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# Empiric Antibiotics for Sepsis

Sara A. Buckman, Isaiah R. Turnbull, and John E. Mazuski

## Abstract

**Background:** Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection. Early recognition and treatment are the cornerstones of management.

**Methods:** Review of the English-language literature.

**Results:** For both sepsis and septic shock “antimicrobials [should be] be initiated as soon as possible and within one hour” (Surviving Sepsis Campaign). The risk of progression from severe sepsis to septic shock increases 8% for each hour before antibiotics are started. Selection of antimicrobial agents is based on a combination of patient factors, predicted infecting organism(s), and local microbial resistance patterns. The initial drugs should have activity against typical gram-positive and gram-negative causative micro-organisms. Anaerobic coverage should be provided for intra-abdominal infections or others where anaerobes are significant pathogens. Empiric antifungal or antiviral therapy may be warranted. For patients with healthcare-associated infections, resistant micro-organisms will further complicate the choice of empiric antimicrobials. Recommendations are given for specific infections.

**Conclusion:** Early administration of broad-spectrum antimicrobial drugs is one of the most important, if not the most important, treatment for patients with sepsis or septic shock. Drugs should be initiated as soon as possible, and the choice of should take into account patient factors, common local pathogens, hospital antibiograms and resistance patterns, and the suspected source of infection. Antimicrobial agent therapy should be de-escalated as soon as possible.

**Keywords:** antimicrobial de-escalation; antimicrobials; sepsis

SEPSIS IS LIFE-THREATENING ORGAN DYSFUNCTION caused by a dysregulated host response to infection [1]. Globally, there are more than 31.5 million cases of sepsis each year, resulting in at least 5.3 million deaths annually [2]. Early recognition and treatment are the cornerstones of management. To accomplish this, it usually is necessary to initiate therapy on the basis of clinical criteria alone, prior to obtaining definitive microbiologic data [3]. Current guidelines recommend initiation of empiric antimicrobial agents within the first hour after the recognition of sepsis or septic shock [4]. These guidelines uniformly emphasize that early antimicrobial drug therapy should be broad-spectrum, as inadequate or inappropriate antibiotics are an important determinant of in-hospital death in critically ill patients in the intensive care unit (ICU) [5–11]. Nonetheless, it may be difficult to provide an appropriate empiric regimen to every patient, given the wide variety of infections that may be present [12]. General guidance is that the regimen should be chosen on the basis of the suspected organism(s) according to the drug susceptibility patterns [13].

Empiric antibiotic selection for septic patients is complicated by the competing obligations to provide broad-spectrum empiric coverage sufficient to avoid inadequate therapy while

simultaneously adhering to good antibiotic stewardship practices. Although patients with a drug-resistant infection are at risk for inappropriate empiric treatment, antibiotic stewardship guidelines might recommend keeping broader-spectrum agents in reserve [14,15]. In this paper, we attempt to resolve this essential tension between the need to treat adequately the individual patient with sepsis or septic shock and the need to preserve effective antimicrobial agents for future patients through appropriate antimicrobial stewardship. We first describe some of the general principles of antimicrobial agent therapy in sepsis and septic shock and then provide some specific guidance with respect to the septic diseases surgical practitioners are likely to encounter in their practices.

## General Principles

### *Timing of antimicrobial drug administration*

The Surviving Sepsis campaign recommends that for both sepsis and septic shock, “antimicrobials be initiated as soon as possible and within one hour” [4]. Early administration of antimicrobial drugs should occur regardless of whether the patient is in the emergency room, ICU, or general care ward.

Moderate data support the recommendation for early antibiotics. One study showed that patients who received antibiotics within one hour of developing hypotension had a higher survival rate to hospital discharge [16]. Another report found the odds of death increased by 9% for each hour antibiotics were delayed in emergency department patients with sepsis, severe sepsis, or septic shock [17]. A third analysis demonstrated that the risk of progression from severe sepsis to septic shock increased 8% for each hour that passed before antibiotics were started [18]. Early antibiotic therapy also may reduce pathogen burden, potentially modifying the host response to infection and reducing subsequent organ dysfunction [19]. Successful initiation of empiric antibiotics for sepsis requires a high clinical suspicion for infection or worsening organ dysfunction and a dosing regimen that creates therapeutic concentrations as soon as possible [20].

