The Journal of Infectious Diseases

SUPPLEMENT ARTICLE

Considerations for Empiric Antimicrobial Therapy in Sepsis and Septic Shock in an Era of Antimicrobial Resistance

Jeffrey R. Strich,[1,2] Emily L. Heil,[3] and Henry Masur[1]

[1]Critical Care Medicine Department, National Institutes of Health Clinical Center, Bethesda, Maryland, USA, [2]United States Public Health Service, Commissioned Corps, Rockville, Maryland, USA, [3]Department of Pharmacy Practice and Science, University of Maryland School of Pharmacy, Baltimore, Maryland, USA

Patients with sepsis present across a spectrum of infection sites and severity of illnesses requiring complex decision making at the bedside as to when prompt antibiotics are indicated and which regimen is warranted. Many hemodynamically stable patients with sepsis and low acuity of illness may benefit from further work up before initiating therapy, whereas patients with septic shock warrant emergent broad-spectrum antibiotics. The precise empiric regimen is determined by assessing patient and epidemiological risk factors, likely source of infection based on presenting signs and symptoms, and severity of illness. Hospitals should implement quality improvement measures to aid in the rapid and accurate diagnosis of septic patients and to ensure antibiotics are given to patients in an expedited fashion after antibiotic order.

Keywords. empiric antibiotics; sepsis; septic shock; antimicrobial resistance.

It is estimated that there are 270 000 deaths a year in the United States due to sepsis and 35 000 deaths attributable to antibiotic resistance [1, 2]. Given the significant burden of sepsis, starting antibiotic therapy is a decision that clinicians face at the bedside on a daily basis, influenced by many different patient factors including presenting signs and symptoms, comorbidities, severity of illness, likelihood of infection, risk associated with delayed antibiotic therapy, and local epidemiology [3]. More simplistically, decisions on starting antibiotic therapy are a balance between the likelihood that a patient actually has infection and the potential harm that antibiotics could cause, such as *Clostridioides difficile* colitis, acute kidney injury, disruption of the gut microbiome, and development of antimicrobial resistance [4, 5]. The global dissemination of antimicrobial resistance further complicates empiric antibiotic therapy decisions and is an independent risk factor for inappropriate empiric therapy [6]. Antibiotic therapy for sepsis can be empiric or targeted, depending on the information available at the time of initial decision. Empiric therapy is generally defined as the initial antibiotic regimen selected in the absence of definitive microbiological pathogen identification and susceptibility testing. This is opposed to targeted or definitive therapy that is the antibiotic regimen selected after pathogen identification and susceptibility testing is completed. After initiation of empiric therapy and utilization of diagnostics testing to aid in identification of the causative pathogen, empiric therapy should be tailored to definitive regimens and/or stopped if the balance of evidence is that infection is unlikely. In this review, we will discuss the clinical impact of delayed or inappropriate antimicrobial therapy and the optimal strategy for choosing empiric antimicrobial regimens for patients with presumed sepsis in this current era of antimicrobial resistance.

TIME TO ANTIBIOTICS AND MORTALITY

Please refer to the paper by Weinberger et al [7] in this issue for a comprehensive review of the relationship between time to antibiotics and mortality. Timely administration of appropriate and effective antimicrobial therapy is a cornerstone of sepsis management. In 2006, a study of 2154 intensive care unit (ICU) subjects by Kumar et al [8] established the importance of antibiotic timing for the subpopulation of septic patients who have shock. Each hour delay in antibiotic administration from time of hypotension onset was associated with a mean decrease in survival of 7.6%. Multiple other studies have supported this finding including Ferrer et al [9] who conducted a retrospective analysis across 165 ICUs in Europe, the United States, and South America including 17 900 patients, 64% of which had septic shock, who received antibiotics after sepsis identification. In this study, the adjusted odds of in-hospital mortality

Correspondence: J. R. Strich, MD, MHS, Critical Care Medicine Department, National Institutes of Health Clinical Center, 10 Center Drive B10, 2C145, Bethesda, MD 20892 (jeffrey.strich@nih.gov).

The Journal of Infectious Diseases® 2020;222(S2):S119–31

DOI: 10.1093/infdis/jiaa221

increased from 1.00 to 1.52 as time to antibiotic administration increased from 0 to more than 6 hours (with 0–1 hour as the reference group) from time of triage.

The Center for Medicare and Medicaid Services (CMS) SEP-1 bundle is intended to encourage healthcare systems to conform to consensus "best practices" to improve the outcome of sepsis and septic shock. Timeliness of antibiotics is an important part of the 3-hour bundle. The impact of similar bundles has been assessed in 2 large retrospective studies, both of which showed improved mortality with shorter time to antibiotics—a relationship that was much stronger for patients with septic shock versus those with sepsis without shock [10, 11]. The only randomized controlled trial of antibiotic timing in patients with presumed sepsis was the PHANTASi trial, which compared the effects of early administration of antibiotics plus usual care (fluid resuscitation and supplementary oxygen) in an ambulance during transport to hospitals in the Netherlands versus usual care alone [12]. Mortality at 28 days was 8% in the intervention group and 8% in the usual care group (relative risk, 0.95; 95% confidence interval [CI], 0.74–1.24) despite antibiotics being prescribed a median of 26 minutes before arriving in the emergency department (ED) in the intervention arm. However, the results should be interpreted with caution due to the low mortality rates in both groups. In addition, in the usual care group, antibiotics were still received on average within 1 hour of presentation to the ED, and there was likely an improvement in recognizing sepsis and time to antibiotics in these patients due to training of emergency medical services personnel.

Sepsis encompasses a very heterogeneous group of patients, some of whom will deteriorate quickly without antibiotics, and some of whom are quite stable and do not benefit from rapid administration of antibiotics [13]. The totality of data indicates that timeliness of antibiotic administration is an important aspect of management for patients with septic shock but not invariably for septic patients without shock. For some patients with sepsis but no shock, prompt antibiotic therapy is important to optimize prognosis (eg, bacterial meningitis, purpura fulminans). For many other patients who are considered to have sepsis, there are adverse consequences associated with "rushing to judgment". It should be noted that 32% of patients with suspected sepsis have noninfectious mimics when additional data are collected [14]. Some of these patients could safely receive limited-spectrum antibiotic therapy rather than broad-spectrum therapy if additional information had been collected that permitted a more focused therapeutic plan.

IMPACT OF INAPPROPRIATE THERAPY ON MORTALITY

Initial antibiotic therapy in sepsis not only needs to be timely, but it needs to be appropriate. Definitions of appropriateness vary. From a prospective perspective, appropriateness can be defined as antimicrobial coverage that provides adequate in vitro activity against all likely pathogens at the clinical infection site of interest [15]. Although from a retrospective perspective, appropriate therapy could be defined as antimicrobial coverage that included in vitro activity against the causative organism. Kumar et al [16] retrospectively determined antibiotic appropriateness, defined as antimicrobials with in vitro activity for the isolated pathogen(s) or appropriate for the underlying clinical syndrome if no pathogen was isolated, for 5715 patients with septic shock. Appropriate antibiotics were initiated in 80.1% of cases, and survival rates were 52% compared to the 19.8% who received inappropriate antibiotics who had a survival rate of 10.3% (odds ratio [OR], 9.45; 95% CI, 7.74–11.54; $P < .0001$) [16]. This effect remained highly associated with risk of death after adjusting for acute physiology and chronic health evaluation (APACHE) II score, comorbidities, hospital site, and other potential risk factors of death. Gaieski et al [17] evaluated 261 patients with severe sepsis or septic shock undergoing early goal-directed therapy. After adjusting for potential confounders, mortality was significantly decreased when time from triage to appropriate antibiotic administration was less than or equal to 1 hour compared to more than 1 hour. Appropriateness of antibiotics was defined similarly to the Kumar et al [16] study as antibiotics for which the causative pathogens were sensitive in vitro or appropriate for the presumed site of infection in culture-negative sepsis.

