Appropriate Antibiotic Therapy

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KEYWORDS

• Sepsis • Antibiotics • Antifungals • Obesity • Resistance • Acute kidney injury • Dosing

KEY POINTS

- Although early retrospective studies found decreased survival associated with each 1-hour delay in antibiotics, prospective studies have not validated these findings; the optimal time benefit of antibiotic delivery within the first 6 hours is not known.
- Inappropriate initial antibiotic therapy is associated with an increase in mortality; it is appropriate to start broad-spectrum antibiotic therapy that provides coverage of the most likely pathogens.
- The use of 2 antibiotics to double-cover gram-negative infections is not routinely required, especially if empiric therapy involves an antipseudomonal penicillin, cephalosporin, or carbapenems.
- Patients who receive both vancomycin and piperacillin/tazobactam may be at greater risk for acute kidney injury.
- The loading dose of antibiotics is the same in patients with and without renal dysfunction. Subsequent doses need to be adjusted in patients with renal dysfunction.

INTRODUCTION

The timely use of appropriate antimicrobials is a cornerstone therapy for patients with sepsis syndromes. Recent publications have sparked debate regarding how the selection and timing of antimicrobial therapy affect the outcomes of patients with severe sepsis and septic shock. The selection of empiric antibiotics for septic patients in the emergency department (ED) likely plays a significant role in patient mortality. Practitioners need to consider many patient-specific factors when tailoring an

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antibiotic regimen to a patient's' clinical presentation. Attention should be directed toward administering the selected antimicrobials in a timely manner. However, recommendations about the timing of administration are lacking: the Surviving Sepsis Campaign (SSC) guidelines have been criticized for their lack of timing advice founded on feasibility trials.[1] Many EDs now stock empiric antimicrobial regimens within the confines of the department rather than in a central pharmacy to enhance the speed and appropriateness of initial therapy. These empiric antimicrobials are often chosen according to local susceptibility patterns and antibiograms. Regimens for appropriate coverage vary according to the suspected disease process, so speed and breadth need to be weighed against the need for a thorough diagnostic work-up to localize the source of infection. The addition of antiviral and antifungal coverage to antibacterial therapy must be considered in certain at-risk patients. Patient-specific characteristics such as renal function, weight, and allergies necessitate antibiotic substitution or dosing adjustments for many critically ill patients.

TIMING OF ANTIMICROBIAL THERAPY

Sepsis has been defined as "life-threatening organ dysfunction due to a dysregulated host response to infection," so it makes intuitive sense that the earlier antimicrobial therapy is instituted, the better outcomes patients will have.[2] Kumar and colleagues[3] found that each hour's delay in antimicrobial administration was associated with a mean decrease in survival of 7.6%. Their multicenter, retrospective study included 2154 patients with hypotension as the start-time marker for septic shock. A second retrospective evaluation, this time of the SSC database, also showed increased in-hospital mortality with each hour's delay in antibiotic administration.[4] Similarly, a retrospective observational study in pediatric intensive care unit (ICU) patients showed an increased mortality risk with each hour's delay from sepsis recognition to antibiotic administration.[5] Note that time-to-intervention studies provide information primarily on correlation, not causation. Given the inherent limitations of retrospective studies and the complex variables that can confound time-to-intervention studies, caution is warranted when interpreting the results.[6]

Prospective studies have failed to validate an increased risk of mortality with delayed antibiotics, as long as they are administered within 6 hours after the diagnosis of sepsis.[7–9] A systematic review and meta-analysis found no significant mortality benefit of administering antibiotics within 3 hours after ED triage or within 1 hour after shock recognition in patients with severe sepsis and septic shock.[10] These data do not suggest that early antibiotic administration is not important, but that the exact time of maximum benefit is yet unknown. Because sepsis is a complex spectrum of illness, many factors affect the risk of death and the length of stay in an ICU. The arbitrarily assigned markers of time to antibiotic administration that are currently used as quality metrics might not be supported by the evidence that emerges from future studies.

APPROPRIATE ANTIBIOTIC SELECTION

After appropriate cultures are obtained, prompt initiation of broad-spectrum empiric antibiotic therapy is essential. Individualizing therapy in the ED is difficult, especially when empiric antimicrobials must be chosen without culture data. Reports suggest that 10% to 40% of initial empiric antimicrobial therapy is inadequate.[11–14] Antibiotic selection should be driven by multiple factors, including the suspected site of infection, local susceptibility patterns, and patient-specific factors. The suspected site of infection suggests common potential pathogens and thus indicates the antibiotics that can achieve an adequate concentration at the site. Local susceptibility patterns,

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guided by institutional antibiograms, aid in the identification of antibiotics with the highest likelihood of coverage for suspected pathogens. Patient-specific factors include organ function, infection history, antibiotic exposure history, surveillance cultures, and allergies.[15] There is little margin for error in patients with severe sepsis, so it is appropriate to start broad-spectrum antibiotic therapy that provides coverage of the most likely gram-positive and gram-negative pathogens.[1] Recommendations for empiric antibiotic regimens for septic patients are presented in **Table 1**.

