Promising strategies including the use of pamindronate and thalidomide have been proposed [37–39].

Other Associations with IBD

Low bone mineral density was found in 31–59% of patients in cross-sectional studies in IBD. A study confirmed low bone mineral density in femur and spine in early spondyloarthropathies, specifically with male gender and decreased functional capacity [40]. Low osteocalcin levels, and cumulative corticosteroid doses were identified as risk factors for osteoporosis [41]. Cases of aseptic osteitis of the clavicle [42] and spontaneous osteonecrosis unrelated to steroid therapy in CD have been reported [43].

Liver Disease and Arthropathy

There are varieties of liver disorders that present with extrahepatic manifestations (EHM). There is an increase in liver-related morbidity and mortality especially in persons 60 years and older. Hence it is imperative to recognize and treat liver disorders with EIMs [44]. Table 69.4 discusses nonviral liver disorders and arthropathy.

Table 69.3 Peripheral and axial arthropathy in colitis

Peripheral arthritis	Axial arthropathy
More common in CD (10–20%) than UC (5–14%) [19] and in women [15]	Sacroiliitis and ankylosing spondylitis (AS)
Episodic, migratory, asymmetric, and usually nonerosive arthritis; commonly involving large joints; may precede (in Crohn's) [23], or follow development of intestinal symptoms	90% of patients with AS have HLA B27 positivity—helpful in early diagnosis [19]
Type I-large joint pauciarticular (acute, self-limiting and parallels IBD); type II-polyarticular (persistent and independent of IBD) [35]	IBD-associated antibody can occur in 55% of AS patients without clinical IBD. ASCA (IgA and/or IgG), pANCA and OmpC antibodies occur in 21%, 30%, and 19% of the AS patients, respectively [89]
Runs parallel to underlying gut disease	Sacroiliitis and AS do not depend on the duration, extent, or severity of bowel involvement [80] and remain progressive irrespective of gut disease
NSAIDs can cause exacerbations in IBD [90]; however COX-2 inhibitors may be safe [19] Responds when underlying IBD improves. Sulfasalazine and infliximab have been used [19] Colectomy appears protective [15]	Treatment involves NSAIDs/COX-2 inhibitors, infliximab and adalimumab. Methotrexate and sulfasalazine not proven useful. Etanercept is useful in AS, but contraindicated in CD [19]

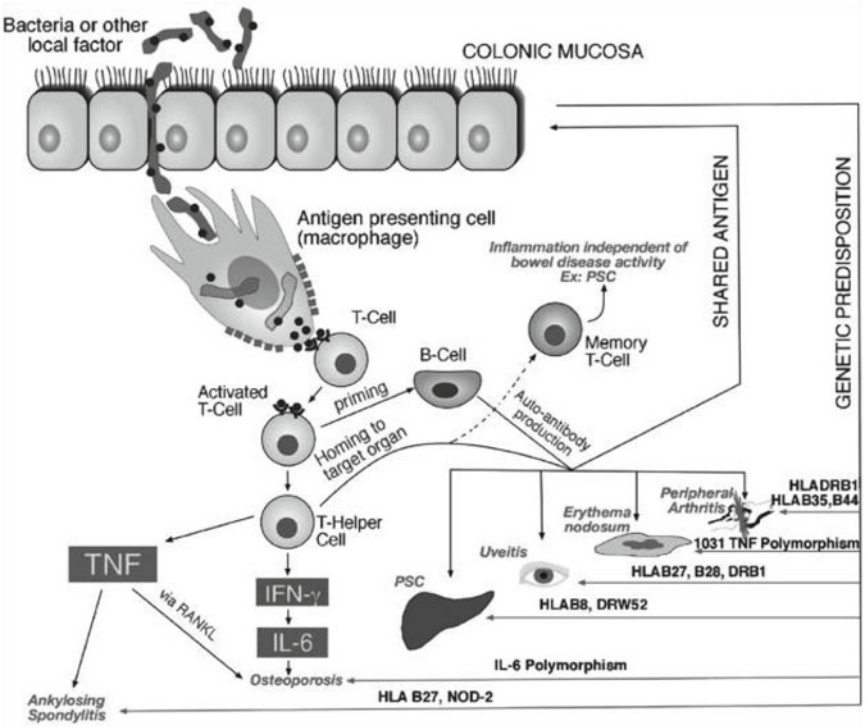

Fig. 69.1 Pathogenesis of extraintestinal manifestations of inflammatory bowel disease. Reprinted with permission from Lippincott Williams and Wilkins Inc. [103]

Hepatitis B

The prevalence of EHM in Hepatitis B is up to 20% and includes myalgia, arthralgias (3%), Sjogren's (3%), Raynaud's (2%), cryoglobulinemia (2%), and polyarteritis nodosa (PAN) [45, 46]. A causal relationship has been established between HBV and PAN with HBV as the inciting agent [47]. The pathophysiology involves intrasynovial immune complexes comprised of HBsAg and antibodies affecting complementary cascade [48]. Polyarthritis during the initial phase with spontaneous remission [49], affecting finger joints similar to RA but nonerosive, associated occasionally with rheumatoid factor positivity is seen [47, 48]. Post-HBV vaccination PAN has been cited [50].

Hepatitis C

Arthralgias and arthritis are the most common EHM of HCV and do not correlate with liver disease severity [44]. Two subtypes are rheumatoid-like symmetrical, polyarticular, nonerosive involving small joints and cryoglobulin-related (older patients with longer HCV infection) mono- or oligoarticular [51]. Testing for anti-cyclic citrullinated peptide helps distinguish HCV arthropathy from rheumatoid arthritis (RA) [44]. Pathogenesis includes synovial damage by viral invasion, cryglobulin-induced immune complexes in synovial fluid [44], increased CD15 expression, and increased angiogenesis; the lesions are characterized by mild synovial lining hyperplasia [52]. Treatment of arthropathy is by NSAIDs, low-dose short-term prednisone, DMARDs (if concomitant RA), antiviral agents, and immune suppressants (for cyroglobulinemia-related arthropathy) [44]. Essential Mixed Cryoglobulinemia (Raynaud's phenomenon, arthralgias, peripheral neuropathy, vasculitis, diffuse glomerulonephritis, and hepatosplenomegaly) with emphasis on lymphoproliferation [53] and rheumatoid factor positivity [54] is noted; the risk factors include increased age, female gender, and longer duration of disease [41].

Polymyositis [55], RA, and systemic lupus erythematosus (SLE) [56] are associations with Sicca syndrome [57]. Pegylated interferon alpha treatment in HCV inducing RA is also reported [58]. Since HCV infection causes a variety of rheumatological symptoms, it is prudent to check for HCV in a patient with undefined rheumatological symptoms [59] as it helps avoid the use of hepatotoxic drugs in those identified with HCV arthropathy. There is a reported association between antineuronal antibodies and mixed cryoglobulinemia [60].

Table 69.4 Nonviral liver disorders and arthropathy

Liver disorder	Related arthropathy
Primary biliary cirrhosis (PBC)	50% in the over 65 years age group [91] Osteoporosis [92], rheumatoid arthritis, scleroderma, CREST syndrome, polymyositis, sarcoidosis, hypertrophic osteoarthropathy [14], Sjogren's syndrome [93] RA and PBC are associated with *CTLA4/ICOS* risk alleles and haplotypes [94]
Autoimmune hepatitis (AIH)	Rheumatoid arthritis, vasculitis, and temporal arteritis common in the over 65-year age group [91] Autoimmune hepatitis-type I in young females—antinuclear antibody positive; type II strongly associated with hepatitis C—anti-LKM1 positive; type III females—antisoluble liver antigen, antinuclear and antismooth muscle positive [14]
Liver cirrhosis	Hypertrophic osteoarthropathy which involves periosteal reactions along shafts of long bones [14] Osteoporosis (risk factors include female sex, cholestasis, and low height and weight) [95] Sterno-clavicular septic arthritis [96]
Hereditary hemochromatosis (HH)	Premature osteoarthritis of wrists, metacarpophalangeal joints (commonly index and middle finger) with limited flexion—iron fist sign [97], knees, and spine with subchondral cysts, joint space narrowing, and osteophyte formation seen in radiography [43] Prevalence of arthropathy is 24–81% in hereditary hemochromatosis; deposition of iron over synovial lining cells differentiates HH from secondary hemochromatosis [97] Ferritin is a proinflammatory cytokine and could be detrimental to joint [97, 98]; damage is irreversible even with regular venesection [97] Iron overload is a major determinant of arthropathy more so than occupational factors [99]. Chondrocalcinosis predicts more severe or extensive disease [97]; female gender predicts more deterioration [100] Osteomalacia, osteoporosis, and renal rickets Present in the elderly and males who are homozygous for the C282Y gene and survive into old age without clinical or biochemical abnormalities [91] Treatment includes NSAIDs, analgesics, and joint arthroplasty [97]
Post liver transplant	Inpatients: osteoarthritis, peripheral neuropathy, and myalgia Outpatients: infection and crystal arthritis secondary to tacrolimus [101]
Malignancy	Hypertrophic osteoarthropathy, polyarthritis and vasculitis [102]

Pancreatic Disorders

Medullary fat necrosis (lytic lesions of bone) may occur in acute pancreatitis. Ductal pancreatic adenocarcinomas are typically a disorder seen in the old [61]. Carcinoma of pancreas may be associated with polyarthritis, usually symmetric involvement of small joints of wrists, hands, and feet and sometimes large joints. Panniculitis, referring to inflammation of subcutaneous fat with necrosis forming multiple subcutaneous nodules resembling erythema nodosum, is seen in carcinoma of pancreas [14], pancreatitis, pancreatic pseudocysts, pancreatic duct stenosis, and vascular pancreatic fistulas [62]. It is associated with arthritis (54–88% involving usually ankles but also hands and feet) [62] and eosinophilia and can precede diagnosis of pancreatic disease by years [41]. Circulating lipase is the inciting agent which apparently causes fat hydrolysis and subsequent inflammation. Arthritis involves multiple osteolytic lesions, loss of joint space, and sometimes periostitis, osteonecrosis, osteosclerosis, and fractures and is independent of the pancreatic process. MRI has the best sensitivity for detection of fatty bone marrow involvement [63]. Early recognition is important to avoid inappropriate treatment to improve joint symptoms [64]. Panniculitis, polyarthritis, and pancreatitis syndrome have been reported in 0.3–3% of pancreatic diseases and are associated with increased mortality [65]. There has been a report of polyarthritis and panniculitis in a patient with pancreatic pseudocyst where the polyarthritis resolved after EUS-guided cyst-gastrostomy [66].

Celiac Disease

Up to 34% of patients with newly diagnosed celiac disease are 60 years and older [61, 67]. It occurs in patients with HLA DQ2 or DQ8 triggered by gluten ingestion causing diarrhea, malabsorption, and malnutrition. The common serologic tests include antitissue transglutaminase IgA and antiendomysial IgA antibodies. Articular involvement is seen in celiac patients and usually presents as acute nonerosive arthritis, involving axial or peripheral joints [68]. A recent study reported sacroiliitis in 70% of celiac patients showing accumulation of synovial fluid, synovitis, erosion with concomitant sclerosis, with the majority clinically asymptomatic while on a gluten-free diet, though subclinically, the joint pathology was progressive [69]. Joint pain may precede the diagnosis by years in advance and respond to a gluten-free diet [70]. Other features include osteomalacia and osteoporosis [63].

Whipple's Disease

Whipple's disease, caused by a bacterium *Tropheryma whipplei*, is a malabsorption syndrome involving the small intestine, also affecting the joints, CNS, and cardiovascular system. Rheumatological manifestations include nondeforming, migratory, symmetrical polyarthritis involving knees, ankles, and wrists. Sacroiliitis can also occur [49]. It has also been reported in the elderly [71]. Arthralgia can precede intestinal and neurological manifestations [72]. A sensitive PCR assay may detect *T. whipplei* DNA in patients with classic symptoms but negative PAS staining on duodenal biopsies [73]. Patients with joint disease must be screened for Whipple's, as it is a fatal condition and the patient should not receive immunosuppressive agents [74]. The efficacy of antibiotics in polyarthritis could be a clue suggesting Whipple's disease [75].

Postsurgical Arthritis

Postbypass articular symptoms begin usually within 3 years of surgery and involve multiple joints, lasting days to weeks, and usually resolve with reanastomosis of the bypassed bowel [49]. Polyarthritis and arthralgias have been reported years after surgery in 8–36% of patients. Female gender and jejunocolic rather than jejunoileal bypass surgery are risk factors for arthropathy. Case report of bowel associated arthritis-dermatitis syndrome (BADAS) has been reported postlaparoscopic gastric bypass (bariatric) surgery [76] and postjejunoileal bypass surgery [77]. Raynaud's phenomenon is noted in a third of patients. Subjective joint pain and tenderness are severe but abrupt episodes of inflammation may also develop. Tenosynovitis of the knee, wrist, ankle, shoulder, and finger joints are common. Marginal erosions may be seen in X-rays with predominance of polymorphs in synovial fluid. HLA B27, antinuclear antibodies are usually negative with positive immune complexes. Treatment involves the use of NSAIDs, glucocorticoids, and tetracycline; the last drug decreases bacterial overgrowth in the gut and can provide prolonged relief. Severe cases require reanastomosis. Spondyloarthropathy has been reported post-Whipple procedure for a biliary tract carcinoma; it also represents a rheumatic syndrome developing from GI disruption [78].

Other Disorders

Wilson's disease is associated with osteomalacia, rickets, chondrocalcinosis, periarticular calcification, and premature osteoarthritis. In one instance, reversal of arthropathy was reported following liver transplantation [79]. Familial Mediterranean fever involves abdominal pain, serosal inflammation, asymmetric nondestructive mono- or oligoarticular disease at times with chronic destruction. Behcet's disease is a triad with oral and genital ulceration, with inflammatory eye disease and presents with self-limiting mono- or oligoarticular disease [80]. Atypical rheumatic manifestations may depict underlying occult neoplasm [81].

Key Points

- A major association between reactive joint pain and HLA-B27 has been found for *Salmonella*, *Shigella*, and *Yersinia* but not for *Campylobacter* and *Escherichia coli*.
- The common presentations in inflammatory bowel disease (IBD) include peripheral arthritis, isolated sacroiliitis, spondylitis, enthesitis, dactylitis, and arthralgias.
- About 36% of IBD patients have at least one extraintestinal manifestation (EIM). Peripheral arthritis in IBD responds when underlying IBD improves while axial arthropathy is progressive irrespective of IBD activity.
- Osteoporosis, rheumatoid arthritis, scleroderma, CREST syndrome, polymyositis, sarcoidosis, hypertrophic osteoarthropathy, Sjogren's syndrome are common manifestations of primary biliary cirrhosis.
- Premature osteoarthritis of wrists, metacarpophalangeal joints (commonly index and middle finger) with limited flexion—iron fist sign, knees and spine with subchondral cysts, joint space narrowing, and osteophyte formation are seen in hereditary hemochromatosis.
- EHM of hepatitis B include myalgia, arthralgias, Sjogren's, Raynaud's, cryoglobulinemia, polyarteritis nodosa (PAN).
- Two subtypes of arthritis in hepatitis C include rheumatoid-like symmetrical, polyarticular, nonerosive involving small joints and cryoglobulin-related (older patients with longer HCV infection) mono- or oligoarticular disease.
- Carcinoma of pancreas may be associated with polyarthritis, usually symmetric involvement of small joints of wrists, hands, and feet and sometimes large joints.
- Panniculitis resembling erythema nodosum is seen in carcinoma of pancreas and pancreatitis.
- Articular involvement in celiac patients usually presents as acute nonerosive arthritis, involving axial or peripheral joints and may precede the diagnosis of celiac disease by years.
- Rheumatological manifestations of Whipple's disease include nondeforming, migratory, symmetrical polyarthritis involving knees, ankles, and wrists and sacroiliitis.

References

1. Carter JD, Hudson AP. Reactive arthritis: clinical aspects and medical management. Rheum Dis Clin North Am. 2009;35(1):21–44.
2. Sieper J, Braun J. Treatment of reactive arthritis with antibiotics. Br J Rheumatol. 1998;37(7):717–20.

