Anti-infective Therapy in Sepsis and Septic Shock

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LEARNING OBJECTIVES

1. Compare and contrast the timing of antimicrobial therapy in patients with sepsis and septic shock.
2. Design an appropriate empiric anti-infective regimen for a patient with sepsis or septic shock for different infection types.
3. Evaluate the effects of sepsis and septic shock on the PK of anti-infective therapy.
4. Apply PK/PD principles to optimize an anti-infective regimen for a patient with sepsis or septic shock.

ABBREVIATIONS IN THIS CHAPTER

ADE	Antimicrobial de-escalation
AKI	Acute kidney injury
APACHE	Acute Physiology and Chronic Health Evaluation
ARC	Augmented renal clearance
ARCTIC	Augmented renal clearance in trauma intensive care (score)
CKD	Chronic kidney disease
ECOFF	Epidemiologic cutoff
fT>MIC	Duration of time that the free drug concentration remains above the MIC during a dosing interval
HAP	Hospital-acquired pneumonia
MDR	Multidrug resistant
MRSA	Methicillin-resistant *Staphylococcus aureus*
PCT	Procalcitonin
PTA	Probability of target attainment
SOFA	Sequential organ failure assessment (score)
SSC	Surviving Sepsis Campaign
TDM	Therapeutic drug monitoring
VAP	Ventilator-associated pneumonia
Vd	Volume of distribution

Table of other common abbreviations.

INTRODUCTION

Sepsis, as defined by the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3), is "life-threatening organ dysfunction caused by a dysregulated host response to infection" (Singer 2016). Septic shock is a subset of sepsis in which a patient experiences derivations in circulatory and cellular parameters. Septic shock manifests as an elevated serum lactate over 2 mmol/L despite adequate fluid resuscitation as well as persistent hypotension, which requires vasopressor administration to sustain a mean arterial pressure of at least 65 mm Hg. Septic shock is associated with a higher mortality rate than sepsis without shock (Paoli 2018; Rhee 2017). Recommendations that guide clinicians in managing both sepsis and septic shock, commonly called the Surviving Sepsis Campaign (SSC) guidelines, are provided and endorsed by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine (Evans 2021).

Sepsis is a major challenge for health care systems, with an incidence of 6%–8% in all hospitalized patients (Paoli 2018; Rhee 2017). Although data vary, it is estimated that 15%–17% of patients die of sepsis (Rhee 2017; Fleischmann 2016). When stratifying by severity, mortality increases as severity increases, with mortality rates ranging from 5.6% in sepsis to 34% in septic shock (Paoli 2018). In all sepsis cases, management relies on prompt identification and initiation of appropriate therapy (Evans 2021).

2021 CLINICAL GUIDELINE UPDATES FOR SEPSIS AND SEPTIC SHOCK

In the 2021 SSC guidelines, several recommendations pertaining to antimicrobial therapy were updated (Evans 2021). Regarding the timing of therapy initiation, previous guidelines recommended administration of antibiotics as soon as possible and within 1 hour

Table 1. Timing of Antimicrobial Administration According to Likelihood of Sepsis and Presence of Shock

	Shock	
Sepsis	**Present (+)**	**Absent (-)**
Definite/ probable	Immediately (ideally within 1 hr) *(Strong recommendation, low-quality evidence)*	Immediately (ideally within 1 hr) *(Strong recommendation, very low-quality evidence)*
Possible	Immediately (ideally within 1 hr) *(Strong recommendation, low-quality evidence)*	Wait; perform rapid assessment for cause of acute illness (infection vs. other cause) *(Best practice statement)* If infection concern continues, administer antimicrobials (ideally within 3 hr) *(Weak recommendation, very low-quality evidence)*

Information from: Evans L, Rhodes A, Alhazzani W, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med 2021;47:1181-247.

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge of the pathophysiology of sepsis and septic shock
- PK parameters that predict antimicrobial efficacy in infectious diseases
- Pharmacology and spectrum of activity of commonly used antimicrobials

Table of common laboratory reference values

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- Surviving Sepsis Campaign (SSC).
- Blot SI, Pea F, Lipman J. The effect of pathophysiology on pharmacokinetics in the critically ill patient – concepts appraised by the example of antimicrobial agents. Adv Drug Deliv Rev 2014;77:3-11.
- Onufrak NJ, Forrest A, Gonzalez D. Pharmacokinetic and pharmacodynamic principles of anti-infective dosing. Clin Ther 2016;38:1930-47.
- Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic shock (Sepsis-3). JAMA 2016; 315:801-10.
- Strich JR, Heil E, Masur H. Considerations for empiric antimicrobial therapy in sepsis and septic shock in an era of antimicrobial resistance. J Infect Dis 2020;222(suppl 2):S119-S131.
- Clinical & Laboratory Standards Institute (CLSI) M100.