#### General considerations regarding spectrum of coverage

Although the principles of antimicrobial stewardship include avoiding injudicious use of broad-spectrum agents, restrictions resulting in inadequate therapy of the patient with sepsis or septic shock are not good stewardship. As indicated previously, inadequate therapy increases the risk of treatment failure or death [11,21]. Moreover, by failing to treat an individual patient adequately, while exposing him or her to agents that will select resistant organisms, inappropriate therapy may increase the development of bacterial resistance.

Selection of antimicrobial agents is based on a combination of patient factors, predicted infecting organism(s), and local microbial resistance patterns. Individual patient factors help to identify those at higher risk of death attributable to inadequate antimicrobial drug coverage. However, in general, any patient meeting the criteria for sepsis or septic shock is a higher-risk patient and should receive broad-spectrum parenteral antibiotics. Assessment of individual risk factors also helps define which patients are at risk for healthcare-associated infections caused by potentially resistant pathogens. Significant medical co-morbidities that may affect drug pharmacokinetics and pharmacodynamics, such as cirrhosis,

renal disease, or malnutrition, also should be taken into consideration when selecting specific agents.

For purposes of choosing an empiric antibiotic regimen, infecting bacteria can be broadly classified as gram-positive, gram-negative, anaerobes, pseudomonads, or resistant (Table 1). In specific cases, fungal and viral pathogens also may play a role. The source of the infection will have a large bearing on the choice of the initial regimen. However, in the setting of sepsis, the initial drugs should have activity against typical gram-positive and gram-negative causative micro-organisms. Anaerobic coverage should be provided for infections, such as intra-abdominal infections (IAI), where anaerobes are significant pathogens. Empiric antifungal or antiviral therapy may be warranted if there is a strong suspicion that either of those classes of pathogens is contributing to the patient's condition. The drugs chosen need to have adequate tissue penetration and activity at the suspected source of infection. Other considerations include the pharmacokinetic and pharmacodynamic properties of the agent, its bactericidal versus bacteriostatic activity, and its inherent toxicity [22, 23].

For patients with healthcare-associated infections, clinicians should be aware of the potential that resistant microorganisms will further complicate the choice of empiric drugs. Antibiotic regimens for these infections should be selected on the basis of known resistant pathogens in the community, as well as hospital and even unit-specific antibiograms (Table 2). Risk factors for infections with resistant organisms include hospitalization, prior residence in another healthcare facility, receipt of home intravenous therapy or wound care, or hemodialysis in the last 90 days. Patients who have received immunosuppressive therapy also are at risk for atypical or resistant pathogens. Patients who have recently (within 90 days) received broad-spectrum antimicrobial drug therapy should be treated for potential healthcare-associated pathogens [21]. Bacteria frequently encountered in healthcare-associated infections include methicillin-resistant *Staphylococcus aureus* and gram-negative bacteria resistant to a number of classes of antibiotics. Gram-negative organisms expressing extended-spectrum beta-lactamase may be resistant to both synthetic penicillins and most cephalosporins. Carbapenem-resistant *Enterobacteriaceae*, including those producing *Klebsiella pneumoniae* carbapenemases (KPCs) or even metallo- $\beta$ -lactamases (NDM-1), are being encountered increasingly in some parts of the world. These latter bacteria

TABLE 1. SELECTED ANTIMICROBIAL AGENTS AND SPECTRUM OF COVERAGE

	Gram +	Gram –	Anaerobes	Pseudomonas	MRSA	ESBL	VRE
Vancomycin	X				X		
Linezolid	X				X		X
Daptomycin	X				X		X
Piperacillin-tazobactam	X	X	X	X			
Meropenem	X	X	X	X		X	
Doripenem	X	X	X	X		X	
Imipenem-cilastatin	X	X	X	X		X	
Ertapenem	X	X	X			X	
Ceftriaxone	X	X					
Cefepime	X	X		X			
Ciprofloxacin	X	X		X			
Levofloxacin	X	X		X			
Metronidazole			X				

ESBL = extended-spectrum  $\beta$ -lactamase producer; MRSA = methicillin-resistant *Staphylococcus aureus*; VRE = vancomycin-resistant enterococci.

