Intensive care has evolved over its 50-year history to yield previously unimaginable recovery from major trauma, multiorgan system failure, and extensive surgery, including organ transplantation. Antimicrobial therapy plays an essential role in combating invasive infections in the intensive care population that are often the ultimate causes of death. However, a parallel evolution of antimicrobial compensation has occurred, engendering resistance and virulence mechanisms to circumvent each new antimicrobial agent. The surgical intensive care unit provides the ultimate microcosm of antimicrobial resistance selection, combining complex and severe underlying illness with invasive devices, bypassed defenses, compromised tissues, and proximity to other high-risk patients, all in one intimate environment. New resistance mechanisms may be introduced from referring institutions or can emerge in response to treatments, and then may spread to others within or outside the ICU. Multidrug-resistant organisms have become a dominant issue in modern health care; a strategic response is essential to short- and long-term success.

The best defense against infection in the surgical ICU is prevention, encompassing meticulous surgical technique that preserves tissue integrity, careful infection control, and care process improvement, accompanied by aggressive and timely diagnostics and judicious use of antimicrobial agents. This chapter will address the latter two strategies, providing general guidance and reference to more in-depth discussions.

General Principles

Infection and Diagnosis

Fever is a common occurrence in the postoperative patient. This can reflect developing infection but may also stem from a myriad of noninfectious sources, most frequently when arising within 48 h of surgery. Differentiating these causes is essential to optimal care and serves to minimize excessive antibiotic use and its after effects. It must also be acknowledged that fever is a natural defense mechanism and is itself only rarely harmful.

In addition to the common causes of postoperative infection – surgical site infection, central venous catheter infection, ventilator-associated pneumonia, urinary tract infection, Clostridium difficile-associated disease, and occasional cholecystitis, sinusitis, meningitis, or epidural catheter infection – fever may be associated with atelectasis, allergic drug reactions (frequently to beta-lactam antibiotics or phenytoin), infusion of blood products, pancreatitis, alcohol withdrawal, malignant hyperthermia, or neuroleptic malignant syndrome.

Interaction of linezolid with monoamine oxidase inhibitors, serotonin re-uptake inhibitors (SSRIs), tramadol, and meperidine can cause the serotonin syndrome, a potentially life-threatening combination of fever, agitation, and autonomic instability.

Similarly, abnormal chest X-rays may reflect pneumonia or can result from numerous noninfectious causes, such as pleural
effusions, congestive heart failure, aspiration pneumonitis, pulmonary hemorrhage, or acute respiratory distress syndrome (ARDS) (see Chap. 22). A diagnosis of pneumonia is the single largest reason for antibiotic use in the ICU, yet clinical diagnosis is only correct about half the time, driving unnecessary antibiotic consumption while risking adverse effects. Careful consideration of the diagnosis is thus imperative.

An early and aggressive diagnostic search for sources of infection helps to optimize anti-infective therapy. Knowing the site of infection is one of the most important determinants of drug choice and administration. Identifying a specific etiologic agent then allows honing initial empiric therapy to the most effective, broad-spectrum regimen that “covers everything” often results in ballooning empiricism, treating symptoms without addressing the source and facilitating the development of resistance.

Cultures should be obtained immediately when suspecting sepsis or significant infection, before initiating antibiotics. These should include peripheral blood cultures; a blood culture from an intravascular catheter in place >48 h or suspected of contamination (total not to exceed three blood cultures in 24 h); urine with urinalysis; tracheal secretions if pneumonia is suspected (quantitative bronchoalveolar lavage is preferable); deep wound cultures; percutaneous drainage cultures if a collection is found; and stool detection of Clostridium difficile if there is diarrhea. Preexisting drainage catheters are often contaminated; cultures from these sources should be approached with great caution.

Diagnostic imaging should be obtained expeditiously. A computed tomography (CT) scan can often help to differentiate pneumonia from pleural effusion or scar, and may identify infarctions, occult abscesses, anastomotic leaks, fistulas, or fluid collections. Some of these may be amenable to percutaneous drainage and culture. Appropriate accompanying chemistry tests should not be omitted, as they may provide (or exclude) a diagnosis more rapidly than cultures.