3. Inman RD. Arthritis and enteritis—an interface of protean manifestations. J Rheumatol. 1987;14(3):406–10.
4. Schiellerup P, Krogfelt KA, Locht H. A comparison of self-reported joint symptoms following infection with different enteric pathogens: effect of HLA-B27. J Rheumatol. 2008;35(3):480–7.
5. Renou F, Wartel G, Raffray L, et al. [Reactive arthritis due to *Escherichia coli* urinary tract infection]. Rev Med Interne. 2011;32(1):e4–5.
6. Kohannim O, Rubin Z, Taylor M. Saline breast implant fluid collection and reactive arthritis in a patient with streptococcal toxic shock syndrome. J Clin Rheumatol. 2011;17(2):89–91.
7. Ota H, Yamaguchi Y, Kojima T, et al. [An elderly case with group B streptococcal bacteremia, subcutaneous abscess and reactive polyarthritis]. Nihon Ronen Igakkai Zasshi. 2007;44(6):761–6.
8. Kotake S, Nanke Y. Chlamydia-associated arthritis and enteropathic arthritis-two important spondyloarthritides. Nihon Rinsho Meneki Gakkai Kaishi. 2011;34(3):121–30.
9. Jacques P, Elewaut D, Mielants H. Interactions between gut inflammation and arthritis/spondylitis. Curr Opin Rheumatol. 2010;22(4):368–74.
10. Braun J, Sieper J. Rheumatologic manifestations of gastrointestinal disorders. Curr Opin Rheumatol. 1999;11(1):68–74.
11. Sieper J, Braun J. Pathogenesis of spondylarthropathies. Persistent bacterial antigen, autoimmunity, or both? Arthritis Rheum. 1995;38(11):1547–54.
12. Inman RD. Antigens, the gastrointestinal tract, and arthritis. Rheum Dis Clin North Am. 1991;17(2):309–21.
13. Ugrinovic S, Mertz A, Wu P, et al. A single nonamer from the *Yersinia* 60-kDa heat shock protein is the target of HLA-B27-restricted CTL response in *Yersinia*-induced reactive arthritis. J Immunol. 1997;159(11):5715–23.
14. Fomberstein B, Yerra N, Pitchumoni CS. Rheumatological complications of GI disorders. Am J Gastroenterol. 1996;91(6):1090–103.
15. Yuksel I, Ataseven H, Basar O, et al. Peripheral arthritis in the course of inflammatory bowel diseases. Dig Dis Sci. 2011;56(1):183–7.
16. Mundwiler ML, Mei L, Landers CJ, Reveille JD, et al. Inflammatory bowel disease serologies in ankylosing spondylitis patients: a pilot study. Arthritis Res Ther. 2009;11(6):R177.
17. De Vos M, Hindryckx P, Laukens D. Novel development in extraintestinal manifestations and spondylarthropathy. Best Pract Res Clin Gastroenterol. 2011;25 Suppl 1:S19–26.
18. Vounotrypidis P, Kouklakis G. The "soft collagen" hypothesis in the pathogenesis of the inflammatory bowel disease and the seronegative spondylarthritides. Med Hypotheses. 2010;75(3):284–6.
19. Brakenhoff LK, van der Heijde DM, Hommes DW. IBD and arthropathies: a practical approach to its diagnosis and management. Gut. 2011;60(10):1426–35.
20. Danoy P, Pryce K, Hadler J, et al. Association of variants at 1q32 and STAT3 with ankylosing spondylitis suggests genetic overlap with Crohn's disease. PLoS Genet. 2010;6(12):e1001195.
21. Reveille JD. The genetic basis of spondyloarthritis. Ann Rheum Dis. 2011;70 Suppl 1:i44–50.
22. Kim SW, Kim ES, Moon CM, et al. Genetic polymorphisms of IL-23R and IL-17A and novel insights into their associations with inflammatory bowel disease. Gut. 2011;60(11):1527–36.
23. Mader R, Segol O, Adawi M, Trougoboff P, Nussinson E. Arthritis or vasculitis as presenting symptoms of Crohn's disease. Rheumatol Int. 2005;25(6):401–5.
24. Lindner AE. Inflammatory bowel disease in the elderly. Clin Geriatr Med. 1999;15(3):487–97.
25. Stallmach A, Hagel S, Gharbi A, et al. Medical and surgical therapy of inflammatory bowel disease in the elderly—prospects and complications. J Crohns Colitis. 2011;5(3):177–88.
26. Vounotrypidis P, Efremidou E, Zezos P, et al. Prevalence of joint hypermobility and patterns of articular manifestations in patients with inflammatory bowel disease. Gastroenterol Res Pract. 2009;2009:924138.
27. Stoffel MP, Csernok E, Herzberg C, et al. Anti-neutrophil cytoplasmic antibodies (ANCA) directed against bactericidal/permeability increasing protein (BPI): a new seromarker for inflammatory bowel disease and associated disorders. Clin Exp Immunol. 1996;104(1):54–9.
28. Fornaciari G, Salvarani C, Beltrami M, et al. Musculoskeletal manifestations in inflammatory bowel disease. Can J Gastroenterol. 2001;15(6):399–403.
29. Palm O, Moum B, Ongre A, Gran JT. Prevalence of ankylosing spondylitis and other spondyloarthropathies among patients with inflammatory bowel disease: a population study (the IBSEN study). J Rheumatol. 2002;29(3):511–5.
30. Bandinelli F, Milla M, Genise S, et al. Ultrasound discloses entheseal involvement in inactive and low active inflammatory bowel disease without clinical signs and symptoms of spondyloarthropathy. Rheumatology (Oxford). 2011;50(7):1275–9.
31. Thomas PD, Keat AC, Forbes A, et al. Extraintestinal manifestations of ulcerative colitis following restorative proctocolectomy. Eur J Gastroenterol Hepatol. 1999;11(9):1001–5.
32. Schapira D, Nachtigal A, Scharf Y. Arthritis as the presenting symptom of diverticulitis. Clin Rheumatol. 1997;16(3):310–3.
33. Alba S, Nascimbeni R, Di Betta E, et al. Arthritis as a rare extraintestinal manifestation of acute sigmoid diverticulitis. Dig Surg. 2001;18(3):233–4.
34. Vavricka SR, Brun L, Ballabeni P, et al. Frequency and risk factors for extraintestinal manifestations in the Swiss inflammatory bowel disease cohort. Am J Gastroenterol. 2011;106(1):110–9.
35. Atzeni F, Ardizzone S, Bertani L, et al. Combined therapeutic approach: inflammatory bowel diseases and peripheral or axial arthritis. World J Gastroenterol. 2009;15(20):2469–71.
36. Padovan M, Castellino G, Govoni M, Trotta F. The treatment of the rheumatological manifestations of the inflammatory bowel diseases. Rheumatol Int. 2006;26(11):953–8.
37. De Keyser F, Van Damme N, De Vos M, et al. Opportunities for immune modulation in the spondyloarthropathies with special reference to gut inflammation. Inflamm Res. 2000;49(2):47–54.
38. Maksymowych WP, Jhangri GS, Fitzgerald AA, et al. A six-month randomized, controlled, double-blind, dose–response comparison of intravenous pamidronate (60 mg versus 10 mg) in the treatment of nonsteroidal antiinflammatory drug-refractory ankylosing spondylitis. Arthritis Rheum. 2002;46(3):766–73.
39. Huang F, Gu J, Zhao W, Zhu J, et al. One-year open-label trial of thalidomide in ankylosing spondylitis. Arthritis Rheum. 2002;47(3):249–54.
40. van der Weijden MA, van Denderen JC, Lems WF, et al. Low bone mineral density is related to male gender and decreased functional capacity in early spondylarthropathies. Clin Rheumatol. 2011;30(4):497–503.
41. Ramos-Remus C, Bahlas S, Vaca-Morales O. Rheumatic features of gastrointestinal tract, hepatic, and pancreatic diseases. Curr Opin Rheumatol. 1997;9(1):56–61.
42. Kotilainen PM, Laxen FO, Manner IK, et al. An aseptic inflammation of the clavicle in a patient with Crohn's disease. A potential manifestation of the SAPHO syndrome. Scand J Rheumatol. 1996;25(2):112–4.
43. Monkemuller KE, Martin R. Other rheumatological complications of GI disorders. Am J Gastroenterol. 1996;91(12):2652.
44. Kemmer NM, Sherman KE. Hepatitis C-related arthropathy: diagnostic and treatment considerations. J Musculoskelet Med. 2010;27(9):351–4.
45. Terrier B, Cacoub P. [Hepatitis B virus, extrahepatic immunologic manifestations and risk of viral reactivation]. Rev Med Interne. 2010;32(10):622–7.

46. Baig S, Alamgir M. The extrahepatic manifestations of hepatitis B virus. J Coll Physicians Surg Pak. 2008;18(7):451–7.
47. Maya R, Gershwin ME, Shoenfeld Y. Hepatitis B virus (HBV) and autoimmune disease. Clin Rev Allergy Immunol. 2008;34(1):85–102.
48. Cacoub P, Terrier B. Hepatitis B-related autoimmune manifestations. Rheum Dis Clin North Am. 2009;35(1):125–37.
49. Mody GM, Cassim B. Rheumatologic manifestations of gastrointestinal disorders. Curr Opin Rheumatol. 1998;10(1):67–72.
50. de Carvalho JF, Pereira RM, Shoenfeld Y. Systemic polyarteritis nodosa following hepatitis B vaccination. Eur J Intern Med. 2008;19(8):575–8.
51. Reimold A. Viruses and arthritis: new challenges in diagnosis, therapy, and immunization. Am J Med Sci. 2010;339(6): 549–56.
52. Ogdie A, Schumacher Jr HR, Dai L, et al. Synovial biopsy findings in arthritis associated with hepatitis C virus infection. J Rheumatol. 2010;37(6):1361–3.
53. Ferri C, La Civita L, Zignego AL. Extrahepatic manifestations of hepatitis C virus infection. Ann Intern Med. 1996;125(4):344; author reply 346.
54. Cosserat J, Cacoub P, Bletry O. Immunological disorders in C virus chronic hepatitis. Nephrol Dial Transplant. 1996;11 Suppl 4:31–5.
55. Ferri C, La Civita L, Fazzi P, et al. Polymyositis, lung fibrosis, and cranial neuropathy in a patient with hepatitis C virus infection. Arthritis Rheum. 1996;39(6):1074–5.
56. Okanoue T, Sakamoto S, Itoh Y, et al. Side effects of high-dose interferon therapy for chronic hepatitis C. J Hepatol. 1996;25(3):283–91.
57. Jorgensen C, Legouffe MC, Perney P, et al. Sicca syndrome associated with hepatitis C virus infection. Arthritis Rheum. 1996;39(7): 1166–71.
58. Yang D, Arkfeld D, Fong TL. Development of anti-CCP-positive rheumatoid arthritis following pegylated interferon-alpha2a treatment for chronic hepatitis C infection. J Rheumatol. 2010;37(8):1777.
59. Lee YH, Ji JD, Yeon JE, et al. Cryoglobulinaemia and rheumatic manifestations in patients with hepatitis C virus infection. Ann Rheum Dis. 1998;57(12):728–31.
60. Alpa M, Ferrero B, Cavallo R, et al. Anti-neuronal antibodies in patients with HCV-related mixed cryoglobulinemia. Autoimmun Rev. 2008;8(1):56–8.
61. Johnson MW, Ellis HJ, Asante MA, Ciclitira PJ. Celiac disease in the elderly. Nat Clin Pract Gastroenterol Hepatol. 2008;5(12):697–706.
62. Borowicz J, Morrison M, Hogan D, Miller R. Subcutaneous fat necrosis/panniculitis and polyarthritis associated with acinar cell carcinoma of the pancreas: a rare presentation of pancreatitis, panniculitis and polyarthritis syndrome. J Drugs Dermatol. 2010;9(9):1145–50.
63. Fraisse T, Boutet O, Tron AM, Prieur E. Pancreatitis, panniculitis, polyarthritis syndrome: an unusual cause of destructive polyarthritis. Joint Bone Spine. 2010;77(6):617–8.
64. Narvaez J, Bianchi MM, Santo P, et al. Pancreatitis, panniculitis, and polyarthritis. Semin Arthritis Rheum. 2010;39(5):417–23.
65. Vasdev V, Bhakuni D, Narayanan K, Jain R. Intramedullary fat necrosis, polyarthritis and panniculitis with pancreatic tumor: a case report. Int J Rheum Dis. 2010;13(4):e74–8.
66. Harris MD, Bucobo JC, Buscaglia JM. Pancreatitis, panniculitis, polyarthritis syndrome successfully treated with EUS-guided cyst-gastrostomy. Gastrointest Endosc. 2010;72(2):456–8.
67. Ruuskanen A, Kaukinen K, Collin P, et al. Positive serum antigliadin antibodies without celiac disease in the elderly population: does it matter? Scand J Gastroenterol. 2010;45(10):1197–202.
68. Efe C, Urun Y, Purnak T, et al. Silent celiac disease presenting with polyarthritis. J Clin Rheumatol. 2010;16(4):195–6.
69. Vereckei E, Mester A, Hodinka L, Poor G. Back pain and sacroiliitis in long-standing adult celiac disease: a cross-sectional and follow-up study. Rheumatol Int. 2010;30(4):455–60.
70. Bourne JT, Kumar P, Huskisson EC, et al. Arthritis and coeliac disease. Ann Rheum Dis. 1985;44(9):592–8.
71. Hehemann K, Heising A. [Whipple's disease in an elderly person (author's transl)]. Leber Magen Darm. 1979;9(6):324–9.
72. Thaler S, Grisanti S, Klingel K, et al. Intermediate uveitis and arthralgia as early symptoms in Whipple's disease. Int J Infect Dis. 2010;14 Suppl 3:e388–9.
73. Ahmadi-Simab K, Schnitzler P. [Whipple's disease with normal duodenal histology and ankylosing spondylitis]. Dtsch Med Wochenschr. 2009;134(4):127–30.
74. Hoppe E, Masson C, Audran M, et al. Whipple's disease diagnosed during biological treatment for joint disease. Joint Bone Spine. 2010;77(4):335–9.
75. Lagier JC, Fenollar F, Halle O, et al. Efficacy of antibiotic therapy in polyarthritis: a clue suggesting Whipple's disease. Int J Antimicrob Agents. 2009;34(4):389–90.
76. Tu J, Chan JJ, Yu LL. Bowel bypass syndrome/bowel-associated dermatosis arthritis syndrome post laparoscopic gastric bypass surgery. Australas J Dermatol. 2011;52(1):e5–7.
77. Patton T, Jukic D, Juhas E. Atypical histopathology in bowel-associated dermatosis-arthritis syndrome: a case report. Dermatol Online J. 2009;15(3):3.
78. Bhangle SD, Kramer N, Rosenstein ED. Spondyloarthropathy after ampullary carcinoma resection: "post-Whipple" disease. J Clin Rheumatol. 2009;15(5):241–3.
79. Nagral A, Sathe K. Reversal of severe Wilson arthropathy by liver transplantation. Indian Pediatr. 2011;48(5):406–7.
80. Ballinger A, Scott DL. Rheumatology and the gut. Br J Hosp Med. 1992;48(7):378–87.
81. Papagoras C, Kountouras J, Brilakis S, et al. Rheumatic-like syndrome as a symptom of underlying gastric cancer. Clin Rheumatol. 2007;26(6):1029–31.
82. Naimushin A, Eliasaf S, Livneh A. [*Clostridium difficile*-associated diarrhea: causes and relationship to reactive arthritis]. Harefuah. 2011;150(1):64–6.
83. Richter J, Muller-Stover I, Strothmeyer H, et al. Arthritis associated with *Strongyloides stercoralis* infection in HLA B-27-positive African. Parasitol Res. 2006;99(6):706–7.
84. Ghotekar LH, Jayanthi S, Mutha SM, et al. Reactive arthritis, psoriasiform lesions and protein loosing enteropathy secondary to strongyloidiasis. J Assoc Physicians India. 2003;51:395–6.
85. Malvy D, Ezzedine KH, Receveur MC, et al. Extra-pulmonary paragonimiasis with unusual arthritis and cutaneous features among a tourist returning from Gabon. Travel Med Infect Dis. 2006;4(6):340–2.
86. Gonzalez-Dominguez J, Roldan R, Villanueva JL, et al. *Isospora belli* reactive arthritis in a patient with AIDS. Ann Rheum Dis. 1994;53(9):618–9.
87. Sing A, Bechtold S, Heesemann J, et al. Reactive arthritis associated with prolonged cryptosporidial infection. J Infect. 2003;47(2): 181–4.
88. Tupchong M, Simor A, Dewar C. Beaver fever—a rare cause of reactive arthritis. J Rheumatol. 1999;26(12):2701–2.
89. de Vries M, van der Horst-Bruinsma I, van Hoogstraten I, et al. pANCA, ASCA, and OmpC antibodies in patients with ankylosing spondylitis without inflammatory bowel disease. J Rheumatol. 2010;37(11):2340–4.
90. Rimbas M, Marinescu M, Voiosu MR, et al. NSAID-induced deleterious effects on the proximal and mid small bowel in seronegative spondyloarthropathy patients. World J Gastroenterol. 2011; 17(8):1030–5.
91. Frith J, Jones D, Newton JL. Chronic liver disease in an ageing population. Age Ageing. 2009;38(1):11–8.

92. Guanabens N, Cerda D, Monegal A, et al. Low bone mass and severity of cholestasis affect fracture risk in patients with primary biliary cirrhosis. Gastroenterology. 2010;138(7):2348–56.
93. Akashi Y, Yoshizawa N, Kubota T, et al. Primary biliary cirrhosis complicated with Sjogren syndrome and multiple myeloma. A case report. Nephron. 1996;73(4):730–2.
94. Walker EJ, Hirschfield GM, Xu C, et al. CTLA4/ICOS gene variants and haplotypes are associated with rheumatoid arthritis and primary biliary cirrhosis in the Canadian population. Arthritis Rheum. 2009;60(4):931–7.
95. Wariaghli G, Mounach A, Achemlal L, et al. Osteoporosis in chronic liver disease: a case-control study. Rheumatol Int. 2010;30(7):893–9.
96. Guerra C, Spillane LL. Sternoclavicular septic arthritis in a patient with end-stage liver disease. Ann Emerg Med. 1996;27(2):264–6.
97. Carroll GJ, Breidahl WH, Olynyk JK. Characteristics of the arthropathy described in hereditary haemochromatosis. Arthritis Care Res (Hoboken). 2011;64(1):9–14.
98. Richette P, Ottaviani S, Vicaut E, Bardin T. Musculoskeletal complications of hereditary hemochromatosis: a case-control study. J Rheumatol. 2010;37(10):2145–50.
99. Carroll GJ, Breidahl WH, Bulsara MK, Olynyk JK. Hereditary hemochromatosis is characterized by a clinically definable arthropathy that correlates with iron load. Arthritis Rheum. 2011;63(1):286–94.
100. Sahinbegovic E, Dallos T, Aigner E, et al. Musculoskeletal disease burden of hereditary hemochromatosis. Arthritis Rheum. 2010;62(12):3792–8.
101. Diep JT, Kerr LD, Barton C, Emre S. Musculoskeletal manifestations in liver transplantation recipients. J Clin Rheumatol. 2008;14(5):257–60.
102. Gheita TA, Ezzat Y, Sayed S, et al. Musculoskeletal manifestations in patients with malignant disease. Clin Rheumatol. 2010;29(2):181–8.
103. Kethu SR. Extraintestinal manifestations of inflammatory bowel diseases. J Clin Gastroenterol. 2006;40(6):468.

Mucocutaneous Manifestations with Gastrointestinal Disease

70

Robert A. Norman and Trupal Patel

Introduction

As the human body ages, changes in metabolism and lifestyle occur, resulting in comorbidty, variably affecting the gastroenterological tract. Aging is associated with gastrointestinal physiological and pathological manifestations [1]. Several gastrointestinal (GI) diseases increase the risk specifically for associated skin disorders. Dermatological manifestations may be coincidental clinical associations, complications of GI illness, or secondary to therapy administered for the GI disorder. Cutaneous manifestations of GI disease in the elderly will be reviewed for various sections of the GI system.

