Choosing Optimal Antimicrobial Therapies

Thomas J. Lynch, PharmD

KEYWORDS

• Antimicrobial therapy • Multidrug resistance • *Streptococcus pneumoniae*
• Methicillin-resistant *Staphylococcus aureus* • *Enterococcus*
• *Pseudomonas aeruginosa* • Group A β-hemolytic *Streptococcus*

KEY POINTS

- Life-threatening infections require immediate and aggressive empiric use of parenteral bactericidal antibiotics.
- The recommended antibiotics are usually broad spectrum, are effective for the presumptive bacterial cause, readily achieve bactericidal concentrations at the site of infection, and are relatively safe to use in high doses.
- Vancomycin is most often used for gram-positive coverage, a carbapenem or piperacillin-tazobactam for gram-negative coverage, and metronidazole or clindamycin for anaerobic coverage.

Selecting appropriate antimicrobial agents for treating infections has always been a difficult task. Unlike selecting drugs to treat other disease processes, there are more variables to address. Not only does one have to consider the pharmacodynamic and pharmacokinetic properties of a drug as it relates to the patient to ensure tolerance and safety, one must also select an agent that the presumed microbe(s) will be susceptible to and that will reach the presumed site of infection with a high enough concentration to at least inhibit further microbial growth.

For treating life-threatening infectious disease emergencies, several properties of the appropriate antimicrobial agent are necessary. More often than not it will have to be given parenterally (intravenously or intramuscularly) to ensure 100% absorption and distribution and have an immediate onset of effect. It should also be bactericidal at achievable plasma and tissue concentrations to destroy and reduce the microbial load, rather than bacteriostatic, which only results in inhibition of further growth, relying on a competent immune system to slow the infectious process.

For the infectious disease emergencies discussed in this article, antimicrobial agents are recommended based on the presumed causative microorganisms and

Disclosures: No funding sources or conflict of interest to report.
Department of Family and Community Medicine, Eastern Virginia Medical School, PO Box 1980, Norfolk, VA 23501, USA
E-mail address: lyncht@evms.edu

Med Clin N Am 96 (2012) 1079–1094
http://dx.doi.org/10.1016/j.mcna.2012.08.006 **medical.theclinics.com**
0025-7125/12/$ – see front matter

site of infection. Once the microorganism has been cultured and sensitivities reported, antimicrobial selection can be streamlined to target the pathogen or pathogens.

HEAD AND NECK INFECTIONS

Meningitis

Infections of the central nervous system (CNS) require the maximum doses of suggested antimicrobial agents in order for the agent to penetrate the blood-brain barrier. Agents such as β-lactam antibiotics and vancomycin penetrate poorly whereas others such as metronidazole have better bioavailability.[1] If meninges are inflamed, there is usually better penetration into the brain, but this is reduced once the meningitis starts to resolve. Vancomycin doses must be adjusted to obtain high serum trough levels of 15 to 20 mg/L.[2]

Empiric antimicrobial therapy for meningitis depends on the age of the patient. About 80% of cases in children and adults are due to *Streptococcus pneumoniae* or *Neisseria meningitidis*. The third-generation cephalosporins, ceftriaxone or cefotaxime, are drugs of choice for meningitis and vancomycin is added in case *S pneumoniae* is highly resistant to the cephalosporins (**Table 1**). Additional agents must be given for neonates and patients over 50 years old because of possible infection by *Listeria monocytogenes* or group B streptococci.[3]

Brain Abscess

Polymicrobial infections are common in patients with brain abscesses. Aerobic and anaerobic streptococci such as *Streptococcus anginosus* along with other anaerobic bacteria such as *Bacteroides fragilis* are common causes. Metronidazole as an antianaerobic agent is usually added to ceftriaxone or cefotaxime because of its excellent penetration into brain abscesses. If the potential source is penetrating trauma or postneurosurgical procedure, then *Staphylococcus aureus* (including methicillin-resistant *S aureus* [MRSA]) and *Pseudomonas aeruginosa* need to be considered as pathogens (see **Table 1**). Vancomycin would be added and the antipseudomonal cephalosporins, ceftazidime or cefepime, would be chosen as the cephalosporins.[4]

Encephalitis

By far the most common cause of encephalitis is infection by herpes simplex virus (HSV). More than 90% of herpes infections are due to HSV-1 and the rest by HSV-2. Intravenous acyclovir is the drug of choice (see **Table 1**). Other more rare viral causes of encephalitis include West Nile virus and Eastern equine encephalitis virus, which are arthropod-borne or arboviruses. At present, no antiviral therapy is available against these viruses.[5]

Jugular Septic Thrombophlebitis

Also known as Lemierre syndrome, jugular septic thrombophlebitis can be a rare complication of oropharyngeal or odontogenic infections. The most likely organisms involved are anaerobic streptococci, *Bacteroides* species, and *Fusobacterium necrophorum*. Three to 6 weeks of an antipseudomonal carbapenem plus metronidazole or ampicillin-sulbactam alone are the therapies of choice (see **Table 1**).[6]

Upper Airway Obstruction

Sudden obstruction of the upper airway usually is caused by acute epiglottitis, especially in children. The most common organism associated with epiglottitis is *Haemophilus influenzae*, although *S aureus*, including MRSA, can also cause it. Because *H influenzae* may be ampicillin resistant, ampicillin-sulbactam, ceftriaxone, or cefotaxime are recommended along with vancomycin to provide activity against MRSA

