Antimicrobial Use in Surgical Intensive Care

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Introduction

Intensive care has evolved over its 60-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 cause of death. However, a parallel evolution of microbial compensation occurs, engendering resistance and virulence mechanisms to circumvent each new antimicrobial agent—penicillin resistance existed before the drug became commercially available. The surgical intensive care unit provides the ultimate microcosm for antimicrobial resistance development, juxtaposing complex and severe underlying illness with invasive devices, bypassed defenses, and compromised tissues, as well as 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 therapeutics, and then may spread to others within or outside the ICU. Multidrug-resistant organisms, promoted by excessive or suboptimal antimicrobial use, have become a dominant concern in modern healthcare, most notably in the intensive care setting; a directed, judicious, but strategic response is essential to both 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 hand hygiene and infection control, removal of invasive devices, and care process improvement, accompanied by aggressive and timely diagnostics and judicious use of antimicrobial agents. This chapter addresses the latter two strategies, providing general guidance and reference to more in-depth discussions.

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General Principles

Infection and Diagnosis

Fever is a common occurrence in the postoperative patient [1]. This can reflect developing infection but also may stem from a myriad of noninfectious sources [2], most frequently arising within 48 h of surgery. Differentiating these causes is essential to optimal care and serves to minimize excessive antibiotic use and its aftereffects. It must also be acknowledged that fever is a natural defense mechanism and is itself only rarely harmful [3].

In addition to the common infectious causes of postoperative fever—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 [4]. Serotonin syndrome, a potentially life-threatening combination of fever, agitation, and autonomic instability, may stem from the use of linezolid when combined with monoamine oxidase inhibitors, serotonin reuptake inhibitors (SSRIs), tramadol, or meperidine [5, 6]. These manifestations may be easily overlooked, given the sedative properties common to several of these drugs.

Similarly, abnormal chest radiographs 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. 25). A diagnosis of pneumonia is the single largest reason for antibiotic use in

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the ICU, yet clinical diagnosis may only be correct about half the time [7], 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 [4, 8]. Knowing the site of infection is the most important determinant of drug choice and administration. Identifying a specific etiologic agent allows honing initial empiric therapy to the most effective, narrowest spectrum agent with the fewest side effects. The alternative strategy of rapidly initiating an aggressive, broad-spectrum regimen that "covers everything" often results in ballooning empiricism, treating symptoms without addressing the source. This delays effective, specific therapy, prolonging ICU length of stay and facilitating 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 (generally limited to no more than three blood cultures in 24–48 h); urine with urinalysis; tracheal secretions if pneumonia is suspected (quantitative bronchoscopic or non-bronchoscopic bronchoalveolar lavage are preferable); deep wound cultures; percutaneous drainage cultures if a collection is found; and stool detection of *C. difficile* if there is diarrhea. Pre-existing drainage catheters are often contaminated within 24–48 h; cultures from these sources should be approached with great caution. Cell counts, particularly from spinal fluid drains, may be invaluable.

Diagnostic imaging should be obtained expeditiously. A computed tomography (CT) scan often helps 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 CT- or ultrasound-guided percutaneous drainage and culture. Appropriate accompanying chemistry tests or cell counts should not be omitted, as they may provide (or exclude) a diagnosis more rapidly than cultures.

Source control is a vital concept when treating ICU-related infections, particularly in a surgical setting [9]. This may include removal of invasive devices or foreign bodies, percutaneous or operative drainage of abscesses, or lavage of septic arthritis or generalized peritonitis. Perforation of the gastrointestinal tract requires drainage and ultimately, repair or creation of a fistula, as persistent drainage coupled with ongoing antimicrobial therapy is a perfect recipe for in vivo development of resistance. Collaboration between critical care, infectious disease, interventional radiology, and surgical teams is ideal [9]. Infectious disease consultation, particularly when initiated early in the course, has been shown to improve antimicrobial utilization and adherence to guidelines, mechanical ventilation days [10], 30-day mortality and readmission, hospital and ICU length of stay, and costs [10, 11].

Surgical site infection is commonly encountered, either during the index hospitalization or upon readmission. In a study of 346 US hospitals participating in the National Surgical Quality Improvement Program (NSQIP), the unplanned readmission rate was 5.7 % for nearly 500,000 operations; surgical site infection was the most common cause of unplanned readmission (19.5 %), precipitating a tenth to over a third of readmissions for various types of surgery [12]. Comprehensive strategies for prevention of surgical site infection are reviewed elsewhere [13].

