20th Edition

HARRISON'S™

PRINCIPLES OF INTERNAL MEDICINE

PREVIEW CHAPTERS FROM THE NEXT EDITION OF HARRISON'S!

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Chapter 1: The Practice of Medicine

The Editors

FIGURE 1-1

ENDURING VALUES OF THE MEDICAL PROFESSION

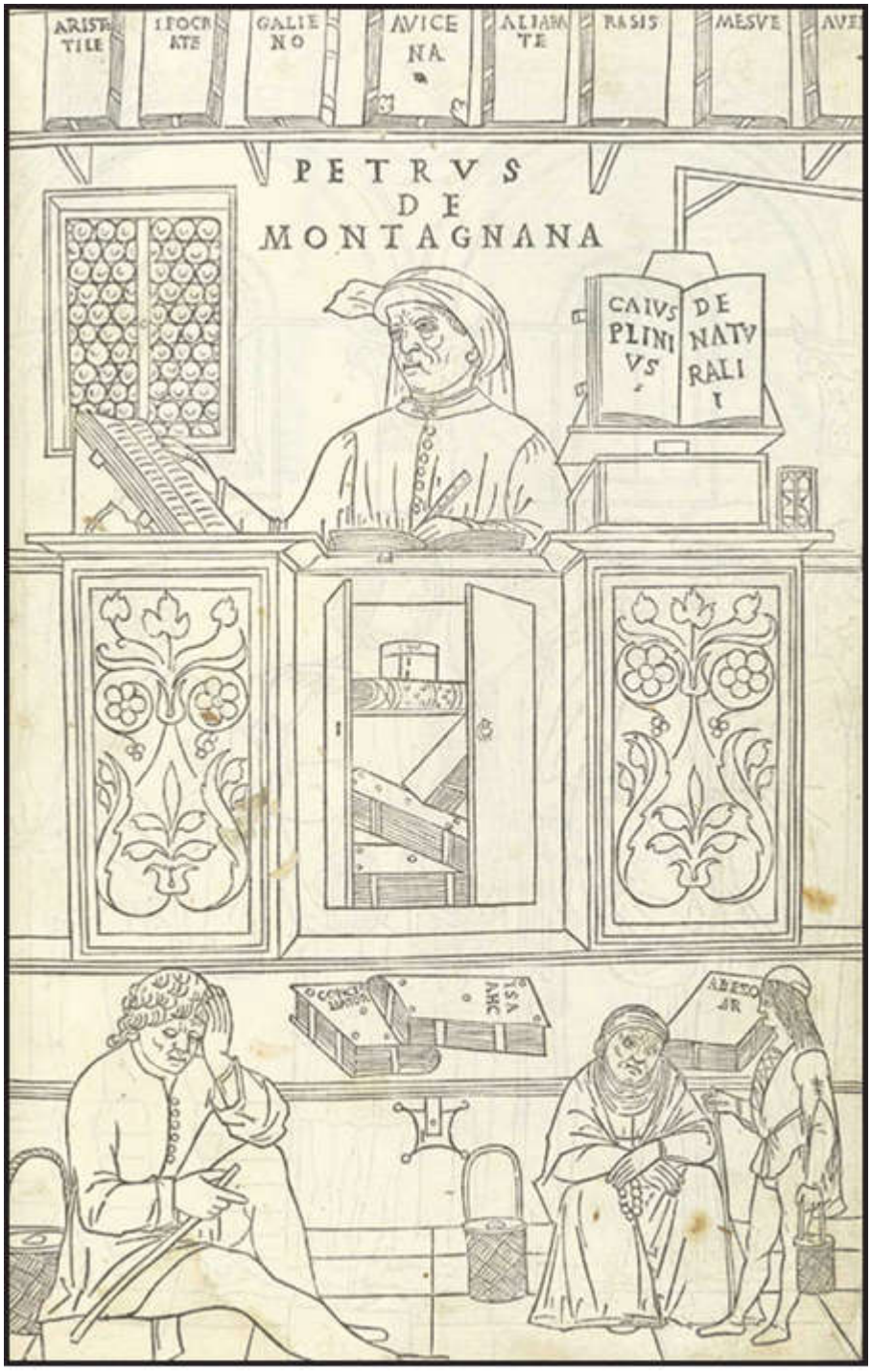
> *No greater opportunity, responsibility, or obligation can fall to the lot of a human being than to become a physician. In the care of the suffering, [the physician] needs technical skill, scientific knowledge, and human understanding.… Tact, sympathy, and understanding are expected of the physician, for the patient is no mere collection of symptoms, signs, disordered functions, damaged organs, and disturbed emotions. [The patient] is human, fearful, and hopeful, seeking relief, help, and reassurance.*
>
> —*Harrison's Principles of Internal Medicine,* 1950

The practice of medicine has changed in significant ways since the first edition of this book appeared in 1950. The advent of molecular genetics, sophisticated new imaging techniques, robotics, and advances in bioinformatics and information technology have contributed to an explosion of scientific information that has changed fundamentally the way physicians define, diagnose, treat, and attempt to prevent disease. This growth of scientific knowledge is ongoing and accelerating.

The widespread use of electronic medical records and the Internet have altered the way physicians access and exchange information as a routine part of medical practice **(Fig. 1-1)**. As today's physicians strive to integrate copious amounts of scientific knowledge into everyday practice, it is critically important to remember two things: first, the ultimate goal of medicine is to prevent disease and, when it occurs, to diagnose it early and provide effective treatment; and second, despite nearly 70 years of scientific advances since the first edition of this text, a trusting relationship between physician and patient still lies at the heart of successful patient care.