Several guidelines exist for the diagnosis and treatment of common ICU-associated infections, including new fever, catheter-related bloodstream infections, urinary tract infection (guidelines to be published in Clinical Infectious Diseases), sepsis, and ventilator-associated pneumonia (see Chaps. 27, 28, 29, and 31).

Antibiotics and Resistance

Bacteria have been present on Earth for 3.5 billion years; antibiotics have been available for less than 70 years. Given their enormous biomass and rapid dividing time, bacteria have evolved nearly unlimited mechanisms of resistance against the antimicrobial armamentarium. These include changes that exclude an antimicrobial agent from the cell (e.g., cell wall thickening in methicillin-resistant Staphylococcus aureus [MRSA] or porin changes in carbapenem-resistant Pseudomonas aeruginosa), alter antimicrobial targets (e.g., changes in cell surface penicillin binding protein sites or in ribosomal protein synthesis enzymes), attack the antimicrobial agent itself (e.g., beta-lactamases that inactivate penicillins and cephalosporins), or actively push an agent out of the cell via efflux pumps. These are only a few of the numerous evasion strategies available to microorganisms. The current crisis of resistance is a result of unfettered use of antibiotics in agriculture and medicine; controlling the rise in resistance will require increased attention to appropriate use of these agents.

Table 32.1 lists some of the common multidrug-resistant organisms encountered in the modern ICU. Prevalence of these problem organisms has been rising steadily, providing growing challenges. Antimicrobial resistance can come from three sources – emergence, influx, and spread. Resistance to an agent emerges under the influence of numerous selective factors, none more influential than the antimicrobial agent itself. Once resistance has developed, it may then spread to other bacteria within the host (e.g., transfer of an extended-spectrum beta-lactamase [ESBL] from Klebsiella pneumoniae to neighboring Escherichia coli in the gut) or may be transported to other patients, usually via the hands of healthcare workers. Similarly, there may be an influx of undetected antimicrobial-resistant organisms into the ICU via newly admitted or transferred patients or colonized staff members. The ICU thus represents a microcosm of the evolutionary pressures favoring resistance: severe underlying illness, numerous invasive procedures, proximity to other compromised patients under emergent conditions, and frequent use of antibiotics and other defense-altering drugs.

Several drugs are worth noting for their abilities to engender or select for resistance. Second- and third-generation cephalosporins, because of extensive gram-negative and anti-streptococcal activity, favor growth of vancomycin-resistant enterococci (VRE). VRE has also been associated with use of both oral and intravenous vancomycin. Numerous agents, most notably clindamycin, fluoroquinolones, and possibly proton pump inhibitors, favor growth of C. difficile. Fluoroquinolones (e.g., ciprofloxacin and levofloxacin) and proton pump inhibitors have also been implicated in nosocomial acquisition of MRSA. Resistance to carbapenems or fluoroquinolones may rapidly emerge during therapy of Pseudomonas infections.
Researchers in New York documented a cascade of events that illustrates the roles of emergence, influx, spread, and the complexity of antimicrobial resistance. In response to an outbreak of ESBL-producing K. pneumoniae infections, they curtailed use of ceftazidime, successfully reducing these infections. However, imipenem use blossomed, leading to outbreaks of imipenem-resistant P. aeruginosa and Acinetobacter baumannii infection. This same clone of A. baumannii, resistant to almost all drugs available, was later found in each of the 15 hospitals throughout Brooklyn, apparently transferred between hospitals along with patient and/or medical staff traffic.18–20

Impact of Hospital-Acquired Infections and Antimicrobial Resistance

Infections acquired in the hospital are among the most significant safety hazards for patients. In a study of medical injuries to patients in 7.45 million hospital discharges, Zhan et al.21 found an excess attributable length of stay of 10.89 days, added cost of $57,727, and excess mortality of 21.96% for patients experiencing postoperative sepsis. Postoperative complications constituted the most serious injuries identified in the study. In a study at Duke, patients with surgical site infections were five times more likely to be readmitted, 60% more likely to spend time in the ICU, spent twice as long in the hospital after surgery, and had twice the mortality rate of uninfected patients.22 In an analysis of this study and others, surgical site infection added an average of $15,646 to the cost of care22,23.