Oral Cavity

Manifestations in the older adult's pharynx and oral cavities include Kaposi's sarcoma and *Candida*. In 1872, Kaposi first described *idiopathisches multiples Pigmentsarkom der Haut*, which has become known as Kaposi sarcoma (KS) [2]. Kaposi's sarcoma presents itself as blue, red, or purple-brown patches, papules, plaques, or cutaneous nodules of the mucosa, larynx, trachea, stomach, liver, and colon; it is prevalent in elderly men of Mediterranean origin [3]. It is a multifocal, vascular, endothelial tumor caused by immunosuppression. Oral lesions are more common in those with AIDS acquired through blood transfusion, sexual transmission, or IV drug use, compared to those with traditional KS (Fig. 70.1).

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Recently, HHV-8 KS associated herpes virus was identified and linked closely with all four types of Kaposi sarcoma, i.e., classic (traditional), endemic (African), epidemic (AIDS related), and iatrogenic (related to immunosuppression) [3, 4]. Nearly all of those with oral lesions manifest the disease in the GI tract. The histopathology in the early stage lesions show irregularly dilated, jagged, anastomising, thin-walled vascular slits containing erythrocytes [5]. Vascular proliferations surrounded by spindle cells that spread are seen in later plaque and nodular stage lesions. Treatment is based on the extent of the disease and patient's immune status. The Klein regimen, using vinblastine, has been shown to effectively treat KS without compromising the immune system [6]. Other treatments include nonintervention, surgical removal of severely affected areas, radiotherapy, chemotherapeutic agents, nonspecific immunotherapy, and cessation of immunosuppressive therapy in iatrogenically immunosuppressed patients.

Humans carry yeast fungi, including various *Candida* species, throughout the gastrointestinal tract as part of the normal commensal flora. *Candida albicans* is the causative species that invades keratinized and nonkeratinized surfaces [7]. Candidiasis presents as beefy, red, moist patches and plaques on skin, nails, and mucous membranes, especially on the tongue (Fig. 70.2). Thrush refers to the white cottage-cheese-like coating of *Candida* that can be scraped off the tongue (Fig. 70.3). *Candida* species are a common cause of intertrigo and fungal infection in elderly, diabetic, and immunocompromised patients.

Gastrointestinal tract candidiasis may be oropharyngeal, esophageal, and nonesophageal. *Candida* species currently are the fourth leading cause of bloodstream infections in the United States, with occurrence at a disproportionately high rate in persons aged 65 years and older [8]. Patients with oropharyngeal candidiasis usually have symptoms of soreness in the oral cavity, burning mouth or tongue, dysphagia, or thrush. Angular chelitis, an inflammatory reaction of candidiasis, causes soreness, erythema, and fissuring in the perioral areas. Esophageal candidiasis presents as dysphagia and odynophagia.

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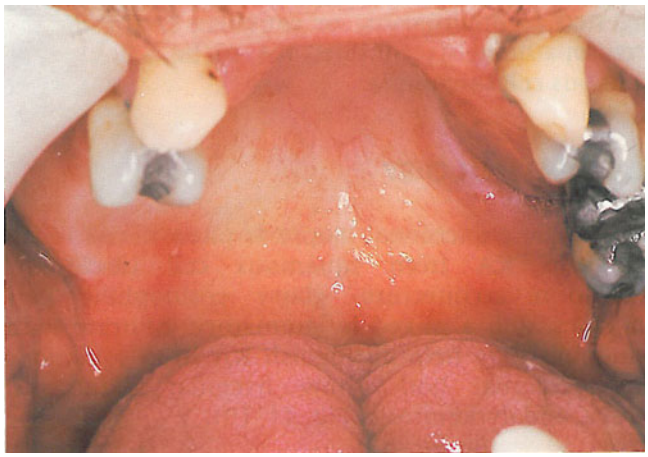

Fig. 70.1 Kaposi's sarcoma of palate in HIV patient

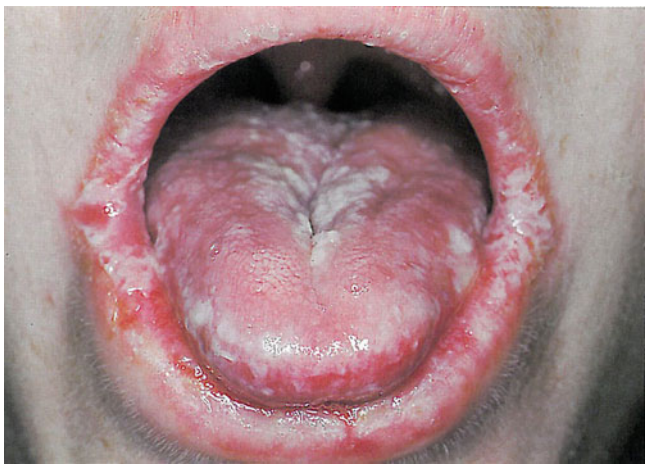

Fig. 70.2 Candiasis of the mouth

Oral candidiasis in adults can be treated with a topical (nyastatin) or oral antifungals (fluconazole) daily depending on the severity of the disease. Treatment of intertrigo associated with candidiasis combines protective agents, antimicrobials, and topical steroids. Petrolatum-based barrier products such as zinc oxide ointment should be applied. A nongreasy alternative is Tetrix, a prescription dimethicone barrier cream. Candidal intertrigo can also be treated with filter paper soaked in Castellani paint [9]. Benzoyl peroxide wash may also be used to cleanse subacute intertrigo. Candidiasis, if not treated, may progress to sepsis, often a fatal complication.

Esophagus and Stomach

Esophageal disease with cutaneous manifestations includes Plummer–Vinson syndrome (PVS), epidermolysis bullosa (EB), scleroderma, and pemphigus vulgaris. PVS, also known as Paterson–Brown Kelly syndrome, denotes the collection of postcricoid dysphagia, upper esophageal webs, and iron deficiency anemia [10]. Signs of PVS include the mucocutaneous findings of brittle, spoon-shaped nails, early loss of teeth, cheilosis, tongue atrophy, and angular stomatitis, along with iron deficiency anemia and the clinical complaint of dysphagia [11]. Diagnosis involves laboratory evaluation to confirm the presence of iron deficiency anemia.

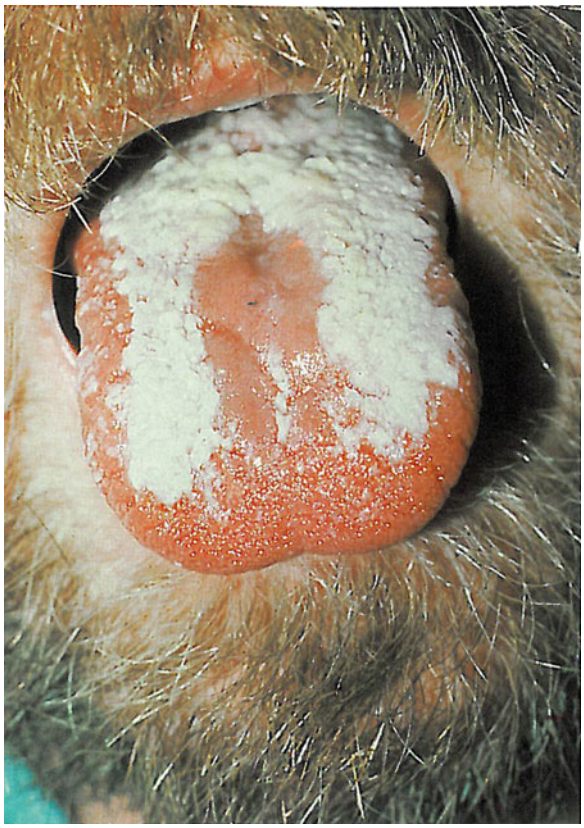

Fig. 70.3 Candiasis showing white exudates

Tylosis describes a group of inherited disorders of keratinization characterized by hyperkeratosis of the palms and soles. Hyperkeratosis of the soles suggests tylosis and calls for evaluation for gastrointestinal malignancy, psoriasis, or eczema. There are several types of inheritance. One rare form is inherited in a dominant fashion. Clinical signs are diffuse hyperkeratosis of the palms and soles and can lead to the development of esophageal cancer [12]. Management of esophageal carcinoma is based on tumor extent. Surgery is the standard treatment option for early stages, but for cancer that is confined to the mucosa, mucosal resection is an alternative [13].

Epidermolysis bullosa describes a rare group of inherited diseases that cause fragile skin [14]. It is characterized by subepidermal blistering of the skin and mucous membranes. Immunologically, EB is characterized by the presence of immunoglobulin G (IgG) autoantibodies (in most patients)

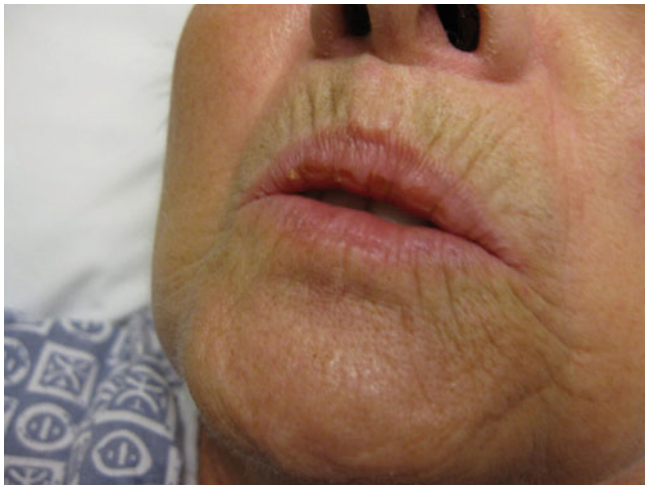

Fig. 70.4 Scleroderma of face

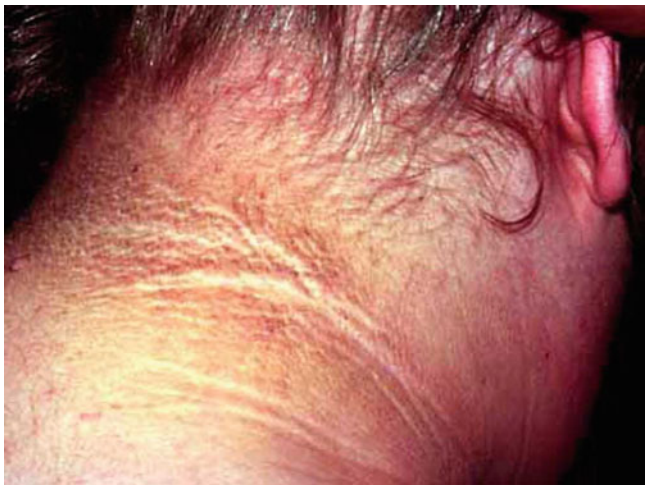

Fig. 70.5 Acanthosis nigricans on neck

targeting the noncollagenous (NC1) domain of type VII collagen. Clinically, there are three forms of EB depending on the layer of blister formation: dystrophic (beneath lamina densa), junctional (within the lamina lucida), and simplex (intraepidermal). They can be distinguished by electron microscopic localization of the basement membrane layer separation. Nutritional deficiency, anemia, and stunted growth may develop over time. Patients with junctional EB have many of the complications of dystrophic EB and may develop pyloric atresia [15]. Therapy includes change to a softer diet and surgical excision.

Scleroderma and systemic sclerosis denote a systematic disease of unknown etiology that causes fibrotic change in the skin, blood vessels, lungs, heart, kidneys, and GI tract [16]. Esophageal symptoms can include premature fullness, reflux esophagitis, dysphagia, and epigastric pain. As many as 90% of patients with scleroderma demonstrate GI manifestations [17]. Manifestations are a result of excess collagen production, enhanced immunologic activity, and improper cellular immunity response. Dermatological manifestations are progressive and begin with edema of face, hands, or feet (Fig. 70.4). The acronym "CREST" has been associated with scleroderma which stands for the symptoms of calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia. The abnormal build up of fibrous tissue in the skin can result in sclerodactyly. This skin tightening is so severe that the fingers curl and lose their mobility. Curved nails or periungual telangiectasia may be present. Telangiectasia was present in 56% of patients with systemic sclerosis in a study and associated with esophageal, heart, and lung disease, calcinosis and pitting scars; the study suggested that telangiectasia may be a marker of esophageal involvement [18]. Raynaud's phenomenon is a vasospastic disorder that causes discoloration of the fingers, toes, and other areas. It is caused by a decrease in blood supply to the various regions. Raynaud's phenomenon is the initial presentation for 70% of patients with scleroderma. Oral administration of ciprofloxacin for 6 months has been shown to reduce the severity of dermal symptoms, through antifibrotic action and without secondary effects [19].

Stevens–Johnson syndrome (SJS) is a mucocutaneous disorder, first described as a febrile erosive stomatitis, severe conjunctivitis, and disseminated cutaneous eruption [20]. Infection, vaccination, drugs, systemic diseases, physical agents, and food have been implicated as causes of SJS, however, drugs are most commonly blamed. Antibiotics are the most common cause of SJS. Other drugs that may cause the disease are analgesics, cough and cold medication, nonsteroidal anti-inflammatory drugs (NSAIDs), psychoepileptics, and antigout drugs. Most patients are treated symptomatically due to the systemic nature of the disease. Fluid management, nutrition, insulin therapy, blood and urine tests are control options. Silver sulfadiazine should be avoided and instead 0.5% silver nitrate or 0.05% chlorhexidine should be used to bathe affected areas. Skin allotransplantation reduces pain, minimizes fluid loss, improves heat control, and prevents bacterial infection. Hyperbaric oxygen can improve healing. Systemic corticosteroid treatment should be short-term, high-dose intravenous therapy. The effect of systemic steroids or IV immune globulin on either the development or the outcome of ocular manifestations in SJS and toxic epidermal necrolysis (TEN) remains understudied.

Acanthosis nigricans (AN) is a brown to black, ill defined, brown-to-black velvety hyperpigmentation of the skin, found in the posterior and lateral folds of the neck, the axilla, and groin (Fig. 70.5). It is associated with several endocrine disorders such as diabetes, hypo- and hyperthyroidism, Cushing's syndrome, and internal malignancy, typically an

adenocarcinoma in the GI tract. This relatively common skin disorder manifests hyperpigmented macules that can progress into palpable plaques. Patients usually present with a thickened, dark skin with pruritis. Skin markings on the palmar surface of the hands are seen, termed acanthosis palmaris. AN can be benign and malignant. Lesions of benign AN may occur at any age, including at birth, but more commonly in the adult population. Malignant acanthosis nigricans occurs more frequently in the elderly [21].

There are speculations as to the etiology of AN with a plethora of systemic diseases associated with AN. Tissue resistance to insulin and factors that stimulate epidermal keratinocyte and dermal fibroblast proliferation may play an important role in the pathogenesis of AN. The definitive cause for AN is not clear, with several possibilities researched. Tumors may activate insulin-like growth factors or their receptors in the epidermis. Many syndromes of AN have been identified sharing common features, including obesity, hyperinsulinemia, and craniosynostosis. These have been subdivided into insulin-resistance syndromes and fibroblast growth factor defects [21]. At low concentrations, insulin binds to insulin receptors; at high concentrations, it binds to insulin-like growth factor receptors on keratinocytes or fibroblasts [22]. Another possibility may be that lytic factors produced by cancer cells may weaken the extracellular matrix. The possibility of an intra-abdominal malignancy should always be considered, especially in the absence of an obvious predisposing condition [23]. There is no gender difference for AN [24]. The disorder is commonly associated with obesity.

The presence of tripe palms heralds an underlying cancer in most; tripe palms refer to the thick velvety palms with prominent dermatoglyphics. The malignancies associated with AN include adenocarcinoma (85% of cases), of which gastric carcinoma is present in 60%. Prognosis is very poor for these patients, with a 1-year mortality rate of greater than 50%. With successful tumor resection, the skin lesions often disappear spontaneously over time. No direct treatment for AN exists, however the underlying disease causing AN can be treated. Oral or topical retinoids have been used in treatment with varying success [25, 26]. Correction of hyperinsulinemia often reduces the burden of hyperkeratotic lesions. Weight reduction in obesity-associated acanthosis nigricans may result in resolution of the dermatosis. AN is treated with a systemic understanding using a variety of methods.

Liver and Pancreas

Hemochromatosis is a metabolic disorder of iron overload leading to excess deposition in hepatocytes, myocardium, and other visceral cells. Dermatologic manifestation of hemochromatosis includes skin hyperpigmentation. Associated disorders include cirrhosis, diabetes mellitus, and cardiac failure. Skin discoloration is a characteristic diffuse gray or brown-bronze color, in the face, neck, arms, genitalia, buccal mucosa, or conjunctiva. Other characteristics include skin atrophy, ichthyosis, partial hair loss (often in the pubis), and koilonychia [27].

The hereditary form of hemochromatosis is inherited as an autosomal recessive trait, with 10% of the American population carrying the mutation in the responsible *HFE*. Two mutations in the *HFE* gene have been described. The first, C282Y, comprises the substitution of tyrosine for cysteine at amino acid position 282. In the second, H63D, aspartic acid is substituted for histidine in position 63 [26]. It is expressed more in males than females, influenced by the menstruation cycle and typically manifests clinically after 40 years of age when body iron stores reach 15–40 g or more [28]. General symptoms comprise chronic fatigue, weakness, lethargy, and apathy. Fatigue is common in hemochromatosis and significantly more in those homozygous for C282Y. The cutaneous hyperpigmentation in hereditary hemochromatosis is primarily due to melanin rather than iron [27]. The increase in synthesis of melanin in melanocytes is caused by iron deposits that damage skin structure which results in the hyperpigmentation often seen in hemochromatosis.

The most common GI manifestation with hemochromatosis is hepatomegaly, seen in nearly 95% of all patients. Cirrhosis may develop in those untreated, leading to complications resulting in hemochromatosis-related deaths. Hepatocellular carcinoma may also be a complication. Treatments include phlebotomy and chelating agents. Phlebotomy does not reduce hyperpigmentation immediately. The efficacy of treatment is influenced by ferritin levels; evaluation of serum ferritin is recommended monthly until the values reach the upper limits of normal (300 μg/L in men and 200 μg/L in women) [29]. Patients with anemia cannot undergo phlebotomy. Here, iron chelation agents (e.g., deferoxamine, deferiprone, deferasirox) are recommended [30]. Nutritional status influences progress and treatment of the disease. Interactions between alcohol intake and dietary iron can increase hydroxyl free radicals that can cause liver cancer [31].