GENERAL CONSIDERATIONS IN CHOOSING EMPIRIC REGIMENS

Before deciding on an empiric regimen for a patient presenting with concern for sepsis, providers must decide what the likely source of infection is, what the likely pathogens are, and how catastrophic the outcome would be if antibiotics were incorrectly withheld. After deciding that antibiotics should be administered, choice of the empiric regimen is the next decision. The Surviving Sepsis Campaign 2016 Guidelines for Management of Sepsis and Septic Shock recommend prescribing broad-spectrum antibiotic(s) in patients with sepsis, without factoring in the severity of outcome, ie, the consequences of withholding antibiotics if infection turned out to be the cause of the syndrome [18]. It is clear that for some syndromes, there is less urgency (ie, infiltrates on chest x-ray in a stable patient with predominantly viral symptoms and no underlying disease), and some syndromes seem almost certainly not to be due to infection.

Instead of universal broad-spectrum antibiotics, the specific antibiotic regimen should be determined using a more cerebral approach. This approach should include acquiring site-specific diagnostics including blood cultures, identifying the probable causative organism based on epidemiological and host risk factors, assessing severity of illness (sepsis with stable blood pressure versus septic shock), determining the likely site of infection, characterizing the probability of a multidrug-resistant

infection, and weighing the consequences of failing to include an active regimen either immediately or, ultimately, in the initial empiric choices. Patient factors include recent infectious exposures, evidence of pertinent colonization, comorbidities, indwelling devices, immunologic status, recent infections, and recent antibiotic exposure in the last 3 months. Furthermore, patient location at the time of acquisition is important to determine (community onset, long-term care exposure, or hospital onset) to help assess the likelihood of specific exposures that might be implicated in colonization or acquisition of an acute disease or resistant pathogen. In general, the empiric regimen focuses on bacterial pathogens, but treatable viruses, fungi, and protozoa should also be considered. When to include specific coverage for methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), and highly resistant Gram-negatives will be discussed below. It is difficult to provide algorithms or tables that take all of these factors into account. Although clinical decision support tools that utilize patient-specific information to make antibiotic therapy predictions are becoming available, clinical machine learning is still not standard of care in most institutions. Therefore, there is no clear substitute for clinical judgment that accounts for all known variables and risk factors when choosing an empiric antibiotic regimen.

Site of Infection

The Infectious Disease Society of America (IDSA) has published guidelines that provide recommendations for empiric therapy based on site and host immune status [19–25]. These recommendations are the basis for suggested regimens in Table 1. Several principles of empiric therapy are worth noting.

1. Local antibiograms should be utilized to guide empiric therapy. The use of antibiograms has been evaluated and has even been determined to be unit specific within hospitals and when utilized increase the likelihood that active agents will be prescribed [26, 27].
2. Risk factors for the likelihood of resistant infection should be evaluated including history of prior infection, known colonization, and ecologic data from the hospital and the community of origin.
3. Identification of infection sources that are removable or drainable is important for optimizing source control. In some cases, such as intravascular line infection and septic shock, removal of the indwelling line quickly can be lifesaving. Furthermore, it has been established that patients with an uncontrolled source of infection are at increased risk of mortality [28–30].
4. Empiric regimens should have adequate tissue penetration for the likely site of infection. For example, piperacillin-tazobactam should be avoided in patients with suspected central nervous system infection because tazobactam does not cross the blood-brain barrier. Tigecycline should be avoided for presumed bacteremia due to low serum concentrations. Daptomycin should be avoided for pneumonia due to drug inactivation by surfactant in the lungs.

Multidrug Therapy

Multidrug therapy, defined as more than 1 antibiotic, is commonly prescribed in patients with suspected or documented sepsis. The severity of the syndrome and consequences of late institution of appropriate therapy influence this decision. For patients who could have septic shock, there is no margin for error, and thus initial multidrug antimicrobial therapy should be prompt and cover all likely pathogens. For hemodynamically stable patients with community-acquired pyelonephritis or pneumonia, a more targeted regimen often with a single agent or narrow spectrum agents is reasonable based on local epidemiology.

Some clinicians advocate for "combination therapy" or "double Gram-negative coverage", defined here as more than 1 drug with activity against the presumed pathogen. This strategy often includes 2 agents with different mechanisms of action but with a similar spectrum of activity. Theoretical benefits of double Gram-negative coverage include potential for synergistic activity, more rapid pathogen clearance, and preventing development of antimicrobial resistance. A recent prospective observational study of patients admitted to the ICU in the Netherlands with severe sepsis and septic shock demonstrated that short courses of adjunctive gentamicin (median duration of 2 days) was associated with an increased risk of renal failure but not with faster reversal of shock or improved survival compared with standard therapy [31]. The results of this study have been questioned given concern for selection bias, infrequent resistance in the region, and the observation that only 4% of patients in both arms did not receive at least 1 in vitro active antibiotic [32]. However, this study may provide evidence that double Gram-negative coverage does not enhance efficacy, and any role of double Gram-negative coverage would be in broadening activity. A randomized clinical trial comparing empiric meropenem and ciprofloxacin versus meropenem alone for suspected ventilator-associated pneumonia (VAP) showed that there was no difference in outcomes between the 2 groups in a setting of low resistance. However, those that had infection due to *Pseudomonas* species, *Acinetobacter* species, and multidrug-resistant Gram-negative bacilli were more likely to receive adequate initial therapy and have microbiological clearance if they received meropenem and ciprofloxacin [33].

The current literature suggests that empiric combination therapy for Gram-negative organisms should be reserved for patients who are severely ill including patients with septic shock at increased risk of multidrug-resistant infections in whom initial in vitro-discordant antibiotic therapy (in vitro nonsusceptible) could have detrimental consequences. This recommendation is

Table 1. Site-Specific Empiric Antibiotic Guideline Recommendations[a]