Table 1
Empiric treatment of life-threatening head and neck infections

Infection	Likely Organism(s)	First-Line Agent(s)	Alternative Agent(s) if Severe Allergy to First Line
Bacterial meningitis Age 1 mo to 50 y	*Streptococcus pneumoniae*, *Neisseria meningitidis*	Vancomycin + ceftriaxone or cefotaxime	Vancomycin + aztreonam
Bacterial meningitis Neonate or age >50 y	*S pneumoniae*, *N meningitidis*, *Listeria monocytogenes*	Vancomycin + ceftriaxone or cefotaxime + ampicillin	Aztreonam in place of cephalosporins and TMP-SMX in place of ampicillin
Brain abscess Community-acquired	*Streptococcus anginosus* *Bacillus fragilis*	Ceftriaxone or cefotaxime + metronidazole	Vancomycin + aztreonam + metronidazole
Brain abscess Nosocomial-acquired	*S anginosus* *B fragilis* *Staphylococcus aureus* *Pseudomonas aeruginosa*	Vancomycin + antipseudomonal cephalosporin + metronidazole	Vancomycin + aztreonam + metronidazole or vancomycin + antipseudomonal carbapenem
Encephalitis	Herpes simplex virus	Acyclovir	
Upper airway obstruction	*Haemophilus influenzae* *S aureus*	Vancomycin + third-generation cephalosporin	Trimethoprim-sulfamethoxazole (TMP-SMX)
Jugular septic thrombophlebitis	*Streptococcus* spp *Peptostreptococcus* spp *Bacteroides* spp *Fusobacterium necrophorum*	Antipseudomonal carbapenem + metronidazole or Ampicillin-sulbactam	Clindamycin

(see **Table 1**). For the severe penicillin-allergic patient, either trimethoprim-sulfamethoxazole or a fluoroquinolone (in adults) may be substituted for the ampicillin-sulbactam or cephalosporin.[7]

PULMONARY INFECTIONS

Pneumonia

When selecting antimicrobial agents for life-threatening pneumonia, it is important to first differentiate between community-acquired (CAP) and hospital-acquired (HAP) or heath care–associated pneumonia (HCAP). The most common bacterial causes of severe CAP are *S pneumoniae*, including drug-resistant strains, and atypical pathogens such as *Chlamydophila pneumoniae*, *Mycoplasma pneumoniae*, and *Legionella pneumophila*. For this reason the intravenous antibiotic combination of choice is a third-generation cephalosporin plus the macrolide, azithromycin, for the atypical pathogens. Respiratory fluoroquinolones (moxifloxacin or levofloxacin) also are usually effective against these pathogens.[8] For severe HAP and HCAP the presumption is that the pathogen(s) may include gram-negative bacilli, multiply drug-resistant (MDR) bacteria, or MRSA. A patient is considered to have HAP if pneumonia occurs at least 48 hours after admission. HCAP should be considered if the patient has a history of recent hospitalization within 90 days, is a resident of a long-term care facility, has received intravenous antibiotics, chemotherapy, or wound care within 30 days, or has attended a hemodialysis clinic. The most prevalent gram-negative organism to consider is *P aeruginosa*. For severe pseudomonal infections it is recommended that 2 agents be used, such as an antipseudomonal carbapenem and fluoroquinolone or the synergistic combination of an antipseudomonal β-lactam (meropenem, doripenem, cefepime, ceftazidime, piperacillin-tazobactam) with and aminoglycoside antibiotic. MDR pathogens may include extended-spectrum β-lactamase (ESBL)-producing bacteria such as *Klebsiella pneumoniae* or *Acinetobacter* species, which are resistant to cephalosporin antibiotics. Therefore for severe HAP or HCAP it is recommended that an antipseudomonal cephalosporin or carbapenem (meropenem or doripenem) be used with an additional antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin). If MRSA is suspected, vancomycin or linezolid should be added (**Table 2**). Although bacteriostatic, linezolid may be preferred because of its better lung-tissue penetration than vancomycin.[9]

Empyema

Empyema is an infection of the pleural space with pus and is usually a result of pneumonia. Pathogens associated with empyema include the same aerobic bacteria that cause pneumonia along with anaerobic bacteria such as *B fragilis*, *Prevetella* species, and *Fusobacterium nucleatum*. In previously healthy individuals the most common aerobic bacteria include *S pneumoniae*, *Streptococcus pyogenes*, and *S aureus*, including MRSA. Also to be considered is *S anginosus*, which is present in the oral cavity and gastrointestinal tract. Once drainage of the pleural space is performed, many antibiotics are available that readily penetrate the pleural space and are bactericidal for the most likely pathogens that cause empyema. Single agents would include piperacillin-tazobactam or a carbapenem. Double therapy would include a ceftriaxone or cefotaxime plus either metronidazole or clindamycin (see **Table 2**). Vancomycin or linezolid could be added if MRSA is a possible cause.[10]

Lung Abscess

Lung abscesses can occur as a complication of aspiration pneumonia and are due to the same bacteria that cause this particular pneumonia, usually anaerobic bacteria