Similarly, antimicrobial resistance typically compounds the already significant clinical and economic impact of infection, causing increases in morbidity and mortality, length of stay, and cost.25 Costs of antimicrobial-resistant infections are often $6,000 to $30,000 greater than with an equivalent infection caused by a susceptible strain.25 In another systematic review, MRSA infection had an attributable cost of $35,367.23

Antimicrobial Therapy

Pharmacodynamics

The effectiveness of certain antimicrobial drugs may depend on the manner of dosing. Fluoroquinolones and the aminoglycosides are concentration dependent and thus are most effective when they achieve high concentrations, surpassing the minimum inhibitory concentration (MIC) of a target organism manyfold. Once-daily dosing of aminoglycosides achieves both high concentrations of drug and very low trough levels, reducing potential toxicity.25 In contrast, penicillins, cephalosporins, macrolides (such as azithromycin), and clindamycin are most effective when they achieve levels above the MIC of the infecting organism for a prolonged period of time. Using shorter administration intervals (or in some circumstances, continuous infusions) may serve to prolong the “time above MIC” and enhance clinical efficacy.

Monitoring Drug Levels

Drug level testing is most commonly used with aminoglycosides because of a relatively narrow toxic-therapeutic window. A trough level is usually adequate in once-daily administration, whereas both the peak and trough should be monitored for synergistic treatment, as in endocarditis. Monitoring vancomycin levels has gained momentum, largely in response to slowly rising vancomycin MICs in staphylococci and the concern for underdosing. Because of very predictable kinetics, efficient monitoring of vancomycin therapy can be accomplished with periodic (e.g., once or twice weekly) trough levels, rather than daily testing.

Dosing Considerations

Most antimicrobial agents are cleared via renal or hepatic metabolism. In patients with compromised renal function, dosing of several antibiotics must be adjusted to avoid accumulation and toxicity. Vancomycin and the aminoglycosides are commonly recognized as requiring dose-adjustment, but the carbapenems and penicillins can also accumulate, causing agitation or lower seizure thresholds. Appropriate dose adjustments are available from several resources, including the Sanford Guide to Antimicrobial Therapy26 (updated yearly) and on the Internet (http://www.hopkins-abxguide.org). Dose adjustment is best initiated after administering a normal first dose. This achieves a rapidly effective drug concentration but avoids subsequent toxic accumulation.

Patients with cirrhosis or severe liver disease are at increased risk for toxicity from certain antimicrobial agents. Chloramphenicol is more likely to cause bone marrow suppression in patients with compromised liver function; dose reduction can avoid this. Other agents – including azithromycin, clarithromycin, and clindamycin – may require reduced doses. Rifampin accumulates in hepatic failure (due to a prolonged half-life), potentially augmenting its already notorious effect on hepatic metabolism of numerous other drugs (most notably anticoagulants) via cytochrome P450. With the ongoing epidemic of obesity, treatment with “average” doses of antibiotics may be inadequate. Although few data exist to guide dosing in the obese patient, the principles of providing peak tissue and serum levels dictate that many agents should be used in higher doses in this setting.27,28

Many clinicians increase cephalosporin doses from 1 to 2 grams for patients weighing more than 80 kg; similarly, vancomycin may be given at 15 mg/kg per dose.

Parenteral to Oral Conversion

Many antimicrobial agents achieve excellent oral absorption and are amenable to conversion from intravenous to oral forms, once other oral medications are tolerated.11,29,30
This can reduce the need for intravenous access and its resultant complications, shorten hospitalization, and reduce costs. Fluoroquinolones, metronidazole, linezolid, clindamycin, trimethoprim-sulfamethoxazole, fluconazole, voriconazole, valacyclovir, and valganciclovir all achieve excellent absorption. It should be noted that orally administered vancomycin is not systemically absorbed and should be used only for treatment of *C. difficile* infection.

Allergy and Other Adverse Effects

Penicillin allergy is perhaps the most frequently encountered, yet least well understood, allergy in health care. Many patients who report histories of allergy to penicillins do not react when re-challenged. In the past, crossover allergy to cephalosporins was estimated to occur in 7–14% of patients with penicillin allergy, yet in a recent review Pichichero estimates that this occurs only rarely, in about 0.5% of those receiving first-generation cephalosporins and almost never with the upper generation cephalosporins. Therefore, cephalosporins can be safely used in most patients reporting penicillin allergy, unless there is history of an immunoglobulin E-mediated reaction, such as anaphylaxis or angioedema. Cross-reactivity between penicillins and carbapenems is controversial and of uncertain significance in clinical practice.