Porphyria cutanea tarda (PCT) is the most common porphyria in adults. It encompasses a group of familial and acquired disorders in which activity of the heme synthetic enzyme uroporphyrinogen decarboxylase (UROD) is deficient [32]. Sporadic PCT typically manifests in adulthood, while double mutations may be severe and observed in early childhood [33].

The patients with the sporadic acquired form of PCT have normal UROD DNA sequences, but are exposed to large polyhalogenated cyclic hydrocarbons. The familial version most often manifests as an autosomal dominant inheritance of a single mutation at the UROD locus. A rare recessive familial type of PCT in which both *UROD* alleles are mutated

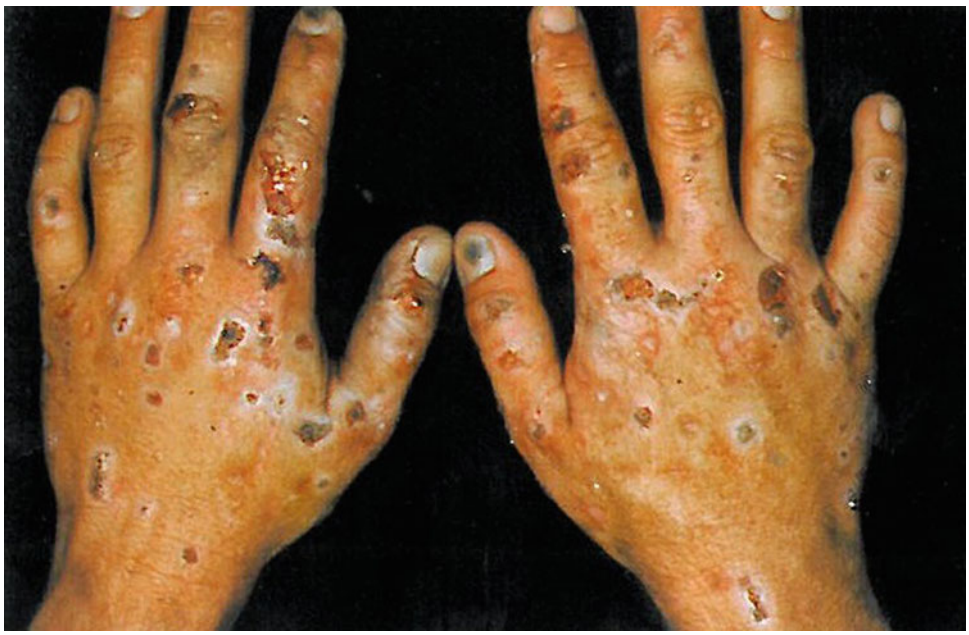

Fig. 70.6 Porphyria cutanea tarda (PCT)

is termed hepatoerythropoietic porphyria [34]. Excess iron enhances formation of toxic oxygen species, increasing oxidative stress and apparently facilitating porphyrinogenesis by catalyzing the formation of oxidation products that inhibit UROD [35]. Diagnosis involves the discovery of increased porphyrins in the blood, liver, stool, and urine.

The major morbidity of PCT is due to skin damage and blistering (Fig. 70.6). Daily activities may be hampered severely. Secondary erosions may cause epidermal loss and infections. Healing is slow and painful, causing atrophic scars. Cutaneous findings are characterized by skin photosensitivity with increased skin fragility, facial hypertrichosis, blisters, scarring with milia formation, and skin hyperpigmentation on the hands and other sun-exposed areas. Urine may be grossly discolored with a tea- or wine-colored tint.

Treatment involves removal of extrinsic triggers. Iron and estrogen supplementation may reduce symptoms. Also, alcohol intake should be cautioned to reduce the creation of increased free radical activity. Patients should avoid sunlight exposure for maximum defense against photosensitivity. Phlebotomy in severe cases may decrease the total iron load and lead to improvement. It may improve scleroderma-like skin manifestations, but not liver cell function. Chelation with desferrioxamine is an alternative means of iron mobilization when phlebotomy is not practical [36]. Human recombinant erythropoietin can stimulate erythropoiesis if the patient is anemic.

Pancreatic fat necrosis describes the association of skin nodules with pancreatic disease. Painful or painless cutaneous lesions are seen on the legs, buttocks, and trunk [37, 38]. Pruritis of lower extremities progresses to skin nodules with tenderness. These nodules drain white, pus-like exudates. An atrophic scar and hyperpigmentation usually results after healing. Patients with pancreatic cancer and pancreatitis have a tendency to manifest pancreatic fat necrosis. Lipolytic enzymes may contribute to development of subcutaneous nodules.

Glucagonoma, a rare tumor of the alpha cells of the pancreas, is characterized by normocytic normochromic anemia, psychological illness, and mild diabetes mellitus is associated with necrolytic migratory erythema (Fig. 70.7).

Lichen planus (LP) is a cutaneous manifestation of a variety of liver diseases. It is a pruritic, papular eruption. Papules are purple, polygonal, and have flat surfaces that affect the skin and mucous membranes. Microscopic examination may detect the presence of white or gray linear marks known as Wickham striae, found anywhere on the epidermis, commonly affecting the wrists, ankles, shins, lower back, and genitalia. Genital involvement is common in men with LP. Vulvar involvement in women can include reticulated papules and severe erosions. Hyperpigmentation, subungual hyperkeratosis, onycholysis, and longitudinal melanonychia can result from lichen planus [39].

Lichen planus is most likely an immunologically mediated reaction. Its origin is unknown but may be associated with ulcerative colitis, alopecia areata, vitiligo, dermatomyositis, morphea, lichen sclerosis, and myasthenia gravis. In a meta-analysis, 16% of patients with lichen planus had hepatitis-C infection [40]. Hepatitis should be considered in patients with widespread or unusual presentations of lichen planus. Atrophy and scarring are seen in the hypertrophic lesions and lesions of the scalp. Cutaneous lichen planus does not

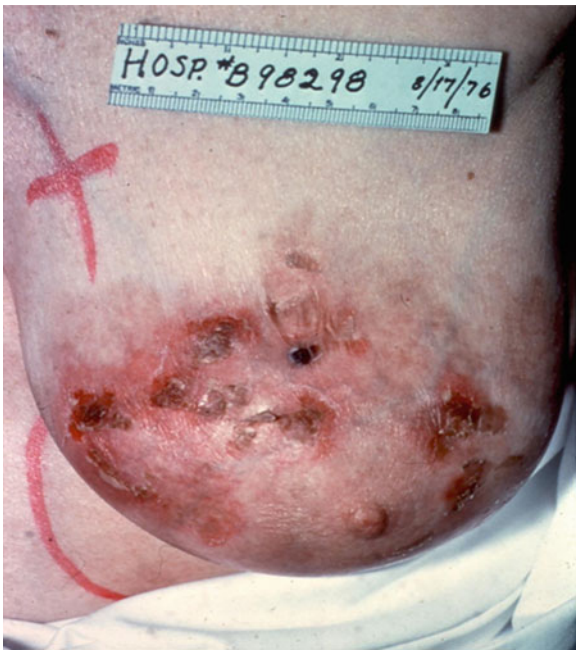

Fig. 70.7 Glucagonoma (courtesy C.S. Pitchumoni, MD)

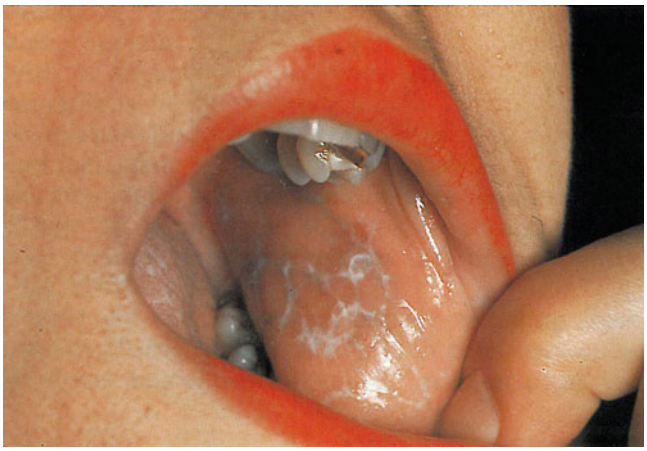

Fig. 70.8 Oral lichen planus

have a higher risk of skin cancer, but ulcerative lesions in the mouth, particularly in men, have a higher incidence of malignant transformation [41] (Fig. 70.8). More than two-thirds of patients are aged 30–60 years; however, lichen planus can occur at any age [42].

LP usually resolves by itself within 8–12 months. Fluorinated topical steroids can be used to treat mild cases. Class I or II ointments are generally used for them. Systemic steroids can be used for symptom control. Many practitioners prefer intramuscular triamcinolone 40–80 mg every 6–8 weeks. Oral acitretin has been shown to be effective [43]. LP of the oral mucosa can be treated with topical steroids. Topical immunomodulators and systemic immunosuppressives are used for more severe cases. These include thalidomide, azathioprine, mycophenolate mofetil, and systemic retinoids.

Intestines

Peutz–Jeghers syndrome (PJS) is an autosomal dominant inherited disorder characterized by intestinal hamartomatous polyps in association with mucocutaneous melanocytic macules. The cause of PJS appears to be a germline mutation of the serine threonine kinase (*STK11*) genes [44, 45]. The risk of cancer increases with the presence of the gastrointestinal polyps [46].

Dermatological manifestations of PJS include mucocutaneous pigmentation and melanin spots, appearing as small, flat, brown spots resembling freckles. The lesions most commonly are found on the lips in 95% of patients. The buccal mucosa, palms of hands, fingers, nose, gingiva, eyelids, and hard palate can also be affected. Cutaneous lesions fade away over time. Ruby and argon lasers successfully eradicate the mouth pigmentation. Care includes regular surveillance for cancers involving the breast, ovary, testicle, cervix, thyroid, and other tissues [47]. Genetic counseling should be provided.

Blue rubber bleb nevus syndrome is a rare sporadic or autosomal dominant disorder characterized by the combination of cutaneous vascular malformations in association with visceral lesions causing GI bleeding [48, 49]. The clinical manifestations most often present in birth or early childhood, although some cases may not be identified until adulthood. The skin lesions range from 1 to over 100 and take three forms: nontender soft nodules that leave behind a blue empty sac that refills rapidly with blood when compressed (blue rubber nipple, Fig. 70.9), blue-black tender macular lesions distributed on the extremities (Fig. 70.10) and trunk, and large hemangiomas (up to 10 cm in diameter) that may interfere with limb or organ function.

Treatment depends on the severity of the diseases. For mild blood loss over time, management includes monitoring, iron replacement, and blood transfusions as needed; endoscopic therapy with bipolar electrocautery or YAG laser may be necessary. A report of blue rubber bleb nevus syndrome indicated the successful use of interferon-beta to treat the manifestations of disseminated intravascular coagulation in a patient with disseminated skin and GI venous malformations [50]. Surgical resection of affected areas may be required.

Gardner syndrome is a variant of familial adenomatous polypsis [51], inherited as an autosomal dominant trait and characterized by GI polyps, multiple osteomas, and skin and soft tissue tumors. Dermatologic manifestations include epidermoid cysts, desmoid, and other benign tumors [52]. Gardner syndrome is genetically linked to band 5q21, the adenomatous polyposis coli locus [53]. The cutaneous findings may require excision if they become severe.

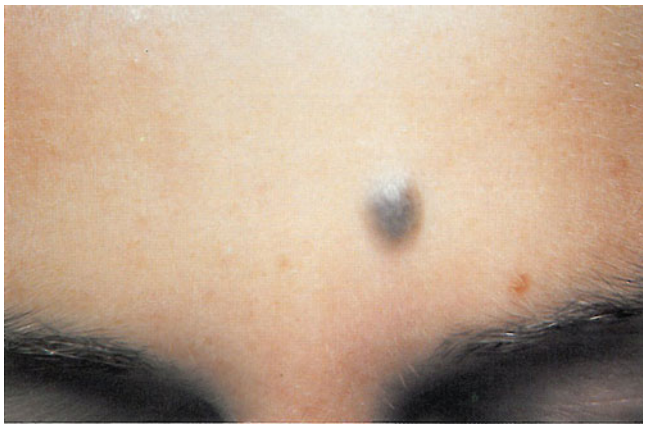

Fig. 70.9 Blue nevus on forehead

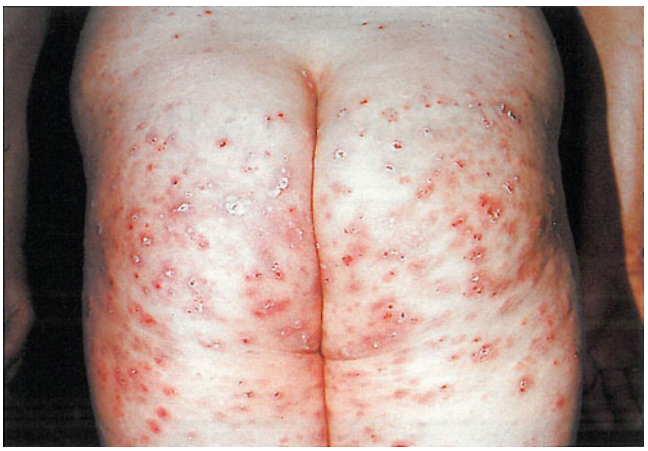

Fig. 70.11 Dermatitis herpetiformis on buttocks

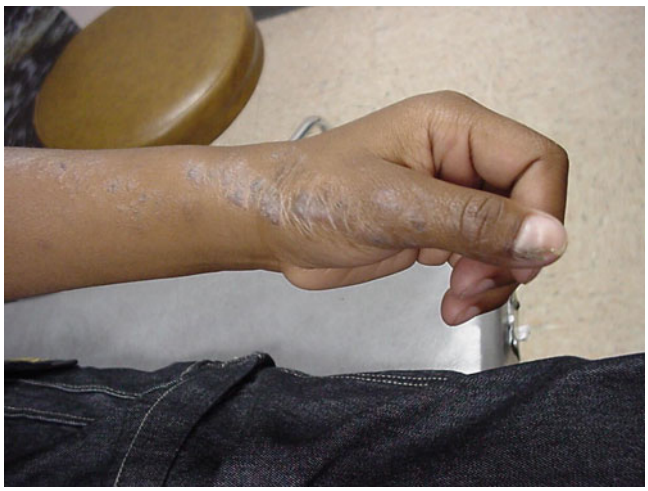

Fig. 70.10 Advanced linear epidermal nevus

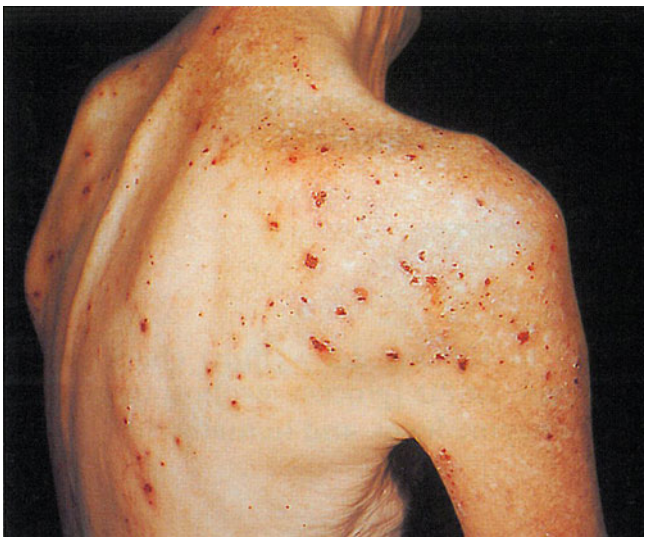

Fig. 70.12 Dermatitis herpetiformis on upper back

Dermatitis herpetiformis (DH) is an autoimmune blistering disorder associated with a gluten-sensitive enteropathy (GSE). It is characterized by localized excoriations, erythematous, urticarial plaques, and papules with vesicles. It is extremely pruritic and manifests on the elbows, knees, back, and buttocks (see Figs. 70.11 and 70.12). Many patients with celiac disease develop dermatitis herpetiformis. Celiac disease (CD) also an autoimmune disorder of the small intestine, affects persons of all ages, manifesting as atrophy of intestinal villi with resultant malabsorption and consequent clinical manifestations [54]. The cause of dermatitis herpetiformis is the deposition of IgA in the papillary dermis triggering an immunologic response to the chronic stimulation of the gut mucosa by dietary gluten. Treatment includes a gluten-free diet and pharmacotherapy [55].

Several cutaneous changes occur in the course of inflammatory bowel disease (IBD) including pyoderma gangrenosum, erythema nodosum, urticaria, and purpura; rarely, the lesions occur before the development of colitis, with leukocytoclastic vasculitis reported several months before the intestinal manifestations became overt [56]. While Crohn's disease affects the intestines, metastatic Crohn's disease is a rare skin manifestation, with granulomatous changes occurring at sites distant from the bowel. The inflammatory postulating skin lesions resolve with corticosteroid therapy [57]. Erythema nodosum refers to nodular, tender inflammatory lesions involving the subcutaneous fat, occurring typically in the legs, especially anterior tibia, more often in women. Lesions are nonspecific and occur with a variety of infections, such as tuberculosis and at times with *Yersinia*, *Campylobacter,* and *Shigella*. Patients with ulcerative colitis and Crohn's disease manifest erythema nodosum when the disease is active in up to 10% of cases. Management involves the use of NSAIDs and addressing the underlying etiology.