Table 2
Empiric treatment of life-threatening pulmonary infections

Infection	Likely Organism(s)	First-Line Agent(s)	Alternative Agent(s) if Severe Allergy to First Line
Pneumonia community-acquired (CAP)	*Streptococcus pneumoniae*, *Legionella pneumophila*, *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*	Ceftriaxone or cefotaxime + azithromycin	Moxifloxacin or levofloxacin (also considered first-line agents)
Pneumonia HAP or HCAP	*S pneumoniae*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Acinetobacter* spp, MRSA	Cefepime or ceftazidime + ciprofloxacin +/− vancomycin	Meropenem or doripenem + gentamicin +/− linezolid
Empyema	*S pneumoniae Streptococcus pyogenes*, *Streptococcus anginosus*, *Staphylococcus aureus*, anaerobes	Piperacillin-tazobactam or carbapenem or ceftriaxone/cefotaxime + metronidazole	Fluoroquinolone + clindamycin
Lung abscess	Mouth flora anaerobes including *Fusobacterium* spp, *Prevatella* spp, and *Peptostreptococcus* spp	Ceftriaxone or cefotaxime + clindamycin or ampicillin-sulbactam alone	Moxifloxacin
Adult respiratory distress syndrome	See sepsis guidelines		

from the oral cavity. Initially a lung abscess is presumed to be polymicrobial and is treated with the combination of ceftriaxone or cefotaxime plus clindamycin (see **Table 2**). Metronidazole, although generally a very effective antianaerobic agent, is specifically inferior for gram-positive anaerobic mouth flora. A parenteral β-lactam plus a β-lactamase inhibitor such as ampicillin-sulbactam or piperacillin-tazobactam can also be used.[11] Alternatives for this polymicrobial infection could include a carbapenem or respiratory fluoroquinolone with anaerobic activity such as moxifloxacin.[12]

Adult Respiratory Distress Syndrome

Among other conditions, adult respiratory distress syndrome may be precipitated by a sepsis syndrome, either as a result of severe pneumonia or infection from an extrapulmonary source. Antimicrobial treatment guidelines for sepsis should be followed.

CARDIAC INFECTIONS

Endocarditis

Infective endocarditis is defined as infected vegetations on the heart valve composed of layers of fibrin, platelets, and bacteria. This resulting tough fibrin mesh lacks vasculature and impairs host response as leukocytes and complement are unable to reach the encased bacteria. Therefore, bacteria can continue to multiply with inoculum counts reaching as high as 10^9 to 10^{10} cfu/mL. Just as leukocytes cannot readily penetrate this fibrin mesh, antibiotics also find it a formidable barrier.[13] Treatment of infective endocarditis requires high doses of intravenous bactericidal antibiotics for an extended period of time, many times in synergistic combination, for a more rapid and reliable killing effect. Presumptive therapy is necessary for initial treatment in life-threatening situations, but the ultimate selection of antibiotics depends on blood culture results and subsequent antimicrobial susceptibility tests. Quantitative minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) determinations may be needed if the infection is due potentially to antibiotic-resistant isolates. Most cases of native valve infective endocarditis are due to either streptococci or staphylococci. *S aureus* is the leading single bacterial cause of acute infective endocarditis. Choice of therapy depends on whether the infecting organism is a penicillin-sensitive streptococcus (MIC $\leq$0.125 mg/L) such as viridans group streptococci or *Streptococcus bovis*, a penicillin-tolerant streptococcus (MIC >0.125 to $\leq$0.5 mg/L), or a penicillin-resistant enterococcus or staphylococcus, including MRSA (**Table 3**). Viridans streptococci are usually mouth flora and include *Streptococcus mitis*, *Streptococcus mutans*, *Streptococcus salivarius*, *Streptococcus sanguis*, and the *Streptococcus intermedius* group (*S intermedius*, *S anginosus*, and *Streptococcus constellatus*). Enterococcus must always be treated with 2 antibiotics, as no single agent is bactericidal for this organism. Duration of treatment should always be counted from the time of the first negative blood culture. The initial therapy for prosthetic valve endocarditis is similar to native valve endocarditis. The most reliable initial antibiotic combination, pending blood culture results, is vancomycin plus gentamicin. Piperacillin-tazobactam, ceftazidime, cefepime, or ciprofloxacin should be added for gram-negative coverage, including *P aeruginosa*, in patients with early prosthetic valve endocarditis.[14]

Pericarditis and Myocarditis

Pericarditis and myocarditis refer to inflammatory processes of the pericardium and myocardium, respectively, which can ultimately lead to heart failure. Viruses seem to be the most likely cause of these inflammatory disorders, but there are few antiviral

Table 3
Infective native valve endocarditis

Documented Infecting Organism	First Line Agent(s)	Treatment Duration	Alternative Agent(s) if Severe Allergy to First Line
Viridans streptococci/ *Streptococcus bovis* with penicillin MIC $\leq$0.12 mg/L	Penicillin G or ceftriaxone	4 wk	Vancomycin
Viridans streptococci/*S bovis* with penicillin MIC >0.12 mg/L and $\leq$0.5 mg/L	Penicillin G or ceftriaxone + high-dose gentamicin	4 wk 2 wk	Vancomycin
Viridans streptococci/*S bovis* with penicillin MIC >0.5 mg/L	See ampicillin-resistant enterococcal endocarditis	—	—
Methicillin-sensitive *Staphylococcus* spp	Nafcillin +/– low-dose gentamicin	6 wk/3–5 d	Vancomycin +/– low-dose gentamicin
Methicillin-resistant *Staphylococcus* spp	Vancomycin	6 wk	Daptomycin
Enterococcus spp susceptible to ampicillin	Ampicillin + low-dose gentamicin	4–6 wk	Vancomycin + low-dose gentamicin
Enterococcus spp resistant to ampicillin	Vancomycin + low-dose gentamicin	6 wk	Daptomycin

therapies available. In rare cases where the specific etiologic agent has been identified, such as tuberculosis or human immunodeficiency virus, targeted antimicrobial therapy can be initiated. However, in most cases supportive care is the treatment of choice along with immunosuppressive therapy where appropriate. When a bacterial cause is likely or documented, antimicrobial therapy is similar to that of infective endocarditis.[15]