FIGURE 1-1

Woodcuts from Johannes de Ketham's *Fasciculus Medicinae*, the first illustrated medical text ever printed, show methods of information access and exchange in medical practice during the early Renaissance. Initially published in 1491 for use by medical students and practitioners, *Fasciculus Medicinae* appeared in six editions over the next 25 years. *Left:* Petrus de Montagnana, a well-known physician and teacher at the University of Padua and author of an anthology of instructive case studies, consults medical texts dating from antiquity up to the early Renaissance. *Right:* A patient with plague is attended by a physician and his attendants. *(Courtesy, U.S. National Library of Medicine.)*



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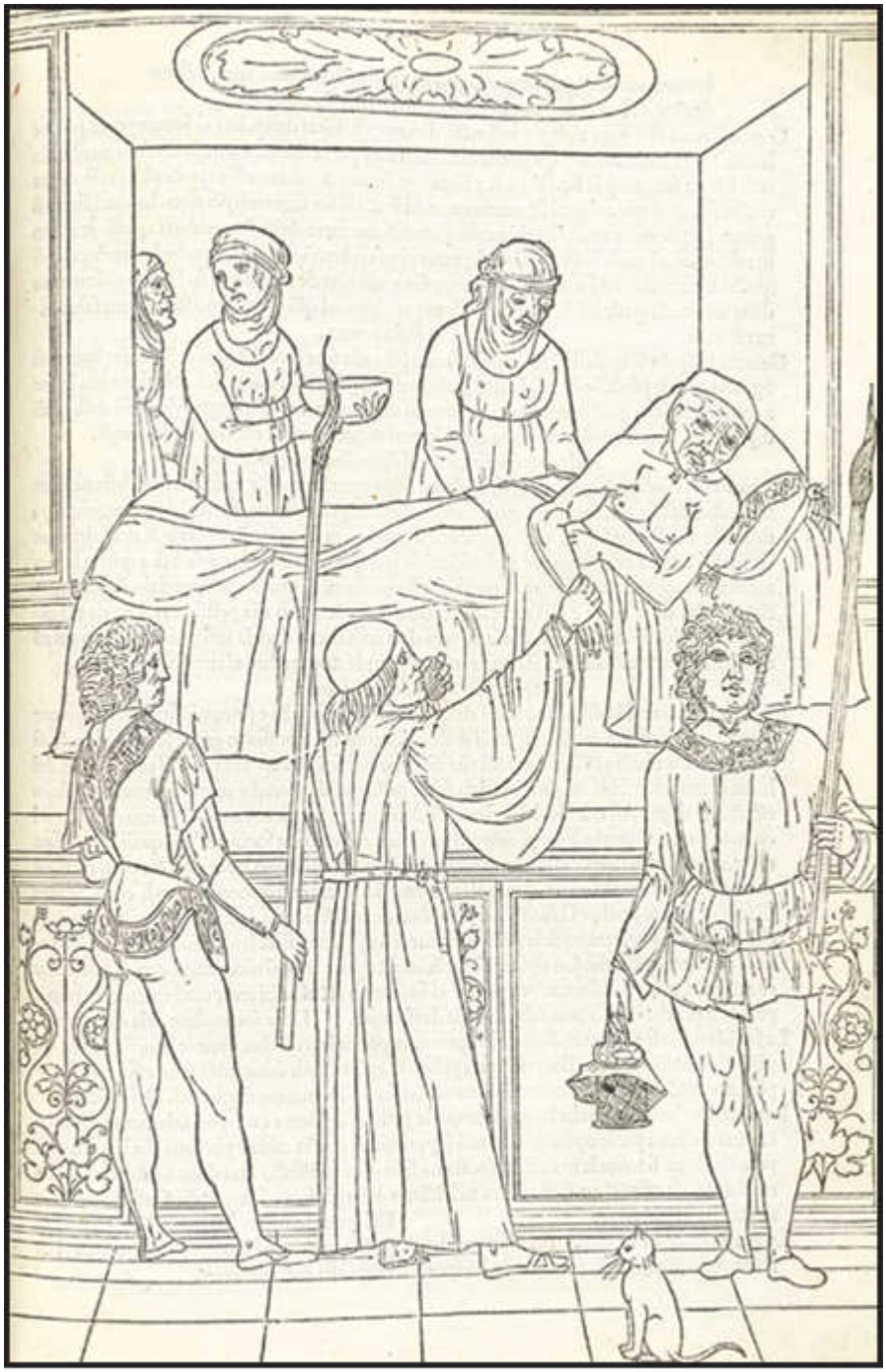

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THE SCIENCE AND ART OF MEDICINE

Deductive reasoning and applied technology form the foundation for the solution to many clinical problems. Spectacular advances in biochemistry, cell biology, and genomics, coupled with newly developed imaging techniques, allow access to the innermost parts of the cell and provide a window into the most remote recesses of the body. Revelations about the nature of genes and single cells have opened a portal for formulating a new molecular basis for the physiology of systems. Increasingly, physicians are learning how subtle changes in many different genes can affect the function of cells and organisms. Researchers are

Chapter 3: Decision-Making in Clinical Medicine

Daniel B. Mark; John B. Wong

INTRODUCTION

Sir William Osler's familiar quote "Medicine is a science of uncertainty and an art of probability" captures well the complex nature of clinical medicine. Although the science of medicine is often taught as if the mechanisms of the human body operate with Newtonian predictability, every aspect of medical practice is infused with an element of irreducible uncertainty that the clinician ignores at her peril. Clinical medicine has deep roots in science, but it is an imprecise science. More than 100 years after the practice of medicine took its modern form, it remains at its core a craft, to which individual doctors bring varying levels of skill and understanding. With the exponential growth in medical literature and other technical information and an ever increasing number of testing and treatment options, twenty-first century physicians who seek excellence in their craft must master a more diverse and complex set of skills than any of the generations that preceded them. This chapter provides an introduction to three of the pillars upon which the craft of modern medicine rests: (1) expertise in clinical reasoning (what it is and how it can be developed); (2) rational diagnostic tests, use and interpretation; and (3) integration of the best available research evidence with clinical judgment in the care of individual patients (*evidence-based medicine* or *EBM* and the tools of EBM).

BRIEF INTRODUCTION TO CLINICAL REASONING

Clinical Expertise

Defining "clinical expertise" remains surprisingly difficult. Chess has an objective ranking system based on skill and performance criteria. Athletics, similarly, have ranking systems to distinguish novices from Olympians. But in medicine, after physicians complete training and pass the boards (or get recertified), no tests or benchmarks are used to identify those who have attained the highest levels of clinical performance. Physicians often consult a few "elite" clinicians for their "special problem-solving prowess" when particularly difficult or obscure cases have baffled everyone else. Yet despite their skill, even such master clinicians typically cannot explain their exact processes and methods, thereby limiting the acquisition and dissemination of the expertise used to achieve their impressive results. Furthermore, clinical virtuosity appears not to be generalizable, e.g., an expert on hypertrophic cardiomyopathy may be no better (and possibly worse) than a first-year medical resident at diagnosing and managing a patient with neutropenia, fever, and hypotension.

Broadly construed, clinical expertise includes not only cognitive dimensions involving the integration of disease knowledge with verbal and visual cues and test interpretation but also potentially the complex fine-motor skills necessary for invasive procedures and tests. In addition, “the complete package” of expertise in medicine requires effective communication and care coordination with patients and members of the medical team. Research on medical expertise remains sparse overall and mostly centered on diagnostic reasoning, so in this chapter, we focus primarily on the cognitive elements of clinical reasoning.