in all patients with sepsis with or without shock (Rhodes 2017). In the 2021 update, recommendations are based on the plausibility (i.e., definite, probable, or possible) of sepsis and the presence or absence of shock and their influence on the timing of antimicrobial administration (Table 1). Although the guidelines do not define the plausibility of infection, according to published information, a possible interpretation for infection can be categorized as definite (i.e., microbiologically confirmed), probable (i.e., clinical presentation is compatible with suspected source of infection with isolation of pathogen), or possible (i.e., clinical presentation is similar to presentation of infection at the potential infection site or evidence suggestive of infection) (Klein Klouwenberg 2015; Calandra 2005). Regarding the choice of anti-infective agents, the 2021 SSC update also provides more specific and expanded recommendations for multidrug-resistant (MDR) gram-negative organisms, methicillin-resistant *Staphylococcus aureus* (MRSA), and fungal pathogens (Table 2). For these recommendations, the update outlines risk factors for each suspected infection (see Box 2).

The guidelines for diagnosis, optimization, and duration of antimicrobial therapy remained relatively unchanged from before. However, in the update, the guidelines suggest against using procalcitonin (PCT) to try to determine whether a patient should be initiated on antimicrobials. Once initiated, clinicians should continue to optimize antimicrobial dosing using strategies that rely on pharmacokinetic/pharmacodynamic (PK/PD) principles. Daily assessment of antimicrobial therapy is recommended for potential opportunities to de-escalate depending on pathogen isolation or to discontinue on the basis of an alternative diagnosis. Furthermore, the update suggests that PCT can continue to be used together with clinical evaluation over clinical evaluation alone to help determine therapy duration.

Table 2. Summary of Current and Previous Antimicrobial Recommendations for Patients with Sepsis or Septic Shock

	2021 Recommendation	2016 Recommendation
MDR gram-negative organisms	High[a] risk of MDR organisms: Suggest using two antimicrobials with gram-negative coverage *(Weak recommendation, very low-quality evidence)* Low[b] risk of MDR organisms: Suggest against using two gram-negative agents *(Weak recommendation, very low-quality evidence)*	"We recommend empiric broad-spectrum therapy with one or more antimicrobials for patients presenting with sepsis or septic shock to cover all likely pathogens (including bacterial and potentially fungal or viral coverage" *(Strong recommendation, moderate-quality evidence)*
MRSA	High[a] risk of MRSA: Suggest using empiric antimicrobials with MRSA coverage *(Best practice statement)* Low[b] risk of MRSA: Suggest against using empiric MRSA coverage *(Weak recommendation, low-quality evidence)*	
Fungal infection	High[a] risk of fungal infection: Suggest using empiric antifungal *(Weak recommendation, low-quality evidence)* Low[b] risk of fungal infection: Suggest against using empiric antifungal *(Weak recommendation, low-quality evidence)*	
Viral infection	No recommendation on antiviral use *(No recommendation)*	

[a]High risk – patient has risk factors specific to ≥ 1 of the pathogens (see Box 2).

[b]Low risk – patient has none of the organism-specific risk factors (see Box 2).

MDR = multidrug resistant.

Information from: Evans L, Rhodes A, Alhazzani W, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med 2021;47:1181-247.

Box 1. Examples of Illnesses That May Mimic Sepsis by System

Central Nervous System
Seizure
Stroke
Hemorrhage

Cardiac
Arrhythmias
Heart failure
Myocardial infarction

Pulmonary
Acute respiratory distress syndrome
Asthma exacerbation
Bronchiectasis exacerbation
Chronic obstructive pulmonary disease exacerbation
Pulmonary embolism

Gastrointestinal
Acute liver failure
Bowel obstruction
Inflammatory bowel disease
Pancreatitis

Endocrine
Adrenal insufficiency
Diabetic ketoacidosis

Hematology/Oncology
Antiphospholipid syndrome
Malignancy
Tumor lysis syndrome

Rheumatologic or Autoimmune Disease
Gout
Rheumatoid arthritis
Systemic lupus erythematosus
Vasculitis

Miscellaneous
Allograft rejection (solid organ transplant recipients)
Hypovolemia
Postoperative period
Tissue ischemia

Drugs or Toxins
Drug overdose
Drug or alcohol withdrawal
Hypersensitivity drug reaction
Medication toxicity
Serotonin syndrome

Information from: Rhee C, Chiotos K, Cosgrove SE, et al. Infectious Diseases Society of America position paper: recommended revisions to the national Severe Sepsis and Septic Shock Early Management Bundle (SEP-1) sepsis quality measure. Clin Infect Dis 2021;72:541-52.