INTRA-ABDOMINAL AND PELVIC INFECTIONS

Acute Peritonitis and Intra-Abdominal Abscess

Peritonitis can develop secondary to perforation of the gastrointestinal tract and spillage of bacterial contents into the peritoneum. The resulting infection is usually polymicrobial and the probable infecting organisms are determined by the site of the perforation along the gastrointestinal tract. The upper intestine usually contains relatively few oral gram-positive microorganisms such lactobacillus and streptococci. The ileum contains a much higher concentration of enteric gram-negative bacteria, such as *Escherichia coli*, gram-positive bacteria such as *Enterococcus*, and an equal number of obligate anaerobes such as *B fragilis*. The colon has, by far, the highest concentration of bacteria (10^{11} cfu/mL) leading to a high incidence of serious intra-abdominal infection if perforation occurs. Hundreds of bacterial species can be present, and anaerobes outnumber aerobic bacteria by a factor of 1000 to 1.[16] Treatment of acute secondary peritonitis therefore must be directed at gram-negative bacteria and anaerobes. Although *Enterococcus* species may be present, antibiotics without enterococcal activity, such as cephalosporins and fluoroquinolones, still

appear to be effective. The selection of antibiotics is further determined by whether the infection is community-acquired or health care–acquired (usually as a result of surgical intervention and presumably due to more resistant organisms) (**Table 4**). Intra-abdominal abscess may occur as a complication of peritonitis; however, the bacteriology is the same. Because antibiotics may not penetrate abscesses very well and there are very high concentrations of bacteria, drainage of the abscess is necessary for antibiotics to be effective.[17]

Cholecystitis and Cholangitis

Cholecystitis and cholangitis usually result from obstruction in the gallbladder or common bile duct, respectively. The most common pathogens associated with cholecystitis are *E coli*, *Klebsiella* species, and *Enterococcus* species. Cholangitis may, in addition, be caused by *Enterobacter* species and anaerobes. For severe biliary tract infections, empiric antibiotic therapy should cover enteric gram-negative organisms and anaerobic bacteria (see **Table 4**). If health care–associated, coverage should be expanded to include *Enterococcus* species.[17]

Pyelonephritis and Perinephric Abscess

Acute pyelonephritis with potentially life-threatening bacteremia requires empiric broad-spectrum intravenous antibiotic therapy. If community-acquired, a fluoroquinolone, piperacillin-tazobactam, or a third-generation cephalosporin may be used. If a Gram stain shows gram-positive cocci, vancomycin should be added for potential MRSA (see **Table 4**). Moxifloxacin should not be used because it is not renally eliminated. Also, if the patient is pregnant, fluoroquinolones are contraindicated. If it is a health care facility–acquired infection, alternative broad-spectrum agents may be needed based on the prevalence of antibiotic-resistant organisms.[18,19]

A perinephric abscess can be a rare complication of a urinary tract infection, and up to 25% of cases may be due to multiple bacterial species. Percutaneous aspiration and drainage will help determine the causative organisms and thus guide antibiotic therapy. Trimethoprim-sulfamethoxazole (TMP-SMX) and fluoroquinolones may be able to better penetrate the abscess site than other antibiotics.[19]

Infectious Colitis

There are several bacterial causes of severe, life-threatening colitis and diarrhea, each of which requires a different antimicrobial approach for treatment (see **Table 4**). Infection due to *Clostridium difficile*, a spore-forming bacteria, is associated with exposure to health care environments, previous antibiotic use, or both. For severe infection oral vancomycin, which is nonabsorbable, is the treatment of choice. Intravenous metronidazole may also be added, although supporting data are lacking. Intravenous vancomycin is ineffective and oral metronidazole is the treatment of choice for milder disease. Several new antibiotics, such as rifaximin, fidaxomicin, and tigecycline, are now available for treating recurrent infection unresponsive to the agents of choice.[20]

Complicated nontyphoidal *Salmonella* infections can usually be treated with a fluoroquinolone or TMP-SMX. However, if life threatening, a third-generation cephalosporin should be added to intravenous fluoroquinolone until susceptibilities are known.[21]

Shigellosis (bacillary dysentery) can be treated with a fluoroquinolone, such as ciprofloxacin, or azithromycin. TMP-SMX should not be used any longer because of the development of widespread resistance.[21]

Campylobacter jejuni gastroenteritis secondary to ingesting undercooked food is usually self-limiting. However, in high-risk individuals, antibiotics are recommended.