Several guidelines exist for the prevention, diagnosis, and treatment of common ICU-associated infections (available at the Infectious Disease Society of America's website) [14], including new fever [4], catheter-associated bloodstream infection [15] and urinary tract infection [16], sepsis [8], intra-abdominal infection [17], and ventilator-associated pneumonia [7]. Treatment of asymptomatic bacteriuria should be avoided, removing a common and significant source of unnecessary and harmful antimicrobial use [18].

Antibiotics and Resistance

Bacteria have been present on Earth for 3.5 billion years; antibiotics have been available for about 75 years. Given their enormous biomass and rapid dividing time, bacteria have evolved nearly unlimited mechanisms of resistance against the antimicrobial armamentarium [19, 20]. These include changes that exclude an antimicrobial agent from the cell (e.g., cell wall thickening in 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) [21], 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 Centers for Disease Control and Prevention, the European CDC, and the World Health Organization recently identified antimicrobial resistance as a world health crisis [22, 23], a result of unfettered use of antibiotics in agriculture and medicine and a dry pipeline of new antimicrobial agents. The predicted impact is unthinkable—300 million deaths in the next 35 years, causing a 2–3.5 % reduction in global GDP [24].

In addition to international and national measures, controlling the rise in resistance will require increased local attention to appropriate use of these agents [25], much of it requiring restraint. In a provocative and edifying study, Hranjec and colleagues describe aggressive versus conservative approaches to suspected infection [26]. Using a quasi-experimental before-and-after design, they examined nearly 1500 admissions to the University of Virginia surgical ICU. In the first year empiric antibiotic therapy was initiated

immediately after obtaining cultures. In the second year a more conservative approach was taken, withholding antibiotics from clinically stable patients until there was objective evidence confirming infection. The conservative approach was associated with more initially appropriate therapy, shorter duration of therapy, and significantly reduced mortality (adjusted odds ratio 0.4 (95 % CI 0.25–0.67). Although rapid initiation of antibiotic therapy in response to sepsis is essential [8], these results suggest that for the stable patient, a more conservative approach may yield improved mortality and better antimicrobial use. Confirmation of this pilot study is needed.

Table 33.1 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 [27–29]. Control of the so-called ESKAPE bugs [30]—*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species—is vital, as this group of organisms increasingly dominates ICU care.

Antimicrobial resistance can arise 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 *K. 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, crowded conditions, and frequent use of antibiotics and other defense-altering drugs.

Table 33.1 Multidrug-resistant organisms commonly encountered in intensive care

Methicillin-resistant *Staphylococcus aureus* (MRSA)
Vancomycin-resistant enterococci (VRE)
Linezolid- and daptomycin-resistant enterococci
Pseudomonas aeruginosa
Fluoroquinolone-resistant *Escherichia coli*
Extended spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae
Carbapenem-resistant Enterobacteriaceae (CRE)
Acinetobacter baumannii
Stenotrophomonas (*Xanthomonas*) *maltophilia*
Clostridium difficile
Candida species

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 that denudes normal gut flora, favor growth of vancomycin-resistant enterococci (VRE). Not unexpectedly, VRE is also associated with the use of both oral and intravenous vancomycin. Numerous agents, most notably clindamycin, fluoroquinolones, cephalosporins, and proton pump inhibitors, favor growth of *C. difficile* [31]. Fluoroquinolones (e.g., ciprofloxacin and levofloxacin) have also been implicated in nosocomial acquisition of MRSA [32]. Resistance to carbapenems or fluoroquinolones may rapidly emerge during therapy of *Pseudomonas* infections [33, 34].

Researchers in New York documented a cascade of events that illustrates the roles of emergence, influx, and spread, as well as the interplay of antimicrobial therapy in the ecology of antimicrobial resistance. In response to an outbreak of ESBL-producing *K. pneumoniae* infections, staff at one hospital curtailed the use of ceftazidime, successfully reducing these infections. However, imipenem use blossomed, leading to outbreaks of imipenem-resistant *P. aeruginosa* and *A. 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 [35–37].