TABLE 2. ANTIMICROBIAL TREATMENT OF SPECIFIC INFECTIONS IN PATIENTS WITH SEPSIS OR SEPTIC SHOCK

	<i>First-line agent(s)</i>	<i>Additive therapy</i>
SSTI		
Suspected monomicrobial caused by <i>S. pyogenes</i>	Penicillin G and clindamycin	
MRSA	Vancomycin OR linezolid	Clindamycin for patients with septic shock
Suspected polymicrobial	Vancomycin OR linezolid OR daptomycin AND piperacillin/tazobactam OR a broad-spectrum carbapenem OR a 3 <sup>rd</sup> or 4 <sup>th</sup> generation cephalosporin plus an anti-anaerobic agent	Clindamycin for patients with septic shock if potentially caused by streptococcal, staphylococcal, or clostridial organisms
NSTI	Vancomycin OR linezolid OR daptomycin AND Piperacillin-tazobactam OR a broad-spectrum carbapenem OR a 3 <sup>rd</sup> or 4 <sup>th</sup> generation cephalosporin plus an anti-anaerobic agent	Clindamycin for patients with septic shock if potentially caused by streptococcal, staphylococcal, or clostridial organisms
Pneumonia		
HAP	Vancomycin OR linezolid AND Piperacillin-tazobactam OR cefepime OR levofloxacin OR imipenem/cilastatin OR meropenem	
VAP	Vancomycin OR linezolid plus piperacillin-tazobactam OR cefepime OR levofloxacin OR imipenem-cilastatin OR meropenem	For septic shock or at higher risk of resistant gram-negative pathogens, use two agents from different classes among the following: Piperacillin-tazobactam, cefepime, ceftazidime, ciprofloxacin, levofloxacin, imipenem-cilastatin, meropenem, aminoglycoside (amikacin, gentamicin, tobramycin), polymyxin (colistin, polymyxin)
IAI		
Higher risk with CA-IAI	Piperacillin-tazobactam OR imipenem-cilastatin OR doripenem OR meropenem OR cefepime plus metronidazole OR ceftazidime plus metronidazole OR aztreonam plus metronidazole plus vancomycin	Add ampicillin or vancomycin If using a cephalosporin-based regimen or a carbapenem other than imipenem-cilastatin
HA-IAI	Piperacillin-tazobactam OR imipenem-cilastatin OR doripenem OR meropenem OR cefepime plus metronidazole OR ceftazidime plus metronidazole OR aztreonam plus metronidazole plus vancomycin	Add second agent from a different class if there is a high incidence of resistant gram-negative pathogens in unit Add vancomycin if high risk of infection with <i>Enterococcus</i> spp. If at high risk for vancomycin-resistant enterococci, add linezolid or daptomycin Add an echinocandin if at high risk for a fungal infection Add a glycopeptide if patient colonized with MRSA or at high risk for colonization
<i>Clostridium difficile</i>		
Severe-fulminant	Oral vancomycin with or without IV metronidazole	Add rectal vancomycin if colonic ileus is present

CA-IAI=community-acquired intra-abdominal infection; HAP=healthcare-associated pneumonia; IAI=intra-abdominal infection; IV=intravenous; MRSA=methicillin-resistant *Staphylococcus aureus*; NSTI=necrotizing soft-tissue infection; SSTI=skin and soft-tissue infection; VAP=ventilator-associated pneumonia.

are resistant to virtually all  $\beta$ -lactam drugs, although some new  $\beta$ -lactamase inhibitors may restore the activity of some beta-lactam antibiotics [24].

#### Multi-drug and combination therapy

Multi-drug therapy encompasses the both use of multiple agents to achieve a broad antimicrobial drug spectrum and the use of multiple antimicrobial agents in combination to target a specific known or suspected pathogen. This latter use is called “combination therapy” in the current Surviving Sepsis Campaign guidelines, in contrast to the more general term “multi-

drug therapy” [4]. The most common indication for combination empiric therapy is a higher risk of a resistant pathogen. Empiric combination therapy can increase the spectrum of coverage, therefore raising the probability of appropriate initial therapy, especially in geographic regions where there is high antimicrobial drug resistance [19,25]. Combination therapy also may lead to a lower risk of emergence of resistance [26]. However, the benefits of combination therapy for the treatment of a specific pathogen are less well defined. Theoretically, use of multiple agents with different mechanisms of action would accelerate pathogen clearance or inhibit the production of microbial virulence factors such as bacterial toxins [27–29]. The disadvantages