Table 4
Empiric treatment of serious intra-abdominal and pelvic infections

Infection	Likely Organism(s)	First-Line Agents	Alternative Agent(s) if Severe Allergy to First Line
Secondary peritonitis and intra-abdominal abscess (community-acquired)	Enteric gram-negative bacteria (*Escherichia coli*, *Klebsiella* spp, *Proteus* spp) Anaerobic bacteria (*Bacteroides* spp)	Piperacillin-tazobactam or antipseudomonal carbapenem	Levofloxacin or aztreonam + metronidazole
Secondary peritonitis and intra-abdominal abscess (health care–associated)	Above organisms + *Pseudomonas aeruginosa* and/or *Staphylococcus aureus*	Above agents + aminoglycoside and vancomycin	Above agents + aminoglycoside and vancomycin
Cholecystitis and cholangitis	Enteric gram-negative bacteria, *Enterococcus* spp, anaerobic bacteria	Piperacillin-tazobactam or carbapenem	Levofloxacin or aztreonam + metronidazole
Pyelonephritis	Enteric gram-negative bacteria	Levofloxacin or ciprofloxacin, piperacillin-tazobactam, or ceftriaxone	Aminoglycoside
Perinephric abscess	Enteric gram-negative bacteria	Levofloxacin or ciprofloxacin	TMP-SMX
Infectious colitis	*Clostridium difficile*	Oral vancomycin +/− intravenous metronidazole	Rifaximin or fidaxomicin
	Salmonella (nontyphoid)	Fluoroquinolone + ceftriaxone	TMP-SMX
	Shigella	Fluoroquinolone	Azithromycin
	Campylobacter jejuni	Azithromycin	Fluoroquinolone
	Yersinia enterocolitica	Fluoroquinolone	Azithromycin

The macrolide azithromycin is the agent of choice. Erythromycin and clarithromycin can also be used, but this increases the risk of metabolic interactions with drugs that inhibit or are metabolized by the cytochrome P450 3A4 enzyme. Fluoroquinolones are now considered alternative agents because there is a high level of *C jejuni* resistance to this class of drugs, attributed to its widespread use in the food animal industry.[21]

Yersinia enterocolitica is a zoonotic infection of rodents, birds, and other wild animals. The organism is transmitted to humans by fleas, and in the resulting infection symptoms of fever, diarrhea, and abdominal pain resemble acute appendicitis. Antibiotics of choice include fluoroquinolones and azithromycin.[21]

E coli serotype O157:H7 is an enterohemorrhagic *E coli* strain (EHEC) that produces a Shiga toxin associated with several severe complications including hemorrhagic colitis, hemolytic uremia syndrome, and thrombotic thrombocytopenic purpura. This EHEC strain is usually consumed in undercooked beef products. The role of antibiotic treatment of *E coli* 0157:H7 remains controversial, and currently no particular antibiotic is recommended. In fact antibiotic treatment may lead to complications such as hemolytic uremic syndrome.[22]

NECROTIZING SOFT-TISSUE INFECTIONS

Necrotizing Fasciitis

Necrotizing fasciitis is a rapidly developing inflammation and infection of both superficial and deep fascia, which can quickly progress to septic shock. A wide variety of bacteria can potentially release toxins that cause necrosis, requiring empiric broad-spectrum antibiotic coverage until Gram stain and culture can help narrow the microbiological etiology. Along with immediate surgical debridement, initial empiric therapy with vancomycin plus a carbapenem is indicated to cover for gram-positive organisms, gram-negative Enterobacteriaciae, and *B fragilis*.[23] Virulent strains of Group A B-hemolytic *Streptococcus* are associated with a so-called flesh-eating necrotizing infection. High-dose penicillin G plus clindamycin is indicated for this particularly gruesome disease (**Table 5**). The clindamycin is added for its ability to reduce the production of bacterial toxins.

Clostridial Myonecrosis

Necrotizing infections involving the muscle are termed myonecrosis. Myonecrosis caused by *Clostridium perfringens*, a gram-positive bacillus, is also known as gas gangrene and is a very painful infection secondary to gas in the wound. Penicillin G

Table 5
Life-threatening necrotizing soft tissue infections

Infection	Likely Organism(s)	First-Line Agents	Alternative Agent(s) if Severe Allergy to First Line
Necrotizing fasciitis	Unknown	Carbapenem or piperacillin-tazobactam + vancomycin + clindamycin	Fluoroquinolone + vancomycin + clindamycin
	Group A β-hemolytic *Streptococcus*	Penicillin G + clindamycin	
Clostridial myonecrosis	*Clostridium perfringens*	Penicillin G + clindamycin	Clindamycin or metronidazole

is the antibiotic of choice, after the diagnosis is confirmed, given along with parenteral clindamycin.[24] Those with a severe penicillin allergy history may be treated with clindamycin or metronidazole alone (see **Table 5**).

SEPSIS SYNDROME

Bloodstream Infections

Sepsis syndrome is a life-threatening condition secondary to infection and consequent end-organ dysfunction, hypotension, and hypoperfusion. In addition to supportive measures, immediate administration of appropriate antimicrobial agents is vital to prevent progression to septic shock and death. It is estimated that for every hour of delay in giving parenteral antibiotics, survival decreases by 8%. The choice of antibiotics for sepsis syndrome depends on the presumed source of the infection, causative organism, and the immune status of the patient. After blood cultures are obtained, a broad-spectrum bactericidal parenteral agent such as piperacillin-tazobactam or a carbapenem, plus vancomycin for gram-positive coverage, should be started.[25,26] Therapy can then be guided by culture results and susceptibility testing (**Table 6**). If sepsis occurs in a neutropenic patient or if *P aeruginosa* is a suspected cause, an aminoglycoside should be added for synergistic effect. If sepsis occurs after broad-spectrum antimicrobial therapy, a fungal organism, such as *Candida*, may be the cause and a parenteral antifungal agent should be considered.