Because clinical reasoning occurs in the heads of clinicians, objective study of the process is difficult. One research method used for this area asks clinicians to “think out loud” as they receive increments of clinical information in a manner meant to simulate a clinical encounter. Another research approach focuses on how doctors should reason diagnostically to identify remediable “errors” rather than on how they actually do reason. Much of what is known about clinical reasoning comes from empirical studies of nonmedical problem-solving behavior. Because of the diverse perspectives contributing to this area, with important contributions from cognitive psychology, medical education, behavioral economics, sociology, informatics, and decision sciences, no single integrated model of clinical reasoning exists, and not infrequently, different terms and reasoning models describe similar phenomena.

Intuitive Versus Analytic Reasoning

A useful contemporary model of reasoning, dual-process theory distinguishes two general systems of cognitive processes. *Intuition* (System 1) provides rapid effortless judgments from memorized associations using pattern recognition and other simplifying “rules of thumb” (i.e., heuristics). For example, a very simple pattern that could be useful in certain situations is “African-American women plus hilar adenopathy equals sarcoid.” Because no effort is involved in recalling the pattern, typically, the clinician is unable to say how those judgments were formulated. In contrast, *Analysis* (System 2), the other form of reasoning in the dual-process model, is slow, methodical, deliberative, and effortful. A student might read about lymph nodes in the lung and from that list (e.g., **Chap. 62**), identify diseases more common in African-American women or examine the patient for skin or eye findings that may occur with sarcoid. These dual processes, of course, represent two exemplars taken from the cognitive continuum. They provide helpful descriptive insights but very little guidance in how to develop expertise in clinical reasoning. How these idealized systems interact in different decision problems, how experts use them differently from novices, and when their use can lead to errors in judgment remain the subject of study and considerable debate.

Pattern recognition, an important part of System 1 reasoning, is a complex cognitive process that appears largely effortless. One can recognize people’s faces, the breed of a dog, an automobile model, or a piece of music from just a few notes within milliseconds without necessarily being able to articulate the specific features that prompted the recognition. Analogously, experienced clinicians often recognize familiar diagnosis patterns very quickly. The key here is having a large library of stored patterns that can be rapidly accessed. In the absence of an extensive stored repertoire of diagnostic patterns, students (as well as more experienced clinicians operating outside their area of expertise and familiarity) often must use the more

laborious System 2 analytic approach along with more intensive and comprehensive data collection to reach the diagnosis.

The following three brief scenarios of a patient with hemoptysis illustrate three distinct patterns that experienced clinicians recognize without effort:

A 46-year-old man presents to his internist with a chief complaint of hemoptysis. An otherwise healthy, nonsmoker, he is recovering from an apparent viral bronchitis. This presentation pattern suggests that the small amount of blood-streaked sputum is due to acute bronchitis, so that a chest x-ray provides sufficient reassurance that a more serious disorder is absent.

In the second scenario, a 46-year-old patient who has the same chief complaint but with a 100-pack-year smoking history, a productive morning cough, with blood-streaked sputum, and weight loss fits the pattern of carcinoma of the lung. Consequently, along with the chest x-ray, the clinician obtains a sputum cytology examination and refers this patient for a chest CT scan.

In the third scenario, the clinician hears a soft diastolic rumbling murmur at the apex on cardiac auscultation in a 46-year-old patient with hemoptysis who immigrated from a developing country and orders an echocardiogram as well, because of possible pulmonary hypertension from suspected rheumatic mitral stenosis.

Pattern recognition by itself is not, however, sufficient for secure diagnosis. Without deliberative systematic reflection, pattern recognition can result in premature closure: mistakenly jumping to the conclusion that one has correct diagnosis before all the relevant data are in. A critical second step, even when the diagnosis seems obvious, is *diagnostic verification*: considering whether the diagnosis adequately accounts for the presenting symptoms and signs and can explain all the ancillary findings. An example of premature closure is contained in the following case, modified from a real clinical encounter. A 45-year-old man presents with a 3-week history of a “flulike” upper respiratory infection (URI) including dyspnea and a productive cough. The Emergency Department (ED) clinician pulled out a “URI assessment form” which defines and standardizes the information gathered. After quickly acquiring the requisite structured examination components and noting in particular the absence of fever and a clear chest examination, the physician prescribed a cough suppressant for acute bronchitis and reassured the patient that his illness was not serious. Following a sleepless night at home with significant dyspnea, the patient developed nausea and vomiting and collapsed. He was brought back to the ED in cardiac arrest and was unable to be resuscitated. His autopsy showed a posterior wall myocardial infarction (MI) and a fresh thrombus in an atherosclerotic right coronary artery. What went wrong? Presumably, the ED clinician felt that the patient was basically healthy (one can be misled by the way the patient appears on examination—a patient that does not “appear sick” may be incorrectly assumed to have an innocuous illness). So in this case, the physician, upon hearing the overview of the patient from the triage nurse, elected to use the URI assessment protocol even before starting the history, closing consideration of the broader range of possibilities and associated tests required to confirm or refute these possibilities. In particular, by concentrating on the abbreviated and focused URI protocol, the clinician

failed to elicit the full dyspnea history, which was precipitated by exertion and accompanied by chest heaviness and relieved by rest, suggesting a far more serious disorder.

Heuristics or rules of thumb are a part of the intuitive system. These cognitive shortcuts provide a quick and easy path to reaching conclusions and making choices, but when used improperly they can lead to errors. Two major research programs have studied heuristics in a mostly non-medical context and have reached very different conclusions about the value of these cognitive tools. The “heuristics and biases” program focuses on how relying on heuristics can lead to cognitive biases and incorrect judgments. Over 100 different cognitive biases have been described. So far, however, there is little evidence that educating physicians and other decision makers to watch for these cognitive biases has any effect on the rate of diagnostic errors. In contrast, the “fast and frugal heuristics” research program explores how and when relying on simple heuristics can produce good decisions. Although many heuristics have relevance to clinical reasoning, only four will be mentioned here.