Although true allergy to vancomycin can occur, the “red man syndrome” is more frequently encountered. This is a nonallergic, infusion-related release of histamine, causing transient flushing of the face, neck, and shoulders, sometimes accompanied by itching and transient hypotension. It can usually be avoided by slowing the rate of administration.

Linezolid is used for treatment of MRSA, VRE, and other multidrug-resistant gram-positive infections. In addition to the serotonin-related effects noted previously, prolonged linezolid use has been associated with depletion of platelets and, less commonly, with marrow suppression of white and red blood cells. These effects appear to resolve quickly upon discontinuation.

Aminoglycosides (e.g., gentamicin, tobramycin, and amikacin) are associated with often irreversible toxicity to the kidney, ear, and vestibular system, and can also cause neuromuscular blockade. Once-daily administration, while maintaining low trough levels, tends to maximize effect but minimize toxicity.

Allergy to sulfa drugs, such as trimethoprim-sulfamethoxazole, may commonly cause rash or, more rarely, aseptic meningitis or myelosuppression. This agent can also interfere with laboratory assays for creatinine, falsely raising concern for declining renal function.

Prolonged exposure to fluoroquinolones has been associated with Achilles tendonitis and rupture, especially in patients with renal insufficiency or transplantation. Fluoroquinolones may also facilitate acquisition of MRSA, presumably by depleting susceptible normal skin flora.

Therapeutic Interactions

Interaction between drugs is a complex topic and will not be dealt with in detail here. The *Sanford Guide to Antimicrobial Therapy* provides comprehensive tables of interactions. Some of the more notable ones include combined use of aminoglycosides with other nephrotoxic agents; altered cytochrome P450 metabolism induced by rifampin; interaction between azoles (e.g., fluconazole or voriconazole) with tacrolimus, cyclosporine, anticoagulants, and phenytoin; and decreased oral absorption of fluoroquinolones by divalent cations, including vitamins with iron, antacids, calcium, and sucralfate.

Special Patient Populations

Expert consultation should be considered for certain patients, including children, women who are pregnant, and patients with cystic fibrosis, human immunodeficiency virus infection, or organ transplantation. Indeed, optimal critical care may require routine incorporation of a pharmacist into the team. Similarly, expert antimicrobial stewardship is vital to optimizing use of these agents, delaying development of resistance, and providing the most cost-effective care.

Pregnant patients have altered volume of distribution and clearance of some drugs (notably ampicillin), as well as concerns about potential effects on the fetus. Metronidazole is a teratogen in animals and should be avoided in pregnancy. Tetracyclines may deposit in bone and tooth enamel, whereas fluoroquinolones can interact with growth plates in bone and should be used only with caution. Penicillins and cephalosporins are generally considered to be safe in pregnancy.

Improving the Quality of Critical Care

Writing in *The New Yorker*, Gawande has argued eloquently that modern intensive care medicine is now so complex that a systems approach is necessary to providing optimal care and eliminating preventable errors. He cites a collaborative project among most of the ICUs in Michigan to reduce catheter-related bloodstream infections (CRBSI). Participants instituted protocols incorporating evidence-based best practices for central venous catheter insertion and care, including daily checklists. Within a few months, CRBSI had been reduced by two-thirds statewide. Similar “bundled” care protocols, applied to ventilator care, urinary catheters, and sepsis offer promise and await further validation.

Prevention

Surgical Prophylaxis

William Halsted, operating in the pre-antibiotic era of the late nineteenth century, identified the principles of asepsis and...
Prophylaxis for Infective Endocarditis

New guidelines from the American Heart Association have drastically reduced the indications for antibiotic prophylaxis of bacterial endocarditis. Appropriate recipients are now limited to those patients with a prior history of endocarditis, a prosthetic valve, cardiac transplantation, or with certain major congenital heart defects. Procedures in these recipients that require prophylaxis are also restricted, including procedures breaching respiratory mucosa, infected skin, or infected musculoskeletal structures. Prophylaxis solely to prevent infective endocarditis is no longer recommended for genitourinary or gastrointestinal tract procedures.

