APPROPRIATE ANTIBIOTIC SELECTION AND USE FOR INTENSIVE CARE UNIT PATIENTS, PART I: RATIONALE FOR ANTIBIOTIC CHOICES

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Mechanism of Antibiotic Action

Antibiotics work by multiple mechanisms, including the inhibition of cell wall synthesis, perturbation of cell wall integrity, inhibition of protein synthesis, and interference with nucleic acid production. β-Lactams attach to penicillin-binding proteins (PBPs) and inhibit the synthesis of peptidoglycans, which are needed for cell wall integrity. Vancomycin inhibits cell wall production by preventing the cross-linking of proteoglycans necessary for cell wall stability. The aminoglycosides, linezolid, clindamycin, and macrolides inhibit protein synthesis at the ribosomal level through multiple mechanisms, whereas metronidazole and the fluoroquinolones interfere with nucleic acid production. An overview of parenteral antibiotics that are commonly used in the intensive care unit (ICU) and their mechanisms of action are presented here [*see Table 1*].

Antimicrobial Resistance

Antimicrobial resistance can result from the intrinsic properties of the organism, adaptation to environmental pressures through chromosomal mutation and horizontal gene transfer, and/or genetic alteration through transferable plasmids.[1]

The most common method of resistance in gram-negative bacteria is enzymatic degradation of the β-lactam antibiotics. These enzymes are classified based on their amino acid sequences and the characteristics of their substrates and inhibitors.[2] Group 1 is composed of cephalosporinases, which use serine for β-lactam hydrolysis and are coded on chromosomes of many Enterobacteriaceae. The resistance by extended-spectrum β-lactamases (ESBLs) is mediated by plasmids that spread microbial resistance across bacterial species and confer additional resistance to fourth-generation cephalosporins. Group 2 has the largest number of enzymes, ESBLs, and serine carbapenemases, which are inhibitor resistant. This group includes *Klebsiella*-producing carbapenemases (KPCs), which can hydrolyze β-lactams of all classes. The metallo-β-lactamases of group 3 are carbapenemases that require divalent zinc ions for substrate hydrolysis.

Sulbactam and tazobactam are heavily modified penicillins that act as β-lactam inhibitors and are used in combination with ampicillin and piperacillin, respectively. When the β-lactamases covalently bind to these molecules, the enzyme activity is inactivated, a concept called "suicide inhibition." These β-lactam/β-lactam inhibitor combinations are useful for the treatment of β-lactamase-producing bacteria.

Porins are trimers of proteins that create transmembrane channels. Although used by bacteria for normal functioning, the porins are the entry portals for some antibiotics. The porin structure in the outer cell membrane of gram-negative bacteria impedes access to the PBP. The chromosome-mediated reduced affinity of PBPs for β-lactams is responsible for the methicillin resistance of *Staphylococcus aureus* (MRSA) and the resistance of *Streptococcus pneumoniae* to penicillin.[3] Vancomycin inhibits cell wall peptidoglycan cross-linking by binding to terminal d-alanine, but the operon-mediated substitution of d-lactate or d-serine for d-alanine confers vancomycin resistance by *Enterococcus faecium* (vancomycin-resistant *Enterococcus* [VRE]).[4] Gram-negative pathogens have intrinsic resistance to vancomycin because their porins are too small to allow its passage into the cell. Efflux transporters in cell membranes pump out antibiotics that have entered the microbes. These are responsible for the intrinsic resistance of some pathogens to fluoroquinolones and the intrinsic and acquired resistance of *P. aeruginosa* to multiple antibiotics.

An increasing number of pathogens are multidrug-resistant organisms

(MDROs).[5,6] These bacteria have several mechanisms to avoid killing, including producing ESBLs, reducing the permeability of porins, enhancing efflux pumps, and altering antibiotic targets. The acronym ESKAPE is a useful mnemonic for the MDROs E. *faecium*, *Staphylococcus aureus* (MRSA), *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp. MDROs also include *Stenotrophomonas maltophilia*, an opportunistic nosocomial pathogen.

The Generating Antibiotic Incentives Now (GAIN) Act, passed in 2012, was created to provide incentives for the development of antibiotics targeted to treat MDROs.[7] The non-β-lactam β-lactamase inhibitor avibactam,[8] combined with ceftazidime (approved in 2015), has activity against KPC and AmpC but not the metallo-β-lactamase NDM-1, which is produced by some *K. pneumoniae*, *Escherichia coli*, and *A. baumannii*. A fifth-generation cephalosporin, ceftolozane, combined with tazobactam,[9] has significant activity against multidrug resistant *P. aeruginosa* (approved in 2014). Three new drugs approved in 2014 to treat some MRSA infections include the long-acting oritavancin, tedizolid, and dalbavancin.[10–12] It is prudent to involve infectious disease (ID) consultants in the care of patients who may require these agents for treatment of these highly resistant pathogens.