When diagnosing patients, clinicians usually develop diagnostic hypotheses based on the similarity of that patient’s symptoms, signs and other data to their mental representations (memorized patterns) of the disease possibilities. In other words, clinicians pattern match to identify the diagnoses which share the most similar findings to the patient at hand. This cognitive shortcut is called the representativeness heuristic. Consider a patient with hypertension and headache, palpitations, and diaphoresis. Based on the representativeness heuristic, clinicians might judge pheochromocytoma to be quite likely given this classic presenting symptom triad suggesting pheochromocytoma. Doing so however, would be incorrect given that other causes of hypertension are much more common than pheochromocytoma and this triad of symptoms can occur in patients who do not have it. Thus, clinicians using the representativeness heuristic may overestimate the likelihood of a particular disease based on its representativeness by failing to recognize the low underlying prevalence (i.e., the prior, or pretest, probabilities). Conversely, atypical presentations of common diseases may lead to underestimating the likelihood of a particular disease. Thus, inexperience with a specific disease and with the breadth of its presentations may also lead to diagnostic delays or errors, e.g., diseases that affect multiple organ systems, such as sarcoid or tuberculosis, may be particularly challenging to diagnose because of the many different patterns they may manifest.

A second commonly used cognitive shortcut, the availability heuristic, involves judgments based on how easily prior similar cases or outcomes can be brought to mind. For example, a clinician may recall a case from a morbidity and mortality conference in which an elderly patient presented with painless dyspnea of acute onset and was evaluated for a pulmonary cause, but eventually found to have acute MI with the diagnostic delay likely contributing to the development of ischemic cardiomyopathy. If the case was associated with a malpractice accusation, such examples may be even more memorable. Errors with the availability heuristic arise from several sources of recall bias. Rare catastrophes are likely to be remembered with a clarity and force disproportionate to their likelihood for future diagnosis—for example, a patient with a sore throat eventually found to have leukemia or a young athlete with leg pain subsequently found to have a sarcoma—and those publicized in the media or recent experience are, of course, easier to recall and therefore more influential on clinical judgments.

gentamicin component is given for only 2–3 weeks have been curative and associated with less nephrotoxicity than those using longer courses. Thus some experts prefer regimens wherein gentamicin is administered for only 2–3 weeks.

If there is high-level resistance to both gentamicin and streptomycin, a synergistic bactericidal effect cannot be achieved with an aminoglycoside; thus an aminoglycoside should not be given. Instead, an 8- to 12-week course of a single cell wall–active agent can be considered; however, high doses of ampicillin combined with ceftriaxone or cefotaxime have been suggested for *E. faecalis* endocarditis (Table 123-4). Nonrandomized comparative studies suggest that ampicillin-ceftriaxone may be as effective as (and less nephrotoxic than) penicillin or ampicillin plus an aminoglycoside in the treatment of *E. faecalis* endocarditis and may provide effective treatment when strains possess high-level resistance to gentamicin and streptomycin. This regimen may also be preferred in patients who are at increased risk for aminoglycoside nephrotoxicity or in lieu of streptomycin.

If the enterococcal isolate is resistant to all of the commonly used agents, suppression of bacteremia followed by surgical treatment should be considered. The role of agents potentially active against multidrug-resistant enterococci (quinupristin/dalfopristin [*E. faecium* only], linezolid, and daptomycin) in the treatment of endocarditis has not been established.

Staphylococci

The regimens used to treat staphylococcal endocarditis (Table 123-4) are based not on coagulase production but rather on the presence or absence of a prosthetic valve or foreign device, the native valve(s) involved (right vs left side), and the susceptibility of the isolate to penicillin, methicillin, and vancomycin. All staphylococci are considered potentially penicillin resistant and, except in specific countries, methicillin resistant. Thus empirical therapy for possible staphylococcal NVE should use a regimen that covers methicillin-resistant organisms. Therapy should be revised to a β-lactam agent if the isolate is susceptible to methicillin. The addition of 3–5 days of gentamicin to a β-lactam antibiotic or vancomycin to enhance therapy for left-sided NVE has not improved survival rates and is associated with nephrotoxicity. Most guidelines do not recommend the routine addition of gentamicin, fusidic acid, or rifampin to regimens for *S. aureus* NVE.

For treatment of NVE due to *methicillin-resistant S. aureus* (MRSA), vancomycin, dosed to achieve trough concentrations of 15–20 μg/mL, is recommended, with the caveat that this regimen may be associated with nephrotoxicity. Although resistance to vancomycin among staphylococci is rare, reduced vancomycin susceptibility among MRSA strains is increasingly encountered. Isolates with a vancomycin MIC of 4–16 μg/mL have intermediate susceptibility and are referred to as *vancomycin-intermediate S. aureus* (VISA). Isolates with a vancomycin MIC of 2 μg/mL may harbor subpopulations with higher MICs. Isolates with these subpopulations, called *heteroresistant VISA* (hVISA), are not detectable by routine susceptibility testing and yet may impair vancomycin efficacy. Because of the pharmacokinetics/pharmacodynamics of vancomycin, killing of MRSA with a vancomycin MIC of >1.0 μg/mL is unpredictable, even with aggressive vancomycin dosing. As an alternative to vancomycin, daptomycin (8–10 mg/kg IV once daily) has provided effective treatment for left-sided NVE caused by documented daptomycin-susceptible VISA, hVISA, or isolates with a vancomycin MIC of >1.0 μg/mL (not approved by the U.S. Food and Drug Administration for this indication). Daptomycin activity against MRSA—even against some isolates with reduced daptomycin susceptibility—is enhanced in combination with nafcillin or ceftaroline. Case series suggest that either high-dose daptomycin combined with nafcillin or ceftaroline or ceftaroline alone (600 mg IV q8h) may be effective treatment for vancomycin-unresponsive MRSA endocarditis. Infectious disease consultation is recommended for treatment of MRSA endocarditis when bacteremia persists despite therapy. The efficacy of linezolid or telavancin for left-sided MRSA endocarditis has not been established. Although it is not advocated by other groups, the British Society for Antimicrobial Chemotherapy recommends the addition of a second drug to vancomycin (rifampin) or to daptomycin (rifampin, gentamicin, or linezolid) for the treatment of MRSA NVE.

Methicillin-susceptible *S. aureus* endocarditis that is uncomplicated and limited to the tricuspid or pulmonic valve can often be treated with a 2-week course that combines oxacillin or nafcillin (but not vancomycin) with gentamicin. However, patients with prolonged fever (≥5 days) during therapy or multiple septic pulmonary emboli should receive standard-duration therapy. Vancomycin plus gentamicin for 2 weeks for right-sided endocarditis caused by MRSA yields suboptimal results; thus this entity is treated for at least 4 weeks with vancomycin or daptomycin (6 mg/kg as a single daily dose).