Therapy

Treatment of established infection in the surgical ICU relies on the principles of good medical–surgical care to minimize the infective burden and maximize host responses; antimicrobial therapy is largely an adjunct. The source of infection should be identified, as detailed previously. Foreign bodies, including prosthetic devices and catheters, frequently require removal when infected. Abscesses and collections must be drained and nonviable tissue debrided in order to facilitate delivery of oxygen, leukocytes, nutrients, and antibiotics to the infected tissue. Optimal nutrition serves not only to improve the immune response but also fluid balance – serum albumin is thus a significant independent prognostic indicator in numerous studies of ICU outcome. In addition, treatment should alter normal flora as little as possible, as these organisms provide a natural defense against replacement by more resistant invading species.

Empiric Therapy

Early empiric therapy must reflect the urgency of the situation. For example, a new fever, elevated white blood cell count, and a new infiltrate on chest radiograph may not require more than a careful examination, diagnostic evaluation, and chest physiotherapy, whereas hemodynamic instability may force rapid initiation of broad-spectrum coverage. Choices of agents should also reflect a patient’s history of exposures, as a newly admitted trauma patient usually bears little risk of carrying resistant organisms, compared to a patient transferred from an oncology floor or a chronic care facility. Antibiotic choices should thus reflect local resistance patterns where the infection originated. An antibiogram specific to the surgical ICU will more accurately direct most antibiotic choices than an institution-wide survey.

Gram-positive coverage is needed for suspected infections involving a breach of the skin (including surgical wounds and intravascular catheters) and for ventilator-associated pneumonia. Vancomycin has been the workhorse empiric choice for decades, as it has activity against streptococci, enterococci, and staphylococci, including MRSA. However, if isolated organisms prove sensitive, penicillin and oxacillin are the drugs of choice for streptococcal and staphylococcal infections, respectively, because of superior activity and narrower spectrum.

With the advent of vancomycin-resistant enterococci (VRE) and rising tolerance among staphylococci to vancomycin, use of linezolid or daptomycin may be needed. VRE is often encountered in biliary surgery, especially surrounding liver transplantation. Daptomycin does not penetrate well into the lung and should not be used for pneumonia.

Gram-negative organisms often contribute to ventilator-associated pneumonia and to surgical wound infections involving the abdomen or genitourinary tract. Vascular catheter infection by gram-negative organisms is less common, unless there is gross contamination of the catheter site. Postoperative meningitis and neutropenia require immediate and aggressive gram-negative coverage, to include *Pseudomonas*; cefepime or ceftazidime provide this and moderate additional gram-positive coverage while achieving adequate central nervous system penetration. Aminoglycosides have broad activity against gram-negative organisms, but are now less frequently used because of concerns about toxicity and
the need for monitoring drug levels. For these reasons, however, they now have regained activity against some of the more resistant pathogens and provide a potent alternative under select circumstances. Conversely, the fluoroquinolones (e.g., ciprofloxacin or levofloxacin) provide broad gram-negative activity and are easy to use, but their popularity has resulted in rapidly declining levels of activity against many major pathogens, moderating their utility. Aztreonam offers an alternative in the settings of beta-lactam allergy or intolerance of aminoglycosides.

Mixed infections of the gastrointestinal tract, including head and neck infections, and invasive infection in diabetics often require an anaerobic spectrum of activity. Clindamycin provides broad anaerobic (and gram-positive) activity and is particularly useful in head and neck infection or for aspiration pneumonia, whereas metronidazole is more often used for abdominal infection. These drugs are used in combination with agents with gram-negative and -positive activity, such as cephalosporins or fluoroquinolones. Alternatively, piperacillin-tazobactam or a carbapenem (imipenem or meropenem) can provide both aerobic and anaerobic coverage. These are appropriate choices in mixed abdominal infections, particularly when more resistant gram-negative organisms are suspected.