Prophylactic Antibiotic Administration for Surgical Patients

The Surgical Care Improvement Project (SCIP) is one of eight Joint Commission electronic clinical quality measures that were initiated as a protocol with the goal of decreasing infections in surgical patients.[13] Three SCIP measures directly address antibiotic administration: (1) prophylactic administration of antibiotics within 1 hour prior to surgical incision; (2) prophylactic antibiotic selection; and (3) prophylactic antibiotic discontinuation within 24 hours after surgery.[3] These goals are largely based on the pharmacologic properties of antibiotics in

DOI 10.2310/7800.8030
04/17

Table 1 Mechanism of Action and Activity of Antibiotics

Antibiotic (Example)	*Mechanism of Action*	*Spectrum of Activity*
Cephalosporins		
First generation (cefazolin)	Inhibition of cell wall synthesis	MSSA, G–
Second generation (cefoxitin)	Inhibition of cell wall synthesis	Extended G–
Third generation (ceftriaxone)	Inhibition of cell wall synthesis	G–, *Streptococcus pneumoniae*
Fourth generation (cefepime)	Inhibition of cell wall synthesis	G–, including *Pseudomonas aeruginosa*
Fifth generation (ceftolozane)	Inhibition of cell wall synthesis	MDRO, *P. aeruginosa*
Penicillins (ampicillin)	Inhibition of cell wall synthesis	*Streptococcus*, susceptible *Enterococcus*
Antistaphylococcal penicillins (nafcillin)	Inhibition of cell wall synthesis	MSSA
Carbapenems (meropenem)	Inhibition of cell wall synthesis	MSSA, G–, anaerobes, ESBL, MDRO
β-Lactam/β-lactam inhibitor (piperacillin-tazobactam)	Inhibition of cell wall synthesis + inactivation of β-lactamase	MSSA, G– including *P. aeruginosa*, anaerobes
Glycopeptides (vancomycin)	Inhibits cell wall synthesis of the polymers *N*-acetylmuramic and *N*-acetylneuraminic acids	MRSA, streptococcal species, susceptible *Enterococcus*
Oxazolidinones (linezolid)	Inhibits protein synthesis by binding to 50S ribosome subunit	MRSA, VRE
Lincosamides (clindamycin)	Inhibits protein synthesis by binding to 50S ribosome subunit	Susceptible *Staphylococcus*, *Streptococcus*, anaerobes
Fluoroquinolones (ciprofloxacin)	Inhibit topoisomerase to prevent unwinding of bacterial DNA	G–, susceptible *P. aeruginosa*, *Salmonella*
metronidazole	Inhibits nucleic acid synthesis by disrupting the DNA of anaerobic cells	Anaerobes
Aminoglycosides (gentamicin)	Inhibits protein synthesis by binding to 30S ribosome subunit, preventing translational accuracy	G–, combined with β-lactam for *Staphylococcus aureus*, *Enterococcus*, *Streptococcus*
Macrolides (azithromycin)	Inhibits protein synthesis by binding to 50S ribosome subunit, preventing transfer RNA transfer	*Mycoplasma pneumoniae*, *Legionella*, GAS
Daptomycin	Inserts in membrane, causing loss of membrane potential, which inhibits DNA and RNA synthesis	MRSA
Rifamycins (rifampin)	Inhibits bacterial RNA synthesis by inhibiting DNA-dependent RNA polymerase	Synergy with other antimicrobials for biofilm penetration; never used alone
Colistin	Displaces ions in outer membrane lipopolysaccharides and solubilizes membranes	G–, MDRO
Aztreonam	Inhibition of cell wall synthesis	G–, *P. aeruginosa*
Tetracyclines (doxycycline)	Binds 30S ribosomal subunit and blocks protein synthesis	*Staphylococcus*, *Stenotrophomonas*, rickettsial infections
Sulfonamides (trimethoprim-sulfamethoxazole)	Disrupts folate synthesis	MRSA, G–

ESBL = extended-spectrum β-lactamase; GAS = group A *Streptococcus*; G– = gram negative; MDRO = multidrug-resistant organism; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-sensitive *Staphylococcus aureus*; VRE = vancomycin-resistant *Enterococcus* sp.

healthy individuals. Although it has been debated that these measures have not met the desired goal of reduction in surgical site infections,[14] the overall concept of this antibiotic stewardship is important to reduce surgical site infections while limiting unnecessary antimicrobial administration. For ICU patients who are scheduled for surgical procedures, a guide[15] for commonly used perioperative antibiotics based on agreed upon recommendations from the Infectious Diseases Society of America (IDSA), the Society for Healthcare Epidemiology of America (SHEA), the Surgical Infection Society (SIS), and the American Society of Hospital Pharmacists is provided here [*see Table 2*]. Evidence to date does not support the use of routine postoperative antibiotics for the purposes of prophylaxis.

Treatment of ICU Infections

When a bacterial infection is suspected, empirical treatment is often initiated several days before the availability of culture and sensitivity results. During this critical period prior to definitive microbiologic diagnosis, the clinician must decide what the most likely pathogen is, the probability of antibiotic resistance, and the effective antibiotic dose to treat the infection based on the patient's pathophysiology until culture results are obtained [*see Table 3*].[16] Effective antibiotic administration with the first hour of hypotension has been associated with increased survival for sepsis.[17] The prompt administration of antimicrobials is critical because, for each hour delay in the administration of appropriate antibiotics, there is an attributable increase in ICU and hospital lengths of stay secondary