Carbapenem-resistant *Enterobacteriaceae* (CRE) have since emerged as a grave threat to public health and to ICU care [38]. These organisms, which inhabit the gastrointestinal tract and contaminate the environment, are now encountered world-wide, following international transit and subsequent clonal outbreaks and spread. Following receipt in transfer of a single infected patient, the National Institutes of Health Clinical Center experienced persistent carbapenem-resistant *K. pneumoniae* infections affecting 18 patients, 6 of whom died [39]. In Chicago rapid regional dissemination was documented following introduction of a patient with CRE infection into a network of acute and long-term care hospitals. Within 1 year a clonal outbreak of CRE was detected in 40 patients in 14 hospitals, 2 LTACHs, and 10 nursing homes [40].

Impact of Hospital-Acquired Infections and Antimicrobial Resistance

Acquired infections are arguably the most significant safety hazards that patients encounter in the hospital. In a study of medical injuries to patients in 7.45 million hospital discharges, Zhan et al. [41] 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 similar studies at Duke and Johns Hopkins, patients with surgical site infections were five times more likely to be re-admitted, 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 [42, 43]. In a recent analysis (used by the Congressional Budget Office), surgical site infection added $11,874–$34,670 to the cost of care [44], accounting for a third of the costs of all hospital-associated infections [45].

Antimicrobial resistance typically compounds the already significant clinical and economic impact of infection, causing increased morbidity and mortality, length of stay, and cost [46]. Costs of antimicrobial-resistant infections are often $6000–$30,000 greater than an equivalent infection caused by a susceptible strain [46]. In a systematic review, MRSA surgical site infection had attributable costs and length of stay of $42,300 and 23 days, respectively [45].

Rapid diagnostics using molecular techniques, such as polymerase chain reaction (PCR) or matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF), may speed identification of pathogens by several days compared to conventional methods, enabling more timely and appropriate therapy while eliminating much of broad-spectrum empiric coverage. Studies integrating MALDI-TOF with an antimicrobial stewardship team improved the time to optimal therapy while reducing hospital length of stay and costs [47].

Antimicrobial Therapy

Infections in the surgical ICU often have poor outcomes, reflecting a confluence of severe underlying illness, multiple invasive devices, compromised defenses, and multiple challenges to antimicrobial dosing and efficacy. Fluid overload, hypoalbuminemia, altered renal and hepatic clearance, perfusion deficits, and antimicrobial resistance all may contribute to reduced anti-infective efficacy. Individualized therapy, with the assistance of software programs, may provide significant assistance in the near future [48, 49].

Pharmacokinetics and Pharmacodynamics

The effectiveness of certain antimicrobial drugs may depend on the manner of dosing. 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. In contrast, 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 [50].

Monitoring Drug Levels

Drug level testing is most commonly used with aminoglycosides because of a relatively narrow toxic-therapeutic window, which often limits their utility. A trough level is adequate in once-daily administration, whereas both the peak and trough should be monitored for synergistic treatment with a beta-lactam antibiotic, as in endocarditis. Monitoring vancomycin levels has gained momentum, largely in response to slowly rising vancomycin MICs in staphylococci and concern for under-dosing. Because of predictable kinetics when renal function remains stable, efficient monitoring of vancomycin therapy can be accomplished by obtaining trough levels once or twice per week, rather than wasteful 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 may also accumulate, causing agitation or lowered seizure thresholds. Dose adjustment is often best initiated following a normal first dose. This achieves a rapidly effective drug concentration with subsequent reduction to avoid toxic accumulation. Appropriate dose adjustment guidance is available from several resources, including the *Sanford Guide to Antimicrobial Therapy* [51] (updated yearly) and the Hopkins ABX Guide [52]. Many hospitals now provide dosing services directed by pharmacy staff.

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, but is now rarely used. 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, also a target of certain protease inhibitors used to treat human immunodeficiency virus (HIV)-infected patients. As with solid organ transplant, early infectious disease consultation is valuable [11, 53].

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 [54, 55]. Many clinicians increase cephalosporin doses from 1 to 2 g for patients weighing more than 80 kg and to 3 g for more than 120 kg [56]; similarly, vancomycin may be given at 15 mg/kg per dose, often with a first loading dose of 20 mg/kg [48, 51].