Inappropriate initial antibiotic therapy is associated with an increase in the mortality. A single-center study of patients with bacteremia found a 34% difference (28% vs 62%) in the mortality among patients given inappropriate antibiotics on the first day of therapy and those given the right antibiotics.[13] In one of the first observational studies on the adequacy of antibiotics specific to patients in the ICU, the mortality was significantly higher in those who received inadequate antimicrobial therapy initially.[11] Further studies have confirmed these findings in patients with gram-negative sepsis, severe sepsis, and septic shock.[12,16]

Although it is important to consider the antimicrobial stewardship principle of using the most narrow-spectrum agent possible for an infection, this practice does not apply in the management of sepsis until culture data are available. However, it is still important to use very broad-spectrum agents such as the carbapenems judiciously, reserving them for patients who have a high likelihood of multidrug-resistant (MDR) infections and in communities in which local susceptibility patterns warrant them.

A classification of infections as health care–associated infections had been used to describe patients at higher risk for MDR organisms. The most recent guidelines have removed this category due to its lack of ability to accurately describe patients who required broad spectrum antibiotic coverage.[17–19] A lack of consensus regarding the power of these risks exists, and recent studies have delineated even more risk factors, including an immunocompromised state, hospitalization during the previous year, previous antibiotic therapy, age greater than 60 years, and Karnofsky index score less than 70.[20–22] Because these risk factors might be overly broad in identifying patients with resistant organisms, Shorr and colleagues[23] designed a clinical score that can be used to assess ED patients' risk of harboring a resistant pathogen (**Table 2**). In a cohort of 977 patients, resistant organisms, defined as methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and extended-spectrum β-lactamases, were isolated 46.7% of the time. The risk score was higher in those with a resistant organism (median 4) than in those without a resistant organism (median 1) ($P<.001$). A score greater than 0 had a high positive predictive value of 84.5% for resistant organisms.[24] In addition, not all risk factors for MDR organisms are equivalent in their prediction of pneumonia caused by resistant pathogens in the community. Hospitalization in the preceding 90 days and residence in a long-term care facility were independent predictors of infection with a resistant pathogen in an observational prospective cohort of patients from the community who were hospitalized with pneumonia.[24,25] Most of the studies using the health care–associated infection classification are limited to respiratory and bloodstream infections. Of note, the health-care associated pneumonia designation was removed from the updated hospital-acquired pneumonia and ventilator-associated pneumonia guidelines as there is increasing evidence that many patients defined as having HCAP are not at high risk for MDRA pathogens and do not account for underlying patient characteristics that are also important determinates for risk of MDR pathogens.[19]

Another important factor in the selection of empiric antibiotic therapy is the patient's reported allergies. Between 15% and 20% of patients report an allergy to β-lactam antibiotics. Patients' self-report of antibiotic allergy has been associated with antimicrobial resistance, increased length of stay, ICU admission, increased costs, and even

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Table 1
Common empiric antibiotic regimens

Suspected Source	Regimen	Comments
Sepsis of unknown origin	• Gram-negative/pseudomonal coverage ◦ Piperacillin/tazobactam, 4.5 g IV q 6 h, or cefepime, 2 g IV q 8 h, or a carbapenem (eg, meropenem, imipenem/cilastatin) ■ Reported β-lactam allergy, but low suspicion for severe or anaphylactic reaction: cefepime, 2 g IV q 8 h, or meropenem, 1 g IV q 8 h. Monitor for reaction ■ Known severe β-lactam allergy: ciprofloxacin, 400 mg IV q 8 h, or aztreonam, 2 g IV q 8 h, if resistance to fluoroquinolones is suspected (eg, prior exposure) ■ Unknown reaction: if critically ill (intubated, pressors), the benefits of appropriately broad/effective antibiotics often outweigh the risk of anaphylaxis ◦ Add amikacin, 25 mg/kg ideal body weight IV × 1, if patient has risk factors for resistant GNR infection. Consult pharmacy for patients with CrCl<30 mL/min or on renal replacement therapy • Gram-positive/MRSA coverage ◦ Vancomycin, 25–30 mg/kg IV ABW load, followed by 15 mg/kg IV q 12 h, or ◦ Linezolid if history of VRE, 600 mg IV q 12 h	A broad-spectrum β-lactam antibiotic should be administered before the anti-MRSA coverage because of its faster infusion times and broader coverage of potential pathogens