Table 2 Common Perioperative Antibiotics

Surgical Procedure	*Recommended Antibiotic**	*Antibiotic if β-Lactam Allergic*†
Cardiac: coronary artery bypass, pacemaker, ventricular assist device	Cefazolin, cefuroxime	Clindamycin, vancomycin
Thoracic, noncardiac	Cefazolin, ampicillin-sulbactam	Clindamycin, vancomycin
Gastrointestinal		
Small intestine, nonobstructive	Cefazolin	Clindamycin + aminoglycoside or aztreonam or fluoroquinolone
Small intestine, obstructive	Cefazolin + metronidazole, cefoxitin, cefotetan	Metronidazole + aminoglycoside or fluoroquinolone
Colorectal	Cefazolin + metronidazole, cefoxitin, cefotetan, ampicillin-sulbactam, ceftriaxone + metronidazole, ertapenem	Clindamycin + aminoglycoside, or aztreonam, or fluoroquinolone, metronidazole + aminoglycoside or fluoroquinolone
Biliary (open/high risk)	Cefazolin, cefoxitin, cefotetan, cetriaxone, ampicillin-sulbactam	Clindamycin + aminoglycoside, or aztreonam, or fluoroquinolone, metronidazole + aminoglycoside or fluoroquinolone
Head and neck	Cefazolin + metronidazole, cefuroxime + metronidazole, ampicillin-sulbactam	Clindamycin, vancomycin
Neurosurgical	Cefazolin	Clindamycin, vancomycin
Orthopedic	Cefazolin	Clindamycin, vancomycin
Urologic (clean contaminated)	Cefazolin + metronidazole, cefoxitin	Fluoroquinolone, aminoglycoside + metronidazole or clindamycin
Vascular	Cefazolin	Clindamycin, vancomycin
Transplantation		
Heart	Cefazolin	Clindamycin, vancomycin
Liver	Piperacillin-tazobactam, cefotaxime + ampicillin	Clindamycin or vancomycin + aminoglycoside or aztreonam or fluoroquinolone
Pancreas/kidney	Cefazolin, fluconazole (high risk of fungal infection)	Clindamycin or vancomycin + aminoglycoside or aztreonam or fluoroquinolone

Recommendations are based on the Surgical Care Improvement Project.[13]
*Administer within 60 minutes before surgical incision (120 minutes for vancomycin or fluoroquinolones).
†For patients with known or at high risk for methicillin-resistant *Staphylococcus aureus* of colonization, it is reasonable to add a single preoperative dose of vancomycin to the recommended agents and use vancomycin instead of clindamycin as an alternative antibiotic if allergic.

to infection.[18] Empirical antibiotic administration in the absence of infection, however, does not improve outcomes and may result in the development of resistant organisms, infection with *Clostridium difficile*, or side effects from the drugs.[19]

While awaiting definitive microbiologic data, the intensivist should rely on the clinical and microbiological history, physical examination, radiology, epidemiologic history, and laboratory studies to help determine the most likely source of infection. Determining the most likely site of infection then allows the clinician to choose empirical antibiotics that will cover the most likely organisms that cause the particular type of infection. Pneumonia and intra-abdominal sites comprised two thirds of infections in septic patients when a pathologic organism was identified.[17] Gram-negative bacteria accounted for 48% of the pathogens, of which 22% were *E. coli*. *S. aureus* was the most likely pathogen (16%) of the 38% that are gram-positive infections.[17]

When choosing empirical antibiotics, consideration should also be given to possible resistance [*see Figure 1*]. Institutions have created antibiograms that characterize the most efficacious use of antibiotics for suspected and confirmed organisms and specific infected sites [*see Table 4*].[20] Antibiograms are hospital specific, may show different susceptibilities between the general hospital population and individual ICUs, and should be used when making decisions regarding empirical antibiotic choices.[21]

DEESCALATION AND DURATION OF ANTIBIOTIC TREATMENT

The deescalation of antibiotics once culture results are known is an essential component of antibiotic stewardship, reducing the risk of selection for resistant organisms, *Clostridium difficile* infection (CDI), antimicrobial toxicity, and drug interactions and overall health care costs.[22,23] In a multicenter study of 67 ICUs, empirical antibiotics for 50% of patients were continued for at least 72 hours in the absence of infection, and treatment for suspected pneumonia accounted for 60% of the patients.[24] Vancomycin and piperacillin-tazobactam were the most frequently prescribed antibiotics.

A common challenge in antibiotic stewardship is the decision regarding duration of therapy. The IDSA has published numerous guidelines on the management of infectious syndromes, which include recommended optimal duration of therapy whenever possible.[25] Increasingly, shorter durations appear to be adequate in a variety of common infections.[25–31] There are many caveats to early discontinuation, including the likelihood of a metastatic infection, site of infection, presence of foreign material, and degree of antibiotic resistance, in addition to comorbidities and advanced age, which may necessitate more extended treatments. The intensivist must balance short-term treatment with the possibility of relapse of infection when therapy fails.

LABORATORY DIAGNOSIS OF BACTERIAL INFECTIONS

When a patient has an unplanned ICU admission, for example, after trauma, respiratory distress, or cardiovascular

Table 3 Empiric Antibiotic Therapy for Suspected Diseases

Suspected Disease	*Preferred Empiric Regimen**
Sepsis, unknown source	vancomycin + ceftriaxone or cefepime + metronidazole
Sepsis, community acquired intra-abdominal source	cefepime, ceftriaxone or ciprofloxacin+ metronidazole; or piperacillin-tazobactam[1]
Sepsis, community acquired urinary source	ceftriaxone or cefepime
Community-acquired pneumonia (CAP)	ceftriaxone + macrolide; consider addition of vancomycin for necrotizing pneumonia or post-influenza CAP[49]
Hospital or ventilator acquired pneumonia	See table 5 for details
Severe non-purulent necrotizing infection/cellulitis or erysipelas	emergent surgical inspection; vancomycin + piperacillin-tazobactam[28]
Severe purulent abscess/skin and soft tissue infection	incision and drainage; vancomycin OR daptomycin or linezolid[28]
Moderate to severe diabetic foot infection	vancomycin + cefepime + metronidazole[50]
Prosthetic joint infection	vancomycin + cefepime in unstable patients when antibiotics cannot be delayed prior to culture
Clostridium difficile colitis	oral vancomycin
Community acquired bacterial meningitis (2-5 y.o.)	vancomycin + ceftriaxone[51]
Community acquired bacterial meningitis (>50 y.o.)	vancomycin + ceftriaxone + ampicillin[51]
Bacterial meningitis after penetrating head trauma, post-neurosurgery or CSF shunt in place	vancomycin + cefepime or ceftazidime or meropenem[51]