of using combination therapy are a greater risk of drug toxicity, especially when aminoglycosides are used; a possibility of superinfection with fungal infections or resistant bacteria; and higher cost [30–32]. In the current Surviving Sepsis Campaign guidelines, combination empiric antimicrobial therapy is recommended for patients with septic shock but not routinely for patients at lower risk of death, such as those with sepsis without septic shock, including those with neutropenia or bacteremia [4]. This recommendation was based on a meta-analysis demonstrating that combination therapy decreased the mortality rate in the highest-risk patients but actually increased deaths in lower-risk patients [33]. If combination empiric therapy is utilized, it should be discontinued once the patient no longer has evidence of septic shock. Combination antimicrobial agent therapy also can be de-escalated to monotherapy once antimicrobial drug susceptibilities are available, except for those infections, such as enterococcal endocarditis, where a benefit of combination therapy has been demonstrated clearly [4,34].

#### De-escalation

“De-escalation” of antimicrobial agents refers to either discontinuing use or narrowing therapy on the basis of culture and sensitivity results. De-escalation generally can be considered at 48–72 h once culture and susceptibility data are available. The action is important to help decrease antimicrobial resistance, to avoid superinfection with other pathogenic or resistant organisms, and to prevent the side effects and costs possible with overuse of broad-spectrum antimicrobial agents [35]. De-escalation also may involve switching the administration route from intravenous to oral or enteral [36]. General criteria for an intravenous to oral/enteral switch are hemodynamic stability, clinical improvement (afebrile, reduction in white blood cell count), a functioning gastrointestinal tract, and ability to deliver oral/enteral medication [37–39].

There are no studies that have suggested that antimicrobial de-escalation is harmful if the infecting organism has been identified or the patient is improving clinically [21,36,40]. One study suggested that de-escalation in patients with severe sepsis and septic shock was associated with a lower mortality rate [41]. Although most of the literature on de-escalation relates to patients with ventilator-associated pneumonia (VAP) and septic shock, de-escalation has proved to be feasible for surgical patients also [42]. However, de-escalation is practiced in only 35%–50% of patients, suggesting that this approach could be utilized much more widely in the interest of promoting effective antimicrobial stewardship [36]. After de-escalation, the patient trajectory should continue to be monitored closely. A worsening of the patient’s condition should prompt further investigation for a recurrent or potential new source of infection, including repeat cultures as needed but not an automatic conclusion that de-escalation has failed.

#### Duration of therapy

The appropriate duration of antimicrobial drug therapy depends on the site of infection as well as the patient’s response to treatment. Duration should be individualized on the basis of the severity of illness, the type of infection, whether source control has been obtained, and diagnostic assessments of improvement or cure [32]. A standard 7–10 days of therapy is acceptable for most patients according to current Surviving Sepsis Campaign guidelines [4]. However, a shorter duration

is appropriate for those patients who have rapid resolution of symptoms or undergone effective source control, such as those with complicated intra-abdominal infections (cIAI) who have received adequate surgery or drainage [34,43]. Procalcitonin measurements have been advocated as a means of decreasing the duration of therapy [4]. Excessive prolongation of antibiotic therapy contributes to the development of antimicrobial drug resistance, amplifies the risk of toxicity, and increases overall antibiotic costs. Along with de-escalation, limiting the duration of therapy can be one of the most effective means of improving antimicrobial stewardship [44].

### Treatment of Specific Infections

#### *Skin and soft-tissue infections*

Skin and soft-tissue infections (SSTI) are common problems for which surgical intervention is undertaken. Both non-necrotizing and necrotizing skin/soft-tissue infections (NSTI) can lead to sepsis and septic shock, although sepsis is particularly common with NSTI. As a general principle, empiric antibiotic therapy of the septic patient with an SSTI should include agents effective against both gram-positive and gram-negative and occasionally anaerobic pathogens. Owing to the high prevalence of methicillin-resistant *S. aureus* (MRSA) strains in North America, treatment should include an agent effective against this organism. Regimens including vancomycin or linezolid in combination with piperacillin-tazobactam, a broad-spectrum carbapenem, or a third- or fourth-generation cephalosporin, potentially with an anti-anaerobic agent such as metronidazole, are appropriate for these patients [45,46].