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Sepsis – Suspected pulmonary source	• CAP ◦ Ceftriaxone, 1–2 g IV q 24 h, and azithromycin, 500 mg daily, or ◦ Ceftriaxone, 1–2 g IV q 24 h, and doxycycline, 100 mg PO BID, or ◦ Levofloxacin, 750 mg, or moxifloxacin, 400 mg, IV/PO daily ◦ Necrotizing or cavitary pneumonia: add MRSA coverage ■ Add linezolid, 600 mg IV/PO q 12 h, to above regimen ■ Note: doxycycline is inadequate for MRSA pneumonia coverage • HCAP ◦ For patients with recent (within last 90 days) intravenous antibiotic exposure ◦ Resistant gram-negative organism coverage ◦ Resistant gram-negative coverage ■ Piperacillin/tazobactam, 4.5 g IV q 6 h, or ■ Cefepime, 2 g IV q 8 h, or ■ Carbapenem (eg, meropenem, 1 g IV q 8 h) ■ Penicillin allergy: fluoroquinolone (eg, ciprofloxacin, 400 mg IV q 8 h) ■ Plus optional gentamicin, 7 mg/kg daily, or amikacin, 20 mg/kg daily (for patients with septic shock while cultures are pending)	• HCAP was a former designation for patients with exposure to health-care settings. The distinction from CAP served to identify patients with a theoretically higher risk for infection with MDR organisms. However, the distinction has been removed from current guidelines because the risk factors for HCAP (below) might not be predictive of infection with resistant pathogens. New guidelines indicate recent intravenous antibiotic use to be the risk factor for resistant pathogens with the most supporting literature • Risk factors for resistant gram-negative organisms: ◦ Hospitalization for $\geq$2 d within the past 90 d ◦ Residence in a long-term care facility ◦ Infusions (eg, home IV antibiotics, chemotherapy) ◦ Hemodialysis patient ◦ Wound care ◦ Family member with MDR organism ◦ Immunocompromised
Sepsis: suspected meningitis	• Vancomycin, 25 mg/kg loading dose, followed by 15 mg/kg q 8–12 h; ceftriaxone, 2 g IV q 12 h, and acyclovir, 10 mg/kg ideal body weight IV q 8 h • After neurosurgery or penetrating trauma, use cefepime, 2 g IV q 8 h, instead of ceftriaxone to cover *Pseudomonas* • Age>50 y, alcohol abuse, or immunocompromised: add ampicillin, 2 g IV q 4 h, to cover *Listeria monocytogenes*	

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Table 1
(*continued*)

Suspected Source	Regimen	Comments
Sepsis: suspected urinary source	• Community patients/no MDR risk factors ○ Ceftriaxone, 1 g IV q 24 h ○ PCN allergic: ciprofloxacin, 500 mg PO BID, or levofloxacin, 750 mg PO daily (renal dose adjustment required) • Foley catheter/risk factors for MDR gram negatives ○ Cefepime, 1 g IV q 8 h, or piperacillin-tazobactam, 3.375 mg IV q 6 h, or levofloxacin, 500 IV q 24 h + gentamicin, 5 mg/kg IBW IV once	Fluoroquinolones (eg, ciprofloxacin and levofloxacin) should be avoided if local antibiogram shows significant resistance to *Escherichia coli* (threshold >10% per IDSA guidelines)
Sepsis: related to central line	Treat as above for sepsis of unknown origin, tailor antibiotics based on blood culture Gram stain	
Sepsis: intra-abdominal source	Treat as above for sepsis of unknown origin; ensure anaerobe coverage is included in the regimen (eg, piperacillin/tazobactam, a carbapenem, or add metronidazole)	

Doses listed in this table are for patients with normal renal function.

Abbreviations: ABW, adjusted body weight; BID, twice a day; CAP, community-acquired pneumonia; CrCl, creatinine clearance; GNR, gram-negative rods; HCAP, health care–associated pneumonia; IBW, ideal body weight; IDSA, Infectious Diseases Society of America; IV, intravenous; MDR, multidrug resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; PCN, penicillin; PO, by mouth; q, every; VRE, vancomycin-resistant enterococci.