* Therapy should be tailored as necessary when culture data become available

collapse, it may be difficult to determine if there is an infection and, if so, what antibiotics should be administered if culture results are not known. Results from the traditional diagnosis method of culture and sensitivity are usually available within 48 to 72 hours. Newer technologies for rapid diagnosis, such as polymerase chain reaction, DNA hybridization, mass spectroscopy, and circulating biomarkers, may allow for more rapid identification of pathogens but are not always readily available at all institutions and may have a high incidence of false positive results.[16] Intensivists should prioritize whenever possible the collection of cultures prior to initiation of antimicrobials and repeat cultures as clinically indicated to increase the likelihood of diagnosis and directed therapy.

HOSPITAL-ASSOCIATED INFECTIONS

Traditionally, infections were considered either community acquired or nosocomial, and this differentiation can be important in decisions regarding empirical antibiotic choices as nosocomial infections are often, but not always, more likely to be caused by more resistant organisms. Nosocomial infections are any infections attributed to exposure within the hospital setting. In addition to surgical site infections, several device-associated hospital-acquired infections are closely monitored by individual institutions and as part of national regulatory requirements and include ventilator-associated pneumonia (VAP), central line–associated bloodstream infections (CLABSIs), and catheter-associated urinary tract infections (CAUTIs).[32]

BLOODSTREAM INFECTIONS

Bacteremia can be thought of as primary, such as from an indwelling central venous catheter or intravenous drug use, or secondary, such as from hematogenous spread from another site of infection, including the lung, urinary tract, intra-abdominal sites, or skin and soft tissue [*see Figure 2*]. If a bloodstream infection is suspected, blood cultures should be obtained prior to the initiation of antibiotics to optimize isolation of the bacteria in culture. With sterile technique, at least two sets of blood culture should be obtained (aerobic and anaerobic bottles), with at least one drawn peripherally.[30] Gram stains of the blood culture growth can help guide empirical antibiotic choices before definitive results are obtained.

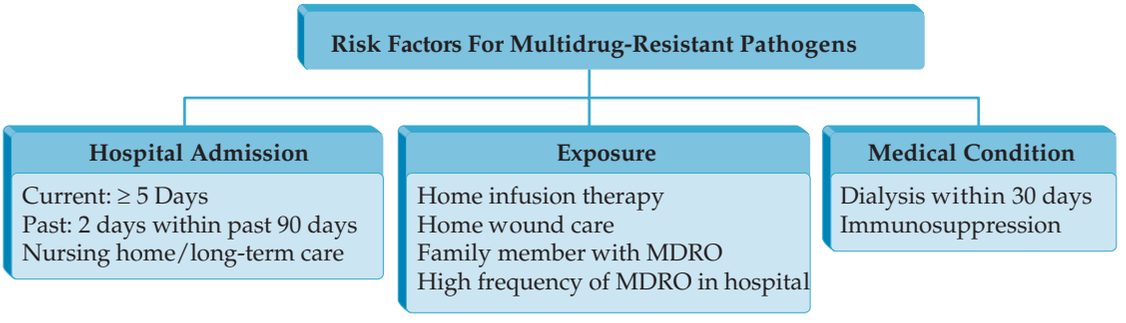

Figure 1 **Risk factors for multidrug-resistant organisms and empirical broad-spectrum treatment.[26,27] MDRO = multidrug-resistant organism.**

Table 4 Sample Antibiogram Demonstrating Percent Susceptible Pathogens to Antibiotics

Pathogen	*Number of Strains*	*Percent Susceptibility at Minimal Inhibitory Concentration*												
		Penicillin	*Ampicillin*	*Piperacillin-Tazobactam*	*Cefazolin*	*Ceftriaxone*	*Cefepime*	*Vancomycin*	*Linezolid*	*Clindamycin*	*Levofloxacin*	*Gentamicin*	*Amikacin*	*Aztreonam*	*Meropenem*
Staphylococcus aureus	3,867	18	—	—	68	—	—	100	100	68	74	—	—	—	—
Staphylococcus—coagulase negative	1,770	16	—	—	49	—	—	100	—	59	56	—	—	—	—
Streptococcus pneumoniae	226	97	—	—	—	99	—	100	—	—	98	—	—	—	—
β-Hemolytic streptococcus Group A	162	100	—	—	100	100	—	—	—	74	99	—	—	—	—
Group B	1,347	100	—	—	100	100	—	100	—	67	99	—	—	—	—
Enterococcus faecalis	106	100	—	—	0	0	—	95	97	0	77	—	—	—	—
Enterococcus faecium	104	5	—	—	0	0	—	25	93	0	4	—	—	—	—
Acinetobacter baumannii	133	—	0	—	0	0	76	—	—	—	82	—	—	0	87
Enterobacter cloacae	505	—	0	78	0	74	93	—	—	—	88	93	100	78	99
Escherichia coli	7,958	—	51	95	82	91	95	—	—	—	78	90	100	94	100
Haemophilus influenzae	96	—	70	—	—	100	—	—	—	—	100	—	—	—	100
Klebsiella pneumoniae	1,800	—	0	90	88	91	94	—	—	—	90	94	99	91	99
Proteus mirabilis	754	76	—	100	55	99	99	—	—	—	81	88	100	99	100
Pseudomonas aeruginosa	1,333	0	—	86	0	0	89	—	—	—	68	84	89	74	83
Salmonella spp.	72	80	—	97	—	99	100	—	—	—	86	—	—	99	100
Serratia marcesens	274	0	—	—	0	94	99	—	—	—	90	98	100	98	100
Stenotrophomonas maltophilia	274	0	—	—	0	0	0	—	—	—	75	0	0	0	0