Site of Infection	Initial Empiric Therapy	Other Considerations
Pulmonary		
CAP [19]	Multidrug therapy with a beta-lactam (ampicillin + sulbactam, ceftriaxone, or ceftaroline) and a macrolide (azithromycin clarithromycin)	Risk factors for MRSA and/or *Pseudomonas aeruginosa*: add vancomycin or linezolid for MRSA coverage; replace standard CAP therapy with pseudomonal coverage such as piperacillin-tazobactam, cefepime, meropenem, or imipenem
	Monotherapy with a respiratory fluoroquinolone (levofloxacin or moxifloxacin)	Recommendation based on "local validation" of risk factors for community onset MRSA or *P aeruginosa* or prior isolation of these organisms in the previous year, particularly from respiratory specimens
HAP/VAP [20]	Multidrug therapy with vancomycin or linezolid and piperacillin-tazobactam, cefepime, ceftazidime, imipenem, meropenem, or aztreonam	Two antipseudomonal antibiotics from different classes (addition of fluoroquinolones, aminoglycosides, or polymyxins) if prior intravenous antibiotic use within 90 days for HAP/VAP and septic shock at time of VAP, ARDS preceding VAP, 5 or more days of hospitalization before VAP, or acute renal replacement therapy before VAP If prior colonization with carbapenem-resistant *Enterobacteriales* or KPC-producing organism ceftazidime-avibactam and meropenem-vaborbactam should be considered but further efficacy data is needed Empiric regimens should be informed by local distribution of pathogens and their antimicrobial susceptibilities
Central nervous system		
Healthcare-associated ventriculitis and meningitis [21]	Vancomycin and cefepime, ceftazidime or meropenem	Beta-lactam choice based on local in vitro susceptibility patterns. If carbapenem-resistant *Acinetobacter* is suspected addition of meropenem and colistin or polymyxin B
Meningitis [22]	Vancomycin and ceftriaxone	Age >50, alcohol abuse or immunocompromised: add ampicillin Penetrating head trauma, CSF shunt or postneurosurgery vancomycin and cefepime, ceftazidime or meropenem Clinical presentation suggestive of *Rickettsial* or *Ehrlichial* disease add doxycycline
Skin and soft tissue		
Necrotizing fasciitis including Fournier gangrene [23]	Multidrug therapy with vancomycin or linezolid and piperacillin-tazobactam, a carbapenem, or ceftriaxone and metronidazole	Prompt surgical consultation is recommended for patient with aggressive infections associated with signs of systemic toxicity or suspicion of necrotizing fasciitis or gas gangrene
Nonpurulent cellulitis/erysipelas (severe) [23]	Vancomycin and piperacillin-tazobactam	Emergent surgical inspection to rule out necrotizing process
Purulent furuncle/ carbuncle/abscess (severe) [23]	Vancomycin, daptomycin, linezolid, telavancin, or ceftaroline	Incision and drainage as indicated
Intra-abdominal		
Community onset extrabiliary (mild) [24]	Cefoxitin, ertapenem, moxifloxacin, or tigecycline	Healthcare setting with high prevalence of ESBL-producing *Enterobacteriales* or >20% of *Pseudomonas* resistant to ceftazidime consider carbapenem or piperacillin-tazobactam
Community onset extrabiliary (severe) [24]	Imipenem-cilastatin, meropenem, doripenem or piperacillin-tazobactam	Healthcare associated: imipenem-cilastatin, meropenem, or piperacillin-tazobactam, levofloxacin or cefepime each along with metronidazole, vancomycin added to each regimen
Community onset biliary (mild to moderate) [24]	Cefazolin, cefuroxime, or ceftriaxone	Empiric therapy should be driven by local microbiological data and source control performed as indicated
Community onset biliary severe or cholangitis [24]	Imipenem-cilastatin, meropenem, or piperacillin-tazobactam, Levofloxacin or cefepime each in combination with metronidazole	
Genitourinary		
Acute pyelonephritis (IDSA archived) [25]	Ceftriaxone, trimethoprim-sulfamethoxazole, or ciprofloxacin	Requiring hospitalization: intravenous fluoroquinolone, aminoglycoside, extended-spectrum cephalosporin, extended-spectrum penicillin, or carbapenem with choice of agents based on local resistance data Do not use fluoroquinolone if >10% resistance prevalence or trimethoprim-sulfamethoxazole in areas of high resistance

Abbreviations: ARDS, acute respiratory distress syndrome; CAP, community acquired pneumonia; CSF, cerebrospinal fluid; ESBL, extended-spectrum beta-lactamase; HAP, hospital-acquired pneumonia; IDSA, Infectious Disease Society of America; KPC, *Klebsiella pneumoniae* carbapenemase; MRSA, methicillin-resistant *Staphylococcus aureus*; VAP, ventilator-associated pneumonia.

[a]Please see individual guidelines for further details.

in line with the IDSA guidelines for the treatment of hospital-acquired pneumonia (HAP) and VAP, which recommend empirically prescribing 2 antipseudomonal antibiotics from different classes for the empiric treatment of VAP only in patients with risk factors for antimicrobial resistance at the time of diagnosis, including prior intravenous antibiotic use within the 90 days, septic shock, preceding *acute* respiratory distress syndrome, hospitalization greater than 5 days, and acute renal replacement therapy before VAP onset or patients in units where >10% of Gram-negative isolates are resistant to an agent being considered for monotherapy [20]. Ultimately, the choice of which second agent should be guided by local antibiogram and epidemiological data. Highlighting this point is a retrospective analysis of patients admitted to a single hospital who developed HAP in which Gram-negative isolates resistant to piperacillin-tazobactam or cefepime only had a 10% chance of having in vitro activity against ciprofloxacin compared with 80% for amikacin [34].

PATHOGEN-SPECIFIC CONSIDERATION FOR EMPIRIC THERAPY REGIMENS

Empiric Therapy for Methicillin-Resistant *Staphylococcus aureus* and Vancomycin-Resistant *Enterococcus*

Failure to treat MRSA and VRE with empiric regimens for life-threatening syndromes can lead to increased mortality. It is estimated that 7% of all patients in the United States are colonized with MRSA at any one time and 8.8% of patients admitted to the ICU are colonized with VRE [35, 36]. Risk factors for infections due to MRSA include recent hospitalization, residence in long-term care facility, recent surgery, hemodialysis, prior antibiotic treatment, and high APACHE score [37]. When infection due to MRSA is a concern in a hospitalized patient, the empiric regimen should include either vancomycin, linezolid, daptomycin, or ceftaroline. Pneumonia should never be treated with daptomycin due to inactivation by pulmonary surfactant, and there is also concern that linezolid may not be optimal for bacteremia given its bacteriostatic activity.

Risk factors for VRE colonization include immunosuppression, neutropenia, renal insufficiency, location in the ICU or oncology ward, and prior antimicrobial use [38, 39]. In a single-center study of patients colonized with VRE, 13.4% of patients subsequently developed VRE bloodstream infections over a 4-year period, with risk factors for subsequent bloodstream infection including vancomycin use, diabetes mellitus, gastrointestinal procedures, and acute renal failure [39]. Empiric regimens for patients with concern for VRE should include either daptomycin or linezolid.

Empiric Therapy for Extend -Cephalosporin Resistant Gram-Negative Bacilli

It is estimated that up to 14% of healthy individuals globally are colonized with extended-spectrum beta-lactamase (ESBL) *Enterobacteriales*, with rates reaching above 40% in Asia and as low as 2% in the Americas but potentially rising [2, 40]. Risk factors to aid in the decision of when to prescribe empiric therapy with activity against ESBLs have been identified in a study that evaluated 1288 patients with bacteremia due to *Escherichia coli* or *Klebsiella pneumoniae* and ceftriaxone minimum inhibitory concentrations ≥2 μg/mL [41]. Using recursive partitioning analysis, the top 5 predictors of ESBL-positive bacteremia were determined to be history of ESBL colonization or infection, chronic indwelling vascular hardware, age greater than 43 years, recent hospitalization in an ESBL high burden region (Latin America excluding the Caribbean, Middle East including Egypt, South Asia, China, and the Mediterranean), and ≥6 days of antibiotic exposure in the prior 6 months. Studies evaluating the development of infection caused by ESBL *Enterobacteriales* in those who are colonized with the same organisms have shown varying results. A study of patients with hematologic malignancy found that patients colonized with ESBL-producing *E coli* are 3.5 times more likely to develop bacteremia with the same strain than those who are not colonized, whereas another study estimated that prior colonization with a third-generation, cephalosporin-resistant *Enterobacteriales* had a positive predictive value of 7.4% for future bacteremia with the same organism and 34.4% for infection [42, 43].

A recent randomized control trial demonstrated improved outcomes for the definitive treatment of third-generation, cephalosporin-resistant *E coli* and *K pneumoniae* infection with carbapenems compared with piperacillin-tazobactam, providing inferential evidence that empiric carbapenems would be superior to β-lactam as empiric therapy [44]. A study that evaluated 659 patients colonized with ESBL-producing *Enterobacteriales* with community-onset sepsis demonstrated that empiric carbapenem therapy was superior to noncarbapenem therapy in univariate analysis, but this finding did not remain significant after risk adjustment [45]. Ultimately, in patients where the preponderance of evidence demonstrates that a patient has a high likelihood of an infection with an ESBL-producing Gram-negative organism, carbapenems should be the empiric agent of choice for the potential ESBL-producing organism.