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Table 2
Risk of resistant pathogens for pneumonia

Risk Factor	Point Value
Recent hospitalization (within 90 d)	4
Presenting from long-term care facility	3
Chronic hemodialysis	2
Admission to ICU within 24 h of ED evaluation	1

death.[24–28] To optimize therapy, a thorough allergy history should be documented, because some so-called reactions to antibiotics are frequently diagnosed inaccurately as allergies. The risk of cross reactivity with cephalosporins, particularly third- and fourth generation, and carbapenems is very low, so the risk/benefit of giving a septic patient potentially suboptimal therapy such as a fluoroquinolone versus a β-lactam with a low risk of cross reactivity should be considered carefully.[29,30]

Empiric antifungal coverage is not indicated for most patients, because fungal infections are typically diagnosed late in the course of hospitalization. The mortality associated with candidal infections can reach as high as 60%.[31,32] Risk factors for invasive candidiasis are categorized as host-related factors (eg, immunosuppressive disease or therapy, neutropenia, age, solid organ transplant) and health care–associated factors (eg, catheter use, total parenteral nutrition, recent surgical interventions, use of broad-spectrum antimicrobial drugs).[33] The Candida Score developed by León and colleagues[34] uses 4 variables for diagnosing probable candidal infection in non-neutropenic hosts: multifocal candida colonization (1), surgery (1), receipt of total parenteral nutrition (1), and clinical signs of severe sepsis (2). A score greater than 2.5 is associated with a greater than 7-fold increase in the likelihood of a documented candida infection. Notably, there was no association between the presence of a central venous catheter and candidal bloodstream infection. The combination of infrequent need for antifungal therapy and delayed culture results leads to delayed treatment and a high mortality among patients with candidal infection. Using the Candida Score in at-risk patients might assist in deciding whether fluconazole or an echinocandin should be ordered preemptively for a critically ill patient.

Irrespective of the conflicting data on time to antibiotic administration, the choice of antibiotics is vital. The use of appropriate antibiotics is associated with a lower mortality and a shorter ICU length of stay.[14,16,35,36] Broad-spectrum antibiotics should be initiated as early as possible. Delays are common, with risk factors including not being seen by an emergency physician, not considering the diagnosis of sepsis initially, and delay of therapy while waiting for diagnostic tests to be performed.[37] Several groups have implemented strategies to remove specific barriers to the timely administration of appropriate antibiotics. Kalich and colleagues[38] implemented an antibiotic-specific sepsis bundle and reported a significant improvement in the initiation of appropriate initial antibiotic therapy for severe sepsis in the ED. Adding appropriate antibiotics to unit-based cabinets also reduced order-to-administration time for first doses.[38,39]

THE ROLE OF CULTURES

Obtaining appropriate blood or tissue cultures before initiating antibiotic therapy is important in identifying the causative organisms. The SSC recommends obtaining cultures before the start of antimicrobial therapy if it can be done without delaying therapy more than 45 minutes (grade 1C).[1] In practice, 2 culture sets, each containing

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an aerobic and anaerobic culture bottle, should be drawn from 2 sites. Although the sepsis guidelines recommend that the volume of blood drawn into culture bottles should be greater than or equal to 10 mL, other infectious disease guidelines suggest that 20 to 40 mL of blood should be drawn, because the volume collected is directly proportional to the yield of pathogens.[1,40] Skin antisepsis can be achieved with tincture of iodine or chlorhexidine gluconate, and the aerobic bottle should be filled first.[40]

Fungal infection can cause delays in growth and difficulty in identification of organisms with routine blood cultures. In addition to cultures, the SSC gives a moderate recommendation for obtaining a 1,3B-D-glucan or antimannan antibody assay when fungal infection is suspected, noting that false-positive results are caused by colonization and advising that the utility of this test in critical care settings needs further investigation.[41] Blood culture yield in sepsis syndromes is variable based on the underlying source of infection. **Table 3** shows rates of positive blood cultures according to suspected site of infection.[42–47]

MISCELLANEOUS

Gram-negative Double Coverage

The use of double coverage as empiric treatment of gram-negative organisms in sepsis remains controversial.[48] Combination therapy can increase the probability of appropriate empiric coverage, improve antibiotic activity through synergy, and potentially prevent or delay the development of resistance.[49] As discussed earlier in this article, the timely initiation of antibiotic therapy with activity against the causative pathogen is essential to decrease mortality and improve outcomes in patients with gram-negative sepsis; therefore, double coverage that increases the likelihood of choosing an effective agent with empiric therapy is the most important consideration for ED patients. A large propensity-matched cohort study of 28 ICUs evaluated the benefit of empiric combination therapy using a broad-spectrum β-lactam plus either an aminoglycoside, fluoroquinolone, or macrolide/clindamycin compared with β-lactam monotherapy in cases of culture-positive septic shock. Although the combination group had a lower 28-day mortality than the β-lactam monotherapy group (36% vs 29%; $P = .0002$), if the β-lactam used was an antipseudomonal penicillin, cephalosporin, or carbapenem, no benefit was seen with the addition of a second agent.[50]