Antibiograms are hospital specific, may show different susceptibilities between the general hospital population and individual intensive care units, and should be used when making decisions regarding empirical antibiotic choices.

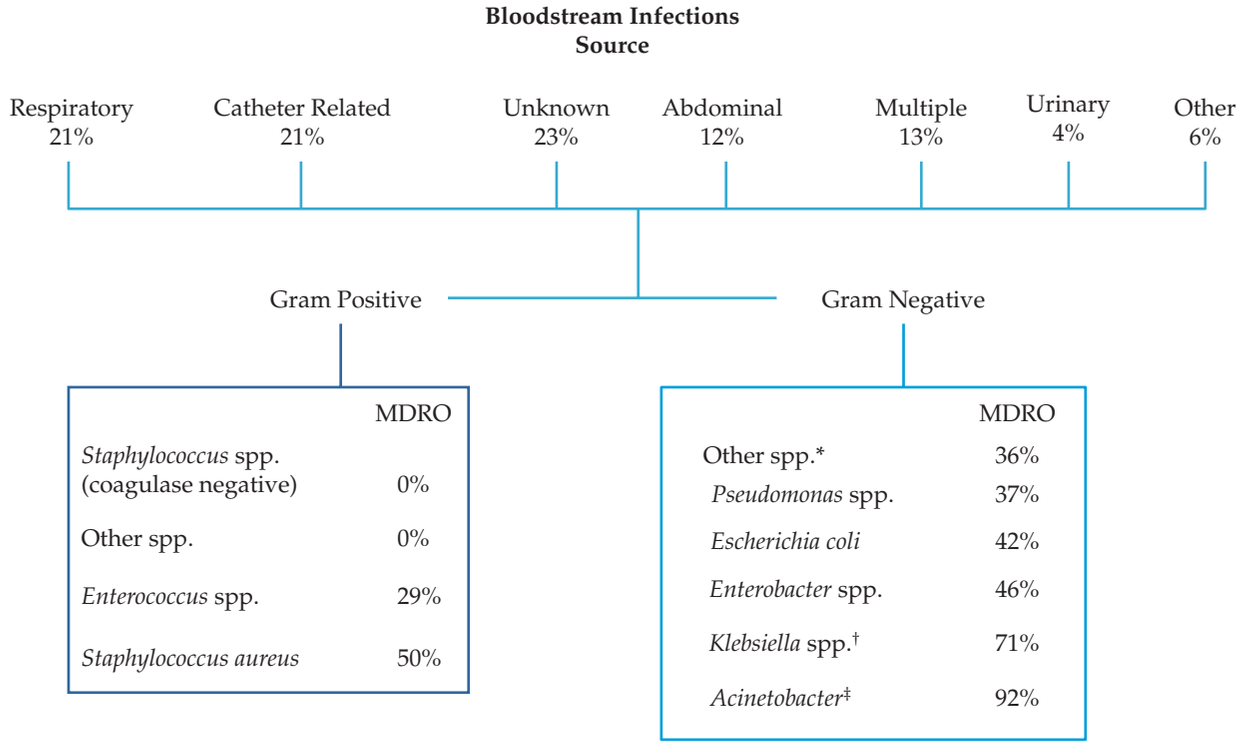

Figure 2 **Sources of bloodstream infections based on a study of 1,156 patients from 162 intensive care units in 24 countries.[48] Although respiratory and catheter-related infections were often evident, there are equal numbers of unknown sources of bacteremia. Among the gram-negative microbes, a high percentage were resident to multiple antibiotics. MDRO = multidrug resistant organism. *Includes *Bacteroides* sp. but 0% MDR. †49% extensively drug resistant. ‡71% extensively drug resistant.**

Current guidelines from the IDSA provide a comprehensive approach for the clinician evaluating and managing a bacteremic patient with short-term venous catheters, arterial catheters, long-term central venous catheters, or ports, taking into consideration the patient's clinical status and the organism recovered. Culturing approaches, including culturing of catheter tips, catheter site exudate when present, and blood cultures, are discussed. In addition to antibiotic therapy based on the organism recovered and patient factors, detailed recommendations regarding the use of antibiotic and ethanol lock therapy when line salvage is attempted are provided.[30] A catheter should not be cultured unless a CLABSI is suspected.[30] Bacteria can produce polysaccharide-rich biofilms that are barriers to antibiotic penetration and protect the bacteria from phagocytes.[30] These pathogens may colonize pacemaker leads, prosthetic cardiac valves, and vascular grafts, leading to endocarditis, osteomyelitis, septic thrombophlebitis, and other metastatic infections.