Empiric Therapy for Carbapenem-Resistant Gram-Negative Bacilli

Prior colonization is often considered as a risk factor when determining the need to empirically provide antibiotics with activity against carbapenem-resistant *Enterobacteriales* (CRE). A single-center study from Israel found that 7.6% of patients who had rectal colonization with a CRE developed a subsequent infection and 8.8% had a clinical culture with CRE [46]. In a multivariate analysis of matched controls who had positive CRE rectal screening, risk factors for a subsequent positive clinical culture included ICU stay, central venous catheter, receipt of antibiotics, and diabetes mellitus. A similar study found that carbapenem-resistant *K pneumoniae* colonization was associated with a 9% chance of subsequent carbapenem-resistant *K*

pneumoniae infection with risk factors of infection including previous invasive procedure, diabetes mellitus, solid tumor, tracheostomy, urinary catheter insertion, and receipt of an antipseudomonal penicillin [47].

The Giannella risk score has been developed to predict the likelihood of carbapenem-resistant *K pneumoniae* bloodstream infection in patients who have rectal colonization [48]. This score includes admission to the ICU (2 points), invasive abdominal procedures (3 points), chemotherapy/radiation therapy (4 points), and colonization at site besides stool (5 points per additional site). A score of 2 points is associated with a 12% probability of CRE bloodstream infection, whereas a score of 12 points is associated with 100% probability for CRE bloodstream infection.

After determining the likelihood that a patient has infection caused by a carbapenem-resistant Gram-negative organism, providers must choose the antibiotic regimen that has the highest probability of demonstrating in vitro activity. Many carbapenem-resistant Gram-negative infections remain susceptible to colistin, which has been shown to increase toxicity and not improve mortality when used empirically [49, 50]. Currently, polymyxins could be considered (particularly when *Acinetobacter baumannii* infection is suspected) as part of a multidrug regimen, but emerging data suggest that novel β-lactam/β-lactamase agents have better safety profiles, and it is likely that these agents will have a more important future role in empiric therapy for high-risk patients [51, 52]. Recent real world evidence suggests that the β-lactam/β-lactamase inhibitor ceftazidime-avibactam is being used empirically [53]. Algorithms have been proposed for the empiric utilization of ceftazidime-avibactam for *K pneumoniae* carbapenemase-producing Gram-negatives, and ceftolozane-tazobactam for carbapenem-resistance *Pseudomonas aeruginosa*, which account for severity of illness, comorbid risk factors, local epidemiology, and prior colonization have been proposed [54]. It remains to be seen how other novel antibiotics will be used in empiric settings such as meropenem-vaborbactam, imipenem-relebactam, eravacycline, plazomicin, and cefiderocol. These investigations are important because outcomes of patients treated with ceftolozane-tazobactam are tied to the timing between initiation of the antibiotic and infection diagnosis [55]. Furthermore, it should be noted that eravacycline, plazomicin, and cefiderocol have a spectrum of activity that includes metallo-β-lactamase-producing organisms, making them potentially useful empirically in patients with geographic and epidemiological risk factors for metallo-β-lactamase [56].

Empiric Antifungals

Candida is often a consideration in patients who need empiric treatment, especially when the patients are neutropenic or have some other relevant immunodeficiency. Other yeasts, including *Histoplasma*, *Coccidioides*, *Blastomyces*, and *Cryptococcus*, can present with life- threatening syndromes that merit empiric therapy. Molds can cause severe morbidity and significant mortality especially in immunosuppressed patients, but molds rarely cause septic shock and usually present subacutely.

Well established risk factors for *Candida* species infection include immunosuppressed status such as neutropenia, chemotherapy, transplant, and chronic liver dysfunction, along with invasive vascular devices, total parenteral nutrition, recent abdominal surgery, high APACHE score, prolonged antibiotic exposure and hospitalization, and number of colonized sites [57, 58].

Based on knowledge that critical illness and degree of colonization increase the likelihood of *Candida* species infection, and lack of data demonstrating improved outcomes with empiric antifungal therapy, the EMPRICUS randomized control trial was performed [59]. In this multicenter study of nonneutropenic, critically ill patients who were colonized at multiple sites by a *Candida* species and developed ICU-acquired sepsis, routine empiric micafungin did not increase fungal infection-free survival at 28 days compared with placebo (hazard ratio, 1.35; 95% CI, 0.87–2.08). Furthermore, in patients with SOFA score >8, there was also no difference in 28-day fungal infection-free survival.

However, there are situations in which empiric antifungal therapy seems plausible and prudent, including esophageal and upper gastrointestinal tract perforation and infections of central lines being used for total parenteral nutrition. If the probability of infection from *Candida* species is high enough, or a patient is critically ill with risk factors and no other cause of fever is identified, empiric therapy with an echinocandin (caspofungin, micafungin, or anidulafungin) should be considered [60]. Guidelines should be consulted for optimal therapy for other yeast, but empiric liposomal amphotericin is almost always adequate therapy for potential life-threatening fungal infection while more information and data are collected.

STRATEGIES TO REDUCE TIME TO INFUSION FOR ANTIBIOTICS

Prompt antimicrobial therapy for sepsis is a logical and plausible approach to improving outcomes for patients with sepsis, even if the data to date are most convincing only in the subpopulations with septic shock and certain specific syndromes such as bacterial meningitis. The time to antibiotic administration can be measured in a variety of ways: "time zero" can be defined as the time when the patient first presented to healthcare providers, the time when the first ominous vital signs or laboratory value became available, the time when a decision was made to treat the patient by entering an order for "stat" antibiotics, or time when diagnostics criteria for sepsis are met, although the latter can often be subjective. Reducing time to antimicrobial therapy for sepsis requires a multifaceted assessment of barriers including delayed recognition of sepsis, lack of optimization

of antimicrobial access, and improvement in administration technique.

Delayed recognition of sepsis and septic shock is a barrier to timely antibiotics and is associated with prolonged time to effective therapy and increased mortality [61–63]. Hospitals should have a performance improvement program to reduce the time from initial patient presentation to the administration of appropriate therapy for all patients who meet a screening definition of sepsis [64]. Commonly studied early warning or data-based recognition systems include Systemic Inflammatory Response Syndrome (SIRS), quick Sepsis-related Organ Failure Assessment (qSOFA), and National Early Warning system, each of which have varying degrees of sensitivity and specificity, reliance on laboratory results, along with ability to be fully automated from an electronic health record (EHR) [65].

The Targeted Real-time Early Warning Score (TREWScore) has been developed in ICU patients to predict development of septic shock and could potentially be used to identify patients at high risk for developing septic shock [66]. Another machine learning-based approach for recognizing severe sepsis was compared with standard of care EHR-based screening in a single-center study [67]. In this study, patients were randomly assigned to the control group (severe sepsis detector based on SIRS criteria and end-organ dysfunction) or intervention group (machine learning algorithm in addition to existing severe sepsis detector). Upon receiving an alert, patients were treated with a severe sepsis bundle. Implementation of the machine learning algorithm resulted in decrease in length of stay and a 12.5% in-hospital mortality decrease ($P = .015$). However, there was no evaluation of how many patients were unnecessarily given broad-spectrum antimicrobial therapy.

Once sepsis has been identified, or is highly suspected, it is important to quantify time from antibiotic order to administration because the time of order entry is an indication that the clinician has decided that antibiotics are necessary (regardless of how appropriately or inappropriately long their decision took). A retrospective analysis of 4429 patients diagnosed with sepsis in an ED at a large academic medical center found that the mean interval between presentation and first antibiotic order, which is the proxy used at the site for sepsis recognition, was 2.5 hours, and then the median interval between order and infusion initiation was an additional 1.3 hours [68]. Antimicrobial lead time (measured as the time from order to administration) of 3–6 hours was associated with an OR of 1.57 (95% CI, 1.26–1.95; $P < .001$) for 28-day mortality and 1.36 (95% CI, 0.9–1.86; $P = .06$) for 6–12 hours. The magnitude and frequency of these delays between antibiotic order and antibiotic administration highlights an important quality improvement opportunity for hospitals to focus not only on enhancing sepsis recognition but also improving the logistics of getting antibiotics administered in a timely manner. Klompas and Rhee [69] have proposed that antibiotic order-to-infusion time for patients with septic shock could be a promising quality metric to improve the care of patients.