Device-Related Infections

Device-related sepsis syndrome can be secondary to peripheral and central intravenous catheters, tunneled catheters, implanted ports, and arterial lines. *S aureus* and coagulase-negative staphylococcal organisms account for 70% to 90% of these infections. Gram-negative bacteria and fungal organisms are also implicated. Therefore, until culture results are available a broad-spectrum bactericidal agent for gram-negative coverage should be started along with vancomycin (see **Table 6**).[25]

TRAVEL-RELATED INFECTIONS

Malaria

For both chloroquine-sensitive and resistant *Plasmodium* species, quinidine gluconate is the only parenteral agent for severe malaria that is approved by the US Food and Drug Administration. Intravenous quinine is available outside the United States. If quinidine gluconate is not available, parenteral artemisinin derivatives are available from the Centers for Disease Control and Prevention (CDC) (**Table 7**).[27] Oral antibiotics such as doxycycline or clindamycin should be added when tolerated.

Table 6
Sepsis syndrome

Source	First-Line Agents	Alternative Agent(s) if Severe Allergy to First Line
Unknown	Piperacillin-tazobactam or carbapenem + vancomycin	Fluoroquinolone + vancomycin
Neutropenic	Piperacillin-tazobactam or carbapenem + aminoglycoside + vancomycin	Fluoroquinolone + aminoglycoside + vancomycin
Device-related	Piperacillin-tazobactam or carbapenem + vancomycin	Fluoroquinolone + vancomycin

Table 7
Travel-related severe infections

Infection	Likely Organism(s)	First-Line Agent(s)	Alternative Agent(s) if Severe Allergy to First Line
Malaria	*Plasmodium* spp	Intravenous quinidine gluconate	Artemisinin derivatives (from CDC)
Dengue fever	*Flavivirus*	Symptomatic treatment only	

Dengue Hemorrhagic Fever

Dengue and dengue hemorrhagic fever are viral illnesses caused by several *Flavivirus* serotypes and transmitted by the mosquito, *Aedes aegypti*. There is currently no known antiviral therapy, and treatment is symptomatic.

POTENTIAL MULTIDRUG-RESISTANT ORGANISMS AND ANTIMICROBIAL AGENTS OF CHOICE

Streptococcus pneumoniae

S pneumoniae (pneumococcus) is a common bacterial cause of CNS and respiratory infections. Resistance in pneumococcus is defined by its susceptibility to penicillin. In 2008, the Clinical Laboratory and Standards Institute revised susceptibility breakpoints to penicillin for meningitis and nonmeningeal infections. For meningitis, penicillin breakpoints are 0.06 mg/L and 0.12 mg/L for sensitive and resistant strains, respectively. For nonmeningeal infections, breakpoints are 2 mg/L, 4 mg/L, and 8 mg/L for sensitive, intermediate, and resistance strains, respectively.[28] Using these new breakpoints it has been estimated that, for non-CNS infections in the United States, 65% of pneumococci are sensitive to oral penicillin and 93% are sensitive to parenteral penicillin or oral amoxicillin. For meningitis, 65% of pneumococci are susceptible to parenteral penicillin. However, these rates may vary considerably depending on locality. As pneumococcus acquires resistance to penicillin, it also becomes resistant to other common non–β-lactam antibiotics such as macrolides, doxycycline, clindamycin, and TMP-SMX. Most isolates remain sensitive to the respiratory fluoroquinolones, and all are susceptible to vancomycin.[29]

Staphylococcus aureus

S aureus is a common bacterial cause of skin and soft-tissue infections and sepsis. It is now estimated that 50% to 60% of *S aureus* infections are due to methicillin-resistant strains. By definition, all MRSA infections are resistant to β-lactam and carbapenem antibiotics. Antimicrobial susceptibility of MRSA depends on whether it is community-acquired (CA) or health care–acquired (HA), 2 phenotypically and genotypically distinct strains. It is essential that culture and sensitivity testing be done for all suspected MRSA infections. Most CA-MRSA strains carry the Panton-Valentine leukocidin gene, which encodes for a cytotoxin that is associated with purulent skin and soft-tissue infections and severe necrotizing pneumonia. Although resistant to β-lactams, CA-MRSA is usually susceptible to such common antibiotics as TMP-SMX, clindamycin, and doxycycline. Infections attributable to HA-MRSA, on the other hand, are resistant to most common antibiotics and the drug of first choice is parenteral vancomycin. Linezolid, a bacteriostatic agent that is available in both parenteral and oral dosage forms, is an alternative but expensive choice for both strains of MRSA. Other new alternative parenteral agents include daptomycin, tigecycline,

and ceftaroline. These antibiotics may take on greater importance as vancomycin intermediate-resistant and fully-resistant strains become more prevalent.[30,31]

Enterococcus

Enterococcus is part of the normal gastrointestinal flora and occasionally may contribute to intra-abdominal, biliary tract, or urinary tract infections. For life-threatening enterococcal infections, such as endocarditis, it is necessary that 2 antibiotics be administered to achieve a bactericidal killing effect; this usually consists of a β-lactam or vancomycin combined with an aminoglycoside. Unlike with other bacterial species, there is no single antibiotic that is bactericidal against *Enterococcus*. Penicillin-susceptible strains can be treated with ampicillin or piperacillin, with vancomycin being used for patients with severe penicillin allergy. Cephalosporins have very weak or no activity. Some *Enterococcus* species, particularly *Enterococcus faecium*, are now resistant to penicillin, ampicillin, and vancomycin (vancomycin-resistant enterococcus or VRE). For these strains options include linezolid, daptomycin, or tigecycline.[32]