Gram-positive bacteria are the most common pathogens, with *S. aureus* being one of the most lethal, with an attributable mortality of 20 to 24%.[33] Even in the setting of community-acquired infection, MRSA should be considered in patients admitted to the ICU with bacteremia.[34] Frequent hospitalizations and residence in rehabilitation and long-term care facilities increase the probability of a bacteremia with resistant microbes such as MRSA. Initial therapy with vancomycin for presumed bacteremia pending culture results is recommended in institutions with a high prevalence of MRSA.[30] Generally, a 4- to 6-week course of antimicrobial therapy is recommended for the treatment of *S. aureus* bacteremia. Studies have shown improved patient outcomes and decreased length of stay in patients with *S. aureus* bacteremia who are managed by ID-trained physicians.[35] Patients with prostheses, foreign bodies, devitalized tissue, and fluid collections may require prolonged treatments of 6 to 8 weeks and close follow-up for months as surveillance for recrudescent infection.[30,33]

Vancomycin-intermediate and vancomycin-resistant *S. aur-eus* infections are rare and should be comanaged with ID consultants. Potential therapeutic agents include linezolid, ceftaroline, and daptomycin. For patients with a risk of mortality for an operative procedure that would be greater than the risk of infection, prolonged treatment followed by long-term suppressive therapy, in many cases ranging from months to years, may be necessary.

Coagulase-negative *Staphylococcus* spp. (CoNS) may be blood culture contaminants but are potentially pathogenic and can cause infections such as endocarditis, particularly in immunocompromised hosts.[33] For CoNS bacteremia not associated with a central line, in select, uncomplicated patients, an abbreviated course of antibiotics may be considered with very close follow-up, with longer durations based on the presence of a line or patient-specific factors as per IDSA guidelines.[30] The isolation of viridans-group streptococci from blood may be indicative of another disease process, for example, *Streptococcus bovis* as an indicator of a malignancy of the colon and *Streptococcus anginosus* signaling a deep organ abscess. *Streptococcus viridans* can be a cause of more significant infection, such as endocarditis, and blood culture results with this organism should be taken seriously; a comprehensive evaluation for metastatic sites of infection should be undertaken.

Enterococci in the blood are often indicative of an invasive urinary tract infection (UTI), intra-abdominal infection, or line-related infection and are the third leading cause of infectious endocarditis.[36] *E. faecalis* and *E. faecium* are naturally resistant to cephalosporins, clindamycin, and aminoglycosides. Most isolates are *E. faecalis*, which is susceptible to the combined therapy of a β-lactam and gentamicin or vancomycin if the patient is allergic to β-lactams. The more frequent use of vancomycin has been associated with increased incidence of VRE; infection with VRE requires treatment with agents such as daptomycin or linezolid. When there is no evidence of endocarditis or metastatic infection, a 7- to 14-day course may be sufficient.[30]

Bacteremias with gram-negative organisms are being seen with increasing frequency, with sources including invasive UTIs, pneumonias, intra-abdominal infections, and CLABSIs. These are more prevalent with age, are the most common causes of bacteremia in women, and are associated with high mortality if associated with endocarditis. Common pathogens include *E. coli*, *K. pneumoniae*, and *Enterobacter* spp.[33] Health care–associated infections, previous exposure to ceftriaxone or ceftazidime, and failure to adequately treat previous infections all favor the development of infection with ESBL-producing organisms.[30]

More highly resistant pathogens have emerged with increased significance. The MDROs *A. baumannii*, *K. pneumoniae*, and *Pseudomonas* spp. are associated with resistance to carbapenems and increased mortality.[37] Initial antibiotic administration should begin with combination therapy based on hospital antibiograms guided by ID consultation until susceptibilities are known.

PNEUMONIA

Hospital-acquired pneumonia (HAP) and VAP are associated with high morbidity and mortality and are leading causes of sepsis.[25] HAP is defined as "pneumonia not incubating at the time of hospital admission and occurring ≥48 hours after admission," in contrast to VAP, which is a "pneumonia occurring >48 hours after endotracheal intubation."[26] Approximately 10% of intubated patients develop pneumonia, the most common nosocomial ICU infection. The chance of VAP increases 3% per day during the first 5 days after intubation[26] and has an attributable mortality of 1 to 13%.[38] Pneumonia identified within the first 4 days of intubation has a better prognosis compared with a late onset, of which 60% is caused by the MDROs *Pseudomonas*, *Acinetobacter*, *Klebsiella*, and *E. coli*.[39] A consistent factor leading to the delay in appropriate therapy is the failure to consider treatment regimens covering resistant organisms. Unfortunately, changing therapy to the correct regimen at a later time has not been shown to reduce the risk of mortality.[26] Oral hygiene care with chlorhexidine mouth rinse is associated with a 40% decrease in the odds of developing VAP, but there is no evidence that mortality, length of ventilator time, and length of ICU stays are changed.