EMPIRIC ANTI-INFECTIVE THERAPY

When to Initiate Empiric Therapy in Sepsis

Relationship Between Timing and Clinical Outcomes

Early time to administration of antibiotic agents remains one of the consistent key principles in treating patients with sepsis. Several studies have shown that early antibiotic initiation is associated with decreased mortality (Peltan 2019; Liu 2017; Seymour 2017; Ferrer 2009). The challenge faced by clinicians is determining the specific time target that provides the greatest mortality benefit but also avoids the risk of overprescribing. As mentioned earlier, the SSC guidelines recommend initiation of antibiotics within 1 hour for all patients with definite or probable sepsis with or without shock as well as for patients with possible septic shock (see Table 1). In patients with possible sepsis without shock, antibiotics can be delayed while prompt investigation of the probable causes of acute illness (infectious vs. noninfectious) occurs. In that instance, investigation of etiology should be carried out within 3 hours, and if concern for infection continues, antibiotics should be administered within that time interval (Evans 2021). Further complicating decision-making, the Centers for Medicare & Medicaid Services implemented the Severe Sepsis and Septic Shock Early Management Bundle (SEP-1) in 2015, enacting a quality reporting measure that requires immediate antibiotic administration for both patients with sepsis and patients with septic shock. Although the literature establishes the need for timely administration, the most appropriate time targets remain controversial because of variable results of overall significance as well as between patients with sepsis with and without shock (Liu 2017; Seymour 2017). The strongest evidence of the mortality benefit of early antibiotic administration is in patients with septic shock (Kalil 2017; Ferrer 2009; Kumar 2006). Furthermore, a recent meta-analysis showed that the benefit of early goal-directed therapy in patients with septic shock stemmed from prompt and appropriate antibiotic therapy (Kalil 2017).

Historically, data have been inconsistent for patients without shock and have failed to show a benefit with early antibiotic use (Alam 2018; Bloos 2017). More recently, studies have compared patients with shock and patients without shock and the impact of timing of antibiotics (Liu 2017; Seymour 2017). In these studies, patients with sepsis without shock had no survival benefit from immediate administration of antibiotics, whereas patients with septic shock did. It seems clearer that mortality in patients without shock increases when antibiotics are not administered within 3–5 hours (Peltan 2019; Alam 2018; Bloos 2017; Seymour 2017). In addition, it seems that for patients with diagnosed sepsis without shock, delaying antibiotics for more than 5 hours is associated with progression to septic shock (Whiles 2017). There appears to be a clear linear increase in mortality with each hour in delay of administration starting after admission upon ED arrival, where the odds of mortality increases by 1.16 in the hospital and by 1.10 at 1 year (Peltan 2019).

Because no clear concern for increased mortality in patients with sepsis without shock is shown until after 5 hours of antibiotic delay, this additional time interval provides clinicians an opportunity for further assessment, which may help prevent unnecessary antibiotics (Weinberger 2020; Peltan 2019). In about one-third of patients with presumed sepsis, noninfectious etiologies may be responsible for the presenting septic picture (see Box 1). Thus, it is imperative to complete swift assessment and use of rapid diagnostics to establish whether the etiology of acute illness is the result of an infectious process and to determine the likelihood of sepsis (Strich 2020; Heffner 2010). This period also provides time to treat patients who have an undifferentiated picture that may be from a noninfectious etiology, allowing clinicians to narrow the differential and more confidently rule in or rule out infection (Weinberger 2020). With this narrowing of diagnostic differential, opportunities should be pursued for modifying the empiric regimen, as recommended by the SSC guidelines, by narrowing or discontinuing antimicrobials altogether (Evans 2021).