Staphylococcal PVE is treated for 6–8 weeks with a multidrug regimen (Table 123-4). Rifampin is an essential component because it kills staphylococci that are adherent to foreign material in a biofilm. Two other agents (selected on the basis of susceptibility testing) are combined with rifampin to prevent in vivo emergence of rifampin resistance. Because many staphylococci (particularly MRSA and

Staphylococcus epidermidis causing PVE) are resistant to gentamicin, the isolate's susceptibility to gentamicin or an alternative agent should be established before rifampin treatment is begun. Possible alternatives for gentamicin include another aminoglycoside, a fluoroquinolone (chosen on the basis of susceptibility), ceftaroline, or another active agent.

Other Organisms

In the absence of meningitis, endocarditis caused by *Streptococcus pneumoniae* isolates with a penicillin MIC of ≤4 μg/mL can be treated with IV penicillin (4 million units every 4 h), ceftriaxone (2 g/d as a single dose), cefotaxime (at a comparable dose), or vancomycin. Ceftriaxone or vancomycin is preferred for pneumococcal strains with a penicillin MIC of ≥2 μg/mL. If meningitis is suspected, treatment with vancomycin plus ceftriaxone—at the doses advised for meningitis—should be initiated until susceptibility results are known. Definitive therapy should then be selected on the basis of meningitis breakpoints (penicillin MIC, 0.06 μg/mL; or ceftriaxone MIC, 0.5 μg/mL). Pneumococcal NVE is treated for 4 weeks and pneumococcal PVE for 6 weeks. *P. aeruginosa* endocarditis is treated with an antipseudomonal β-lactam (piperacillin or a cephalosporin) and high doses of tobramycin (8 mg/kg per day in three divided doses). Endocarditis caused by Enterobacteriaceae is treated with a potent β-lactam antibiotic plus an aminoglycoside. Corynebacterial endocarditis is treated with penicillin plus an aminoglycoside (if the organism is susceptible to the aminoglycoside) or with vancomycin, which is highly bactericidal for most strains. Therapy for *Candida* endocarditis consists of a lipid formulation of amphotericin B (3–5 mg/kg IV qd) plus flucytosine (25 mg/kg PO q6h) or a high-dose echinocandin (caspofungin or micafungin, 150 mg IV qd; or anidulafungin, 200 mg IV qd). Early surgery is advised, as is long-term (if not indefinite) suppression with an oral azole.

Empirical Therapy and Treatment for Culture-Negative Endocarditis

In designing therapy to be administered before culture results are known or when cultures are truly negative, clinical clues to etiology (e.g., acute vs. subacute presentation, NVE, early or late PVE, the patient's predispositions) as well as epidemiologic clues (region of residence, animal exposure) must be considered. Thus empirical therapy for acute endocarditis in an injection drug user or for health care–associated NVE should cover MRSA and potentially antibiotic-resistant gram-negative bacilli. Treatment with vancomycin plus gentamicin or cefepime, initiated immediately after blood cultures are obtained, covers these organisms as well as many other potential causes. For empirical treatment of NVE with a subacute presentation, vancomycin plus ceftriaxone is reasonable. For blood culture–pending PVE, vancomycin, gentamicin, and cefepime should be used if the prosthetic valve has been in place for ≤1 year. Empirical therapy for infected prosthetic valves in place for >1 year is similar to that for culture-negative NVE. Therapy is revised once a pathogen has been identified.

In the treatment of blood culture–negative episodes, marantic endocarditis and the antiphospholipid antibody syndrome must be considered. Fastidious organisms should be investigated by serologic testing. In the absence of prior antibiotic therapy, it is unlikely that infection due to *S. aureus*, CoNS, enterococci, or Enterobacteriaceae will present with negative blood cultures; thus, in this situation, recommended empirical therapy targets not these organisms but rather fastidious streptococci, nutritionally variant organisms, the HACEK group, and *Bartonella* species. Pending the availability of diagnostic data, blood culture–negative subacute NVE is treated with vancomycin plus ampicillin-sulbactam (12 g every 24 h) or ceftriaxone; doxycycline (100 mg twice daily) is added for enhanced *Bartonella* coverage. If cultures are negative because of prior antibiotic administration, pathogens that are likely to be inhibited by the specific prior therapy should be considered.

CIED Endocarditis

Antimicrobial therapy for CIED endocarditis (as well as for generator pocket and lead infection) is adjunctive to complete removal of the device. The antimicrobial selected is based on the causative organism and should be used as recommended for NVE (Table 123-4). Bacteremic CIED infection may be complicated by coincident left-sided NVE, PVE, or remote-site infection (e.g., osteomyelitis) and may require modification of antimicrobial therapy. A 4- to 6-week course of endocarditis-targeted therapy is recommended for patients with CIED endocarditis and for those with bacteremia that continues during ongoing antimicrobial therapy after device removal. Generator pocket infection without bacteremia is treated with a 10- to 14-day course, some of which can be given orally. In the absence of another source, *S. aureus* bacteremia (and persistent CoNS bacteremia) in patients with a CIED is likely to be indicative of CIED or valvular endocarditis and should be managed accordingly. However, not all bloodstream infections in these patients indicate endocarditis. If evidence suggesting endocarditis is lacking, bloodstream infection due to gram-negative bacilli, streptococci, enterococci, and *Candida* species may not indicate endocarditis and can be treated with an abbreviated course of antimicrobial therapy. However, in the absence of another source, bacteremia relapse after antimicrobial therapy increases the likelihood of CIED

endocarditis and warrants treatment as such. Attempted salvage of an infected CIED with antibiotics alone is usually unsuccessful and should be reserved for patients whose devices cannot be removed or who refuse removal.

Outpatient Antimicrobial Therapy

Fully compliant, clinically stable patients who are no longer bacteremic, are not febrile, and have no clinical or echocardiographic findings that suggest an impending complication may complete therapy as outpatients. Careful follow-up and a stable home setting are necessary, as are predictable IV access and use of antimicrobial agents that are stable in solution. Recommended regimens should not be compromised to accommodate outpatient therapy.

Monitoring Antimicrobial Therapy

Antibiotic toxicity, including allergic reactions, occurs in 25–40% of endocarditis patients and commonly arises after several weeks of therapy. Blood tests to detect renal, hepatic, and hematologic toxicity should be performed periodically. Serum concentrations of aminoglycosides and vancomycin should be monitored periodically and doses adjusted to optimize treatment and to avoid or address toxicity.