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 [25, 57, 58]. This can reduce need for intravenous access and its complications, shorten hospitalization, and reduce cost. Fluoroquinolones, metronidazole, linezolid, clindamycin, doxycycline, rifampin, trimethoprim-sulfamethoxazole, fluconazole, voriconazole, valacyclovir, and valganciclovir all achieve excellent oral 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 understood allergy in healthcare. Many patients who report allergy to penicillins do not react when re-challenged. Delineating the manifestations of purported allergy is valuable, as misattributed allergy relegates patients to alternate, and in many cases inferior, agents. In the past, crossover allergy to cephalosporins was estimated to occur in 7–14 % of patients with penicillin allergy, yet Pichichero estimates that this occurs only rarely, in about 0.5 % of those receiving first-generation cephalosporins and almost never with upper generation cephalosporins [59, 60]. 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, with previous estimates ranging from 0 to 50 %, but of uncertain significance in clinical practice. In a study of 104 patients with IgE-mediated reactions to penicillin confirmed by skin tests, only 1 (0.9 %) had an IgE-mediated reaction to meropenem; the other 103 tolerated escalating doses without adverse effects [61].

Although true allergy to vancomycin can occur, the "red man syndrome" is more frequently encountered. This is a non-allergic, infusion-related release of histamine, causing transient flushing in a "mantle" distribution over the face, neck, and shoulders, sometimes accompanied by itching and transient hypotension. It can usually be avoided by slowing the rate of infusion.

Linezolid is used for treatment of MRSA, VRE, and other multidrug-resistant Gram-positive infections. In addition to the serotonin-related effects noted above, 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 [62].

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 [50]. Particular caution should be exercised with renal compromise.

Allergy to sulfa drugs, such as trimethoprim-sulfamethoxazole, may commonly cause rash or, more rarely, aseptic meningitis or myelosuppression. This agent can also cause mild interference with laboratory assays for creatinine, falsely raising concern for compromised 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 [32], presumably by depleting susceptible normal skin flora and opening an ecologic niche. Certain fluoroquinolones and macrolides have been associated with prolonged QTc intervals and *torsades de pointe*, although several implicated agents were removed from the market and clinical significance remains uncertain.

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 [51]. Some of the more notable ones include: combined use of aminoglycosides with other nephrotoxic agents; altered cytochrome P450 metabolism of anticoagulants, narcotics, and steroids 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. As much as a 70 % reduction in absorption, can be avoided by delaying administration of divalent cations 2 h after administration of a fluoroquinolone.

Special Patient Populations

Expert consultation should be considered for certain patients, including children, women who are pregnant, and patients with cystic fibrosis, HIV infection, or organ transplantation [53]. Indeed, optimal critical care may require routine incorporation of a pharmacist into the team [10]. Similarly, expert antimicrobial stewardship is vital to optimizing use of these agents, delaying development of resistance, and providing the most cost-effective care [25, 57]. Indeed, in a CDC evaluation of patients discharged from 323 hospitals 55.7 % of patients received antibiotics; in 37.2 % of those antibiotic use could have been improved. Subsequent models suggested that a 30 % reduction in broad-spectrum antimicrobial use in this population would result in a 26 % reduction in *C. difficile* infection [63].

Younger patients may have dramatically greater renal clearance than other critically ill patients, leading to inadequate drug levels. 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 immature 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 provide optimal care and eliminate preventable errors [64]. He cites a collaborative project among most of the ICUs in Michigan to reduce catheter-related bloodstream infections (CRBSI) [65]. Participants instituted protocols incorporating evidence-based best practices for central venous catheter insertion and care, including daily check lists. Within a few months, CRBSI had been reduced by two-thirds statewide [65]. Other "bundled" care protocols, applied to guidelines for ventilator care, urinary catheters [16], and sepsis [8] 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 hemostasis as elements of surgical technique that would minimize infection. He advocated the use of sharp dissection and fine sutures, gentle handling of tissues, and complete wound closure [66]. Over a century later, perioperative antimicrobial prophylaxis is a vital adjunctive measure to these mainstays of infection prevention. Although the details of prophylaxis for elective surgery are altered in emergent operations on previously hospitalized ICU patients, the principles remain. The purpose of prophylaxis is to prevent intrinsic and extrinsic bacterial contamination of the surgical site that occurs during an operation from developing into a postoperative infection. The ideal prophylactic agent would be active against the major potential infecting agents; not induce resistance; effectively penetrate relevant tissues; have a long enough half-life to maintain effective levels throughout the procedure (re-dosing as necessary); have low toxicity and potential for allergy; have few interactions with anesthetic agents and muscle relaxants; and be cost effective [56, 67, 68]. It should be administered within an hour before the procedure (within 2 h for vancomycin and fluoroquinolones) [69]. Postoperative doses provide no added benefit. In a review of 28 studies there was no clear advantage to either multiple- or single-dose prophylaxis (odds ratio 1.06, 95 % CI, 0.89–1.25) [70]. Furthermore, unnecessary postoperative doses may cause harm, including allergy or anaphylaxis, prolonged bleeding times, *C. difficile* colitis, and selection of resistant organisms. This is particularly important in surgical ICU patients, who may require prolonged care and risk progressive acquisition of multidrug-resistant organisms [71]. Similarly, "prophylaxis" of drains, tubes, and catheters is both ineffective and hazardous, as is an attempt to "maintain sterility of the wound" [56, 72, 73].