Visceral Neoplasms

Muir–Torre syndrome (MTS) is a syndrome that combines sebaceous neoplasms with visceral malignancies. These include sebaceous adenoma, sebaceous epithelioma, sebaceous carcinoma, and gastrointestinal or genitourinary carcinomas. Sebaceous adenoma is the characteristic marker of MTS. These fairly rare benign tumors usually appear as yellow papules or nodules in adults. Sebaceous carcinomas most commonly occur on the eyelids, where they generally arise from the meibomian glands and the glands of Zeiss. They also occur on ears, feet, penis, and the labia. MTS has an autosomal dominant pattern of inheritance in 59% of cases and a high degree of penetrance with variable expression. This condition is associated with an inherited defect in one copy of a DNA mismatch repair gene (*MMR*), which eventually leads to microsatellite instability (MSI) [58]. The two major MMR proteins involved are hMLH1 and hMSH2. Approximately, 70% of tumors associated with the MTS have MSI. While germline disruption of hMLH1 and hMSH2 is evenly distributed in HNPCC, disruption of hMSH2 occurs in over 90% of MTS patients [59].

Treatment of MTS involves regular screening for GI and genitourinary cancers. In many patients, the skin cancers associated with MTS tend to have a nonaggressive course. However, approximately 60% of patients reportedly develop metastatic disease, with a 50% survival rate calculated at 12 years. Lesions outside the head and neck may take a more aggressive course. Age at presentation of MTS ranges from young adulthood to the elderly, with a median age of 53 years [60].

Cowden disease, a rare disease of autosomal dominant inheritance is characterized by hamartomas in various tissues. Cutaneous manifestations include trichilemmomas, acral keratoses, and oral papillomas. Oral lesions are common. Papules are 1–3 mm with a smooth surface and a whitish appearance and are present in the gingival, labial, and palatal surfaces of the mouth in over 80% of patients and acral keratoses are flesh-colored or slightly pigmented smooth or verrucoid papules on the dorsal hands and feet, occurring in over 60% of patients [61]. The disease is associated with a variety of malignancies, including breast, thyroid, endometrial, cervical, and colon cancer. GI polyposis occurs in at least 35% of patients with Cowden disease. The common sites of polyposis are colon and rectum, although polyps can occur in the esophagus, stomach, gallbladder, and small bowel. Cowden disease (multiple hamartoma syndrome) is caused by a mutation in the *PTEN* tumor suppressor gene (also termed *MMAC1* or *TEP1*) on band 10q23.3. Identical mutations in *PTEN* have been described in Bannayan–Ruvulcaba–Riley syndrome (BRRS). Cutaneous manifestations of Cowden disease are similar in both sexes. Systemic treatments (i.e., acitretin) may control some cutaneous manifestations of the disease; however, recurrence of lesions is typical after treatment is discontinued [62]. A thorough initial GI evaluation is indicated, with appropriate follow-up care.

Cronkhite–Canada syndrome (CCS) is a rare, sporadically occurring, noninherited disorder reported in 1955 by Leonard Cronkhite Jr. and Wilma Canada in patients with generalized gastrointestinal polyps, cutaneous pigmentation, alopecia, and onychodystrophy. Ectodermal changes (i.e., hyperpigmentation, alopecia, nail dystrophy) result from malabsorption and protein loss. Most patients are over 50 years old at presentation. As the etiology is unknown, treatment is mainly symptomatic, with the goals to correct fluid, electrolyte, and protein loss, and regulate stool frequency. The most effective treatment is combination therapy composed of systemic corticosteroids with an antiplasmin, an elemental diet, antibiotics, and hyperalimentation (nutritional supplements). CCS may be associated with carcinoma of the GI tract.

Rare Manifestations: Parasitic Diseases

Strongyloides is a helminthic pathogen associated with infection that is clinically characterized by watery diarrhea, abdominal cramping, and urticarial rash. *Strongyloides stercoralis* infection is acquired when an individual walks barefoot in contaminated soil. The infective filariform larvae enter the body through the feet by burrowing into the skin. Strongyloidiasis generally presents with diffuse nonspecific GI, dermatologic, or respiratory symptoms, and can cause diarrhea and cachexia in immunocompromised patients who are at a higher risk of disease. Benzimidazoles such as thiabendazole, mebendazole, and albendazole are antihelmintic agents used to disrupt energy production in the parasites.

Leishmaniasis is another parasitic mucocutaneous disease. Sandfly bites transmit leishmaniasis; however, infection potentially may be transmitted via a congenital route, through blood transfusions, or through contaminated needle sticks. Mucocutaneous leishmaniasis is considered a New World disease and includes infection by *Leishmania mexicana, L. amazonensis, L. braziliensis, L. guyanensis,* and *L. panamensis.* Mucocutaneous disease affects the mucous membranes of the mouth, nose, and soft palate, causing at times extensive midfacial mutilation and, occasionally, death resulting from airway or nutritional compromise. Local therapy for cutaneous symptoms includes cryotherapy, infiltration of sodium stibgluconate, local heat therapy, and various topical paromomycin preparations. Pentavalent antimonials are generally first-line therapy for cutaneous and mucocutaneous diseases.

Additional Considerations in Older Adults

Nutritional deficiencies are common in the geriatric population, especially in those individuals with poor caretaker support. Vitamin C deficiency can cause scurvy, resulting in follicular keratosis (an outgrowth at the base of hair), bleeding of gums and teeth, and delayed wound healing. Ariboflavinosis, caused by lack of vitamin B_2 can result in magenta tongue, seborrhea, cheliosis, and conjunctivitis (Fig. 70.13). Dermatologic manifestations of zinc deficiency include hair loss, skin lesions, diarrhea, and wasting of body tissue, besides acne; cutaneous signs include hair loss and white spots, bands, or lines on fingernails, termed leukonychia. Supplementation of vitamins and minerals is recommended in those who do not receive adequate nutrition.

Older patients are on medications for numerous disorders, including gastrointestinal disease; adverse drug events may present as a variety of skin lesions warranting a careful medication review. Geriatric patients, especially those bedbound and in institutions, often have fecal or urinary incontinence, with perianal incontinence-associated dermatitis, a disorder that has received little attention; the disorder must be distinguished from often coexisting pressure ulcers [63]. Treatment goals of incontinence dermatitis include removal of irritants from the skin, eradication of associated infections such as candidiasis, and contain or divert incontinent urine and stool [63]. And finally, several skin manifestations may be the result of intestinal malabsorption and motility disorders, rather than a primary immunologic or genetic disorders; the skin may thus be considered "the mirror of the gut" [64].

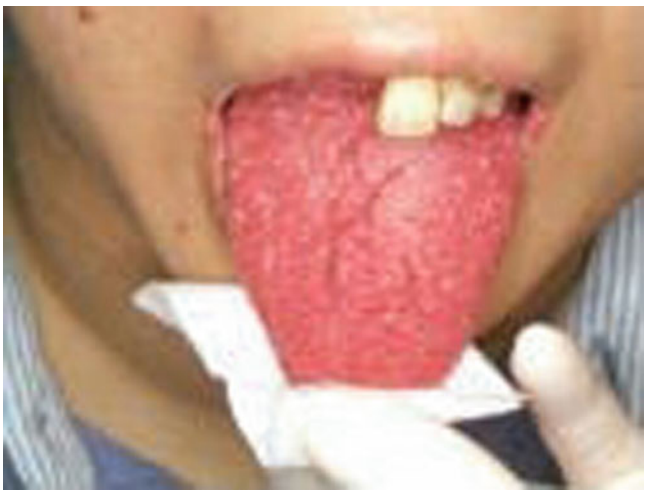

Fig. 70.13 Glossitis due to B_2 deficiency

Key Points

- Skin manifestations are common in GI disease and vary in severity.
- Topical therapy, pharmacotherapy, changes in diet, topical steroids, systemic steroids, and surgery are options in treatment for these dermal disorders.
- Several systemic disorders such as malnutrition, diabetes, hypo- and hyperthyroidism, obesity, and immunosuppressed states can manifest as a variety of mucocutaneous manifestations.
- A careful skin examination may be the clue to presence of underlying disease such as a malignancy in the GI tract.
- Medications used for these skin disorders include topical and systemic steroids, at times in combination with topical or oral antifungals.
- Other treatments include nonintervention, surgical removal of severely affected areas, radiotherapy, chemotherapeutic agents, nonspecific immunotherapy, and cessation of immunosuppressive therapy in those who are iatrogenically immunosuppressed.
- For geriatric patients with malnutrition, supplementation of vitamins and minerals is recommended in those who do not receive adequate nutrition, as skin manifestations are common in the malnourished group.

References

1. Forciea MA, Lavizzo-Mourne R, Schwab EP. Geriatric secrets. 2nd ed. Philadelphia: Hanley and Belfus; 2000. p. 127.
2. Schwartz RA, Lambert WC, Van Voorhees AS, et al. Kaposi sarcoma. http://emedicine.medscape.com/article/1083998-overview. Accessed 14 Feb 2011.
3. Schwartz RA, Cohen PF. Kaposi's sarcoma. In: Newcomer VD, Young Jr EM, editors. Geriatric dermatology: clinical diagnosis and practical therapy. New York: Igaku-Shoin; 1989. p. 645–52.
4. Allan AE, Shoji T, Li N, et al. Two cases of Kaposi's sarcoma mimicking Stewart-Treves syndrome found to be human herpesvirus-8 positive. Am J Dermatopathol. 2001;23(5):431–6.
5. Young Jr EM, Newcomer VD, Kligman AM. Kaposi's sarcoma. In: Geriatric dermatology: color atlas and practitioner's guide. Philadelphia: Lea and Febiger; 1993. p. 202–3.
6. Klein E, Schwartz RA, Laor Y, et al. Treatment of Kaposi's sarcoma with vinblastine. Cancer. 1980;45:427–31.
7. Young Jr EM, Newcomer VD, Kligman AM. Superficial fungal infections. In: Geriatric dermatology: color atlas and practitioner's guide. Philadelphia: Lea and Febiger; 1993. p. 107–9.
8. Sheinfeld NS, Lambiase MC, Lehman DS, Allan JM. Candidiasis, cutaneous. http://emedicine.medscape.com/article/1090632-overview. Accessed 20 Feb 2011.
9. Sundaram SV, Srinivas CR, Thirumurthy M. Candidal intertrigo: treatment with filter paper soaked in Castellani's paint. Indian J Dermatol Venereol Leprol. 2006;72(5):386–7.
10. Atmatzidis K, Papaziogas B, Pavlidis T, et al. Plummer-Vinson syndrome. Dis Esophagus. 2003;16(2):154–7.

11. Hoffman RM, Jaffe PE. Plummer-Vinson syndrome. A case report and literature review. Arch Intern Med. 1995;155(18):2008–11.
12. Harper PS, Harper RMJ, Howell Evans AW. Carcinoma of the oesophagus with tylosis. Q J Med. 1970;39:317–33.
13. May A, Gossner L, Behrens A, et al. A prospective randomized trial of two different endoscopic resection techniques for early stage cancer of the esophagus. Gastrointest Endosc. 2003;58(2): 167–75.
14. Woodley DT, Chen M. Epidermolysis bullosa: then and now. J Am Acad Dermatol. 2004;51(1 Suppl):S55–7.
15. Berger TG, Detlefs RL, Donatucci CF. Junctional epidermolysis bullosa, pyloric atresia, and genitourinary disease. Pediatr Dermatol. 1986;3(2):130–4.
16. Steen VD, Medsger Jr TA. Severe organ involvement in systemic sclerosis with diffuse scleroderma. Arthritis Rheum. 2000;43(11): 2437–44.
17. Rose S, Young MA, Reynolds JC. Gastrointestinal manifestations of scleroderma. Gastroenterol Clin North Am. 1998;27(3):563–94.
18. Ashida R, Ihn H, Mimura Y, et al. Clinical and laboratory features of Japanese patients with scleroderma and telangiectasia. Clin Exp Dermatol. 2009;34(7):761–3.
19. Ruben EC, Manuel VR, Agustin OR, et al. Ciprofloxin utility as antifibrotic in the skin of patients with scleroderma. J Dermatol. 2010;37(4):323–9.
20. Lyell A. Toxic epidermal necrolysis: an eruption resembling scalding of the skin. Br J Dermatol. 1956;68(11):355–61.
21. Miller JH, Rapini RP. Acanthosis nigricans. http://emedicine.medscape.com/article/1102488-overview. Accessed 20 Feb 2011.
22. Verrando P, Ortonne JP. Insulin binding properties of normal and transformed human epidermal cultured keratinocytes. J Invest Dermatol. 1985;85:328–32.
23. Longshore SJ, Taylor JS, Kennedy A, Nurko S. Malignant acanthosis nigricans and endometrioid adenocarcinoma of the parametrium: the search for malignancy. J Am Acad Dermatol. 2003;49(3): 541–3.
24. Sinha S, Schwartz RA. Juvenile acanthosis nigricans. J Am Acad Dermatol. 2007;57(3):502–8.
25. Ozdemir M, Toy H, Mevlitoglu I, et al. Generalized idiopathic acanthosis nigricans treated with acitreitn. J Dermatolog Treat. 2006;17:54–6.
26. Darmstadt GL, Yokel BK, Horn TD. Treatment of acanthosis nigricans with tretinoin. Arch Dermatol. 1991;127:1139–40.
27. Chevrant-Breton J, Simon M, Bourel M, Ferrand B. Cutaneous manifestations of idiopathic hermochromatosis. Study of 100 cases. Arch Dermatol. 1977;113(2):161–5.
28. Brandhagen DJ, Fairbanks VF, Baldus W. Recognition and management of hereditary hemochromatosis. Am Fam Physician. 2002;65:853–60.
29. Drobnik J, Schwartz RA. Hemochromatosis. http://emedicine.medscape.com/article/1104743-overview. Accessed 24 Feb 2011.
30. Hazin R, Abu-Rajab Tamimi TI, Abuzetun JY, et al. Recognizing and treating cutaneous signs of liver disease. Cleve Clin J Med. 2009;76(10):599–606.
31. Asare GA, Bronz M, Naidoo V, Kew MC. Synergistic interaction between excess hepatic iron and alcohol ingestion in hepatic mutagenesis. Toxicology. 2008;254(1–2):11–8.
32. Kappas A, Sassa S, Galbraith RA, et al. The porphyrias. In: Scriver CR, Beaudet AL, Sly WS, Valle D, editors. The metabolic basis of inherited disease. New York: McGraw-Hill; 1995. p. 2103–59.
33. Elder GH, Smith SG, Herrero C, et al. Hepatoerythropoietic porphyria: a new uroporphyrinogen decarboxylase defect or homozygous porphyria cutanea tarda? Lancet. 1981;1(8226):916–9.
34. Moran-Jimenez MJ, Ged C, Romana M, et al. Uroporphyrinogen decarboxylase: complete human gene sequence and molecular study of three families with hepatoerythropoietic porphyria. Am J Hum Genet. 1996;58(4):712–21.
35. Rocchi E, Cassanelli M, Borghi A, et al. Liver iron overload and desferrioxamine treatment of porphyria cutanea tarda. Dermatologica. 1991;182(1):27–31.
36. Bonkovsky HL, Lambrecht RW, Shan Y. Iron as a co-morbid factor in nonhemochromatotic liver disease. Alcohol. 2003;30(2): 137–44.
37. Bonkovsky HL, Poh-Fitzpatrick M, Pimstone N, et al. Porphyria cutanea tarda, hepatitis C, and HFE gene mutations in North America. Hepatology. 1998;27(6):1661–9.
38. Lambiase P, Seery JP, Taylor-Robinson SD, et al. Resolution of panniculitis after placement of pancreatic duct stent in chronic pancreatitis. Am J Gastroenterol. 1996;91(9):1835–7.
39. Chuang T-Y, Stitle L. Lichen planus. http://emedicine.medscape.com/article/1123213-overview. Accessed 1 Mar 2011.
40. Shengyuan L, Songpo Y, Wen W, et al. Hepatitis C virus and lichen planus: a reciprocal association determined by a meta-analysis. Arch Dermatol. 2009;145(9):1040–7.
41. Ingafou M, Leao JC, Porter SR, Scully C. Oral lichen planus: a retrospective study of 690 British patients. Oral Dis. 2006; 12(5):463–8.
42. Balasubramaniam P, Ogboli M, Moss C. Lichen planus in children: review of 26 cases. Clin Exp Dermatol. 2008;33(4):457–9.
43. Cribier B, Frances C, Chosidow O. Treatment of lichen planus. An evidence-based medicine analysis of efficacy. Arch Dermatol. 1998;134(12):1521–30.
44. Hemminki A, Markie D, Tomlinson I, et al. A serine/threonine kinase gene defective in Peutz-Jeghers syndrome. Nature. 1998;391(6663):184–7.
45. Jenne DE, Reimann H, Nezu J, et al. Peutz-Jeghers syndrome is caused by mutations in a novel serine threonine kinase. Nat Genet. 1998;18(1):38–43.
46. Brosens LA, van Hattem WA, Jansen M, et al. Gastrointestinal polyposis syndromes. Curr Mol Med. 2007;7(1):29–46.
47. Boardman LA, Thibodeau SN, Schaid DJ, et al. Increased risk for cancer in patients with the Peutz-Jeghers syndrome. Ann Intern Med. 1998;128(11):896–9.
48. Oranje AP. Blue rubber bleb nevus syndrome. Pediatr Dermatol. 1986;3(4):304–10 [Medline].
49. Oksüzoglu BC, Oksüzoglu G, Cakir U, et al. Blue rubber bleb nevus syndrome. Am J Gastroenterol. 1996;91(4):780–2.
50. Apak H, Celkan T, Ozkan A, et al. Blue rubber bleb nevus syndrome associated with consumption coagulopathy: treatment with interferon. Dermatology. 2004;208(4):345–8.
51. Gu GL, Wang SL, Wei XM, Bai L. Diagnosis and treatment of Gardner syndrome with gastric polyposis: a case report and review of the literature. World J Gastroenterol. 2008;14(13): 2121–3.
52. Ascari-Raccagni A, Baldari U, Righini MG. Cutaneous symptoms of Gardner's syndrome. J Eur Acad Dermatol Venereol. 1999; 12(1):80–1.
53. Elkharwily A, Gottlieb K. The pancreas in familial adenomatous polyposis. J Pancreas. 2008;9(1):9–18.
54. Barta Z, Zold E, Nagy A, Zeher M, Csipo I. Celiac disease and microscopic colitis: a report of 4 cases. World J Gastroenterol. 2011;17(16):2150–4.
55. Smith JB, Taylor TB, Zone JJ. The site of blister formation in dermatitis herpetiformis is within the lamina lucida. J Am Acad Dermatol. 1992;27(2 Pt 1):209–13.
56. Akbulut S, Ozaslan E, Topal F, et al. Ulcerative colitis presenting as leukocytoclastic vasculitis of skin. World J Gastroenterol. 2008;14(15):2448–50.
57. Eames T, Landthaler M, Karrer S. Crohn's disease: an important differential diagnosis of granulomatous skin diseases. Eur J Dermatol. 2009;19(4):360–4.
58. Honchel R, Halling KC, Schaid DJ, et al. Microsatellite instability in Muir-Torre syndrome. Cancer Res. 1994;54(5):1159–63.