Blood cultures should be repeated daily until sterile in patients with endocarditis due to *S. aureus* or difficult-to-treat organisms, rechecked if there is recrudescent fever, and performed again 4–6 weeks after therapy to document cure. Blood cultures become sterile within 2 days after the start of appropriate therapy when infection is caused by viridans streptococci, enterococci, or HACEK organisms. In *S. aureus* endocarditis, β-lactam therapy results in sterile cultures in 3–5 days, whereas in MRSA endocarditis, positive cultures may persist for 7–9 days with vancomycin or daptomycin treatment. MRSA bacteremia persisting despite an adequate dosage of vancomycin or daptomycin may indicate emergence of reduced susceptibility in the infecting strain and point to a need for alternative therapy. When fever persists for 7 days despite appropriate antibiotic therapy, patients should be evaluated for paravalvular abscess, extracardiac abscesses (spleen, kidney), or complications (embolic events). Recrudescent fever raises the possibility of these complications but also of drug reactions or complications of hospitalization. Vegetations become smaller with effective therapy; however, 3 months after cure, 50% are unchanged and 25% are slightly larger or smaller.

Antithrombotic Therapy

A decision to initiate antithrombotic (anticoagulant or antiplatelet) therapy in patients with infective endocarditis requires careful consideration of the risks and benefits, including temporal considerations of each. Patients with infective endocarditis are at risk for emboli, for hemorrhagic transformation of embolic strokes, and for intracerebral hemorrhage from septic arteritis or ruptured mycotic aneurysms. Antithrombotic therapy can render this bleeding catastrophic. Neither anticoagulant nor antiplatelet therapy reduces the risk of emboli in patients with NVE, and thus such treatment is not indicated for that purpose. However, patients with infective endocarditis may have coexisting conditions wherein anticoagulation is indicated. Thus, in the absence of a contraindication (i.e., no clinical or imaging evidence of a recent large embolic stroke, intracerebral hemorrhage, or mycotic aneurysm), anticoagulant therapy is given to patients who have a mechanical prosthetic valve, atrial fibrillation with either mitral stenosis or a CHADS2 score ≥2, or deep-vein thrombophlebitis. Most experts prefer to use unfractionated or low-molecular-weight heparin for ease of reversal. Anticoagulant therapy should be reversed, at least temporarily, in most patients who have had an acute ischemic stroke or an intracerebral hemorrhage.

SURGICAL TREATMENT

Intracardiac and central nervous system complications of endocarditis are important causes of morbidity and death. In some cases, effective treatment for these complications requires surgery. The indications for cardiac surgical treatment of endocarditis (Table 123-5) have been derived from observational studies and expert opinion. The strength of individual indications varies; thus the risks and benefits as well as the timing of surgery must be individualized (Table 123-6). These complex considerations are best weighed by a team that includes cardiologists, cardiac surgeons, infectious disease physicians, and neurologists if there have been neurologic complications. From 25 to 40% of patients with left-sided endocarditis undergo cardiac surgery during active infection, with slightly higher surgery rates for PVE than NVE. Intracardiac complications and CHF are the most commonly cited indications for surgery. The benefit of surgery has been assessed primarily in studies comparing populations of medically and surgically treated patients matched for the necessity of surgery, with adjustments for predictors of death (comorbidities) and the timing of surgical intervention (a correction for survival bias). Although study results vary, surgery for NVE based on current indications appears to convey a significant survival benefit (27–55%) that becomes increasingly apparent among patients with the most pressing indications and with follow-up

for ≥6 months. The effect of surgery for PVE is more nuanced, with survival benefits accruing largely to those with intracardiac complications. Of note, surgery itself carries mortality risks that may offset survival benefits in patients with lesser indications.

Indications

Congestive Heart Failure

Moderate to severe refractory CHF caused by new or worsening valve dysfunction or intracardiac fistulae is the major indication for cardiac surgery. Surgery can relieve functional stenosis due to large vegetations or restore competence to damaged regurgitant valves by repair or replacement. At 6–12 months of follow-up, the mortality rate is 50% among patients with left-sided NVE or PVE and moderate to severe heart failure due to valve dysfunction who are treated medically, while that among matched patients treated surgically is 15%. The survival benefit with surgery is inversely related to the severity of preoperative CHF; thus surgery should not be delayed in the face of deteriorating hemodynamics.

Perivalvular Infection

This complication, which is most common with aortic valve infection, occurs in 10–15% of patients with NVE and in 45–60% of those with PVE. It is suggested clinically by persistent unexplained fever during appropriate therapy, new electrocardiographic conduction disturbances, or pericarditis. TEE with color Doppler is the test of choice to detect perivalvular abscesses (sensitivity, ≥85%). Occasionally, three-dimensional TEE and FDG-PET/CT demonstrate perivalvular infection not detected by TEE. For optimal outcome, surgery is required, especially when fever persists, fistulae develop, prostheses are dehisced and unstable, or infection relapses after appropriate treatment. Cardiac rhythm must be monitored since high-grade heart block may require insertion of a pacemaker.

Uncontrolled Infection

Continued positive blood cultures or otherwise unexplained persistent fevers despite optimal antibiotic therapy may reflect uncontrolled infection that warrants surgery. Surgical treatment is also advised for endocarditis caused by organisms against which effective antimicrobial therapy is lacking (e.g., yeasts, fungi, *P. aeruginosa*, other highly antibiotic-resistant bacteria, *Brucella* species).

S. aureus Endocarditis

The mortality rate for *S. aureus* PVE exceeds 50% with medical treatment but is reduced to 25% with surgical treatment. When patients have intracardiac complications, surgical treatment reduces the mortality rate twentyfold. However, surgery is not routinely advised for uncomplicated *S. aureus* PVE. Surgical treatment should be considered for patients with MRSA left-sided NVE who remain septic and unresponsive to alternative antibiotics. Isolated tricuspid-valve *S. aureus* endocarditis, even with persistent fever, rarely requires surgery.

Prevention of Systemic Emboli

Persisting morbidity and/or death may result from cerebral or coronary artery emboli. Antithrombotic therapy does not prevent systemic emboli in NVE. The frequency of embolization decreases rapidly with effective antimicrobial therapy. Thus, to further reduce emboli through cardiac surgery, the surgery must be performed very early. Predicting a high risk of systemic embolization by echocardiographic determination of vegetation size and anatomy does not identify those patients in whom surgery to prevent emboli will result in increased survival. In a small randomized trial in patients who were at low risk of surgery-related mortality and had large vegetations (>10 mm) and significant valve dysfunction, emboli were prevented by early surgery (≤48 h after diagnosis), but there was no survival benefit. Rarely is the indication for surgery solely to prevent systemic emboli; however, this goal may be an additional benefit of early surgery for other indications. Valve repair, with the consequent avoidance of a prosthesis, improves the benefit-to-risk ratio of surgery performed to eliminate vegetations.