In a study of 593 patients with bacteremia caused by *P aeruginosa*, including MDR and extensively drug-resistant strains, Peña and colleagues[51] found no difference in the 30-day mortality in the group treated with combination therapy (most often a β-lactam plus an aminoglycoside) and those who received single-drug therapy. There was also no association of combination therapy with survival among patients who received 2 antibiotics that both covered the infecting organism, an observation that questions the clinical utility of synergy. However, the study included multiple antibiotic

Table 3
Blood culture yield according to infectious source

Site of Infection	Blood Cultures Positive (%)
CAP	6–14[42,43]
Pyelonephritis/complicated UTI	20–30[44]
Meningitis	80–90[45]
Cellulitis	5–8[46]
Neutropenia	10[47]

Abbreviation: UTI, urinary tract infection.

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combinations and was not designed to establish whether synergy is drug dependent. Prevention of resistance is an important goal of combination therapy, but this strategy is probably best reserved for MDR organisms, which require a longer duration of treatment. In vitro data showed that monotherapy is associated with a more rapid increase in minimum inhibitory concentration (MIC) and therefore development of resistance isolates compared with combination therapy, although in vivo data are lacking.[52] If the infecting organism has an increased MIC to the drug being used, and if it is unknown whether pharmacokinetic and pharmacodynamic targets can be attained, the addition of a second agent could help overcome the deficit.[53] Ultimately, the decision to use empiric combination therapy for sepsis should be made with consideration of local epidemiology and individual patient characteristics. In areas in which resistance to broad-spectrum β-lactam therapy is anticipated, the addition of an aminoglycoside until culture data and susceptibilities are available is reasonable but must be considered in conjunction with risks (eg, the presence or risk of renal dysfunction) and benefits (eg, for patients with previous antibiotic and hospital exposure or colonized with MDR organisms).

Acute Kidney Injury Risk with the Combination of Vancomycin and Piperacillin/Tazobactam

Two abstracts presented at the 2012 meeting of the Society of Critical Care Medicine suggested that patients who receive vancomycin plus piperacillin-tazobactam or piperacillin-tazobactam alone have a higher risk of developing acute kidney injury (AKI) than do patients who receive vancomycin alone. Hellwig and colleagues[54] performed a retrospective evaluation of all adult patients who were admitted to Sanford USD Medical Center over a 6-month period and who then received vancomycin plus or minus piperacillin-tazobactam for more than 48 hours. AKI was defined as an increase of serum creatinine level greater than 0.5 mg/dL or a 50% increase from baseline. Among the 735 patients whose records were analyzed, the incidence of AKI was 4.9% for those who received vancomycin alone, 11.1% for those who received piperacillin-tazobactam alone, and 18.6% for those who received a combination of vancomycin plus piperacillin-tazobactam (vancomycin vs piperacillin-tazobactam, $P = .014$; vancomycin vs combination, $P = .005$). Similar results were found when only the ICU patients were considered: 6.0%, 12.2%, and 21.2%, respectively (vancomycin vs piperacillin-tazobactam, $P = .279$; vancomycin vs combination, $P = .005$). Min and colleagues[55] evaluated 140 surgical ICU patients over the course of a year who received vancomycin plus or minus piperacillin-tazobactam for at least 48 hours. AKI was defined as an increase in serum creatinine level more than 1.5 times baseline during antibiotic therapy. The investigators controlled for severity of illness and concomitant use of other nephrotoxic antibiotics. The incidence of AKI was higher in the vancomycin plus piperacillin-tazobactam group than in the vancomycin-alone group (40.5% vs 9.0%; $P<.001$).

There have since been 7 additional studies published on this topic, including a recent prospective evaluation (**Table 4**). Moenster and colleagues[56] conducted a retrospective cohort study of all diabetic patients with osteomyelitis treated with vancomycin plus either piperacillin-tazobactam or cefepime for at least 72 hours at a Veterans' Affairs Medical Center between January 2006 and December 2011. The primary outcome was development of AKI, defined as an increase in serum creatinine level of 0.5 mg/dL or 50% of baseline. One-hundred and thirty-nine patients met the inclusion criteria: 109 in the piperacillin-tazobactam group and 30 in the cefepime group. AKI developed in 29.3% (32 out of 109) of the patients who received vancomycin plus piperacillin-tazobactam compared with 13.3% (4 out of 30) of those treated

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Table 4
Summary of studies evaluating risk of acute kidney injury with piperacillin-tazobactam