Necrotizing infections are associated with a high mortality rate and considerable morbidity. Aggressive surgical debridement, broad-spectrum antibiotic therapy, and full supportive care in an ICU are keys to the treatment of these patients. These infections fall into three categories: Type I or polymicrobial NSTI caused by mixtures of aerobic and anaerobic organisms; Type II or monomicrobial NSTI, typically caused by *Streptococcus pyogenes* (group A  $\beta$ -hemolytic streptococci), although *S. aureus* infections also can fall into this category; and the uncommon Type III NSTI associated with *Vibrio* spp. [47]. Monomicrobial infections caused by *Clostridium* spp., such as gas gangrene, can be considered a Type II infection or placed in a distinct category.

Regardless of the classification, initial empiric antibiotic therapy for NSTI should be broad and include coverage of gram-positive, gram-negative, and anaerobic organisms. Because MRSA may be present, empiric regimens should include vancomycin, linezolid, or daptomycin. Piperacillin-tazobactam, a broad-spectrum carbapenem, or a third- or fourth-generation cephalosporin plus an anti-anaerobic agent also should be part of the empiric therapy [45,46]. Because of the difficulty in distinguishing between a Type I and Type II infection, high-dose clindamycin may be included in the regimen to control potential *Streptococcus pyogenes*. Local prevalence of resistant pathogens as well as hospital- or unit-specific antibiograms and patient-specific risk factors such as allergies, recent exposure to the healthcare setting, or recent use of antimicrobial agents should be factored in when choosing a drug regimen. Once culture results are available, therapy should be tailored to treat the confirmed pathogens. For Type I infections, anti-MRSA agents are not needed if MRSA is not found in cultures, and

anti-gram-negative agents can be discontinued if *Pseudomonas* spp. or other problematic pathogens are not encountered. However, therapy still generally will require an agent or agents effective against common gram-positive, gram-negative, and anaerobic species. Monomicrobial infections caused by Group A  $\beta$ -hemolytic streptococci should be treated with a penicillin and a protein-synthesis inhibitor such as clindamycin or linezolid; the latter generally can be discontinued when signs of sepsis have subsided [45,46]. Monomicrobial clostridial infections are treated similarly using high-dose penicillin and high-dose clindamycin. Treatment for Type III NSTI caused by *Vibrio* spp. should include doxycycline and ceftriaxone or cefotaxime [48]. Antibiotics should be continued until the patient has shown significant improvement and has been without a fever for 48–72 h and further debridement is no longer necessary [46].

Toxic shock syndrome (TSS) is a fulminant condition caused by toxins elaborated by a gram-positive organism, usually *S. pyogenes* or *S. aureus*. It often is part of a localized, sometimes clinically unapparent, SSTI. However, mortality rates as high as 70% have been reported for streptococcal TSS [48,49]. Empiric antimicrobial therapy should include agents effective against drug-resistant organisms, in addition to clindamycin or linezolid for reduction of superantigen production [50–53]. Initial regimens for group A streptococcal TSS include penicillin G and clindamycin, or linezolid if the patient is intolerant to  $\beta$ -lactam drugs [53,54]. In areas with a high prevalence of MRSA, the initial regimen should include either vancomycin and clindamycin or linezolid monotherapy [53]. Antibiotics should be de-escalated when culture and susceptibility data are available.

#### *Hospital-acquired and ventilator-associated pneumonia*

Hospital-acquired pneumonia (HAP) and VAP are frequent complications in surgical patients, especially those who have sustained traumatic injuries or burns [55]. The Infectious Diseases Society of America and American Thoracic Society (IDSA/ATS) guidelines released in 2016 define HAP as an episode of pneumonia developing 48 h or more after hospital admission which is not associated with mechanical ventilation, whereas VAP is a pneumonia developing greater than 48 h after endotracheal intubation [34].