59. Ponti G, Losi L, Pedroni M, et al. Value of MLH1 and MSH2 mutations in the appearance of Muir-Torre syndrome phenotype in HNPCC patients presenting sebaceous gland tumors or keratoacanthomas. J Invest Dermatol. 2006;126(10):2302–7.
60. Burger B, Itin P. Muir-Torre syndrome. Dermatology. 2008; 217(1):56–7.
61. Adkisson K, Fiala KH. Cowden disease (multiple hamartoma syndrome). http://emedicine.medscape.com/article/1093383-overview. Accessed 15 Mar 2011.
62. Cnudde F, Boulard F, Muller P, et al. Cowden disease: treatment with acitretine. Ann Dermatol Venereol. 1996;123(11):739–41.
63. Gray M. Optimal management of incontinence-associated dermatitis in the elderly. Am J Clin Dermatol. 2010;11(3):201–10.
64. Abenavoli L, Proietti I, Vonghia L, et al. Intestinal malabsorption and skin disorders. Dig Dis. 2008;26(2):167–74.

HIV Disease

71

C.S. Pitchumoni and Alexander Brun

Gastrointestinal Manifestations of HIV Disease

Introduction

To date, more than 60 million people have become infected with the human immunodeficiency virus (HIV) since the beginning of the epidemic in 1981, with 2.7 million newly infected people in 2010 [1, 2]. The prevalence of HIV infection in adults ≥50 years of age (older people/adults) is rapidly increasing (25% in 2006 [3], compared to 20% in 2001 [4]). The US Senate Special Committee on Aging predicts that in the year 2015 50% of people infected with HIV will be ≥50 years old [5]. With the advent of highly active antiretroviral therapy (HAART), the progression of HIV infection to acquired immune deficiency syndrome (AIDS) and related deaths has declined. References to patients with AIDS imply a CD4 count of <200/mm^3 and/or the presence of opportunistic disorder(s). Because of the rise in incidence and improvement in survival time, AIDS is becoming increasingly important in geriatric practice (see Table 71.1).

Risk Factors for HIV Infection in Older Adults

Sexual contact and injection drug use as risk factors are common in both young and old adults. Sexual contact amongst men who have sex with men (MSM) is the most common mode of transmission amongst males of all ages in America, followed by injection drug use, heterosexual sex, and blood transfusion. However, heterosexual sex is the most frequent route of exposure to HIV in older women, with drug abuse being second in line [6].

Contrary to perceptions, older adults remain sexually active into late life, with the availability of medication for erectile dysfunction enhancing their sexuality. Despite the stereotypes, older adults engage in risky behavior including unprotected sex, often involving multiple partners and prostitutes, in part because they do not consider themselves at risk of contracting sexually transmitted diseases or fear resulting pregnancy [7]. Many healthcare providers do not ask about HIV risk factors in patients ≥50 years old because they do not perceive this age group as one in danger of acquiring HIV infection [8]. Failure to recognize this risk and unwillingness to discuss sexual problems with their doctors often leads to late presentation and delayed diagnosis in those ≥50 years of age [9, 10]. Delayed diagnosis in older adults is associated with higher levels of mortality, particularly in the MSM group (see Table 71.2) [11–13].

Age-related physiological changes increase the chance of acquiring HIV. In both sexes, aging is associated with thymic atrophy and decreased cell-mediated immunity [14]. Anal mucosal tear is more common due to thinning of epithelial structures in older men and increases the chances of acquiring HIV in MSM. Increased friability and vaginal mucosal atrophy in postmenopausal women predispose them to mucosal breakdown during intercourse, thus increasing the likelihood of infection transmission [15].

Clinical Features and Gastrointestinal Manifestations

Gastrointestinal (GI) complications are among the most common clinical features of AIDS, largely a result of opportunistic infections [16]. Assessment and management of GI

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Table 71.1 Changing patterns of HIV demographics in the USA[a]

Parameter	1999	2007/2008[b]
Diagnosis of HIV infection	Data is not available	41,269 (2008) <50 years old: 34,481 ≥50 years old: 6,788
Diagnosis of AIDS	46,400	37,151 (2008) <50 years old: 28,961 ≥50 years old: 8,190
Deaths of persons with a diagnosis of HIV infection	Data is not available	16,661 (2007) <50 years old: 9,859 ≥50 years old: 6,802
Deaths of persons with an AIDS diagnosis	16,432	17,619 (2007) <50 years old: 10,531 ≥50 years old: 7,088
Persons living with a diagnosis of HIV infection	113,02	580,370 (2007) <50 years old: 415,230 ≥50 years old: 165,140
Persons living with an AIDS diagnosis	290,547	459,595 (2007) <50 years old: 304,114 ≥50 years old: 155,481

[a]Data compiled from 1999 and 2008 CDC Surveillance reports [6, 43]
[b]HIV infection is reported in 37 states

Table 71.2 Effect of late presentation and delayed diagnosis

Sexual orientation	*Ratio*
Men who have sex with men present late	Older MSM almost 2 times as likely to present late than younger MSM (40% vs. 21%) [13]
Heterosexuals present late	53% of older heterosexual men present late, compared to 45% of younger heterosexual men [13] 51% of older heterosexual women present late, compared to 36% of heterosexual women [13]
Men who have sex with men diagnosed late	10 times more likely to die within a year of diagnosis, compared to those diagnosed early [11]
Heterosexuals diagnosed late	9 times more likely to die than heterosexuals diagnosed early [12]
Age	*Ratio*
Older adults diagnosed late	2.4 times more likely to die within a year of diagnosis than younger adults diagnosed late [13] 14 times more likely to die within a year of diagnosis, compared to older adults diagnosed early [13]

manifestations varies with the nature and persistence of symptoms, as well as the degree of immunosupression [17]. With HAART, GI complaints are often considered secondary to non-HIV related conditions, age associated changes in gut structure and motility, or drug toxicity from antiretroviral agents [18, 19].

1. Malnutrition and wasting
   Malnutrition and weight loss are widely prevalent problems in all HIV/AIDS patients, as they are common symptoms of various diseases, opportunistic infections, as well as drug-induced anorexia and nausea. "Wasting syndrome" occurs in the final clinical stage of AIDS and is characterized by involuntary weight loss >10% of baseline body weight over a 1–2 month period, accompanied by fever or night sweats that fail to resolve with antibiotics, or diarrhea occurring more than 3 times daily for over a month in duration [20]. Management includes treatment of HIV infection and prevention of opportunistic infections with HAART, addressing comorbidities and improving appetite with pharmacologic agents (see Table 71.3).
2. Esophageal and gastric manifestations
   Dysphagia in HIV patients with thrush and a CD4 count of <200/mm^3 usually indicates *Candida* esophagitis (see Table 71.4). Cytomegalovirus (CMV), the second most frequent esophageal infection, usually causes deep mucosal ulcerations and occurs when CD4 count falls below 50/mm^3. In comparison to *Candida* esophagitis, dysphagia is much less common in patients with CMV and the pain is more focal; chief complaints include odynophagia or severe chest pain [21]. Esophageal strictures occur as a complication of esophagitis from CMV. CMV is not to be confused with idiopathic ulcerations; although the latter closely resembles CMV both clinically and endoscopically, their main distinguishing feature is the lack of viral cytopathic effect evident on histology and immunohistochemical studies. Ulcerated lesions may also be caused by the herpes simplex virus (HSV) (see Table 71.4).

   In patients who exhibit oral thrush in addition to dysphagia and/or odynophagia, treatment is initiated with fluconazole [22]. If empirical treatment fails to resolve the symptoms after 1 week, endoscopy with biopsy of the ulcer base and histological examination is the next step to establish the etiology. Treatment of CMV involves 2–3 weeks of intravenous ganciclovir or valganciclovir. HSV is usually managed by oral intake of acyclovir. Over 90% of idiopathic ulcers respond to oral glucocorticoids [23] and thalidomide is effective in severe, refractory cases [24].

   Other rare causes include *Mycobacterium tuberculosis*, *Mycobacterium* avium complex (MAC), histoplasmosis, *Cryptosporidium*, Kaposi's sarcoma, and lymphoma.

   Gastric disorders in HIV infection and AIDS result from opportunistic infections, malignancies, and other causes unrelated to HIV. While the prevalence of *Helicobacter pylori* is lower in those with HIV due to their recurrent use of antimicrobial therapy, peptic ulcer disease is still common in this group [25]. Decrease in secretion of gastric acid and intrinsic factors in patients with HIV lead to malabsorption of iron, vitamin B12, and medications including Indinavir, Atazanvir, Ketoconazole, and Itraconazole. Kaposi's sarcoma most commonly involves the stomach. It typically presents as a violet-blue submucosal mass without ulceration and can be confirmed with biopsy and histological examination. Up to 50% of patients have concomitant cutaneous involvement. AIDS-associated lymphomas are usually multifocal, but on rare

Table 71.3 Wasting syndrome in AIDS [20, 44]

Common causes	Clinical features	Diagnosis	Management
Viremia Opportunistic infections Anorexia and nausea induced by medications including HAART GI conditions that affect nutritional intake or absorption	weight loss of >10% with *either* (a) diarrhea for longer than 1 month more than 3 times daily, or (b) fever or night sweats lasting over a month that do not respond to antibiotics or antimalarial agents	Clinical diagnosis	Immune reconstruction and prevention of opportunistic infections with HAART therapy Treat diarrhea and comorbidities Increase caloric intake with appetite stimulants such as dronabinol and megestrol, steroids including oxandrolone and nandrolone

Table 71.4 Esophagitis [21–23, 45, 46]

Common causes	Clinical features	Diagnosis	Management
Candida esophagitis	Thrush, dysphagia, odynophagia	Upper endoscopy (shows plaques) Biopsy (confirms desquamated epithelial cells with yeast forms, fungal invasion in the superficial epithelium)	Fluconazole
Cytomegalovirus (CMV)	Odynophagia, substernal chest pain; dysphagia is less common	Upper endoscopy (demonstrates large and deep lacerations) Biopsy (shows CMV inclusions)	Ganciclovir or valganciclovir
Herpes simplex virus (HSV)	Oral lesions, odynophagia	Upper endoscopy (reveals shallow, small ulcers) Biopsy (shows HSV inclusions)	Acyclovir
Idiopathic	Same as CMV	Lack of viral cytopathic effect evident on histology and immunohistochemical studies	Prednisone or thalidomide

occasions can be related to *H. pylori* leading to gastric mucosa-associated lymphoid tissue (MALT) lymphomas. Biopsy and immunohistochemical staining are needed for diagnosis.

3. Diarrheal diseases

Diarrhea, a common complaint in AIDS, may be caused by infections (bacterial, viral, fungal, parasitic, opportunistic), medications and dietary intolerance (see Table 71.5) [26]. Immunodeficiency renders patients with AIDS particularly vulnerable to prolonged and severe diarrhea [27]. Small intestinal dysfunction and mucosal damage not attributable to intestinal pathogens is termed "HIV enteropathy." It is characterized by chronic diarrhea, advanced HIV disease (CD4 <100/mm^3) and lack of an identifiable pathogen [28]. Symptoms may improve with HAART. HIV enteropathy may result from indirect effects of HIV on enteric homeostasis.

A detailed history, clinical features, and CD4 count help narrow the differential diagnosis (see Table 71.5). Initial evaluation should include stool cultures for bacteria, ova and parasites. If the etiology cannot be discerned, colonoscopy with multiple mucosal biopsies is performed. Most cases of diarrhea are self-limiting and can be managed conservatively with rehydration, dietary modification, and relief of symptoms. Otherwise, management is directed against the causative agent. Common gram-negative enteric pathogens should be treated empirically with appropriate antibiotics (see Table 71.5). Hospitalization is indicated in patients with CD4 count <200/mm^3 with signs of systemic involvement, or in the presence of severe dehydration, significant electrolyte imbalance or acidosis [29].

4. Anorectal problems

Anorectal disease (warts, fissures, and ulcers) is present in many patients with HIV infection/AIDS, particularly in MSM [30]. Typical manifestations include pain, rectal discharge, blood in stool, and pruritus. Sexually transmitted infections such as *Chlamydia trachomatis*, human papilloma virus (HPV), *Neisseria gonorrhoeae, Treponema pallidum*, and HSV are common pathogens. Etiology and stage of HIV disease will direct the management strategy, with surgical intervention reserved for cases when less invasive means have failed [31]. Although physical examination may suggest the cause of anorectal symptoms, definitive diagnosis is established by anoscopy and sigmoidoscopy with mucosal biopsy.

5. Hepatobiliary complications

Hepatomegaly is a common finding on physical examination. Abnormal liver tests are common in HIV infection/AIDS. Liver test abnormalities are secondary to hepatitis, biliary tract disease, neoplasms, opportunistic infections, and/or medications. In the HAART era, liver test abnormalities commonly result from chronic viral hepatitis or drug toxicity [32].

The predominant causes of hepatitis in HIV-infected patients include hepatitis B and C virus, CMV and HIV

Table 71.5 Diarrhea (bacterial, viral, parasitic, and fungal infections, HIV enteropathy, and noninfectious causes) [18, 26–29, 47–49]

Common causes	Clinical features	Diagnosis	Management
Bacterial infections			
Salmonella	Large volume, watery stool, nausea, vomiting, fever, dehydration, upper abdominal cramps, self limiting, preceded by contaminated food/water intake	Blood cultures for bacteria Stool culture[a] and sensitivity for bacteria, white blood cell count, red blood cell count *C. difficile* toxin essay	Empiric therapy using ciprofloxacin or ceftriaxone
Shigella	Small volume, nausea, vomiting, bloody stool, tenesmus, frequent bowel movement, lower abdominal cramps	Stool ova and parasite examination Cultures of rectal tissue for bacteria	Empiric therapy using ciprofloxacin or azithromycin
Campylobacter		Colonoscopy, endoscopy, sigmoidoscopy	Empirical therapy using ciprofloxacin
Clostridium difficile	Small volume, tenesmus, frequent bowel movement, lower abdominal cramps, history of antibiotics or hospitalization	Biopsy	Metronidazole, vancomycin
Mycobacterium tuberculosis	Prolonged fever, night sweats, abdominal pain		Rifampin, ethambutol, isoniazid, pyrazinamide Clarithromycin + ethambutol or antiretroviral therapy accompanied by drugs for symptomatic relief
Mycobacterium avium complex (MAC)	Large volume, watery stool, upper abdominal cramps, low CD4 count, prolonged fever, night sweats, weight loss, malabsorption, hepatomegaly		
Viral infections			
Norwalk virus	Nausea, vomiting, watery stool, abdominal discomfort, myalgias	Same as bacterial infections	Supportive care
Rotavirus	Subclinical to severe diarrhea, can cause chronic symptomatic diarrhea	Retinal exam for possible CMV retinitis	Supportive care
Cytomegalovirus (CMV)	Small volumes, CD4 <100/mm^3 and often <50/mm^3	CMV requires biopsy for definitive diagnosis and stool test is negative	Ganciclovir, foscarnet, acyclovir, antiretroviral therapy
	Weight loss, fevers, colitis, bright red blood per rectum, lower abdominal pain, tenesmus, frequent bowel movement	Endoscopy reveals subepithelial hemorrhage and mucosal ulcerations	
Herpes simplex virus (HSV)	Painful oral lesions, dysphagia, taste change	Visual exam may be sufficient to diagnose HSV	Acyclovir, famciclovir or valacyclovir given orally or intravenously in severe cases
Parasitic infections			
Giardia lamblia	Large volume, gas, upper abdominal cramps, bloating, watery and foul smelling stool	Same as bacterial infections Giardia antigen test	Metronidazole or tinidazole
Entamoeba histolytica	Small volume, frequent bowel movement, tenesmus, lower abdominal cramps, mucoid or bloody stool		
Cryptosporidium	Large volume, watery stool, dehydration, nausea, vomiting, upper abdominal pain, severe weight loss		Nitazoxanide, paromomycin, antiretroviral therapy
Microsporidia	Large volume, mild severity, watery stool, nonbloody stool, no fever, malabsorption, absence of abdominal pain, weight loss present but not severe, CD4 <100/mm^3		Albendazole
Isospora belli	Watery stool, abdominal discomfort, steatorrhea, nausea, vomiting, weight loss, malabsorption		Trimethoprim, sulfamethoxazole

(continued)

Table 71.5 (continued)

Common causes	Clinical features	Diagnosis	Management
Fungal infections			
Histoplasmosis	Fever, sweats, muscle aches, headache, dry cough, chest pain, appetite loss	Fungal smear Urine culture Blood culture Histoplasmosis antigen	Amphotericin B followed by itraconazole for approximately 3 weeks
Coccidioidomycosis	Fever, cough, headaches, rash, and myalgias		
Cryptococcosis	Headache, fever, nausea, vomiting, behavioral changes		
HIV enteropathy			
	Chronic diarrhea not attributable to intestinal pathogens	Diagnosis is by exclusion (i.e., diagnostic methods fail to identify and intestinal pathogen) Low-grade mucosal atrophy of the small bowel with a decrease in mitotic figures	HAART, octreotide, antimotility drugs, symptomatic therapy with luminal agents (fiber supplements, cholestyramine, kaolin)
Noninfectious causes			
Drug induced diarrhea (antiretroviral therapy and antibiotics)			
Neoplasms			

[a]Stool samples usually provide a definitive diagnosis for *Salmonella, Shigella,* and *Campylobacter* and *C. difficile*

Table 71.6 Hepatobiliary complications [32, 38, 40, 50]

Common causes	Clinical features	Diagnosis	Management
Hepatitis	Jaundice, hepatomegaly, fever, nausea, vomiting, abdominal tenderness, amphotericin, diarrhea	Elevated liver enzymes Liver scans Stool-blood culture Ultrasonography CT Magnetic resonance cholangiography Liver biopsy ERCP	HAART, interferon + ribavirin for Hepatitis C. In addition, protease inhibitor for genotype 1
Medication-induced liver injury	Same as hepatitis + use of antiretroviral agents, azoles, rifampin, isoniazid, sulfonamides		Usually dose related; therapy should be changed when transaminase levels exceed 5 times the upper limit of normal
Neoplasms	Kaposi's sarcoma: dark red/purple nodules in the portal regions, filled with densely packed spindle-shaped endothelial cells that form slit-like vascular channels		Radiotherapy, chemotherapy; depends on extent and location of the tumor
Biliary tract diseases	Acalculous cholecystitis: right upper quadrant pain, fever, vomiting, CD4 count <100/mm^3, history of prior infection with CMV		Laparoscopic cholecystectomy for acalculous cholecystitis,
	AIDS cholangiopathy: papillary stenosis, sclerosing cholangitis, extrahepatic biliary stenosis, CD4 count <200/mm^3		Sphincterotomy for symptomatic relief in aids cholangiopathy HAART

itself (see Table 71.6). HIV coinfection accelerates the progression of and resulting liver injury from the hepatitis C virus. Recent studies demonstrate an increased risk of liver damage and subsequent morbidity and mortality in coinfection, compared with chronic hepatitis B virus alone [33, 34]. Infection with hepatitis B and C may progress to cirrhosis and primary hepatocellular carcinoma. Hepatitis E virus is an established cause of acute hepatitis. It can be fulminant in patients with chronic liver disease [35]. Over the past few years, however, a number of cases of chronic hepatitis caused by hepatitis E virus genotype 3 have been reported in patients with HIV [36]. *M. tuberculosis* is the most common opportunistic infection in AIDS patients [37, 38]. Mycobacterial and fungal infections may cause granulomatous disease. Hepatic involvement generally reflects a disseminated process and is not the direct cause of morbidity or mortality. Peliosis hepatis is a rare condition which is associated with immunodeficiency. Blood-filled cysts of various sizes are histologically characteristic of peliosis hepatitis. Although spontaneous regression may occur, hepatic failure, portal hypertension, and hemorrhage are possible complications.