There are many strategies that can improve time to infusion for the first dose of antibiotics in septic patients including improving access to antibiotics in EDs, floors, and ICUs and creating interdisciplinary teams that rapidly respond to patients with suspected sepsis. These teams, often part of a "code sepsis" response, typically include a clinical pharmacist on the team who either brings a sepsis kit that can provide prompt beside delivery of antibiotics and fluids for resuscitation or ensures initiation of antibiotics after blood cultures have been drawn within 1 hour of sepsis recognition. Code sepsis teams can provide a significant reduction in time to appropriate empiric antibiotic therapy, as demonstrated by one such ED that reduced time to empiric antimicrobial prescription from 126 minutes to 78 minutes after implementing an interdisciplinary code sepsis team in patients meeting the CMS case definition of sepsis for SEP-1 [70]. The team also improved appropriateness of initial antibiotic therapy, defined as an antibiotic regimen approved for the treatment of severe sepsis or septic shock according to the National Hospital Inpatient Quality Measures manual, by approximately 1 hour, presumably due to the expertise the team members had compared to other ED providers. With regards to acquiring blood cultures that are important to guide de-escalation, antibiotics should not be delayed for substantial periods of time while antibiotics are obtained.

Hospitals should be encouraged to develop quality improvement projects to closely evaluate their current processes for delivering antibiotics to patients and to evaluate opportunities to decrease time between order and administration. A "low-hanging fruit" intervention is to ensure that commonly used antibiotics can be easily and quickly accessed in EDs and ICUs by storing doses in automated dispensing cabinets. Not all antibiotics are available in formulations that permit automated dispensing cabinet storage versus requiring preparation and dispensation from the pharmacy, so the decision of what to stock should be determined based on institutional sepsis protocols using local antibiogram data in conjunction with consultation with pharmacists to determine what is feasible.

Most commonly used antibiotics in sepsis are available as either premixed bags or could be used with adaptor systems that allow nurses to mix powdered single-dose vials with diluents in a sterile, closed system, both of which facilitate storage in high-risk areas. Although this is a seemingly simple intervention, there is potential for significant impact. A single-center community ED demonstrated a mean door-to-antibiotic time from 167 minutes to 97 minutes when broad-spectrum empiric antibiotics were included in the ED automated dispensing cabinets [71].

First-dose antibiotic orders that originate from high-acuity areas such as EDs should be defaulted to a "stat" priority to ensure timely approval for pharmacist verification. Pharmacists

Table 2. Commonly Used Antibiotics for Empiric Broad-Spectrum Coverage in Sepsis

Drug	Standard Dose for Sepsis	Infusion Length	Renal Dose Adjustments Required?	Stability After Reconstitution
Drugs With Broad-Spectrum Gram-Negative Coverage Including *Pseudomonas*				
Piperacillin/tazobactam [75]	4.5g IV q6h	Initial dose: 30 minutes Subsequent doses: 30 minutes to 4 hours	Yes at CrCl <40 mL/min	24 hours at room temperature and up to 1 week refrigerated
Ceftazidime [76]	2g IV q8h	Initial dose: can be administered IV push over 3–5 minutes or by intermittent infusion over 15 to 30 minutes Subsequent doses: 30 minutes to 4 hours	Yes at CrCl <50 mL/min	12 hours at room temperature or 3 days under refrigeration
Cefepime [77, 78]	2g IV q8h	Initial dose: can be administered IV push over 3–5 minutes or by intermittent infusion over 30 minutes Subsequent doses: 30 minutes to 4 hours	Yes at CrCl <60 mL/min	24 hours at room temperature and up to 1 week refrigerated
Imipenem/cilastatin [79]	1g IV q6h	Doses <500 mg should be infused over 20–30 minutes doses >500 mg should be infused over 40–60 minutes	Yes at CrCl <60 mL/min	4 hours at room temperature and 24 hours under refrigeration
Meropenem [80]	1–2g IV q8h	Initial dose: doses up to 1g can be administered IV push over 3–5 minutes, or by intermittent infusion over 30 minutes Subsequent doses: 30 minutes to 3 hours	Yes at CrCl <50 mL/min	4 hours at room temperature (in SWFI or sodium chloride 0.9%) or 24 hours under refrigeration
Ciprofloxacin [93]	400 mg IV q8h	Infuse over 60 minutes	Yes at CrCl <50 mL/min	14 days at room temperature or under refrigeration
Levofloxacin [94]	750 mg IV q24h	Doses ≤500 mg infuse over 60 minutes, 750 mg infuse over 90 minutes. Rapid infusion can lead to hypotension	Yes at CrCl <50 mL/min	72 hours at room temperature or 14 days under refrigeration
Drugs With Broad-Spectrum Gram-Positive Coverage Including MRSA				
Vancomycin [81]	15 to 20 mg/kg IV q8–12h	Minimum infusion time of 60 minutes, with additional 30 minutes added for each 500 mg beyond 1000 mg (eg, administer 1000 mg over 60 minutes and 1500 mg over 90 minutes)	Yes, at CrCl <90 mL/min and as guided by therapeutic drug monitoring	14 days under refrigeration
Linezolid [82]	600 mg IV/PO q12h	Over 30 to 120 minutes	No	Premade bags stable until expiration date on packaging when maintained in their overwrap
Daptomycin [83] (not for use in sepsis with suspected pulmonary source)	6 to 8 mg/kg IV q24h	IV push over 2 minutes or IV infusion over 30 minutes	Yes, at CrCl <30 mL/min	12 hours at room temperature and up to 48 hours under refrigeration
Ceftaroline [84]	600 mg IV q12h	Infuse over 60 minutes	Yes at CrCl <50 mL/min	6 hours at room temperature or within 24 hours under refrigeration
Antifungal Agents				
Micafungin [95]	100 mg IV q24h	Infuse over 60 minutes, more rapid infusions may result in more frequent histamine-mediated reactions	No	24 hours at room temperature
Caspofungin [96]	70 mg IV loading dose on day 1, then 50 mg daily thereafter	Infuse over 60 minutes, more rapid infusions may result in more frequent histamine-mediated reactions	No	24 hours at room temperature

Abbreviations: CrCl, creatinine clearance; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*; PO, per os; SWFI, sterile water for injection.

should be equipped with electronic tools to allow them to rapidly evaluate doses, allergies, and drug interactions so as not to delay time to order verification.

An essential education pearl for nursing staff is the order of administration of antibiotics in patients with sepsis or septic shock. Often patients are being started on broad-spectrum empiric therapy that provides coverage of MRSA and *Pseudomonas* species. In general, the regimen includes a broad-spectrum β-lactam (eg, piperacillin/tazobactam, cefepime, meropenem) plus an agent with MRSA coverage such as vancomycin. The β-lactam should be administered first before the MRSA coverage given the broader spectrum activity and shorter infusion times for initial dosing.

A great deal of focus is given to the first dose of antibiotics in septic patients, but having a plan in place to prevent delays of subsequent doses is also needed. A retrospective analysis of 828 patients with sepsis and septic shock in an ED setting found that one third of patients experienced a delay in receiving their second antibiotic dose of greater than or equal to 25% of the intended dosing interval, particularly with antibiotics given at more

frequent dosing intervals (eg, every 6 or 8 hours) [72]. Antibiotics are often given as a single dose in the ED, but using symptom-based treatment pathways or sepsis protocols and order-sets with scheduled antibiotics beyond the initial dose can (1) ensure that subsequent doses are given and (2) provide standardization to improve appropriateness of antibiotic selection [73]. Other means of impacting timeliness of antibiotics include administering the initial doses with faster infusion times; however, it should be noted that the primary decision in choosing an antibiotic should be its spectrum of activity and likelihood of in vitro activity over the rapidity in which it can be administered. Although prolonged infusions of β-lactams are known to improve pharmacokinetic/pharmacodynamic target attainment, the initial doses should always be given as a bolus to ensure that time to peak concentrations are not delayed [74]. Table 2 demonstrates the standard infusion times for antibiotics commonly used in sepsis [75–84].