The IDSA/ATS guidelines provide recommendations for antimicrobial drug treatment of HAP and VAP. Empiric regimens for VAP should include agents effective against *S. aureus* and gram-negative bacilli, including *P. aeruginosa*. It is recommended that either vancomycin or linezolid be part of the initial regimen if the patient is at risk for an infection caused by MRSA. Such patients include those with septic shock, acute respiratory distress syndrome before VAP, prior intravenous antibiotic use within 90 days, hospitalization for five or more days prior to the diagnosis of VAP, acute renal replacement therapy before VAP, and those being treated in ICUs where the incidence of MRSA isolates is greater than 10%–20%. If MRSA coverage is not indicated, the empiric regimen should include an agent effective against methicillin-susceptible *S. aureus* (MSSA) and gram-negative bacilli, such as piperacillin-tazobactam, cefepime, levofloxacin, imipenem/cilastatin, or meropenem. For patients in an ICU where >10% of gram-negative isolates are resistant to a monotherapy agent, or if local antimicrobial sus-

ceptibility rates are not known, two antipseudomonal antimicrobial drugs should be started empirically [34].

Once culture results are available, pathogen-directed therapy can be provided. The IDSA/ATS guidelines favor de-escalation of antibiotics once definitive results are available but indicate that clinical trials that weigh the potential influence of de-escalation on decreasing antimicrobial drug resistance versus the potential for it to increase the risk of recurrent pneumonia are needed urgently. For patients with a confirmed pneumonia caused by *P. aeruginosa*, there is low-quality evidence suggesting that combination therapy be continued if the patient remains in septic shock or is considered to be at high risk of death. The recommended duration of therapy for most patients with VAP is seven days, although shorter or longer durations may be appropriate for selected patients [34].

Treatment of patients with suspected HAP parallels that described for VAP. Empiric treatment should include coverage of *S. aureus*, including MRSA if the patient is at higher risk of MRSA pneumonia according to the criteria described above. Empiric treatment for MSSA and gram-negative bacilli is similar to that for VAP and includes antibiotics active against *P. aeruginosa* and other gram-negative bacilli. Two antipseudomonal antibiotics of different classes should be started empirically if there is a high likelihood of resistant gram-negative isolates. As with VAP, antibiotic therapy should be de-escalated, if feasible, and discontinued after seven days [34].

#### *Intra-abdominal infections*

Intra-abdominal infections are a common problem faced by general surgeons. They traditionally have been categorized as uncomplicated or complicated, with uncomplicated IAI being those infections limited to a hollow viscus, whereas cIAI are those with extension into a normally sterile area of the abdomen [56]. Patients with cIAI also may be described as having secondary or tertiary peritonitis, single or multiple intra-abdominal abscesses, or an intra-abdominal phlegmon [57]. Patients can be designated as having either a community-acquired IAI (CA-IAI) or healthcare-associated/hospital-acquired IAI (HA-IAI). Those patients who have an infection developing >48 h after an initial operation, have been hospitalized for >48 h during the previous 90 days, have resided in a skilled nursing or other long-term care facility, have received home infusion or wound care, or dialysis within the previous 30 days, or who have undergone treatment with broad-spectrum antibiotics for five days or more during the previous 90 days are considered to have HA-IAI. All other patients are deemed to have a CA-IAI; these patients are further stratified as being at lower or higher risk of an adverse outcome. Recent guidelines developed by the Surgical Infection Society (SIS) suggest that patients with sepsis or septic shock and those with high Acute Physiology and Chronic Health Evaluation (APACHE) II scores are higher-risk patients. In addition, multiple factors, including age 70 years or greater, malignant disease, hypoalbuminemia, and major compromise of cardiovascular, hepatic or renal function also place the patient at higher risk of an adverse outcome. Finally, patients with diffuse peritonitis, an elevated Mannheim peritonitis index score, and those with delayed or inadequate initial source control should be considered at higher risk [57].

Treatment of patients with cIAI should include medical stabilization, source control, and antibiotic therapy. The empiric drug therapy for cIAI should include coverage against aerobic

gram-negative Enterobacteriaceae, aerobic streptococci, and obligate enteric anaerobic organisms. Treatment options for lower-risk CA-IAI include ertapenem or moxifloxacin or combination therapy with cefotaxime or ceftriaxone plus metronidazole or ciprofloxacin plus metronidazole. Fluoroquinolones should be used only if there is a significant reaction to  $\beta$ -lactam antibiotics. Levofloxacin may be substituted for ciprofloxacin if it is the only formulary fluoroquinolone option.

Because patients with cIAI presenting with sepsis or septic shock are considered higher-risk patients, certain regimens generally are recommended. For these patients, therapeutic options include piperacillin-tazobactam, imipenem-cilastatin, doripenem or meropenem, cefepime or ceftazidime plus metronidazole, or aztreonam plus metronidazole plus vancomycin. Addition of ampicillin or vancomycin to provide coverage of *Enterococcus* spp. should be considered if using a cephalosporin-based regimen or a broad-spectrum carbapenem other than imipenem-cilastatin [57].