Cied Endocarditis

Removal of all hardware is recommended for patients with established CIED endocarditis as well as for pocket or intracardiac lead infection. Percutaneous lead extraction is preferred; with retained hardware after attempted percutaneous extraction, surgical removal should be considered. With lead vegetations >2 cm, there is a risk of a pulmonary embolism; nevertheless, the need for surgical removal of the CIED is unclear. Removal of the infected CIED during the initial hospitalization is associated with increased 30-day and 1-year survival rates over those attained with antibiotic therapy and attempted device retention. The CIED, if needed, can be reimplanted at a new site after at least 10–14 days of effective antimicrobial therapy. CIEDs should be replaced when patients undergo surgery for endocarditis.

Chapter 156: Diseases Caused by Gram-Negative Enteric Bacilli

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FIGURE 156-1

GENERAL FEATURES AND PRINCIPLES

The post-antibiotic era has begun. For most people, this is the first time in their lives that an effective treatment for a bacterial infection may not exist. The Enterobacteriaceae are at the forefront of this evolving public health crisis. For example, the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) have designated carbapenem-resistant Enterobacteriaceae as representing a threat level of "urgent" and "priority one, critical," respectively. Enterobacteriaceae are responsible for a significant proportion of the deaths attributed to resistant bacteria, the number of which has been estimated at 23,000 and 25,000 annually in the United States and the European Union, respectively, with numbers three- to fivefold greater (per capita) in low- and middle-income countries (e.g., Thailand). These pathogens cause a wide variety of infections involving diverse anatomic sites in both healthy and compromised hosts. Therefore, a thorough knowledge of clinical presentations and appropriate therapeutic choices is necessary for optimal outcomes. *Escherichia coli*, *Klebsiella*, *Proteus*, *Enterobacter*, *Serratia*, *Citrobacter*, *Morganella*, *Providencia*, *Cronobacter*, and *Edwardsiella* are enteric gram-negative bacilli (GNB) that are members of the family Enterobacteriaceae. *Salmonella*, *Shigella*, and *Yersinia*, also in the family Enterobacteriaceae, are discussed in **Chaps. 160**, **161**, **and 166**, respectively.

EPIDEMIOLOGY

E. coli, *Klebsiella*, *Proteus*, *Enterobacter*, *Serratia*, *Citrobacter*, *Morganella*, *Providencia*, *Cronobacter*, and *Edwardsiella* are components of the normal animal and human colonic microbiota and/or the microbiota in various environmental habitats, including long-term-care facilities (LTCFs) and hospitals. As a result, except for certain pathotypes of intestinal pathogenic *E. coli*, these genera are global pathogens. The incidence of infection due to these agents is increasing because of the combination of an aging population and increasing antimicrobial resistance. In healthy humans, *E. coli* is the predominant species of GNB in the colonic microbiota; *Klebsiella* and *Proteus* are less prevalent. GNB (primarily *E. coli*, *Klebsiella*, and *Proteus*) colonize the oropharynx and skin of healthy individuals only transiently. By contrast, in LTCFs and hospital settings, a variety of GNB emerge as the dominant colonizers of both mucosal and skin surfaces, particularly in association with antimicrobial use, severe illness, and extended length of stay. LTCFs are emerging as an

important reservoir for resistant GNB. This colonization may lead to subsequent infection; for example, oropharyngeal colonization may lead to pneumonia, and colonic/perineal colonization may lead to urinary tract infection (UTI). The use of ampicillin or amoxicillin was associated with an increased risk of subsequent infection due to the hypervirulent pathotype of *Klebsiella pneumoniae* in Taiwan; this association suggests that changes in the quantity or prevalence of colonizing bacteria may significantly influence the risk of infection. *Serratia* and *Enterobacter* infection may be acquired directly through a variety of infusates (e.g., medications, blood products). *Edwardsiella* infections are acquired through freshwater and marine environment exposures and are most common in Southeast Asia.

STRUCTURE AND FUNCTION

Enteric GNB possess an extracytoplasmic outer membrane consisting of a lipid bilayer with associated proteins, lipoproteins, and polysaccharides (capsule, lipopolysaccharide). The outer membrane interfaces with the external environment, including the human host. A variety of components of the outer membrane are critical determinants in pathogenesis (e.g., capsule) and antimicrobial resistance (e.g., permeability barrier, efflux pumps). In addition, secreted products play an important role in both host infection (e.g., iron acquisition molecules) and environmental niche survival and colonization (e.g., type VI secretion systems).

PATHOGENESIS

Multiple bacterial virulence factors are required for the pathogenesis of infections caused by GNB. Possession of specialized virulence genes defines pathogens and enables them to infect the host efficiently. Hosts and their cognate pathogens have been co-adapting throughout evolutionary history. During the host–pathogen "chess match" over time, various and redundant strategies have emerged in both the pathogens and their hosts **(Table 156-1)**.

TABLE 156-1

Interactions of Extraintestinal Pathogenic *Escherichia coli* with the Human Host: A Paradigm for Extracellular, Extraintestinal Gram-Negative Bacterial Pathogens

Bacterial Goal	Host Obstacle	Bacterial Solution
Extraintestinal attachment	Flow of urine, mucociliary escalator	Multiple adhesins (e.g., type 1, S, and F1C fimbriae; P pili)
Nutrient acquisition for growth	Nutrient sequestration (e.g., iron via intracellular storage and extracellular scavenging via lactoferrin and transferrin)	Cellular lysis (e.g., hemolysin), multiple mechanisms for competing for iron (e.g., siderophores) and other nutrients
Initial avoidance of host bactericidal activity	Complement, phagocytic cells, antimicrobial peptides	Capsular polysaccharide, lipopolysaccharide
Dissemination (within host and between hosts)	Intact tissue barriers	Irritant tissue damage resulting in increased excretion (e.g., toxins such as hemolysin), invasion of brain endothelium
Late avoidance of host bactericidal activity	Acquired immunity (e.g., specific antibodies), treatment with antibiotics	Cell entry, acquisition of antimicrobial resistance

Intestinal pathogenic (diarrheagenic) mechanisms are discussed below. The members of the Enterobacteriaceae family that cause extraintestinal infections are primarily extracellular pathogens and therefore share certain pathogenic features. The principal components of host defense against Enterobacteriaceae, regardless of species, are innate immunity (including intact skin and mucosal barriers; the withholding of nutrients; and the activities of complement, antimicrobial peptides, and professional phagocytes) and humoral immunity. Both susceptibility to and severity of infection are increased with dysfunction or deficiencies of these host components. By contrast, the virulence traits of intestinal pathogenic *E. coli*—i.e., the distinctive strains that can cause diarrheal disease—are for the most part different from those of extraintestinal pathogenic *E. coli* (ExPEC) and other GNB that cause extraintestinal infections. This distinction reflects site-specific differences in host environments and defense mechanisms.