Biliary disorders in AIDS patients can be classified into non-HIV-associated diseases (e.g., gallstones), AIDS cholangiopathy (AC), and acalculous cholecystitis. Patients usually present with right upper quadrant pain in a setting of cholestatic pattern of laboratory abnormalities (see Table 71.7). *Cryptosporidium parvum* is the most common

Table 71.7 Abdominal pain [18, 40, 41, 48]

Common causes	Clinical features	Diagnosis	Management
Infection by *Cryptosporidium*, CMV and MAC in the absence of perforation or obstruction	Dull, mild and intermittent pain accompanied by nausea and vomiting	Stool cultures, sigmoidoscopy, stool ova and parasite examination	HAART therapy for opportunistic infections Chemotherapy or radiation for lymphoma or Kaposi's sarcoma related illnesses Antibiotic or antineoplastic regimens for symptomatic relief
Obstruction in the stomach, small bowel or colon	Severe nausea and vomiting with accompanying pain	Abdominal ultrasonography and endoscopy are required to establish diagnosis	Surgical management for obstruction, perforation, acalculous cholecystitis
Infection in the presence of perforation	Severe pain with peritoneal irritation points to perforation in the small bowel or colon	Imaging modalities, surgical exploration and laparoscopy may be necessary in presence of ascites	Sphincterotomy for AIDS cholangiopathy
Biliary tract diseases	Right upper quadrant pain and abnormal liver biochemical tests	Ultrasonography or computed topography, magnetic resonance cholangiography, endoscopic retrograde cholangiopancreatography and liver biopsy	

organism associated with AC [39]. The four types of cholangiographic abnormalities seen in AC are papillary stenosis, intra/extrahepatic sclerosing cholangitis, combination of papillary stenosis and sclerosing cholangitis, as well as extrahepatic duct strictures. In patients with AC, endoscopic retrograde cholangiopancreatography (ERCP) helps diagnose and reduce pain by sphincterotomy. Since it does not extend survival, treatment is aimed at raising CD4 count and lowering the viral load. Cholecystectomy or percutaneous cholecystostomy are viable management options for acalculous cholecystitis [40].

6. Pancreatic diseases
   Pancreatic diseases in patients with HIV are caused by alcohol abuse, hyperlipidemia, cholelithiasis, medication toxicity, HIV-related opportunistic infections, and occasionally neoplastic infiltration [18]. The main culprits are pentamidine, dideoxyinosine, and trimethoprin-sulfamethoxazole. Common HIV-related pathogens leading to pancreatitis are CMV, *M. tuberculosis, M. avium, Cryptococcus*, HSV, *Toxoplasma gondii, Pneumocystis jirovecii*, and protozoa. On rare occasions, lymphoma or Kaposi's sarcoma can invade the pancreas and present itself with mass effect on adjacent duodenum and/or exocrine insufficiency if the pancreatic duct is obstructed. Higher baseline CD4 counts are associated with decreased risk of pancreatitis.
7. Gastrointestinal neoplasms
   Kaposi's sarcoma (KS) is the most common HIV-related tumor of the GI tract; other neoplasms include non-Hodgkin's lymphoma, squamous cell carcinoma of the rectum or anus, and cloacogenic carcinoma of the rectum [41]. Anorectal carcinomas occur with greater frequency in MSM as a result of chronic perianal herpes or HPV acquired through sexual contact and can be detected using cytologic specimens of the anal canal [42].

KS is generally asymptomatic unless extensive; HAART improves prognosis. Lymphomas are aggressive (high-grade B-cell in origin) with short survival that correlates with degree of immunocompromise. Barium contrast X-ray studies, abdominal ultrasound, and CT scans can be diagnostic, but biopsies provide definitive diagnosis.

Key Points

- Risk factors for HIV infection in older adults include risky sexual behavior, physiological changes with age, and parenteral drug use.
- Nonspecific gastrointestinal manifestations and weight loss are common initial presentations of AIDS, largely a result of the aging process, opportunistic infections, drug toxicity, and other non-HIV related causes.
- *Candida albicans*, Cytomegalovirus, and HSV are the most common infectious agents that cause esophagitis in older HIV infected individuals.
- Immunodeficiency in AIDS patients renders patients particularly susceptible to prolonged and severe diarrhea. Chronic diarrhea in a setting of advanced AIDS without an identifiable pathogen is termed "HIV enteropathy."
- In patients on HAART, the main etiology of abnormal hepatic function tests is medications and chronic viral hepatitis.
- The two main HIV-related biliary diseases are AIDS cholangiopathy and acalculous cholecystitis.
- Didanosine is a common cause of asymptomatic hyperamylasemia, pancreatitis, and in rare cases, fulminant pancreatic toxicity.
- Kaposi's sarcoma is the most common HIV-related tumor of the GI tract.

References

1. Joint United Nations Programme on HIV/AIDS (UNAIDS). The global aids epidemic: 09 global facts and figures. World Health Organization. 2009 (cited 25 Dec 2010). http://data.unaids.org/pub/FactSheet/2009/20091124_fs_global_en.pdf.
2. Joint United Nations Programme on HIV/AIDS (UNAIDS). Global report: UNAIDS Report on the global AIDS epidemic. 2010 (cited 25 Dec 2010). http://www.unaids.org/globalreport/documents/20101123_GlobalReport_full_en.pdf.
3. US Department of Health and Human Services, Centers for Disease Control and Prevention (CDC), HIV prevalence estimates—United States, 2006. Morbidity and mortality weekly report. 2008 (cited 25 Dec 2010). http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5739a2.htm.
4. US Department of Health and Human Services, Centers for Disease Control and Prevention (CDC). Cases of HIV infection and AIDS in the United States and Dependent Areas, 2005. HIV/AIDS Surveillance Report. 2007 (cited 25 Dec 2010). http://www.cdc.gov/hiv/surveillance/resources/reports/2005report/.
5. Statement of Senator Gordon H. Smith. HIV over fifty: exploring the new threat. United States Senate Special Committee on Aging, Aging hearing. 2005 (cited 25 Dec 2010). http://www.aging.senate.gov/events/hr141gs.pdf.
6. US Department of Health and Human Services, Centers for Disease Control and Prevention. HIV surveillance report 2008. 2010 (cited 4 Jan 2011). http://www.cdc.gov/hiv/surveillance/resources/reports/2008report/.
7. Gott CM. Sexual activity and risk-taking in later life. Health Soc Care Community. 2001;9(2):72–8.
8. Skiest DJ, Keiser P. Human immunodeficiency virus infection in patients older than 50 years. A survey of primary care physicians' beliefs, practices, and knowledge. Arch Fam Med. 1997;6(3):289–94.
9. Lindau ST, Schumm LP, Laumann EO, Levinson W, O'Muircheartaigh CA, Waite LJ. A study of sexuality and health among older adults in the United States. N Engl J Med. 2007;357(8):762–74.
10. Althoff KN, Gebo KA, Gange SJ, Klein MB, Brooks JT, Hogg RS, et al. CD4 count at presentation for HIV care in the United States and Canada: Are those over 50 years more likely to have a delayed presentation? AIDS Res Ther. 2010;7(1):45.
11. Chadborn TR, Baster K, Delpech VC, Sabin CA, Sinka K, Rice BD, et al. No time to wait: how many HIV-infected homosexual men are diagnosed late and consequently die? (England and Wales, 1993-2002). AIDS. 2005;19(5):513–20.
12. Chadborn TR, Delpech VC, Sabin CA, Sinka K, Evans BG. The late diagnosis and consequent short-term mortality of HIV-infected heterosexuals (England and Wales, 2000–2004). AIDS. 2006;20(18):2371–9.
13. Smith RD, Delpech VC, Brown AE, Rice BD. HIV transmission and high rates of late diagnoses among adults aged 50 years and over. AIDS. 2010;24(13):2109–15.
14. Kalayjian RC, Landay A, Pollard RB, Taub DD, Gross BH, Francis IR, et al. Age-related immune dysfunction in health and in human immunodeficiency virus (HIV) disease: association of age and HIV infection with naive CD8+ cell depletion, reduced expression of CD28 on CD8+ cells, and reduced thymic volumes. J Infect Dis. 2003;187(12):1924–33.
15. Shah S, Mildvan D. HIV and aging. Curr Infect Dis Rep. 2006;8(3):241–7.
16. Egger M, May M, Chene G, Phillips AN, Ledergerber B, Dabis F, et al. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. Lancet. 2002;360(9327):119–29.
17. Chu C, Selwyn PA. Complications of HIV infection: a systems-based approach. Am Fam Physician. 2011;83(4):395–406.
18. Wallace MR, Brann OS. Gastrointestinal manifestations of HIV infection. Curr Gastroenterol Rep. 2000;2(4):283–93.
19. Edmunds-Ogbuokiri J. Clinically significant drug interactions in the HIV-infected elderly. HIV Clinician. 2011;23(2):12–5.
20. World Health Organization. WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children: WHO Press. 2007 (cited 18 Dec 2010). http://www.who.int/hiv/pub/guidelines/HIVstaging150307.pdf.
21. Wilcox CM, Schwartz DA, Clark WS. Esophageal ulceration in human immunodeficiency virus infection. Causes, response to therapy, and long-term outcome. Ann Intern Med. 1995;123(2):143–9.
22. Wilcox CM, Alexander LN, Clark WS, Thompson 3rd SE. Fluconazole compared with endoscopy for human immunodeficiency virus-infected patients with esophageal symptoms. Gastroenterology. 1996;110(6):1803–9.
23. Alexander LN, Wilcox CM. A prospective trial of thalidomide for the treatment of HIV-associated idiopathic esophageal ulcers. AIDS Res Hum Retroviruses. 1997;13(4):301–4.
24. Thompson C. Thalidomide effective for AIDS-related oral ulcers. Lancet. 1995;346(8985):1289.
25. Fialho AB, Braga-Neto MB, Guerra EJ, Fialho AM, Fernandes KC, Sun JL, et al. Low prevalence of *H. pylori* infection in HIV-positive patients in the Northeast of Brazil. BMC Gastroenterol. 2011;11:13.
26. Loftus CG. Gastrointestinal Infections, Clostridium difficile-Associated Disease, and Diverticular Disease. In: Hauser SC, editor. Mayo Clinic gastroenterology and hepatology board review. 4th ed. New York: Oxford University Press; 2011. p. 193–205.
27. Hill A, Balkin A. Risk factors for gastrointestinal adverse events in HIV treated and untreated patients. AIDS Rev. 2009;11(1):30–8.
28. Nyabilondi E, Wehbeh W, David R. HIV enteropathy: case report and review of advances in pathogenesis, diagnosis, and treatments. Infect Dis Clin Pract (Baltim Md). 2010;18(5):293–5.
29. Beatty GW. Diarrhea in patients infected with HIV presenting to the emergency department. Emerg Med Clin North Am. 2010;28(2):299–310. Table of contents.
30. Abramowitz L, Benabderrahmane D, Baron G, Walker F, Yeni P, Duval X. Systematic evaluation and description of anal pathology in HIV-infected patients during the HAART era. Dis Colon Rectum. 2009;52(6):1130–6.
31. Nadal SR, Manzione CR, Horta S. Comparison of perianal diseases in HIV-positive patients during periods before and after protease inhibitors use: what changed in the 21st century. Dis Colon Rectum. 2008;51(10):1491–4.
32. Novoa AM, de Olalla PG, Clos R, Orcau A, Rodriguez-Sanz M, Cayla JA. Increase in the non-HIV-related deaths among AIDS cases in the HAART era. Curr HIV Res. 2008;6(1):77–81.
33. Thio CL, Seaberg EC, Skolasky Jr R, Phair J, Visscher B, Munoz A, et al. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). Lancet. 2002;360(9349):1921–6.
34. Gilson RJ, Hawkins AE, Beecham MR, Ross E, Waite J, Briggs M, et al. Interactions between HIV and hepatitis B virus in homosexual men: effects on the natural history of infection. AIDS. 1997;11(5):597–606.
35. Kamar N, Garrouste C, Haagsma EB, Garrigue V, Pischke S, Chauvet C, et al. Factors associated with chronic hepatitis in patients with hepatitis e virus infection who have received solid organ transplants. Gastroenterology. 2011;140(5):1481–9.
36. Dalton HR, Bendall RP, Keane FE, Tedder RS, Ijaz S. Persistent carriage of hepatitis E virus in patients with HIV infection. N Engl J Med. 2009;361(10):1025–7.

37. Amarapurkar AD, Sangle NA. Histological spectrum of liver in HIV - autopsy study. Ann Hepatol. 2005;4(1):47–51.
38. Aaron L, Saadoun D, Calatroni I, Launay O, Memain N, Vincent V, et al. Tuberculosis in HIV-infected patients: a comprehensive review. Clin Microbiol Infect. 2004;10(5):388–98.
39. Enns R. AIDS cholangiopathy: "an endangered disease". Am J Gastroenterol. 2003;98(10):2111–2.
40. Winbladh A, Gullstrand P, Svanvik J, Sandstrom P. Systematic review of cholecystostomy as a treatment option in acute cholecystitis. HPB (Oxford). 2009;11(3):183–93.
41. Dal Maso L, Franceschi S. Epidemiology of non-Hodgkin lymphomas and other haemolymphopoietic neoplasms in people with AIDS. Lancet Oncol. 2003;4(2):110–9.
42. Cranston RD, Hart SD, Gornbein JA, Hirschowitz SL, Cortina G, Moe AA. The prevalence, and predictive value, of abnormal anal cytology to diagnose anal dysplasia in a population of HIV-positive men who have sex with men. Int J STD AIDS. 2007;18(2):77–80.
43. US Department of Health and Human Services, Centers for Disease Control and Prevention (CDC). HIV/AIDS Surveillance Report U.S. HIV and AIDS cases reported through December 1999;11(2):5–44 (cited 5 Jan 2011). http://www.cdc.gov/hiv/topics/surveillance/resources/reports/pdf/hasr1102.pdf.
44. Dworkin MS, Williamson JM. AIDS wasting syndrome: trends, influence on opportunistic infections, and survival. J Acquir Immune Defic Syndr. 2003;33(2):267–73.
45. Wilcox CM, Rodgers W, Lazenby A. Prospective comparison of brush cytology, viral culture, and histology for the diagnosis of ulcerative esophagitis in AIDS. Clin Gastroenterol Hepatol. 2004;2(7):564–7.
46. Thom K, Forrest G. Gastrointestinal infections in immunocompromised hosts. Curr Opin Gastroenterol. 2006;22(1):18–23.
47. Nguyen N, Holodniy M. HIV infection in the elderly. Clin Interv Aging. 2008;3(3):453–72.
48. Blanshard C. Gastrointestinal manifestations of HIV infection. Hosp Med. 1999;60(1):24–8.
49. Lewthwaite P, Gill GV, Hart CA, Beeching NJ. Gastrointestinal parasites in the immunocompromised. Curr Opin Infect Dis. 2005;18(5):427–35.
50. Becker S. Liver toxicity in epidemiological cohorts. Clin Infect Dis. 2004;38 Suppl 2:S49–55.

Gastrointestinal Disorders in the Older Adult: The Psychiatrist's Role

72

Alberto Cortes-Ladino

Introduction

The gastrointestinal tract is phylogenetically the oldest system in the body and hence most likely to be used to express emotions that cannot be dealt with through the regular channels.

Franz Gabriel Alexander, Hungarian physician and psychoanalyst, known as the father of psychosomatic medicine, reported in 1934 that, "The abdomen has aptly been called *the sounding board of the emotions"* and, "In spite of the fact that this relation between psyche and soma is well known, it is surprising how little attention is given to this matter in the actual management of gastrointestinal disorders" [1]. Despite the research and experience obtained ever since, the lack of precision in the diagnosis of symptomatic gastrointestinal disorders without structural abnormalities remains [2]. The presence of medical comorbidity with mental illness has been associated with less improvement after treatment, worse quality of life, poorer adherence to treatment, slower recovery, greater suicide risk, and higher cost utilization [3–5].