The requirements of SEP-1 and the recommendation for immediate antimicrobial administration for all patients with suspected sepsis may lead to infection overdiagnosis and subsequent antibiotic overuse (Rhee 2021). Up to 43% of patients admitted to the ICU with a diagnosis who are subsequently treated for presumed sepsis are later found to have very little to no likelihood of infection (Klein Klouwenberg 2015). Up to 20% of patients administered antibiotics in the hospital have one adverse reaction, and up to 20% of those who have an adverse event have been prescribed antibiotics when not indicated (Tamma 2017). The most common adverse reactions from antibiotics include acute kidney injury (AKI), allergic or hypersensitivity reactions, thrombocytopenia, increased antibiotic resistance, and disruption of the gut microbiome, which may lead to *Clostridioides difficile* infection (Evans 2021; Rhee 2021; Bhalodi 2019; Tamma 2017). Weighing the risk of providing prompt yet potentially unnecessary antibiotic use against the risk of withholding antimicrobials is crucial and hence should be considered when patients are experiencing sepsis symptoms without shock.

Considerations when Choosing an Empiric Regimen

Importance of Agent Selection

Ineffective empiric agent selection in sepsis can lead to poor outcomes (Strich 2020; Kollef 2019; Paul 2010). When selecting an initial regimen, the clinician must consider a patient's current clinical status and level of severity, medical and microbiologic history, presence of risk factors for resistant organisms, location of infection acquisition, and local resistance patterns. These factors are important to assess to avoid choosing a regimen that is too narrow, which can lead

to inadequate coverage, as well as to avoid choosing an inappropriately broad regimen, which can lead to adverse effects and antibiotic resistance. Appropriate initial therapy selection in sepsis correlates with decreased mortality, shorter length of stay, and reduced potential for treatment failure (Bassetti 2020).

Clinical Severity

Clinicians should align antimicrobials and the spectrum of coverage with the patient's severity of illness. When determining severity of illness, it is important to remember that presentation of infection and sepsis is not uniform across all patient populations. Thus, determining severity of illness should be based on the plausibility of sepsis, and the appropriate antimicrobials should promptly be initiated if concern for definite/probable sepsis with or without shock is present.

The subset of sepsis with the highest severity of illness (highest mortality) is septic shock. Thus, timely administration and selection are essential. A retrospective analysis of 5715 patients with septic shock studied the appropriateness of empiric regimens, defined as antimicrobials with in vitro activity against the pathogens isolated or the appropriate regimen for the underlying clinical syndrome with no isolated pathogen (Kumar 2009). The appropriate regimen was initiated in 80.1% of patients, 52% of whom survived. For the 19.8% of patients who received inappropriate empiric regimens, survival was 10.3% (OR 9.4; 95% CI, 7.7–11.5; p<0.0001). These findings show that choosing an adequate empiric regimen is imperative to decrease mortality among patients with septic shock. If concern for septic shock exists, the infection site should be determined together with a careful review of the risk factors for resistant organisms when choosing the most appropriate empiric regimen.

Suspected Infection Site

With the heterogeneity that exists in sepsis, the suspected infection site must be determined to anticipate possible pathogens and reliably select proper empiric coverage. The most common infection sites causing sepsis include respiratory, urinary tract, intra-abdominal, and skin and soft tissue, with varying incidence and mortality rates depending on site (Table 3). Cultures should only be obtained from sites considered a source of infection, including blood, rather than cultures obtained from all sites (Evans 2021; Rhodes 2017). Ideally, cultures should be collected immediately (i.e., within 45 minutes) before initiating antimicrobial therapy, but antimicrobial therapy should not be delayed by culture collection. Once possible sources are determined and cultures are obtained, selection of appropriate regimens should rely on clinical practice guidelines according to type and location of infection. If several sources are suspected, it may be reasonable to defer to the infection, necessitating the broadest spectrum of coverage. Hence, antimicrobial therapy may need to be customized from guideline-recommended empiric regimens to consider the likely pathogens for each potential source of infection to ensure the selected agents have adequate tissue penetration to each site.

Table 3. Infection Sites in Patients with Severe Sepsis[a]

Infection Site	Occurrence (%)	Mortality (%)
Respiratory	44.0	32.9
Bacteremia, site unspecified	17.3	41.2
Genitourinary	9.1	16.1
Abdominal	8.6	19.5
Wound/soft tissue	6.6	20.6
Device related	2.2	18.1
CNS	0.8	29.5
Endocarditis	0.6	33.1
Other/unspecified	10.8	15.4

[a]Data are based on epidemiology of severe sepsis definitions.

Information from: Angus DC, Linde-Zwirble WT, Lidicker J, et al. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med 2001;29:1303-10.