Blood cultures prior to the initiation of antibiotics are recommended (given the high rate of bacteremias secondary to pneumonia), and noninvasive semiquantitative cultures are the preferred method for obtaining respiratory cultures for HAP, both VAP and non-VAP.[27] Clinical criteria alone, rather than the use of C-reactive protein, procalcitonin, or soluble triggering receptor expressed on myeloid cells (sTREM-1), is recommended for making the decision to initiate antibiotic treatment.[26]

Treatment of pneumonia is based on the American Thoracic Society (ATS) and IDSA guidelines,[26] which emphasize the use of an antibiogram to aid in decisions regarding empirical antibiotics. The IDSA/ATS-recommended empirical treatment strategies for both non-VAP and VAP based on risk factors for MRSA and other MDROs are outlined here [*see Table 5*].[26] The risk factors for multidrug-resistant pathogens in pneumonia are common to most patients admitted to an ICU [*see Figure 2*]. Initial therapy necessitates the administration of antibiotics at optimal doses of a different class to cover suspected multidrug-resistant pathogens.[6,26]

Risk factors for MDROs antecedent prior to the diagnosis of VAP include septic shock, acute respiratory distress syndrome (ARDS), intravenous antibiotic in the preceding 90 days, hospitalization for 5 days or more, and renal replacement therapy.[26] *P. aeruginosa* is the most common gram-negative MDRO in VAP.[21] Initial treatment should consist of combined therapy incorporating cefepime, ceftazidime, imipenem, meropenem or piperacillin/tazobactam plus ciprofloxacin, levofloxacin, or an aminoglycoside.[26] This expanded coverage may also be indicated for the empirical treatment of MDRO *K. pneumoniae*. *Acinetobacter* and *Stenotrophomonas* are most commonly isolated in the respiratory samples of critically ill patients and are problematic secondary to increasing resistance, biofilm production, and the potential for outbreaks to occur within a unit. It is recommended that ID consultants be involved in the management of infections with these organisms given their drug resistance profiles.

Vancomycin is the first-line antibiotic for MRSA pneumonia; however, adequate dosing, monitored by drug levels, is required to ensure both efficacy and safety, especially in patients with renal insufficiency.[26,40] Linezolid, although not superior to vancomycin, may be preferable for patients with renal insufficiency. Daptomycin should never be used for a pulmonary infection as it is inactivated by surfactant, rendering it ineffective at treating infections in this location.

As for the treatment of all infections, deescalation when culture results are known and the limitation of treatment to an appropriate duration are important to reduce resistance. Most patients who receive appropriate therapy should have a good clinical response in the first 6 days of therapy. For patients with VAP, a 7-day course of treatment, compared with a more traditional 10- to 15-day course, reduced the incidence of MDROs.[26,41] *Pseudomonas*, *Acinetobacter,* and *Stenotrophomonas* have a higher rate of recurrence of infection with short-term therapy.[41]

URINARY TRACT INFECTIONS

UTIs account for a significant number of health care–acquired infections.[42] Indwelling urinary catheters are associated with 75% of nosocomial UTIs[42] and increase the risk of infection by 3 to 10% per urinary catheter day, and 1 to 4% of patients with a UTI will develop sepsis.[43] Prevention of CAUTI is a national priority, and key elements include (1) only placing indwelling urinary catheters for appropriate indications; (2) catheter insertion and maintenance technique; and (3) frequent reassessment for continued need and immediate removal when the catheter is no longer needed.

The term *complicated urinary tract infection* (cUTI) is used for infections in association with at least one of the following factors that will decrease the efficacy of therapy: an abnormal genitourinary tract including bladder catheterization, urinary retention, nephroli-

Table 5 Empirical Treatment of Hospital-Acquired Pneumonia (Non-VAP and VAP) in the ICU[26]*

Non-VAP			*VAP*		
Low mortality risk, low MRSA† risk	Low mortality risk, risk of MRSA	High mortality risk, antibiotics within 90 days	Treatment with antibiotic from each of the following classes:		
One of the following: piperacillin-tazobactam, cefepime, levofloxacin, imipenem, meropenem	One of the following: piperacillin-tazobactam, cefepime, levofloxacin, ciprofloxacin, imipenem, meropenem, aztreonam + vancomycin‡ or linezolid	Two of the following§: piperacillin-tazobactam cefepime, levofloxacin, ciprofloxacin, imipenem, meropenem, aztreonam‖ + vancomycin‡ or linezolid	G+ coverage with MRSA activity Vancomycin‡ or linezolid	G– coverage with antipseudomonal activity (β-lactam) piperacillin-tazobactam, cefepime, ceftazidime, imipenem, meropenem, aztreonam‖	G– coverage with antipseudomonal activity (non-β-lactam) Levofloxacin, ciprofloxacin, amikacin, gentamicin, tobramycin, colistin,¶ polymyxin¶

G– = gram negative; G+ = gram positive; ICU = intensive care unit; MRSA = methicillin-resistant *Staphylococcus aureus*; VAP = ventilator-associated pneumonia.
*For the treatment of multidrug-resistant organisms and methicillin-sensitive and methicillin-resistant pathogens, infectious disease consultation is prudent to guide antibiotic choices.
†If the patient has a risk of gram-negative infections or preexisting lung disease such as bronchiectasis or cystic fibrosis, treatment with two antipseudomonal agents is recommended.
‡Target goal is trough level 15 to 20 mg/mL. Consider loading dose of 25 to 30 mg/kg for severe illness.
§Avoid administering two β-lactams.
‖Include coverage for methicillin-susceptible *S. aureus* if used for β-lactam-allergic patient.
¶Reserved for high prevalence of multidrug-resistant organisms.

thiasis, immunocompromise, and infection with an MDRO. Cultures should be obtained in patients with symptoms of a UTI and an indwelling catheter. If still needed, the catheter is replaced, before the initiation of antibiotic therapy. The diagnosis is confirmed when there is no other identifiable source of infection with growth of 10^5 or more colony-forming units/mL of at least one pathogenic bacterial species. Indwelling urinary catheters develop biofilm within hours of initial placement, and cultures obtained from urinary catheters will commonly demonstrate bacteriuria. Thus, cultures should only be obtained in symptomatic patients. Enterobacteriaceae cause 89% of infections.[42] *E. coli* has been isolated from almost 50% of patients with cUTI, followed by *K. pneumoniae* (14.5%), *P. mirabilis* (6.4%), and *Enterobacter cloacae* (4.6%).[42]