Prophylaxis for Infective Endocarditis

New guidelines from the American Heart Association have drastically reduced the indications for antibiotic prophylaxis of bacterial endocarditis [74, 75]. 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 above. 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 long-term 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 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 or cefazolin [76] 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, 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 chest, abdomen, or genitourinary tract. Vascular catheter infection by Gram-negative organisms is less common, unless there is gross contamination of the catheter site; femoral catheter placement is to be avoided whenever possible. Postoperative meningitis and neutropenia require immediate and aggressive Gram-negative coverage, to include *P. aeruginosa*; cefepime or ceftazidime provides 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 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 *C. parapsilosis* 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 provides 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 few 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

Table 33.2 Risk factors for multidrug resistance [71]

Age
Male sex
Length of stay
Diabetes mellitus
Renal failure
Injection drug use
Use of invasive devices
Surgery involving the gastrointestinal tract
Solid organ transplantation
Prior antimicrobial use (particularly cephalosporins and fluoroquinolones)
Exposure to healthcare facilities
Transfer from a long-term care facility

significant expense and potential drug interactions, commonly resulting in restricted access.

Indications for empiric antifungal therapy are usually limited and include candidemia or infection of an intravenous catheter. Secondary peritonitis may frequently involve significant yeast, as can organ transplantation. The invasive behavior of *Candida* infection is somewhat unpredictable, leading to controversy regarding the role of empiric therapy in high-risk patients [77]. Most candiduria is asymptomatic, rather than true urinary tract infection, and rarely results in candidemia [78]. Symptomatic *Candida* UTI, however, warrants treatment. Other than fluconazole (or rarely used amphotericin B or flucytosine), most antifungal agents do not concentrate adequately within the bladder and upper urinary tract; voriconazole, posaconazole, and the echinocandins do not provide reliable therapy in the genitourinary tract. Bladder irrigation with antimicrobial agents is not recommended.

Multidrug-Resistant Organisms

Multidrug-resistant organisms (Table 33.2) 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, long-term acute care facilities, or dialysis units [71]. Prior MRSA colonization or infection commonly persists, often for months or years, leading many institutions to identify such patients on re-admission 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.

In reality, broad-spectrum empiric antimicrobial therapy is common and de-escalation occurs relatively infrequently. In a study of empiric antibiotic therapy in six hospitals, 60 % of 6812 patients were treated with antibiotics, 30 % of whom were both afebrile and had a normal white blood cell count [79]. Appropriate cultures were obtained in only 59 %; 42 % were positive. By the 5th day of therapy, fewer than one in four patients had de-escalation or narrowing of the antibiotic regimen, usually in response to a positive culture or a negative imaging study. Editorialists, commenting on the "vastly underappreciated" collateral ecologic damage of antimicrobial misuse, suggested forcing an "antibiotic time-out" 3–5 days into each course of empiric therapy [80]. Critical review of the need for antimicrobial use, invasive devices, and sedation should be part of the daily routine clinical evaluation.

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 [8] suggest 7–10 days of antibiotic therapy is usually appropriate, guided by clinical response. Guidelines for treatment of complicated intra-abdominal infections suggest limiting therapy to 4–7 days, unless source control is inadequate [17].

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 requires 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.

In a multicenter trial treating ventilator-associated pneumonia, the results of Chastre, et al. are instructive [81]. 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 2–3 weeks, confirmed by subsequent meta-analysis of 4 randomized controlled trials comparing 7–8 days to 10–15 days of therapy [82]. Duration may be shorter still in those who respond rapidly but may require more

extended courses in the patient who is slow to respond [83]. The use of inhaled, aerosolized antibiotics delivers high concentrations of antibiotic directly to the lung, potentially reducing adverse systemic effects. Early studies, whether of treatment or as an effort to reduce multidrug-resistant organism colonization of the lung, hold promise and warrant further investigation [84].

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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