Risk Factors for Drug Resistance

In addition to evaluating patients for potential source and infection site, clinicians should evaluate patients for risk factors for resistant organisms. Several general factors can influence a patient's risk of developing an infection caused by a resistant organism, including a recent prolonged hospital or facility stay, prior antibiotic exposure in the past 3 months, colonization with resistant organisms, comorbidities (e.g., diabetes, renal failure), immunosuppression (e.g., neutropenia, HIV), and the presence of indwelling devices (e.g., central venous catheter, urinary catheter, chronic hemodialysis catheter) (Strich 2020; Kollef 2019). The updated SSC guidelines also provide risk factors specific to each type of resistant organism (Box 2). In addition, determining the patient's likely location at the time of contraction, whether in the community, long-term care, or hospital, can help a clinician understand the likelihood of the presence of resistant organisms. Community-onset infections are much less likely caused by resistant organisms; thus, broad-spectrum antimicrobial regimens should be avoided unless risk factors are present (Rhee 2020). To design an appropriate empiric regimen, clinicians should carefully review the possibility of resistant organisms, including severity of illness, risk factors, location, and local prevalence (both in-hospital and community).

Box 2. Examples of Risk Factors for MRSA and MDR Organisms; Fungal and Viral Infections

Risk Factors for MRSA Organisms

- Hemodialysis
- History of recurrent skin infections or chronic wounds
- History of MRSA infection or colonization[a]
- Presence of invasive devices
- Recent hospital admissions
- Recent IV antibiotics
- Severity of illness (septic shock)

Risk Factors for MDR Gram-negative Organisms

- Broad-spectrum antibiotic use within the preceding 90 days
- Hospital-acquired/health care–associated infection
- Hospitalization abroad within the preceding 90 days
- Local prevalence of antibiotic-resistant organisms
- Proven infection or colonization with antibiotic-resistant organisms within the preceding year
- Travel to a highly endemic country within the preceding 90 days (see https://resistancemap.cddep.org/)

Risk Factors for *Candida* Sepsis

- Acute kidney injury and hemodialysis
- Broad-spectrum antibiotics > 72 hr
- *Candida* colonization at several sites
- Central venous catheters and other intravascular devices
- Emergency GI or hepatobiliary surgery
- GI tract perforations and anastomotic leaks
- Immunosuppression
- Longer ICU length of stay
- Neutropenia
- Individuals who inject drugs
- Prior surgery
- Severe thermal injury
- Severity of illness (high APACHE score)
- Surrogate markers such as serum β-D-glucan assay
- Total parenteral nutrition

Risk Factors for Endemic Fungal Infections (*Cryptococcus*, *Histoplasma*, Blastomyces, Coccidioidomycosis)

- Certain biologic response modifiers (e.g., monoclonal antibody)
- Diabetes
- Hematopoietic stem cell transplantation
- High-dose corticosteroid therapy
- HIV infection
- Presence of fungal antigen markers such as histoplasma assays
- Solid organ transplantation

Risk Factors for Invasive Mold Infections

- Certain biologic response modifiers (e.g., monoclonal antibody)
- Presence of mold antigen markers such as serum or bronchoalveolar lavage galactomannan assay
- Hematopoietic stem cell transplantation
- High-dose corticosteroid therapy
- Neutropenia
- Solid organ transplantation

Risk Factors for Viral Infections

- Hematologic malignancies
- Hematopoietic stem cell transplantation
- HIV infection
- Neutropenia
- Solid organ transplantation

[a]Study findings vary with respect to persistence of colonization. Clinical judgment may be needed to determine whether anti-MRSA treatment is warranted.

APACHE = Acute Physiology and Chronic Health Evaluation; IV = intravenous(ly); MDR = multidrug-resistant; MSRA = methicillin-resistant *Staphylococcus aureus*.

Information from: Evans L, Rhodes A, Alhazzani W, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med 2021;47:1181-247; Shenoy ES, Paras ML, Noubary F, et al. Natural history of colonization with methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE): a systematic review. BMC Infect Dis 2014;14:177.

Considerations for MDR Gram-negative Infections

Gram-negative organisms are a commonly encountered challenge in patients with sepsis. The increased rates of gram-negative resistance as well as the ability of these bacteria to acquire a wide range of resistance mechanisms have led to investigation of combination therapy for treating these infections. Because several studies have shown that early administration of adequate intravenous antibiotics is one of the key interventions that improves survival in sepsis and septic shock, use of empiric combination therapy for gram-negative bacilli (especially *Pseudomonas aeruginosa*) was studied as a way to increase the chances that the selected antibiotic regimen would be adequate while awaiting culture results and susceptibilities. The most commonly studied regimens are a combination of an antipseudomonal β-lactam with either an aminoglycoside or a fluoroquinolone because they have a similar spectrum of activity but different mechanisms of action. Many studies comparing combination therapy with monotherapy have provided somewhat inconsistent results, given that most evidence has been observational and hampered by heterogeneity as well as selection and immortal time bias as the result of different dosing regimens, therapy durations, and single-center trial designs. However, when taken together, most systematic reviews and meta-analyses found little to no difference in key outcomes such as mortality, cure rates, and hospital length of stay (Evans 2021; Strich 2020; Tabah 2020; Sjövall 2017; Vardakas 2013). Hence, it seems that as long as the empiric antibiotic has adequate coverage according to local epidemiologic data, a second antibiotic is unlikely to provide additional benefit.