Pseudomonas aeruginosa

P aeruginosa is an opportunistic organism that easily colonizes moist surfaces and is usually associated with nosocomial bacterial infections. Several broad-spectrum β-lactam antibiotics have been developed over the last several decades specifically with activity against *P aeruginosa*. These agents include piperacillin-tazobactam, the cephalosporins ceftazidime and cefepime, and the carbapenems imipenem, meropenem, and doripenem. For infections such as bacteremia and pneumonia, the highest doses recommended should be used in order for serum and tissue levels of antibiotic to be above the MIC for more than 50% of the time. Initial treatment with an antipseudomonal β-lactam and fluoroquinolone or aminoglycoside improves the likelihood that one or the other antibiotic class will be effective until sensitivity results are available. There is still controversy regarding whether to continue high-dose aminoglycoside therapy for a synergistic bactericidal effect. Multiresistant strains are now emerging that will not respond to β-lactam, fluoroquinolone, or aminoglycoside therapy. In such cases old antibiotics such as colistin and polymyxin are being tried.[33]

MONITORING PARAMETERS FOR SELECTED ANTIMICROBIAL AGENTS

Bactericidal antibiotics can generally be divided into 2 categories based on how they best kill bacteria. Knowing the difference in these mechanisms helps in determining the best dosing strategies to ensure early success in treating a life-threatening infection. β-Lactam antibiotics such as the penicillins, cephalosporins, and carbapenems kill bacteria in a time-dependent manner. Vancomycin falls in this same category. Active growth inhibition only occurs as long as antibiotic concentration at the site of infection is above the MIC. For antibiotics to be bactericidal, concentrations usually have to be 4 to 5 times higher than the MIC. This level can be measured in vitro and is known as the minimum bactericidal concentration or MBC. With inappropriately low doses and/or prolonged dosing intervals, time-dependent antibiotics will not be effective for serious infections.[34] The second category of antibiotics kills bacteria in a concentration-dependent manner and includes the aminoglycosides, fluoroquinolones, and daptomycin. For this group of antibiotics, peak levels should be at least 8 to 10 times the MIC for a bactericidal effect. As serum concentration levels decline after a dose, bactericidal activity continues (postantibiotic effect). If a bacteria MIC is relatively high and/or the site of infection is difficult for antibiotics to penetrate,

concentrations of single antibiotics will not achieve bactericidal levels, which is often the case for treating endocarditis or infections due to *Enterococcus* and *P aeruginosa.*[34] In these cases, the use of 2 agents with different mechanisms of action is necessary for either an additive or synergistic bactericidal effect. Although somewhat controversial, it may also be necessary to expose a positive bacterial culture to a patient's serum containing antibiotics to measure serum bactericidal titers (SBT) as a guide to therapy. For endocarditis, SBTs of 1:8 or greater are recommended.[35]

The recommended antibiotic regimens in this article are based on current national bacterial-resistant trends. To ensure optimal success, it is necessary to follow local and regional antibiotic resistance data. Local data are made available every 6 to 12 months by diagnostic laboratories at the local hospitals.

Several antibiotics require routine measurement of serum levels to guide treatment. The most important is vancomycin, which is frequently used in empiric regimens to cover for MRSA. Because the MIC for MRSA has been gradually rising over the last few years (MIC creep), new guidelines now recommend that vancomycin trough levels be 15 to 20 mg/L.[2] Peak levels are not measured. These new target levels require higher doses that can potentially cause nephrotoxicity. Therefore it is also necessary to routinely monitor renal function. Aminoglycoside antibiotics traditionally required frequent serum-level determinations when dosed as a time-dependent antibiotic because of their nephrotoxic potential. Once it was discovered that bactericidal activity is concentration dependent, once-daily high-dose therapy is now the norm. If more frequent low-dose therapy is required, peak and trough serum levels should be monitored on a regular basis.

SUMMARY

Life-threatening infectious disease emergencies require immediate, aggressive parenteral administration of antimicrobial agents to ensure high bactericidal concentrations of drug at the site of infection. Usually initial treatment is empiric until culture results and antimicrobial sensitivities are reported. This approach necessitates the use of broad-spectrum bactericidal agents that will eradicate the presumed infecting organism(s), which potentially could be multidrug resistant. For infections potentially attributable to gram-positive bacteria, vancomycin is commonly used because it will be effective for highly resistant strains such as MRSA and multidrug-resistant *S pneumoniae.* For gram-negative infections, broad-spectrum β-lactams, such as ceftriaxone, piperacillin-tazobactam, and the carbapenems, are commonly chosen. Excellent alternatives include the fluoroquinolone antibiotics. For nosocomial infections whereby *P aeruginosa* and other highly resistant organisms may be the cause, antipseudomonal β-lactams such as cefepime, ceftazidime, piperacillin-tazobactam, or doripenem may be used as well as the fluoroquinolone, ciprofloxacin. For anaerobic infections, it is usually necessary to add either metronidazole or clindamycin. Once an infection is under control and the culture and sensitivity results are reported, it is important to switch to the most narrow-spectrum agent possible. Taking this action will decrease the potential for adverse drug effects and the risk of development of antibiotic-induced resistance.