Antifungal Therapy

Antifungal therapy options have evolved from amphotericin B and its lipid preparations to the azoles (mostly fluconazole and voriconazole) and echinocandins (e.g., caspofungin and micafungin). Fluconazole has provided reliable activity against Candida albicans and more variable action against some other Candida species, but emergence of fluconazole-resistant C. albicans and the more intrinsically resistant species (e.g., C. krusei and Torulopsis glabrata) have raised caution in some locations. Voriconazole has activity against some of these more resistant species, as well as potent activity against Aspergillus species. Both agents have significant drug interactions related to hepatic metabolism. The echinocandins boast essentially none of the renal toxicity of amphotericin and fewer drug interactions while having activity against numerous other fungi. Newly released posaconazole provides potent antifungal activity that is broader yet, including mucormycosis. Each of these agents (other than now-generic fluconazole) generates significant expense, commonly resulting in restricted access. Most antifungal agents, other than fluconazole, do not provide reliable therapy within the bladder.

Indications for empiric antifungal therapy are usually limited and include yeast urinary tract infection and either candidemia or contamination of an intravenous catheter. Secondary peritonitis may frequently involve significant yeast, as can organ transplantation. The behavior of invasive Candida infection is somewhat unpredictable, leading to controversy regarding the role of empiric therapy in high-risk patients.

| Table 32.2. Risk factors for multidrug resistance. |
|-----------------------------|-----------------------------|
| Age                         | Male sex                    |
| Length of stay              | Diabetes mellitus           |
| Renal failure               | Injection drug use          |
| Use of invasive devices     | Surgery involving the gastrointestinal tract |
| Exposure to healthcare facilities | Prior antimicrobial use (particularly cephalosporins and fluoroquinolones) |
| Transfer from a long-term care facility |

Multidrug-Resistant Organisms

Multidrug-resistant organisms (Table 32.2) should be suspected in patients: hospitalized within the past year; admitted to the hospital for more than 2–3 days; exposed to recent antimicrobial use; or in contact with healthcare settings, such as nursing homes, rehabilitation facilities, or dialysis units. Prior MRSA colonization or infection commonly persists, often for months or years, leading many institutions to identify such patients on readmission so that appropriate isolation and treatment can be instituted.

De-Escalation

Initial empiric therapy should be altered as microbiologic data become available. The Gram stain may provide rapid information – pneumonia due to S. aureus or P. aeruginosa is usually not subtle, so a negative Gram stain suggests an alternative etiology. Once a pathogen is identified, an optimal, high potency agent should be chosen, with a narrow spectrum of activity and minimal side effects. One should avoid the temptation to continue a “big gun” because of initial success, when a honed regimen has been identified.

Monitoring response to therapy relies primarily on clinical assessment, including hemodynamics, as well as white blood cell and platelet counts and renal and acid–base function. Duration of therapy will often depend on these measures, as controlled studies of optimal courses of therapy are often lacking. Therapy should be continued just long enough to maximize response, while minimizing subsequent development of resistance or toxicity. The Surviving Sepsis Campaign guidelines suggest 7–10 days of antibiotic therapy is usually appropriate, guided by clinical response.

An important exception is bacteremia, which should usually be treated for a minimum of 2 weeks for uncomplicated infection. For bacteremia due to S. aureus, treatment should be extended to 4 or more weeks when there is evidence of deep infection, such as endocarditis. Osteomyelitis, prosthetic infection, or involvement of a non-removable focus require extended treatment. A longer course of therapy is also often warranted in patients with neutropenia, diabetes.
mellitus, severe malnutrition, or cirrhosis. Correcting these underlying conditions contributes significantly to improved recovery.

The results of Chastre et al. are instructive. In a multicenter trial treating ventilator-associated pneumonia, the authors found that most patients responded as well to 8 days of therapy as to 15, yet were exposed to fewer antibiotics and were thus less likely to develop subsequent resistance. This seminal study changed a long-standing practice of treating pneumonia for 3 weeks or more and provides a model for future investigation.

Conclusions

Antimicrobial agents offer a high probability of success against formerly devastating infections, accompanied by little complicating toxicity. Tempering this optimism is the observation that subsequent overuse has stimulated a modern crisis of resistance, exacerbated by a dearth of newly developed antibiotics. For the practitioner of intensive care medicine, growing antimicrobial resistance adds complexity to care of the individual patient but also to other patients in the ICU, as antibiotics exert their ecologic effect in the surrounding microbiologic environment. The solution to this “perfect storm” is careful diagnosis, thoughtful treatment, and judicious restraint, allied with systematic preventive measures to optimize safe care and remove the hazards that promote infection.

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