One exception to this may be the risk of MDR gram-negative pathogens where combination therapy increases the likelihood of adequate initial therapy (Evans 2021; Heyland

2008). In this respect, there are two important considerations. First, the patient's risk of MDR pathogens should be assessed (see Box 2). Second, the local and/or institutional prevalence of antibiotic-resistant microorganisms should be considered (Evans 2021; Kalil 2016). This approach is supported by the SSC guidelines (Evans 2021). Furthermore, the clinical practice guidelines for managing hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) suggest double-coverage of gram-negative bacilli for patients with risk factors for MDR pathogens as well as for those receiving care in units where more than 10% of VAPs are resistant to the antibiotic being considered for monotherapy (Kalil 2016).

Of importance, combination antibiotic therapy may also carry an increased risk of adverse effects. A prospective cohort study of patients with sepsis or septic shock found that even a short course of adjunctive gentamicin (median duration 2 days, interquartile range 1–3 days) increased the risk of AKI (OR 1.39; 95% CI, 1.00–1.94) (Ong 2017). Box 3 summarizes points to consider for empiric combination therapy.

Considerations for MRSA Coverage

When determining whether MRSA is a possible pathogen, considerations may include geographic location, location of acquisition (e.g., community vs. hospital), and infection site. In a 24-hour point prevalence study worldwide across 1150 ICUs and 88 countries, MRSA accounted for 5% of all infections among all critically ill patients, with the highest rates documented in the North American region at 10% (Vincent 2020). With respect to acquisition, in a study of 17,430 patients with culture-positive community-onset sepsis in the United States, MRSA accounted for 11.7% of cases (Rhee 2020). Of the documented MRSA infections in critically ill patients around the world, most (55%) were located in the respiratory tract, followed by the blood (21%) and skin (8%) (Vincent 2020).

Because MRSA is usually isolated from the respiratory tract, clinicians should determine respiratory MRSA colonization status by the rapid MRSA PCR assay. The MRSA PCR has shown a negative predictive value (NPV) of over 95%, which can effectively rule out MRSA pneumonia (Parente 2018; Smith 2017; Johnson 2015). A recent study reviewing the impact of time between the assay and the collection of a respiratory sample showed that the NPV of the assay remained consistently high for up to 2 weeks after collection, with no significant difference when looking at a patient's location of isolation (ICU vs. floor) (Turner 2021). A high NPV of MRSA nares was also found for other non-respiratory infections such as skin soft tissue infections, intra-abdominal infections, and bacteremia (Mergenhagen 2020). Consequently, the MRSA PCR can be used by clinicians to rule out MRSA infection and avoid unnecessary antibiotics. In contrast, the positive predictive value of MRSA nares screen is 35%–55% and should not be used to diagnose MRSA infections (Parente 2018). If a MRSA nares screen is unavailable or another source of infection is suspected, a careful review of MRSA risk factors is warranted (see Box 2) (Evans 2021).

The choice of intravenous anti-MRSA agents generally relies on the suspected infection site and local antibiogram data. Intravenous vancomycin is usually prescribed as an empiric agent of choice. Recently, the consensus guidelines for vancomycin were revised to provide recommendations on dosing in serious MRSA infections (Rybak 2020). Therefore, they endorsed a change with vancomycin therapeutic drug monitoring (TDM) for dose optimization to use the PK/PD target of the AUC over 24 hours ($AUC_{0\text{-}24hr}$)/MIC ratio within a range of 400–600. If a patient cannot receive vancomycin, linezolid, daptomycin, or ceftaroline may be reasonable alternatives, though their use will depend on formulary restrictions and suspected infection site.