Study	Design	Population	AKI Incidence (%)		*P* Value
			Pip-Tazo + Vanc	Comparator	
Hellwig et al,[54] 2011	Retrospective	Mixed (n = 735)	All: 18.6 ICU: 21.2	All: 4.9 (vanc alone), 11.1 (pip-tazo alone) ICU: 6 (vanc alone), 12.2 (pip-tazo alone)	All: .0001 (vanc vs combination) ICU: .005 (vanc vs combination)
Min et al,[55] 2011	Retrospective	ICU (n = 140)	40.5	9 (vanc alone)	<.001
Moenster et al,[56] 2014	Retrospective	Mixed (n = 139)	29.3	13.3 (vanc + cefepime)	.099
Gomes et al,[57] 2014	Retrospective	Mixed (n = 224)	34.8	12.5 (vanc + cefepime)	.003
Meaney et al,[58] 2014	Retrospective	Internal medicine (n = 125)	22.4	No comparator	NA
Burgess et al,[59] 2014	Retrospective	Mixed (n = 191)	16.3	8.1 (vanc alone)	.041
Peyko et al,[60] 2016	Prospective	Mixed (n = 85)	37.3	7.7 (vanc + cefepime or meropenem)	.005
Karino et al,[61] 2016	Retrospective + case control	Mixed (n = 320)	33	No comparator, but similar for intermittent or extended pip-tazo infusions	NA
Hammond et al,[62] 2016	Retrospective	ICU (n = 122)	32.7	28.8 (vanc + cefepime)	.647

Abbreviations: NA, not available; pip-tazo, piperacillin-tazobactam; vanc, vancomycin.

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with vancomycin plus cefepime ($P = .099$). A multiple logistic regression analysis identified weight and average vancomycin trough as the only significant predictors of AKI. The investigators were unable to detect a statistically significant difference in the incidence of AKI between the groups; however, power was not met.

A second retrospective matched cohort examined 224 patients receiving vancomycin plus piperacillin-tazobactam or vancomycin plus cefepime for more than 48 hours.[57] The patients in this study had no preexisting kidney disease. AKI was defined according to the Acute Kidney Injury Network criteria. Its incidence was higher in the piperacillin-tazobactam plus vancomycin group (34.8%) than in the cefepime plus vancomycin group (12.5%) in the unmatched analysis ($P<.0001$). After adjusting for potential sources of bias through propensity score–matched pairs and conditional logistic regression, piperacillin-tazobactam plus vancomycin combination therapy ($P = .003$) was found to be an independent predictor of AKI. There were no significant differences in time to development of AKI or hospital length of stay between the groups.

Meaney and colleagues[58] retrospectively evaluated 125 adult internal medicine patients who received at least 72 hours of vancomycin treatment. Nephrotoxicity, defined as an increase in serum creatinine level of 0.5 mg/dL or 50% more than baseline (whichever was larger), occurred in 17 (13.6%) of the 125 patients. On multivariable logistic regression analysis, after controlling for hypotensive episodes, Charlson Comorbidity Index, and baseline creatinine clearance, concomitant use of piperacillin-tazobactam was associated with an increased incidence of vancomycin-associated nephrotoxicity (adjusted odds ratio, 5.36; 95% confidence interval, 1.41–20.5). Thirteen of the 58 patients (22.4%) receiving the combination developed nephrotoxicity. The investigators concluded that vancomycin-associated nephrotoxicity is prevalent among internal medicine patients, with 5.36-fold higher odds if piperacillin-tazobactam is administered concomitantly.

Burgess and Drew[59] retrospectively reviewed the records of 191 internal medicine and ICU patients, treated at 1 medical center, who received vancomycin or vancomycin plus piperacillin-tazobactam for at least 48 hours. AKI was defined as an increase in serum creatinine level more than 1.5 times baseline during antibiotic therapy. Nephrotoxicity developed in 8 (8.1%) of the 99 patients in the vancomycin group and in 15 (16.3%) of the 92 patients in the combination group (1-sided χ^2 test, $P = .041$). A steady-state vancomycin trough concentration of 15 μg/mL or greater was also associated with an increased risk of the development of nephrotoxicity.

Results of the first prospective study designed to evaluate the incidence of AKI were published recently.[60] The investigators conducted an open-label cohort study at a community academic medical center, which involved adult patients over a 3-month period who received either the combination of piperacillin-tazobactam plus vancomycin or the combination of cefepime or meropenem plus vancomycin for more than 72 hours. AKI was defined using specific criteria introduced by the Kidney Disease: Improving Global Outcomes (KDIGO) AKI Work Group in 2012. Eighty-five patients were enrolled (59 in the piperacillin-tazobactam plus vancomycin group and 26 in the cefepime/meropenem plus vancomycin group). The incidence of AKI was significantly higher in the piperacillin-tazobactam plus vancomycin group (37.3%) (7.7%; $\chi^2 = 7.80$, $P = .005$). There was no difference in the mean steady-state vancomycin trough levels between groups. The study did not reach the projected sample size of 120 patients and the piperacillin-tazobactam group had disproportionately more patients, both of which decrease the power of the study's findings. Development of AKI was based strictly on the KDIGO definition, and follow-up contact was not made to ascertain the clinical significance of the AKI.