There are multiple signs of psychological distress present in patients with GI disturbances, but the most widely studied due to their frequency and potential severity are discussed here.

Major Psychiatric Syndromes Influencing the Diagnosis and Treatment of Gastrointestinal Illness in Older Adults

Depression and Mixed Anxiety-Depression

Foremost, a depressive disorder, which interferes with the ability to function, is not a normal part of aging, although temporary "blue" moods are normal. Due to the erroneous conception that persistent depression is a normal response to the development of medical complications and gradual loss of independence, Major Depressive Disorder is greatly underdiagnosed in the old [6–8]

In cancer patients, there is a well-studied association between gastrointestinal cancer and an increased incidence of depression. Higher rates were seen in cancer of the stomach (20.2%), followed by pancreas (17.3%) and colon (8.6%) possibly due to the release of cytokines in some cases [9–14]. In a comprehensive review of over 50 psychiatric consultation studies of depression in cancer patients, 25% of patients with advanced bowel cancer presented with depression, compared to 50% of patients with pancreatic cancer; 13% of those with colon cancer, and 40% of geriatric patients with oropharyngeal cancer [13].

The risk of mixed anxiety–depression symptoms, contrary to the common belief, decreases with every 10-year increase in age. While 17% of patients in their 30's manifested mixed anxiety–depression symptoms, only 10% of those in their 60s reported these symptoms. Generally, increasing age brings with it lessons of experience and a greater sense of fulfillment. Clinically, it highlights the importance of identifying mixed anxiety–depression in younger, not older, patients [14].

Older individuals are at greater risk for depression and suicidal acts whether they are physically healthy of not. In addition to the loss of good health, the elderly patient often has sustained other losses, including physical ability, financial stability, and death of loved ones [15].

In a recent study based on data from the Primary Care Research in Substance Abuse and Mental Health for the Elderly (PRISM-E), the findings indicated that the DSM criteria are not decisive in determining remission from major depression, whereas addressing medical comorbidity was important to optimize such remission [16]. Among nursing home dwellers, the presence of depression is related to a greater risk of hospital admissions due to medical comorbidities including gastrointestinal problems, independent of their functional status. Hence, the recognition and appropriate treatment of depression would result in a lower inpatient

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services utilization, mortality, and cost-effective issues for the health care system [17, 18].

Likewise, factors like failure to thrive, dietary and health behavior are associated with depression and mortality in a study of community-dwelling elderly. Low-grade inflammation and low plasma vitamin C levels were independently associated with depression and mortality, which would explain that, in contrast with the nursing home population, physical dysfunction might partly mediate this association [19].

A cross-sectional study with 413 patients showing that elderly individuals with depression, fecal incontinence, and cognitive and functional limitations, manifest poor nutritional status, with a higher risk for hospitalizations; these patients tend to have lower blood hemoglobin, serum total protein, and albumin, and higher incidence of geriatric syndromes [20]. A case–control study with 108 elderly patients revealed that those with Generalized Anxiety Disorder presented higher rates of diabetes and gastrointestinal conditions, suggesting the benefit of screening for anxiety in older individuals presenting with gastrointestinal illness [21]. A prospective survey in 92 elderly, terminally ill cancer patients, found depression and hopelessness to be the strongest, independent predictors of desire for hastened death, whereas, interestingly, no association was found between either presence of pain or pain intensity and desire for hastened death, confirming results of previous research in that topic [22–25]

Treatment

When treating depression in the elderly, medications are started at low dose, and the dosage is increased more slowly than with a younger patient. Also, drugs with fewer anticholinergic effects are preferred due to greater sensitivity of the elderly to anticholinergic complications such as delirium, urinary retention, constipation, and cardiac arrhythmias. Evidence continues to support the use of antidepressants of the selective serotonin reuptake inhibitors (SSRIs) class which prescribed initially because they have fewer sedative and autonomic effects than the tricyclic antidepressants (TCAs). Antidepressants are well tolerated by elderly people and is, overall, as effective as in young adults. Of note, every antidepressant medication carries a warning from the FDA, in which patients of all ages should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. See Table 72.1 for doses of the antidepressants most commonly used in the elderly [26–28].

Table 72.1 Antidepressant medications commonly used in the elderly

Drug and class	Starting daily dose (mg)	Therapeutic daily dose (mg)
Fluoxetine (SSRI)	10	20–60
Sertraline (SSRI)	25	50–200
Paroxetine (SSRI)	10	10–40
Bupropion (NDRI)	75	200–300
Venlafaxine (SNRI)	18.75	75–225
Mirtazapine (TeCA)	7.5	15–45
Modafinil (Analeptic)	100	200–400
Citalopram (SSRI)	20	20–40
Escitalopram (SSRI)	10	10–40

SSRI selective serotonin reuptake inhibitor; *NDRI* norepinephrine-dopamine reuptake inhibitor; SNRI *serotonin-norepinephrine reuptake inhibitor*; *TeCA* tetracyclic antidepressant

Delirium

In the hospital setting, approximately 15% of elderly patients are reported to exhibit delirium on admission and another 10–40% are diagnosed with delirium during the hospitalization [29, 30]. In the nursing home setting, up to 60% of residents aged 75 years or older may be delirious cross-sectionally [31]. Elderly patients who develop delirium during a hospitalization have an estimated 22–76% chance of dying during that admission [32].

Delirium is the most common and serious neuropsychiatric complication in different types of cancer including liver, gastric, pancreatic, and colon cancer. Likewise, this acute confusional state is developed due to metabolic disorders such as hepatic encephalopathy, thiamine deficiency, hypoalbuminemia; systemic illness like postoperative states (bowel resection due to trauma and cancer, intestinal obstruction, perforation, or severe diverticular disease) [32–34].

Another factor commonly associated with the development of delirium is the abuse of laxatives, mainly among the elderly, possibly due to the belief that daily bowel movements are needed to maintain good health. Laxatives of the stimulant class are more frequently abused, yielding in a confusional state related to electrolyte imbalance and acid/base changes that can be life threatening [35]

Polypharmacy, common in the old, can result in adverse drug effects (ADEs), which may present as a variety of neuropsychological disorders and gastrointestinal (GI) syndromes; the former may include depression, cognitive impairment, and agitation amongst others, while the GI manifestations range from dry mouth and appetite disturbances, to constipation, diarrhea, and abdominal discomfort [36]. Delirium may be the only presenting feature of the life-threatening Serotonin Syndrome, resulting from the drug interaction involving the SSRI antidepressant citalopram and fluconazole, in frail, susceptible individuals such as cancer and elderly patients [37].

Chemotherapy agents have also been associated with delirium during the treatment of solid tumors and hematologic malignancies. Delirium due to ifosfamide toxicity is observed in 5–30% of patients with cancer; ifosfamide also

causes nausea and vomiting in over half of the patients, besides anorexia, diarrhea, and in some cases, constipation. Delirium due to the neuropsychiatric toxicity of ifosfamide is successfully treated with methylene blue that can be used either orally or intravenously [38]. Fatal gastrointestinal ADEs from neuroleptic medications are reported, such as death from constipation and bowel obstruction induced by clozapine, an antipsychotic commonly used in the treatment of schizophrenia not controlled with other neuroleptics, or when the schizophrenia presents with prominent negative symptoms [39].

Neuroleptics have become a crucial component of treatment of delirium, targeting agitation, paranoia, and hallucinations. The list of medications used in the management of delirium is provided in Table 72.2; however, primarily one must address the cause of delirium and inciting factors, and it involves correction of volume, electrolyte imbalance, treatment of infection, or withdrawing a medication that may have predisposed to delirium.

In a double-blind, randomized study comparing haloperidol, chlorpromazine, and lorazepam in the treatment of delirium, lorazepam alone was ineffective in the treatment of delirium. Moreover, lorazepam alone exacerbated delirium and increased cognitive impairment [32, 40]. However, since the use of lorazepam is acceptable in the treatment of alcohol withdrawal delirium, and the use of neuroleptics could decrease the threshold for seizures, the management of delirium syndrome should be on a case-by-case basis.

In another study, olanzapine appeared highly effective in patients younger than 70 years, while another atypical, risperidone, was more effective in controlling delirium symptoms in patients older than 70 years, with a history of dementia [41].

The important side effects of first-generation (typical) antipsychotics involve the dopaminergic system (galactorrhea) with extrapyramidal effects (parkinsonism, akathisia, dystonia, tardive dyskinesia), cholinergic system (urinary retention, constipation, visual disturbances), and histaminergic system (sedation). Among the atypical antipsychotics, weight gain, increased risk of diabetes, metabolic syndrome, stroke and cataract development are the most significant. Regardless of the typical or atypical character of the antipsychotics, all of them increase the risk of prolongation of the QTc interval and reduce the threshold for seizures.

Table 72.2 Medications commonly used to manage delirium

Drug	Daily dose range (mg)	Route
Haloperidol	0.25–5 mg every 2–12 h	IV, PO, SC, IM
Olanzapine	2.5–20 mg every 12–24 h	PO
Risperidone	0.5–3 mg every 12–24 h	PO
Quetiapine	12.5–200 mg every 12–24 h	PO
Lorazepam	O.5–2 mg every 1–4 h	PO, IV, IM
Midazolam	30–100 mg every 24 h	IV, SC

Special Considerations in Older Adults

In general, gold standard depression measures are not appropriate for use in geriatric cancer patients due to lack of validation and possibly fail to assess common symptoms of depression in this population [42]. Anxiety and depression are common in older adults, especially so in chronic disease, contributing to impairments and disabilities; higher rates are seen in inflammatory bowel disease, and may lead to deteriorating trends of the GI disease [43]. Screening for anxiety and depression in the older adult with GI illness, and timely referrals by the gastroenterologist or the primary physician/geriatrician to a psychiatrist for comanagement can be a useful strategy in the older age group [43].

Key Points

- Older patients with chronic GI illness may have a psychiatric disorder as the basis for complaints; on the other hand, the GI illness may contribute to depression or delirium from the complications of illness or treatment provided.
- The most common psychiatric comorbidities in this setting are depression, anxiety, and delirium.
- Antidepressants of the SSRI type and related, remain as first line for treatment of depression in the elderly.
- Whether typical or atypical, antipsychotics are helpful in controlling symptoms of delirium, but side effects must be taken into account when used in those with specific medical problems.

References

1. Alexander F. The influence of psychologic factors on gastrointestinal disturbances: A Symposium. 1: General principles, objectives and preliminary results. Psychoanalyt Quart. 1934;3:501.
2. Drossman DA, Creed FH, Olden KW, et al. Psychosocial aspects of the functional gastrointestinal disorders. Gut. 1999;45:1125–30.
3. Fava M, Uebelacker LA, Alpert JE, et al. Major depressive subtypes and treatment response. Biol Psychiatry. 1997;42(7):568–76.
4. Gaynes BN, Magruder KM, Burns BJ, et al. Does a coexisting anxiety disorder predict persistence of depressive illness in primary care patients with major depression? Gen Hosp Psychiatry. 1999;21(3):158–67.
5. Brown C, Schulberg HC, Madonia MJ, et al. Treatment outcomes for primary care patients with major depression and lifetime anxiety disorders. Am J Psychiatry. 1996;153(10):1293–300.
6. Older adults: Depression and suicide facts (Fact sheet). http://www.nimh.nih.gov/health/publications/older-adults-depression-and-suicide-facts. Accessed 10 Dec 2010.
7. Depression Guideline Panel. Depression in primary care, vol. 1. Detection and diagnosis. Clinical practice guideline, No. 5. AHCPR Publication No. 93-0550. Rockville, MD: Agency for Health Care, Policy and Research; 1993.
8. Lebowitz BD, Pearson JL, Schneider LS, et al. Diagnosis and treatment of depression in late life. Consensus statement update. JAMA. 1997;278(14):1186–90.

9. Zabora J, BrintzenhofeSzoc K, Curbow B, et al. The prevalence of psychological distress by cancer site. Psychooncology. 2001; 10(1):19.
10. Carney CP, Jones L, Woolson RF, et al. Relationship between depression and pancreatic cancer in the general population. Psychosom Med. 2003;65(5):884–8.
11. Massie M. Prevalence of depression in patients with cancer. J Natl Cancer Inst Monogr. 2004;32:57–71.
12. Musselman DL, Miller AH, Porter MR, et al. Higher than normal plasma interleukin-6 concentrations in cancer patients with depression: preliminary findings. Am J Psychiatry. 2001;158(8):1252–7.
13. Massie MJ. Depressive disorders. In: Holland JC et al., editors. Psychooncology. New York: Oxford University Press; 2010. p. 311–8.
14. Brintzenhofe-Szoc KM, Levin TT, Li Y, et al. Mixed anxiety-depression symptoms in a large cancer cohort: prevalence by cancer type. Psychosomatics. 2009;504(4):383–91.
15. Magni G. Assessments of depression in an elderly medical population. J Affect Disord. 1986;11:121.
16. Azar AR, Chopra MP, Cho LY, et al. Remission in major depression: results from a geriatric primary care population. Int J Gertiatr Psychiatry. 2011;26(1):28–55.
17. Miu DK, Chan CK. Prognostic value of depressive symptoms on mortality, morbidity and nursing home admission in older people. Geriatr Gerontol Int. 2010;11(2):174–9. doi:10.1111/j. 1447-0594. 2010.00665.x.
18. Lyness JM, Niculescu A, Tu X, et al. The relationship of medical comorbidity and depression in older primary care patients. Psychosomatics. 2006;47(5):435–9.
19. Hamer M, Bates CJ, Mishra GD. Depression, physical function, and risk of mortality: national diet and nutrition survey in adults older than 65 years. Am J Gertiatr Psychiatry. 2010;19(1):72–8.
20. Saka B, Kaya O, Ozturk GB, et al. Malnutrition in the elderly and its relationship with other geriatric syndromes. Clin Nutr. 2010; 29(6):748.
21. Wetherell JL, Ayers CR, Nuevo R, et al. Medical conditions and depressive, anxiety, and somatic symptoms in older adults with and without generalized anxiety disorder. Aging Ment Health. 2010; 14(6):764–8.
22. Bretibart W, Rosenfeld B, Pessin H, et al. Depression, hopelessness, and desire for hastened death in terminally ill patients with cancer. JAMA. 2000;284(22):2907–11.
23. Bretibart W, Rosenfeld B, Passik S. Interest in physician assisted suicide among ambulatory HIV-infected patients. J Am Psychiatry. 1996;153:238–42.
24. Emanule EJ, Fairclough DL, Daniels ER, et al. Euthanasia and physician assisted suicide: attitudes and experiences of oncology patients, oncologists, and the public. Lancet. 1996;347:1805–10.
25. Chochinov HM, Wilson KG, Enns M, et al. Depression, hopelessness, and suicidal ideation. Psychosomatics. 1998;39:366–70.
26. National Alliance on Mental Illness: Depression in older adults Fact Sheet. http://www.nami.org/template. Reviewed by Ken Duckworth, M.D., Oct 2009.
27. Arean PA, Mackin RS, Vargas-Dwyer E, et al. Treating depression in disabled, low-income elderly: a conceptual model and recommendations for care. Int J Geriatr Psychiatry. 2010;25(8):765–9.
28. Alexopoulos GS. Depression in the elderly. Lancet. 2005; 365(9475):1961–70. Review.
29. Kolbeinsson H, Jonsson A. Delirium and dementia in acute medical admissions of elderly patients in Iceland. Acta Psychiatr Scand. 1993;87:123–7.
30. Lipowski ZJ. Delirium (acute confusional states). JAMA. 1987;258:1789–92.
31. Sandberg O, Gustafson Y, Brannstrom B, et al. Prevalence of dementia, delirium and psychiatric symptoms in various care settings for the elderly. Scand J Soc Med. 1998;26:56–62.
32. Friedlander M, Breitbart W. Delirium in palliative care. Oncology (Williston Park). 2004;18(12):1541–53.
33. American Psychiatric Association. Practice guidelines for the treatment of patients with delirium. Am J Psychiatry. 1999;156 suppl 5:118–26.
34. Fann JR. The epidemiology of delirium: a review of studies and methodological issues. Semin Clin Neuropsychiatry. 2000;5(2):64–74.
35. Roerig JL, Steffen KJ, Mitchell JE, et al. Laxative abuse: epidemiology, diagnosis and management. Drugs. 2010;70(12):1487–503. Review.
36. Cecile M, Seux V, Pauly V, et al. Adverse drug events in hospitalized elderly patients in a geriatric medicine unit: study of prevalence and risk factors. Rev Med Interne. 2009;30(5):393–400.
37. Levin TT, Cortes-Ladino A, Weiss M, et al. Life-threatening toxicity due to a citalopram - fluconazole interaction: case reports and discussion. Gen Hosp Psychiatry. 2008;30(4):372–7.
38. Alici-Evcimen Y, Breitbart W. Ifosfamide neuropsychiatric toxicity in patients with cancer. Psychooncology. 2007; 16(10):956–60.
39. Levin TT, Barrett J, Mendelowitz A. Death from clozapine-induced constipation. Psychosomatics. 2002;43(1):71–3.
40. Breitbart W, Marotta R, Platt M. A double-blind comparison trial of haloperidol, chlorpromazine, and lorazepam in the treatment of delirium in hospitalized AIDS patients. Am J Psychiatry. 1996;153:231–7.
41. Breitbart W, Tremblay A, Gibson C. An open trial of olanzapine for the treatment of delirium in hospitalized cancer patients. Psychosomatics. 2002;43:175–6.
42. Nelson CJ, Cho C, Berk AR, et al. Are gold standard depression measures appropriate for use in geriatric cancer patients? A systematic evaluation of self-report depression instruments used with geriatric, cancer, and geriatric cancer samples. J Clin Oncol. 2010;28(2):348–56.
43. Graff LA, Walker JR, Bernstein CN. It's not just about the gut: managing depression and anxiety in inflammatory bowel disease. Pract Gastroenterol. 2010;34(7):11–25.

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