If a patient needs an anti-MRSA antibiotic, the next decision is the timing of administration in relation to other concurrent empiric antimicrobials. Depending on intravenous access and compatibility, it may be challenging to determine which antimicrobial agent should be administered first. In a recent observational study of patients with suspected bloodstream infections, those who received a β-lactam before vancomycin had a lower 7-day mortality (OR 0.45; 95% CI, 0.24–0.83). As a result, it is strongly recommended to administer a broad-spectrum β-lactam (or alternatively a fluoroquinolone) with gram-negative activity first (Amoah 2021). Additional considerations pertaining to the timing of antimicrobials should include the likelihood of microorganisms at the suspected infection site, infusion time of antimicrobials, PK/PD parameters (i.e., time- vs. concentration-dependent), ease of accessibility (e.g., sent from pharmacy vs. available in an automated dispensing cabinet), and readiness for

Box 3. Considerations for Empiric Combination Therapy for Gram-negative Microorganisms

- Assess patient's risk of MDR pathogens
- Review local and/or institutional prevalence of MDR pathogens
- Review local antibiogram data to determine which second agent would be most appropriate to add
- Assess risk of adverse effects with combination therapy

MDR = multidrug resistant.

Information from: Evans L, Rhodes A, Alhazzani W, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med 2021;47:1181-247; 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; Ong DSY, Frencken JF, Klouwenberg PMC, et al. 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.

administration (e.g., compounded, needs reconstitution, or premixed solution).

Considerations for Fungal Infections

Sepsis caused by fungal infections is rare but carries significant morbidity and mortality. However, data remain uncertain on when to add an antifungal as an empiric agent and whether there is a clear mortality benefit. In a trial of febrile ICU patients at high risk of invasive candidiasis, no benefit was seen with adding empiric fluconazole over placebo (Schuster 2008). Furthermore, adding micafungin in patients without neutropenia with ICU-acquired sepsis provided no mortality benefit compared with no antifungal therapy (Timsit 2016). The SSC guidelines suggest only those at high risk of fungal infections should receive empiric antifungal therapy; therefore, a review of risk factors for fungal infection (i.e., *Candida*, endemic fungi, invasive mold) is essential (see Box 2) (Evans 2021). However, many of the risk factors outlined by the SSC guidelines as well as the candidiasis guidelines are broad and undifferentiated, leading to difficulty in determining who is at highest risk (Evans 2021; Pappas 2016). In a recent meta-analysis examining the likely risk factors for invasive *Candida* infections (ICIs), the authors not only confirmed some of the well-known risk factors for ICIs (e.g., *Candida* colonization, broad-spectrum antibiotics, total parenteral nutrition, and abdominal surgery), but also identified other risk factors to consider, including receipt of blood transfusions, medical interventions such as mechanical ventilation, renal replacement therapy, and diabetes (Thomas-Rüddel 2022). The authors also stated that many of the risk factors for ICIs are related and highly dependent on one another. To determine the degree of risk of developing sepsis because of a fungal infection, clinicians must consider the suspected infection site and the likelihood of a fungal pathogen, together with the number and type of risk factors present. In addition, local fungal epidemiology (i.e., possible endemic fungi) and the prevalence of antifungal resistance, such as with certain *Candida* spp., should be considered when deciding on an empiric antifungal regimen (Thomas-Rüddel 2022; Evans 2021; Pappas 2016).

Role of Antiviral Therapy

The 2021 SSC guidelines have no recommendation on the use of antiviral agents because the primary cause of sepsis is rarely viral infections. Particularly at risk of severe disease because of viral infections are patients who are immunocompromised (see Box 2). Historically, influenza was a common cause of sepsis from a viral source; however, with the spread of the SARS-CoV-2 infection in 2020 and the subsequent pandemic, cases of sepsis caused by viral infections have increased.

Because of a lack of data showing positive effects of antivirals as well as the rapidly and ever-changing information on SARS-CoV-2, the SSC panel chose not to provide a recommendation. Concern for viral pathogens (e.g., herpes simplex virus, Epstein-Barr virus, cytomegalovirus, respiratory viruses, influenza, SARS-CoV-2) in those at risk should be determined on the basis of patient history. If viral treatment is indicated, clinicians should see the specific clinical practice guidelines that address management.

Local Prevalence and Resistance Patterns

Finally, it is critical to consider local antibiogram data to determine which agents are most appropriate for monotherapy coverage or to enhance antibiotic coverage in combination therapy. The concept of using local antibiogram data for enhancing combination therapy was shown in a retrospective study of HAP pathogens. The investigators found that among gram-negative microorganisms resistant to piperacillin/tazobactam or cefepime, ciprofloxacin was active against less than 10% of isolates, whereas amikacin was active against more than 80% (Beardsley 2006). Clinicians can also use antibiogram data to develop institutional guidelines and make formulary decisions for optimal antimicrobial use.