EMPIRIC ANTIBIOTIC DE-ESCALATION

After the initiation of empiric antibiotics, prescribers should review the appropriateness of the antibiotic regimen chosen for opportunities to de-escalate or potentially even stop therapy. If the totality of diagnostic work suggests that the patient did not have sepsis and infection was unlikely, antibiotics should be discontinued. Antimicrobial stewardship program guidelines recommend a prescriber-led review of the antibiotic regimen that requires persuasive and enforced prompting of prescribers to achieve meaningful impact [85]. Examples of tools to aid prescribers to consider de-escalation include checklists, which when used in the ICU setting have resulted in reduced duration of antibiotic therapy, 72-hour antibiotics time-outs prompted by the HER, which have been shown to increase the rate of de-escalation, and antibiotic stop orders, which have been particularly helpful in stopping empiric vancomycin utilization [86–88]. In addition, de-escalation of antibiotics in patient who are determined to have culture-negative sepsis has been shown to be safe, including a study of critically ill surgical patients [89].

CONCLUSIONS

Sepsis is a syndrome that includes infection-related organ dysfunction that is not immediately life threatening, and infection-related organ dysfunction including shock that is immediately life threatening. For patients in whom the likelihood of infection is low, and the urgency of treatment is minimal, there are major advantages to avoiding a rush to judgment and obtaining serial observations and additional testing before initiating antibiotic therapy. Antibiotic therapy, even for a few doses, can lead to unnecessary cost, major toxicity, clinically important changes in microbial flora, and enhancement of drug resistance. For patients where the likelihood of infection is high but acuity is low, there may be ample time to collect data so that the initial antimicrobial regimen is targeted rather than broad. For patients where the acuity is high, or the outcome is likely to be affected adversely by delayed therapy, it is appropriate and prudent for hospitals to develop systems in which patients are expeditiously recognized and promptly treated with an antimicrobial regimen that is broad enough to cover all plausibly likely pathogens.

Distinguishing patients who need urgent antibiotic therapy from those who do not requires clinical judgment. Empiric therapy for patient who are deemed to warrant therapy for sepsis should be based on patient risk factors including site of infection, severity of illness, and immunosuppression status along with epidemiological factors such as location of infection acquisition (community vs healthcare setting) and antibiogram data. Infectious disease practitioners should play an active role in these decisions, because data would suggest that infectious disease consultation before bacteremia improves the chances of appropriate therapy [90, 91]. Improved rapid diagnostics will be imperative in the future to aid empiric therapy by decreasing time to appropriate therapy and decreasing unnecessary exposure to broad-spectrum antibiotics [92]. Finally, time to antibiotics, measured from order entry to initiation of patient infusion, is a parameter that all healthcare facilities can work to improve.

Notes

Disclaimer. The opinions expressed in this article are those of the authors and do not represent any position or policy of the National Institutes of Health, the US Department of Health and Human Services, or the US Government.

Financial support. This study was funded by the Intramural Research Program of the National Institutes of Health Clinical Center.

Supplement sponsorship. This supplement is sponsored by bioMérieux, the Gordon and Betty Moore Foundation and Beckman Coulter.

Potential conflicts of interest. E. L. H. reports grants from ALK-Abello. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Rhee C, Dantes R, Epstein L, et al. Incidence and trends of sepsis in US hospitals using clinical vs claims data, 2009–2014. JAMA **2017**; 318:1241–9.
2. Centers for Disease Control and Prevention. Antibiotic threats in the United States. **2019**.
3. Prescott HC, Iwashyna TJ. Improving sepsis treatment by embracing diagnostic uncertainty. Ann Am Thorac Soc **2019**; 16:426–9.
4. Cressman AM, MacFadden DR, Verma AA, Razak F, Daneman N. Empiric antibiotic treatment thresholds for serious bacterial infections: a scenario-based survey study. Clin Infect Dis **2019**; 69:930–7.

5. Kollef MH, Burnham JP. Antibiotic thresholds for sepsis and septic shock. Clin Infect Dis **2019**; 69:938–40.
6. Zilberberg MD, Nathanson BH, Sulham K, Fan W, Shorr AF. Carbapenem resistance, inappropriate empiric treatment and outcomes among patients hospitalized with *Enterobacteriaceae* urinary tract infection, pneumonia and sepsis. BMC Infect Dis **2017**; 17:279.
7. Weinberger J, Rhee C, Klompas, M. Time-to-antibiotics in suspected sepsis. J Infect Dis **2020**.
8. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med **2006**; 34:1589–96.
9. Ferrer R, Martin-Loeches I, Phillips G, et al. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. Crit Care Med **2014**; 42:1749–55.
10. Seymour CW, Gesten F, Prescott HC, et al. Time to treatment and mortality during mandated emergency care for sepsis. N Engl J Med **2017**; 376:2235–44.
11. Liu VX, Fielding-Singh V, Greene JD, et al. The timing of early antibiotics and hospital mortality in sepsis. Am J Respir Crit Care Med **2017**; 196:856–63.
12. Alam N, Oskam E, Stassen PM, et al.; PHANTASi Trial Investigators and the ORCA (Onderzoeks Consortium Acute Geneeskunde) Research Consortium the Netherlands. Prehospital antibiotics in the ambulance for sepsis: a multicentre, open label, randomised trial. Lancet Respir Med **2018**; 6:40–50.
13. Whiles BB, Deis AS, Simpson SQ. Increased time to initial antimicrobial administration is associated with progression to septic shock in severe sepsis patients. Crit Care Med **2017**; 45:623–9.
14. Heffner AC, Horton JM, Marchick MR, Jones AE. Etiology of illness in patients with severe sepsis admitted to the hospital from the emergency department. Clin Infect Dis **2010**; 50:814–20.
15. McGregor JC, Rich SE, Harris AD, et al. A systematic review of the methods used to assess the association between appropriate antibiotic therapy and mortality in bacteremic patients. Clin Infect Dis **2007**; 45:329–37.
16. Kumar A, Ellis P, Arabi Y, et al.; Cooperative Antimicrobial Therapy of Septic Shock Database Research Group. Initiation of inappropriate antimicrobial therapy results in a fivefold reduction of survival in human septic shock. Chest **2009**; 136:1237–48.
17. Gaieski DF, Mikkelsen ME, Band RA, et al. Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department. Crit Care Med **2010**; 38:1045–53.
18. Rhodes A, Evans LE, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Crit Care Med **2017**; 45:486–552.
19. Metlay JP, Waterer GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med **2019**; 200:e45–67.
20. Kalil AC, Metersky ML, Klompas M, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis **2016**; 63:e61–111.
21. Tunkel AR, Hasbun R, Bhimraj A, et al. 2017 Infectious Diseases Society of America's Clinical Practice Guidelines for healthcare-associated ventriculitis and meningitis. Clin Infect Dis **2017**; 64:e34–65.
22. Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis **2004**; 39:1267–84.
23. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis **2014**; 59:147–59.
24. Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Clin Infect Dis **2010**; 50:133–64.
25. Gupta K, Hooton 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.
26. Kaufman D, Haas CE, Edinger R, Hollick G. Antibiotic susceptibility in the surgical intensive care unit compared with the hospital-wide antibiogram. Arch Surg **1998**; 133:1041–5.
27. Green DL. Selection of an empiric antibiotic regimen for hospital-acquired pneumonia using a unit and culture-type specific antibiogram. J Intensive Care Med **2005**; 20:296–301.
28. Karvellas CJ, Abraldes JG, Zepeda-Gomez S, et al.; Cooperative Antimicrobial Therapy of Septic Shock (CATSS) Database Research Group. The impact of delayed biliary decompression and anti-microbial therapy in 260 patients with cholangitis-associated septic shock. Aliment Pharmacol Ther **2016**; 44:755–66.
29. Buck DL, Vester-Andersen M, Møller MH; Danish Clinical Register of Emergency Surgery. Surgical delay is a critical