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Two additional studies were published in 2016.[61,62] Karino and colleagues[61] performed a combination of retrospective cohort and case-control studies with a primary objective to evaluate the incidence of AKI between intermittent versus extended infusions of piperacillin/tazobactam in combination with vancomycin. Overall, AKI occurred in 105 out of 320 (33%) of the cohort receiving combination therapy. There were similar rates in those receiving intermittent (53 out of 160 [33.1%]) and extended infusions (52 out of 160 [32.5%]) of piperacillin/tazobactam. The investigators identified the following independent risk factors for AKI: having a documented gram-positive infection, the presence of sepsis, receipt of a vancomycin loading dose, and receipt of any concomitant nephrotoxin.

Hammond and colleagues[62] conducted a retrospective cohort study of 122 ICU patients (medical, surgical, and neuroscience) who received at least 48 hours of combination therapy with vancomycin and piperacillin-tazobactam (49 patients) or vancomycin and cefepime (73 patients). The primary outcome was development of AKI as determined by the Acute Kidney Injury Network criteria. Overall, 37 patients (30.3%) developed AKI. The incidence of AKI was similar in the piperacillin-tazobactam group compared with the cefepime group (32.7% vs 28.8%, $P = .647$).

It seems time to acknowledge that there is an association between piperacillin-tazobactam and risk of AKI (with vancomycin). There have been 9 different groups with internal medicine and ICU patients, including a prospective study, showing this adverse effect. In 3 of the retrospective studies, it is difficult to conclude that piperacillin-tazobactam is the primary cause of increased AKI compared with vancomycin alone. If the groups are equally sick, the rationale for using 2 antibiotics rather than 1 is unclear. The prospective study by Peyko and colleagues[60] supports the association, even with vancomycin trough levels the same in each group. Proposed mechanisms for AKI induced by piperacillin-tazobactam include acute interstitial nephritis and toxic effects on the renal tubule. In ICU patients specifically, the results have been conflicting. All 3 ICU studies reported a high rate of AKI with vancomycin plus piperacillin-tazobactam (21.2%–40.5%).[54,55,62] Two of the ICU studies showed a significantly higher rate in the combination group compared with vancomycin alone; the other did not show a difference when piperacillin-tazobactam was replaced with cefepime. A prospective study in ICU patients is needed. The AKI association should be taken into account when developing sepsis order sets and treatment plans.

Dosing Considerations

Critically ill obese patients

Although there is a paucity of data to guide dosing of antimicrobials in critically ill obese patients, some conclusions can be drawn from existing kinetic studies. An increased volume of distribution has been noted in obese patients compared with matched controls.[63] Lean body mass and plasma volume are both increased. Other important pharmacokinetic/pharmacodynamic parameters to consider include the duration the antimicrobial agent binds to the organism and the concentration. Time-dependent antimicrobials, such as penicillins, cephalosporins, carbapenems, aztreonam, macrolides, tetracyclines, vancomycin, and clindamycin, achieve maximum bactericidal effect the longer the drug's concentration is greater than the MIC for a particular bacterial species, which is often quantified as the time greater than the MIC. Concentration-dependent antimicrobials, such as fluoroquinolones and aminoglycosides, achieve maximum bactericidal effect as the serum concentration increases. The peak concentration/MIC is used to evaluate concentration-dependent antimicrobials.

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Assuming normal renal and hepatic function, the available data support using the high end of the dosing range for most antimicrobials in critically ill obese patients.[64,65] For penicillins, cephalosporins, carbapenems, and fluoroquinolones, the authors suggest using the high end of the dosing range. For example, if the plan is to use piperacillin/tazobactam, 3.375 g intravenously every 6 hours, for a complicated intra-abdominal infection, the authors suggest using 4.5 g instead. Guideline recommendations for dosing vancomycin in critically ill obese patients suggest a weight-based initial dose of 25 to 30 mg/kg to a maximum of 2 g.[66,67] A recent study provides some guidance on achieving therapeutic vancomycin trough levels quickly with a divided-dose strategy.[68] Obese-specific, divided-load dosing achieved trough concentrations of 10 to 20 g/mL for 89% of obese patients within 12 hours after initial dosing and 97% of obese patients within 24 hours after initial dosing. Subsequent vancomycin dosing should be adjusted based on renal function, trough levels, and possible area under the curve/MIC ratios. Although the nephrotoxicity associated with vancomycin is less than was previously thought, aminoglycosides can still cause nephrotoxicity and ototoxicity even with therapeutic levels. The 2 most-studied dosing strategies are traditional (lower doses more frequently) and once daily. In obese patients weighing more than 30% greater than their ideal body weight (IBW), an adjusted body weight (ABW) is used for dosing:

$$\text{ABW (kg)} = \text{IBW} + 0.4 \times (\text{actual body weight} - \text{IBW})$$