Short-term therapy is adequate for most uncomplicated UTIs. *Enterococcus* in asymptomatic bacteriuria often does not require antimicrobial treatment, particularly if associated with an indwelling catheter, where its simple removal is recommended. Cephalosporins are more than 90% effective against non–ESBL-producing *E. coli*, in contrast to fluoroquinolones, which are less than 70% effective for non-ESBLs.[42] Empirical therapy should consider treatment of resistant pathogens based on a patient's historical microbiology as well as on regional and institutional flora. In a study of inpatients with UTIs from 24 hospitals over a 2-year period, approximately 7% of *E. coli* and 10% of *K. pneumoniae* produced ESBL.[42] The carbapenems are most effective against ESBL-producing *E. coli* but less so against *K. pneumoniae* because of carbapenemase production. There is increasing resistance of *P. aeruginosa* to the fluoroquinolones. Fosfomycin, an older antibiotic, has been the subject of renewed interest as a treatment option for MDROs. Newer agents, ceftolozane-tazobactam[44] and ceftazidime-avibactam,[45] are targeted at highly resistant *E. coli*, *K. pneumoniae*, and *P. aeruginosa*, which are implicated in cUTIs. An ID consultant should guide the use of these agents.

INTRA-ABDOMINAL INFECTION

Abdominal infections are the second most common cause of sepsis and secondary peritonitis. The basic management principle is operative source control of a perforated viscus, lavage of intraperitoneal soilage, or percutaneous drainage of a fluid collection with the administration of appropriate antibiotics.[27] Empirical coverage for high-risk patients admitted from the community should include broad-spectrum agents that will cover *E. faecalis*, gram-negative aerobic pathogens, and anaerobes. These include piperacillin-tazobactam, a carbapenem, a cephalosporin–β-lactamase inhibitor,[44,45] or a combination of metronidazole plus cefepime, ceftazidime, or a fluoroquinolone.[27] As for cUTIs, fluoroquinolone-resistant *E. coli* has increased. Empirical therapy for health care–associated pathogens necessitates treatment for enterococci, ESBL-producing Enterobacteriaceae, MDROs such as *P. aeruginosa*, and *A. baumannii*.[27,46] Coverage of *E. faecium* for 4 to 7 days once source control has been achieved is warranted for patients with known VRE colonization.[27] A recent study showed that after source control, a 3- to 5-day antibiotic course for uncomplicated intra-abdominal infections had the same outcome as longer therapy, with 20% recurrence of infection in both groups.[47]

Broad-spectrum antibiotic use, resulting in alteration of intestinal flora, is a major risk factor for CDI.[29] This pathogen is the leading cause of nosocomial diarrhea. Diagnosis is made by the presence of diarrhea and either a stool test positive for toxigenic *C. difficile*, the detection of toxins, or the findings of pseudomembranous colitis.[29]

The first step in the treatment of CDI is the deescalation or discontinuation of the current antibiotic regimen. Conventional treatment for a first episode of CDI is a 10- to 14-day regimen: oral metronidazole 500 mg every 8 hours for mild to moderate infections or oral vancomycin 125 mg or oral vancomycin 500 mg every 6 hours for initial severe infections.[28] Severe, complicated CDI is treated by combination therapy with oral vancomycin 500 mg every 6 hours and intravenous metronidazole 500 mg every 8 hours.[29] Vancomycin retention enemas (500 mg in 100 mL normal saline) can be used in lieu of oral administration if an ileus is present. The macrolide fidaxomicin (200 mg oral twice daily for 10 days) has a similar cure rate to the 125 mg vancomycin dose but may be superior in preventing a second recurrence within 28 days. ID and surgical consultation is recommended for severe CDIs.

SKIN AND SOFT TISSUE INFECTIONS

Skin and soft tissue infections (SSTIs) have a broad spectrum of presentation in ICU patients.[28] The most common SSTIs admitted to an ICU are necrotizing fasciitis and Fournier gangrene following the primary therapy of surgical resection. These infections should be suspected in the setting of erythema, drainage, or crepitus in the skin or soft tissue with hemodynamic compromise. Broad-spectrum antibiotic coverage with vancomycin, linezolid, or daptomycin plus piperacillin-tazobactam, a carbapenem, ceftriaxone with metronidazole, or a fluoroquinolone with metronidazole is initially required as these are often polymicrobial infections. Penicillin, combined with clindamycin for suppression of toxins and cytokines, is indicated for group A streptococcal fasciitis as well as gas gangrene from *Clostridium perfringens* and other *Clostridium* spp.

Conclusion

The appropriate selection of antibiotics is a fundamental responsibility of the intensivist with consideration of the correct antibiotic at the right dose and the right time of administration to treat both resistant and multidrug-resistant organisms. The intensivist, as an antibiotic steward, is central to the delivery of safe and effective patient care and the prevention of antimicrobial resistance.

Financial Disclosures: Richard M Pino, MD, PhD, FCCM, Molly Paras, MD, and Erica S Shenoy, MD, PhD, have no relevant financial relationships to disclose.

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Review Clinical Trial Meta-analysis Guideline

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