determinant of survival in perforated peptic ulcer. Br J Surg **2013**; 100:1045–9.
30. Wong CH, Chang HC, Pasupathy S, Khin LW, Tan JL, Low CO. Necrotizing fasciitis: clinical presentation, microbiology, and determinants of mortality. J Bone Joint Surg Am **2003**; 85:1454–60.
31. Ong DSY, Frencken JF, Klein Klouwenberg PMC, et al.; MARS Consortium. Short-course adjunctive gentamicin as empirical therapy in patients with severe sepsis and septic shock: a prospective observational cohort study. Clin Infect Dis **2017**; 64:1731–6.
32. Lipcsey M, Castegren M, Furebring M, Sjölin J. Should the aminoglycoside β-lactam combination be abandoned in all severely ill patients with presumed gram-negative infection? Clin Infect Dis **2018**; 66:480–2.
33. Heyland DK, Dodek P, Muscedere J, Day A, Cook D; Canadian Critical Care Trials Group. Randomized trial of combination versus monotherapy for the empiric treatment of suspected ventilator-associated pneumonia. Crit Care Med **2008**; 36:737–44.
34. Beardsley JR, Williamson JC, Johnson JW, Ohl CA, Karchmer TB, Bowton DL. Using local microbiologic data to develop institution-specific guidelines for the treatment of hospital-acquired pneumonia. Chest **2006**; 130:787–93.
35. Jarvis WR, Jarvis AA, Chinn RY. National prevalence of methicillin-resistant *Staphylococcus aureus* in inpatients at United States health care facilities, 2010. Am J Infect Control **2012**; 40:194–200.
36. Ziakas PD, Thapa R, Rice LB, Mylonakis E. Trends and significance of VRE colonization in the ICU: a meta-analysis of published studies. PLoS One **2013**; 8:e75658.
37. Callejo-Torre F, Eiros Bouza JM, Olaechea Astigarraga P, et al. Risk factors for methicillin-resistant *Staphylococcus aureus* colonisation or infection in intensive care units and their reliability for predicting MRSA on ICU admission. Infez Med **2016**; 24:201–9.
38. Bhorade SM, Christenson J, Pohlman AS, Arnow PM, Hall JB. The incidence of and clinical variables associated with vancomycin-resistant enterococcal colonization in mechanically ventilated patients. Chest **1999**; 115:1085–91.
39. Zaas AK, Song X, Tucker P, Perl TM. Risk factors for development of vancomycin-resistant enterococcal bloodstream infection in patients with cancer who are colonized with vancomycin-resistant enterococci. Clin Infect Dis **2002**; 35:1139–46.
40. Karanika S, Karantanos T, Arvanitis M, Grigoras C, Mylonakis E. Fecal colonization with extended-spectrum beta-lactamase-producing *Enterobacteriaceae* and risk factors among healthy individuals: a systematic review and metaanalysis. Clin Infect Dis **2016**; 63:310–8.
41. Goodman KE, Lessler J, Cosgrove SE, et al.; Antibacterial Resistance Leadership Group. A clinical decision tree to predict whether a bacteremic patient is infected with an extended-spectrum β-lactamase-producing organism. Clin Infect Dis **2016**; 63:896–903.
42. Cornejo-Juárez P, Suárez-Cuenca JA, Volkow-Fernández P, et al. Fecal ESBL *Escherichia coli* carriage as a risk factor for bacteremia in patients with hematological malignancies. Support Care Cancer **2016**; 24:253–9.
43. Rottier WC, Bamberg YR, Dorigo-Zetsma JW, van der Linden PD, Ammerlaan HS, Bonten MJ. Predictive value of prior colonization and antibiotic use for third-generation cephalosporin-resistant enterobacteriaceae bacteremia in patients with sepsis. Clin Infect Dis **2015**; 60:1622–30.
44. Harris PNA, Tambyah PA, Lye DC, et al.; MERINO Trial Investigators and the Australasian Society for Infectious Disease Clinical Research Network (ASID-CRN). Effect of piperacillin-tazobactam vs meropenem on 30-day mortality for patients with *E coli* or *Klebsiella pneumoniae* bloodstream infection and ceftriaxone resistance: a randomized clinical trial. JAMA **2018**; 320:984–94.
45. Stupica D, Lusa L, Klevisar MN, et al. Should we consider faecal colonisation with extended-spectrum β-lactamase-producing *Enterobacteriaceae* in empirical therapy of community-onset sepsis? Int J Antimicrob Agents **2017**; 50:564–71.
46. Schechner V, Kotlovsky T, Kazma M, et al. Asymptomatic rectal carriage of blaKPC producing carbapenem-resistant *Enterobacteriaceae*: who is prone to become clinically infected? Clin Microbiol Infect **2013**; 19:451–6.
47. Borer A, Saidel-Odes L, Eskira S, et al. Risk factors for developing clinical infection with carbapenem-resistant *Klebsiella pneumoniae* in hospital patients initially only colonized with carbapenem-resistant *K pneumoniae*. Am J Infect Control **2012**; 40:421–5.
48. Giannella M, Trecarichi EM, De Rosa FG, et al. Risk factors for carbapenem-resistant *Klebsiella pneumoniae* bloodstream infection among rectal carriers: a prospective observational multicentre study. Clin Microbiol Infect **2014**; 20:1357–62.
49. Cisneros JM, Rosso-Fernández CM, Roca-Oporto C, et al.; Magic Bullet Working Group WP1. Colistin versus meropenem in the empirical treatment of ventilator-associated pneumonia (Magic Bullet study): an investigator-driven, open-label, randomized, noninferiority controlled trial. Crit Care **2019**; 23:383.
50. Zak-Doron Y, Dishon Benattar Y, Pfeffer I, et al.; AIDA Study Group. The association between empirical antibiotic treatment and mortality in severe infections caused by carbapenem-resistant gram-negative bacteria: a prospective study. Clin Infect Dis **2018**; 67:1815–23.
51. Pogue JM, Kaye KS, Veve MP, et al. Ceftolozane/tazobactam vs polymyxin or aminoglycoside-based regimens for the