Options for empiric antibiotic therapy for patients with HA-IAI include piperacillin-tazobactam, doripenem, imipenem-cilastatin, meropenem, cefepime or ceftazidime plus metronidazole, or aztreonam plus metronidazole plus vancomycin. If there is a high incidence of resistant gram-negative bacteria in the local setting, a second agent from a different class may be added. In patients with a risk of infection with *Enterococcus* spp., addition of vancomycin is recommended, and for patients at high risk for infection with vancomycin-resistant enterococci, linezolid or daptomycin is recommended. Patients at high risk for fungal infections, including those who have recently received long courses of broad-spectrum antibiotic therapy, those heavily colonized with *Candida*, and those with upper-gastrointestinal perforations, recurrent bowel perforations, or surgically treated pancreatitis should receive empiric antifungal therapy. For severely ill patients with sepsis or septic shock, an empiric echinocandin is the drug of choice; it may be de-escalated to fluconazole as the patient's condition improves. Although IAI caused by MRSA is uncommon, empiric use of a glycopeptide may be warranted in those patients already colonized with or at high risk for colonization with MRSA [57].

De-escalation according to definitive culture results is appropriate in patients receiving broad-spectrum therapy, although agents effective against common *Enterobacteriaceae* as well as anaerobic micro-organisms should be continued. Short-course (four days) antibiotic therapy is now recommended. A large SIS-sponsored trial demonstrated equivalent outcomes with shorter as opposed to longer courses of therapy in patients who had adequate source control [43]. In subgroup analyses, no benefit of longer courses of drugs was observed in higher-risk patients or those presenting with sepsis [58–60].

### *Clostridium difficile* infection

*Clostridium difficile* infection (CDI) is the most common nosocomial infection affecting the gastrointestinal tract. In fact, *C. difficile* has surpassed MRSA as the most common pathogen causing a hospital-associated bacterial infection [61,62]. The most common risk factor for CDI is antibiotic use. Other risk factors are greater age, prior hospitalization, severe underlying disease, chronic kidney disease, gastrointestinal surgical procedures, and immunodeficiency [63–67]. Symptoms range from mild diarrhea to fulminant colitis; the latter may result in multisystem organ dysfunction and,

eventually, death [68]. Patients with severe CDI have significant systemic symptoms and frequently meet the criteria for sepsis or septic shock [69].

The diagnosis is based on both clinical and laboratory findings. Most commonly, it is based on a stool test positive for a *C. difficile* toxin in a patient with diarrhea; however, in particularly severe cases in which no diarrhea is present, colonoscopic or histopathologic evidence of pseudomembranous colitis may establish the cause of the signs and symptoms [70]. The IDSA and Society for Healthcare Epidemiology of America (SHEA) published clinical practice guidelines in 2010 for the management of CDI. When CDI is diagnosed, the suspected offending agent and any unnecessary antibiotics should be discontinued as soon as possible. Patients with mild to moderate CDI can receive metronidazole for 10–14 days. For severe or fulminant CDI, however, oral vancomycin, with per rectum vancomycin if colonic ileus is present, is the treatment of choice [70,71]. Although it has not been tested in a rigorous fashion, intravenous metronidazole frequently is used in combination with oral or enteral vancomycin in severely ill patients. Surgical treatment should be considered in critically ill patients who have a serum lactic acid concentration >5 mmol/L or a white blood cell count >50,000/mcL, as these markers are associated with a higher mortality rate [70,72].

### Conclusion

Early administration of broad-spectrum antibiotics is one of the most important, if not the most important, treatment for patients with sepsis or septic shock. Drug therapy should be initiated as soon as possible, preferably within the first hour of diagnosis. The choice of drugs should take into account patient factors, common local pathogens, hospital antibiograms and resistance patterns, and the suspected source of the infection. Antibiotic therapy should be de-escalated as soon as possible on the basis of definitive culture results. The duration of antimicrobial agent therapy should be based on the type of infection and the patient's clinical response; increasingly, shorter courses of therapy have been found to be not only sufficient but preferable for many of these conditions.

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