A given enterobacterial strain usually possesses multiple adhesins for binding to a variety of host cells (e.g., in *E. coli*: type 1, S, and F1C fimbriae; P pili). Nutrient acquisition (e.g., of iron via siderophores) requires many genes that are necessary but not sufficient for pathogenesis. The ability to resist the bactericidal activity of complement and phagocytes in the absence of antibody (e.g., as conferred by capsule or the O antigen component of lipopolysaccharide) is one of the defining traits of an extracellular pathogen. Tissue damage (e.g., as mediated by *E. coli* hemolysin) may facilitate nutrient acquisition and spread within the host. Without doubt, many important virulence genes await identification **(Chap. 116)**.

The ability to induce septic shock is another defining feature of these genera. GNB are the most common causes of this potentially lethal syndrome. Pathogen-associated molecular pattern molecules (PAMPs; e.g., the lipid A moiety of lipopolysaccharide) stimulate a proinflammatory host response via pattern recognition receptors (e.g., Toll-like or C-type lectin receptors) that activate host defense signaling pathways; if overly exuberant, this response results in shock **(Chap. 297)**. Direct bacterial damage of host tissue (e.g., by toxins) or collateral damage from the host response can result in the release of damage-associated molecular pattern molecules (DAMPs; e.g., HMGB1) that can propagate a detrimental proinflammatory host response.

Many antigenic variants (serotypes) exist in most genera of GNB. For example, *E. coli* has more than 150 O (somatic) antigens, 80 K (capsular) antigens, and 53 H (flagellar) antigens. This antigenic variability, which permits immune evasion and allows recurrent infection by different strains of the same species, has impeded vaccine development **(Chap. 118)**.

INFECTIOUS SYNDROMES

Depending on both the host and the pathogen, GNB can infect nearly every organ or body cavity. *E. coli* can cause either intestinal or extraintestinal infection, depending on the particular pathotype, and *Edwardsiella tarda* can cause both intestinal and extraintestinal infection. *Klebsiella* causes primarily extraintestinal infection, but a toxin-producing variant of *Klebsiella oxytoca* has been associated with hemorrhagic colitis.

E. coli and—to a lesser degree—*Klebsiella* account for most extraintestinal infections due to GNB. These species (for *K. pneumoniae*, primarily its hypervirulent pathotype) are the most virulent pathogens within this group, as demonstrated by their ability to cause severe infections in healthy, ambulatory hosts from the community. However, the other genera of GNB are also important extraintestinal pathogens, especially among LTCF residents and hospitalized patients, in large part because of the intrinsic or acquired antimicrobial resistance of these organisms and the increasing number of individuals with compromised host defenses. The mortality rate is substantial in many GNB infections and correlates with severity of illness and underlying host status. Especially problematic are pneumonia, sepsis, and septic shock (arising from any site of infection), for which the associated mortality rates are 20–60%.

DIAGNOSIS

Isolation of GNB from sterile sites almost always implies infection, whereas their isolation from nonsterile sites, particularly from open wounds and the respiratory tract, requires clinical correlation to differentiate

colonization from infection. Clinical microbiology laboratories are increasingly incorporating newer molecular-based methodologies (e.g., matrix-assisted laser desorption–ionization–time-of-flight mass spectrometry [MALDI-TOF-MS] and polymerase chain reaction [PCR]) to enhance the sensitivity, accuracy, and rapidity of reporting on pathogen identification and resistance genes (e.g., *bla*KPC, NDM, OXA, CTX). This information can be used to increase the timeliness of initiation and/or the accurate selection of empirical antimicrobial therapy, thereby improving outcomes.

TREATMENT

TREATMENT

Infections Caused by Gram-Negative Enteric Bacilli

 Initiation of appropriate empirical antimicrobial therapy early in the course of GNB infections (particularly serious ones) leads to improved outcomes **(See also Chap. 139)**. The ever-increasing prevalence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) GNB; the lag between published and current resistance rates; and variations in antimicrobial susceptibility by species, geographic location, regional antimicrobial use, and hospital site (e.g., intensive care units [ICUs] versus wards) necessitate familiarity with evolving patterns of antimicrobial resistance for the selection of appropriate empirical therapy. Factors predictive of resistance in a given isolate include recent antimicrobial use, a health care association (e.g., recent or ongoing hospitalization, dialysis, residence in an LTCF), or international travel (e.g., to Asia, Latin America, Africa, Eastern Europe). Resistance rates will almost certainly increase over time and will likely be higher than shown here by the time this chapter is published. Data for 2008–2014 from the U.S. National Healthcare Safety Network indicates that the prevalence of the extended-spectrum β-lactamase (ESBL) phenotype among Enterobacteriaceae isolates varied by health care setting—i.e., 16% for short-term care, 38.6% for long-term care, and 10.7% for inpatient rehabilitation facilities—as did the prevalence of carbapenem resistance (2.8%, 12%, and 1.9%, respectively). Global ESBL rates for Enterobacteriaceae isolates from hospitalized patients were roughly similar in North America, Western Europe, Australia, and New Zealand and were higher in Latin America, Eastern Europe, and Asia. Perhaps even more concerning is the reported isolation of carbapenem-resistant Enterobacteriaceae (mediated primarily by New Delhi metallo-β-lactamase [NDM]) from ambulatory patients without known risk factors.

For appropriately selected patients, it may be prudent initially, pending antimicrobial susceptibility results, to use two potentially active agents as a way to increase the likelihood that at least one agent will be active against the patient's organism. If broad-spectrum treatment has been initiated, it is important to switch to the most appropriate narrower-spectrum agent once antimicrobial susceptibility results become available. Such responsible antimicrobial stewardship should help disrupt the ever-escalating cycle of selection for increasingly resistant bacteria, decrease the likelihood of *Clostridium difficile* infection, decrease costs, and maximize the useful longevity of available antimicrobial agents. Likewise, it is important to avoid treatment of patients who are colonized but not infected (e.g., who have a positive sputum culture without evidence of pneumonia or a positive urine culture without clinical manifestations of UTI).