REFERENCES

1. Lutsar I, McCracken GH, Friedland IR. Antibiotic pharmacodynamics in cerebrospinal fluid. Clin Infect Dis 1998;27:1117–27.
2. Rybak M, Lomaestro B, Rotschafer JC, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System

Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. Am J Health Syst Pharm 2009;66:82–98.
3. Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis 2004;39:1267–84.
4. Tunkel AR, Glaser CA, Bloch KC, et al. The management of encephalitis: Clinical practice guidelines by the Infectious Disease Society of America. Clin Infect Dis 2008;47:303–27.
5. Mathisen GE, Johnson JP. Brain abscess. Clin Infect Dis 1997;25:763–79.
6. Chow AW. Infections of the oral cavity, neck, and head. In: Mandell GL, Bennett JE, Dolin R, editors. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. Philadelphia: Churchill Livingstone; 2010. p. 855–71.
7. Guildfred LA, Lyhne D, Becker BC. Acute epiglottitis: epidemiology, clinical presentation, management and outcome. J Laryngol Otol 2008;122:818–23.
8. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Disease Society of America/American Thoracic Society Consensus Guidelines on the management of community acquired pneumonia in adults. Clin Infect Dis 2007;44:S27–72.
9. American Thoracic Society, Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 2005;171: 388–416.
10. Septimus EJ. Pleural effusion and empyema. In: Mandell GL, Bennett JE, Dolin R, editors. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. Philadelphia: Churchill Livingstone; 2010. p. 917–23.
11. Levison ME. Anaerobic pleuropulmonary infection. Curr Opin Infect Dis 2001;14: 187–91.
12. Ott SR, Allewelt M, Lorenz J, et al. Moxifloxacin vs ampicillin/sulbactam in aspiration pneumonia and primary lung abscess. Infection 2008;36:23–30.
13. McDonald JR. Acute infective endocarditis. Infect Dis Clin North Am 2009;23: 643–64.
14. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications. A statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council of Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association. Circulation 2005;111:e394–434.
15. Knowlton KU, Savoia MC, Oxman MN. Myocarditis and pericarditis. In: Mandell GL, Bennett JE, Dolin R, editors. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. Philadelphia: Churchill Livingstone; 2010. p. 1153–71.
16. Levison ME, Bush LM. Peritonitis and intraperitoneal abscesses. In: Mandell GL, Bennett JE, Dolin R, editors. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. Philadelphia: Churchill Livingstone; 2010. p. 1011–34.
17. Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infections in adults and children: guidelines by the Surgical Infection Society and the Infectious Disease Society of America. Clin Infect Dis 2010;50:13–64.
18. Gupta K, Hooten TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis 2011;52: e103–20.

19. Sobel JD, Kaye D. Urinary tract infections. In: Mandell GL, Bennett JE, Dolin R, editors. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. Philadelphia: Churchill Livingstone; 2010. p. 957–85.
20. Cohen SH, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults: 2010 update by the Society for Healthcare Epidemiology of America and the Infectious Disease Society of America. Infect Control Hosp Epidemiol 2010;31:431–55.
21. DuPont HL. Approach to the patient with infectious colitis. Curr Opin Gastroenterol 2012;28:39–46.
22. Pennington H. *Escherichia coli* 0157. Lancet 2010;376:1428–35.
23. Anaya D, Dellinger P. Necrotizing soft tissue infection: diagnosis and management. Clin Infect Dis 2007;44:705–10.
24. Pasternack MS, Swartz MN. Myositis and myonecrosis. In: Mandell GL, Bennett JE, Dolin R, editors. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. Philadelphia: Churchill Livingstone; 2010. p. 1313–22.
25. Munford RS, Suffredini AF. Sepsis, severe sepsis, and septic shock. In: Mandell GL, Bennett JE, Dolin R, editors. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. Philadelphia: Churchill Livingstone; 2010. p. 987–1010.
26. Freifield AG, Ej Bow, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis 2011;52:e56–93.
27. Centers for Disease Control and Prevention (CDC). Availability and use of parenteral quinidine gluconate for severe or complicated malaria. MMWR Morb Mortal Wkly Rep 2000;49:1138–40.
28. Centers for Disease Control and Prevention (CDC). Effects of new penicillin susceptibility breakpoints for *Streptococcus pneumoniae*—United States, 2006-2007. MMWR Morb Mortal Wkly Rep 2008;57:1353–7.
29. Musher DM. *Streptococcus pneumoniae*. In: Mandell GL, Bennett JE, Dolin R, editors. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. Philadelphia: Churchill Livingstone; 2010. p. 2623–42.
30. Yok-Ai Q, Moreillon P. *Staphylococcus aureus* (including staphylococcal toxic shock). In: Mandell GL, Bennett JE, Dolin R, editors. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. Philadelphia: Churchill Livingstone; 2010. p. 2543–78.
31. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Disease Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. Clin Infect Dis 2011;52:1–38.
32. Arias CA, Murray BE. *Enterococcus* species, *Streptococcus bovis* group, and *Leuconostoc* species. In: Mandell GL, Bennett JE, Dolin R, editors. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. Philadelphia: Churchill Livingstone; 2010. p. 2642–53.
33. Pier GB, Ramphal R. *Pseudomonas aeruginosa*. In: Mandell GL, Bennett JE, Dolin R, editors. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. Philadelphia: Churchill Livingstone; 2010. p. 2835–60.
34. Bergman SJ, Speil C, Short M, et al. Pharmacokinetic and pharmacodynamic aspects of antibiotic use in high-risk populations. Infect Dis Clin North Am 2007;21:821–46.
35. Stratton CW. Serum bactericidal test. Clin Microbiol Rev 1988;1:19–26.