treatment of drug-resistant *Pseudomonas aeruginosa*. Clin Infect Dis **2019**. doi: 10.1093/cid/ciz816.
52. van Duin D, Lok JJ, Earley M, et al.; Antibacterial Resistance Leadership Group. Colistin versus ceftazidime-avibactam in the treatment of infections due to carbapenem-resistant *Enterobacteriaceae*. Clin Infect Dis **2018**; 66:163–71.
53. Strich JR, Ricotta E, Warner S, et al. Pharmacoepidemiology of ceftazidime-avibactam use: a retrospective cohort analysis of 210 US hospitals. Clin Infect Dis **2020**; pii: ciaa061. doi: 10.1093/cid/ciaa061.
54. Montravers P, Bassetti M. The ideal patient profile for new beta-lactam/beta-lactamase inhibitors. Curr Opin Infect Dis **2018**; 31:587–93.
55. Gallagher JC, Satlin MJ, Elabor A, et al. Ceftolozane-tazobactam for the treatment of multidrug-resistant *Pseudomonas aeruginosa* infections: a multicenter study. Open Forum Infect Dis **2018**; 5:ofy280.
56. van Duin D, Doi Y. The global epidemiology of carbapenemase-producing *Enterobacteriaceae*. Virulence **2017**; 8:460–9.
57. Blumberg HM, Jarvis WR, Soucie JM, et al.; National Epidemiology of Mycoses Survey(NEMIS) Study Group. Risk factors for candidal bloodstream infections in surgical intensive care unit patients: the NEMIS prospective multicenter study. The National Epidemiology of Mycosis Survey. Clin Infect Dis **2001**; 33:177–86.
58. Pittet D, Monod M, Suter PM, Frenk E, Auckenthaler R. *Candida* colonization and subsequent infections in critically ill surgical patients. Ann Surg **1994**; 220:751–8.
59. Timsit JF, Azoulay E, Schwebel C, et al.; EMPIRICUS Trial Group. Empirical micafungin treatment and survival without invasive fungal infection in adults with ICU-acquired sepsis, *Candida* colonization, and multiple organ failure: the EMPIRICUS Randomized Clinical Trial. JAMA **2016**; 316:1555–64.
60. Pappas PG, Kauffman CA, Andes DR, et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis **2016**; 62:e1–50.
61. Machado FR, Salomão R, Rigato O, et al. Late recognition and illness severity are determinants of early death in severe septic patients. Clinics (Sao Paulo) **2013**; 68:586–91.
62. Gatewood MO, Wemple M, Greco S, Kritek PA, Durvasula R. A quality improvement project to improve early sepsis care in the emergency department. BMJ Qual Saf **2015**; 24:787–95.
63. Jones SL, Ashton CM, Kiehne L, et al. Reductions in sepsis mortality and costs after design and implementation of a nurse-based early recognition and response program. Jt Comm J Qual Patient Saf **2015**; 41:483–91.
64. Rhodes A, Evans LE, Alhazzani W, et al. Surviving sepsis campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Med **2017**; 43:304–77.
65. Usman OA, Usman AA, Ward MA. Comparison of SIRS, qSOFA, and NEWS for the early identification of sepsis in the Emergency Department. Am J Emerg Med **2019**; 37:1490–7.
66. Henry KE, Hager DN, Pronovost PJ, Saria S. A targeted real-time early warning score (TREWScore) for septic shock. Sci Transl Med **2015**; 7:299ra122.
67. Shimabukuro DW, Barton CW, Feldman MD, Mataraso SJ, Das R. Effect of a machine learning-based severe sepsis prediction algorithm on patient survival and hospital length of stay: a randomised clinical trial. BMJ Open Respir Res **2017**; 4:e000234.
68. Kashiouris MG, Zemore Z, Kimball Z, et al. Supply chain delays in antimicrobial administration after the initial clinician order and mortality in patients with sepsis. Crit Care Med **2019**; 47:1388–95.
69. Klompas M, Rhee C. Antibiotic order-to-infusion time for patients with septic shock: a potential new quality metric. Crit Care Med **2019**; 47:1467–70.
70. Whitfield PL, Ratliff PD, Lockhart LL, et al. Implementation of an adult code sepsis protocol and its impact on SEP-1 core measure perfect score attainment in the ED. Am J Emerg Med **2019**. doi: 10.1016/j.ajem.2019.07.002.
71. Hitti EA, Lewin JJ 3rd, Lopez J, et al. Improving door-to-antibiotic time in severely septic emergency department patients. J Emerg Med **2012**; 42:462–9.
72. Leisman D, Huang V, Zhou Q, et al. Delayed second dose antibiotics for patients admitted from the emergency department with sepsis: prevalence, risk factors, and outcomes. Crit Care Med **2017**; 45:956–65.
73. Thiel SW, Asghar MF, Micek ST, Reichley RM, Doherty JA, Kollef MH. Hospital-wide impact of a standardized order set for the management of bacteremic severe sepsis. Crit Care Med **2009**; 37:819–24.
74. Vardakas KZ, Voulgaris GL, Maliaros A, Samonis G, Falagas ME. Prolonged versus short-term intravenous infusion of antipseudomonal β-lactams for patients with sepsis: a systematic review and meta-analysis of randomised trials. Lancet Infect Dis **2018**; 18:108–20.
75. Piperacillin/tazobactam (Zosyn®) [prescribing information]. Philadelphia, PA: Pfizer IP; **2017**.
76. Ceftazidime (Fortaz®) [prescribing information]. Buena, NJ: Baxter Healthcare Corporation; **2017**.
77. Cefepime (Maxipime®) [prescribing information]. Lake Forest, IL: Hospira ILF; **2012**.
78. Garrelts JC, Wagner DJ. The pharmacokinetics, safety, and tolerance of cefepime administered as an intravenous bolus or as a rapid infusion. Ann Pharmacother **1999**; 33:1258–61.
79. Imipenem (Primaxin®) [prescribing information]. Whitehouse Station, NJ: Merck & Co IWS; **2016**.

80. Meropenem (Merrem®) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP**; 2016**.
81. Vancomycin (Vancocin®) [prescribing information]. Rockford, IL: Mylan Institutional LLC; **2018**.
82. Linezolid (Zyvox®) [prescribing information]. New York, NY: Pfizer IP; **2008**.
83. Daptomycin (Cubicin®) [prescribing information]. Whitehouse Station, NJ: Merck & Co IWS; **2018**.
84. Ceftaroline (Teflaro®) [prescribing information]. St. Louis, MO: Forest Pharmaceuticals ISL; **2010**.
85. Barlam TF, Cosgrove SE, Abbo LM, et al. Implementing an antibiotic stewardship program: guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis **2016**; 62:e51–77.
86. Weiss CH, Persell SD, Wunderink RG, Baker DW. Empiric antibiotic, mechanical ventilation, and central venous catheter duration as potential factors mediating the effect of a checklist prompting intervention on mortality: an exploratory analysis. BMC Health Serv Res **2012**; 12:198.
87. Guglielmo BJ, Dudas V, Maewal I, et al. Impact of a series of interventions in vancomycin prescribing on use and prevalence of vancomycin-resistant enterococci. Jt Comm J Qual Patient Saf **2005**; 31:469–75.
88. Wolfe JR, Bryant AM, Khoury JA. Impact of an automated antibiotic time-out alert on the de-escalation of broad-spectrum antibiotics at a large community teaching hospital. Infect Control Hosp Epidemiol **2019**; 40:1287–9.
89. Turza KC, Politano AD, Rosenberger LH, Riccio LM, McLeod M, Sawyer RG. De-escalation of antibiotics does not increase mortality in critically ill surgical patients. Surg Infect (Larchmt) **2016**; 17:48–52.
90. Kerremans JJ, Verbrugh HA, Vos MC. Frequency of microbiologically correct antibiotic therapy increased by infectious disease consultations and microbiological results. J Clin Microbiol **2012**; 50:2066–8.
91. Raineri E, Pan A, Mondello P, Acquarolo A, Candiani A, Crema L. Role of the infectious diseases specialist consultant on the appropriateness of antimicrobial therapy prescription in an intensive care unit. Am J Infect Control **2008**; 36:283–90.
92. Messacar K, Parker SK, Todd JK, Dominguez SR. Implementation of rapid molecular infectious disease diagnostics: the role of diagnostic and antimicrobial stewardship. J Clin Microbiol **2017**; 55:715–23.
93. Ciprofloxacin (Cipro) [prescribing information]. Wayne, NJ: Bayer HealthCare Pharmaceuticals Inc. **2016.**
94. Levofloxacin (Levaquin) [prescribing information]. Lake Forest, IL: Raritan; **2008**.
95. Micafungin (Mycamine) [prescribing information]. Northbrook, IL: Astellas Pharma US IN; **2019**.
96. Caspofungin (Cancidas) [prescribing information]. Whitehouse Station, NJ: Merck and Co. IWS; **2005**.