Levels (including peak, trough, and random) then guide dosing. Renal function (including serum creatinine and urine output) should be monitored along with auditory function.

Pharmacokinetic/pharmacodynamic considerations

Basic pharmacokinetic and pharmacodynamic principles should play a role in the selection and dosing of initial antibiotic therapy. Important distinctions between antibiotic agents include their killing mechanism (concentration vs time) and their character (bacteriostatic vs bactericidal). Time-dependent antibacterial agents (eg, β-lactams) work best when the serum concentration exceeds the organism's MIC for the duration of the dosing interval; therefore, frequency of administration is the most important factor in their dosing. In contrast, concentration-dependent antibacterial drugs (eg, aminoglycosides, fluoroquinolones) work best when the peak serum concentrations are maximized. Therefore, optimizing either the interval for time-dependent antibacterials or the dose for concentration-dependent antibacterials maximizes the likelihood of target attainment. Bactericidal agents cause death by disrupting the bacterial cell and primarily affecting the cell wall or membrane (eg, β-lactams, daptomycin) or the bacterial DNA (eg, fluoroquinolones). Bacteriostatic agents inhibit replication without killing the organism and primarily inhibit protein synthesis. These distinctions are not absolute but, in the case of sepsis, bactericidal agents are preferred.[15,69]

Adequate dosing also depends on the drug's ability to get to the target site of action. Antibiotic concentrations achieved in serum are often not adequate at other sites of infection, such as the cerebrospinal fluid (CSF) or bone. For example, cefazolin, a first-generation cephalosporin, achieves poor CSF concentrations and is not a good agent to use for methicillin-sensitive *S aureus* (MSSA) meningitis, even though it is an excellent agent for MSSA bacteremia.[70] In contrast, tigecycline achieves excellent tissue concentrations but inadequate serum concentrations for use in sepsis.[71] For patients with renal dysfunction, dose reduction to prevent accumulation should be

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considered. For young septic patients who are hypermetabolic, higher doses may be needed to avoid underdosing.

In the ED, the initial antibiotic dose is important because it is often continued once the patient is admitted.[72] Even patients with renal dysfunction can generally be prescribed a 1-time dose similar to that for a patient with normally functioning kidneys. Subsequent doses should be adjusted based on renal and hepatic parameters. The use of order sets in electronic medical records can serve as a method for implementing evidence-based dose ordering in the ED.[73,74] ED order sets should take into account individual institutional practices with regard to preference for 1-time antibiotic doses versus standing orders. Each approach has advantages and disadvantages. One-time orders allow a loading dose and fewer calculations up front, but antibiotics that need frequent dosing (eg, every 6 hours) might be forgotten if a patient has a long boarding time in the ED while waiting for an inpatient bed to become available. Standing orders solve the problem of overlooking subsequent doses. However, laboratory values (eg, serum creatinine level) measured after the first dose is administered may call for a change in the dose or interval. Without prompts in place, patients could receive supratherapeutic drug doses, possibly increasing the risk of organ injury (eg, AKI). Although there is not a clear best practice for this issue, awareness of the problem is a good first step.

SUMMARY

Antibiotics remain a cornerstone therapy for sepsis syndromes in ED patients. Antibiotics should be given early, and the antimicrobial spectrum should be broad enough to cover the most likely pathogens. Blood and tissue cultures should be obtained before administration of an antibiotic if possible in a timely fashion. Debate remains as to the feasibility of giving antibiotics within a 60-minute time frame and the time point at which outcomes worsen with each additional hour of delay. Patient-specific factors, the presumed site of infection, allergies, and local susceptibility patterns determine what antimicrobials should be prescribed empirically. The routine use of double gram-negative coverage is not supported by evidence. Patient weight and renal comorbidities could alter the dose of antibiotics chosen, and these factors should be evaluated carefully in each patient. Overall, the advice expressed by the German microbiologist Paul Ehrlich[75] in 1913 seems to stand the test of time: “Frapper fort et frapper vite” (Hit hard and hit fast).

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