DEFINITIVE ANTI-INFECTIVE THERAPY

Once the susceptibilities of the causative microorganisms are available, antimicrobial therapy can be de-escalated accordingly. The outcomes associated with antimicrobial de-escalation (ADE) in critically ill patients are somewhat inconsistent because studies used differing definitions of ADE and were largely observational. Most studies found no difference in ICU or hospital length of stay (Tabah 2020). One multicenter randomized controlled trial of 117 patients with severe sepsis found no difference in 28-day mortality between groups who received ADE and those who continued on an empiric regimen (31% vs. 23%, respectively; p=0.55) (Leone 2014). A recent review of 20 observational studies found that ADE was associated with lower mortality (RR 0.71; 95% CI, 0.63–0.80); however, this finding should be interpreted with caution because of the observational study design and large heterogeneity (Lakbar 2020). Factors associated with failure to de-escalate antimicrobials (i.e., continuing broad-spectrum therapy) include presence of MDR microorganisms, polymicrobial infections, infections with high risk of undiagnosed pathogens (e.g., intra-abdominal infections), hematologic malignancy, fungal sepsis, and higher organ dysfunction scores (Salahuddin 2016; Tabah 2016). These findings indicate that, in general, clinicians are more likely to de-escalate antimicrobial therapy in patients who have lower severity of illness and are clinically improving (Evans 2021; Tabah 2020).

Despite the lack of high-quality data, the general consensus is that ADE is safe in critically ill patients. The SSC guidelines suggest daily assessment for de-escalation of antimicrobials (weak recommendation with very low-quality evidence) (Evans 2021). A recently published European

position statement also favors ADE but highlights the need to separately assess therapy duration because of concerns that ADE may increase the therapy duration. Data from cohort studies have been inconsistent, with some reporting similar durations and others noting a decrease or increase in duration (Tabah 2020). The only randomized controlled trial showed an increased duration of therapy with an ADE strategy compared with continuation of empiric therapy (14.1 ± 13.4 days vs. 9.9 ± 6.6 days, p=0.04, respectively) (Leone 2014). Similarly, in the mortality outcome studies mentioned earlier, evidence is difficult to interpret because of heterogeneity and observational study design. It is possible that ADE increases the chance of errors when clinicians count treatment-days, especially when ADE leads to a change in antimicrobial therapy. Hence, it appears reasonable to pay special attention to therapy duration after ADE as part of a comprehensive antimicrobial stewardship effort (Tabah 2020).

Combination therapy has been investigated for definitive treatment of gram-negative bacilli because of early findings that it had synergistic effects and reduced the emergence of antibiotic resistance. However, these findings were based on in vitro and animal studies and have not been confirmed in clinical trials (Giamarellou 1986; Pechere 1986). Similar to empiric treatment, most studies showed no difference in patient outcomes such as mortality, treatment failure, length of stay, or acquisition of resistance between combination therapy and monotherapy (Babich 2021; Evans 2021; Vardakas 2013; Bliziotis 2011). The SSC guidelines suggest against gram-negative double-coverage for definitive treatment once susceptibilities are known (weak recommendation with very weak quality of evidence), but the authors acknowledge that combination therapy may be warranted in the presence of MDR pathogens (Evans 2021). Indeed, treatment of MDR gram-negative bacilli requires a multifaceted approach because they are associated with high morbidity and mortality. The European Society of Clinical Microbiology and Infectious Diseases and the Infectious Diseases Society of America recently published guidelines for the treatment of infections caused by MDR gram-negative bacilli, including extended-spectrum β-lactamase–producing Enterobacterales, AmpC β-lactamase–producing Enterobacterales, and carbapenemase-producing gram-negative bacilli (Enterobacterales, *P. aeruginosa*, *Acinetobacter baumannii*) (Paul 2022; Tamma 2022, 2021).

Of interest, the 2016 HAP/VAP clinical practice guidelines recommend combination therapy for definitive treatment of *P. aeruginosa* in patients with septic shock or at high risk of death (weak recommendation, very low-quality evidence). This recommendation appears to be based on a meta-analysis, which found that the benefits of combination therapy largely depend on the mortality risk of patients. Although the pooled OR indicated no overall mortality difference with combination therapy (OR 0.86; 95% CI, 0.71–1.03; p=0.094), there was a mortality benefit in patients who had a greater than 25% mortality risk (high risk) (OR 0.51; 95% CI, 0.41–0.64; p=0.002) and those with septic shock (OR 0.49; 95% CI, 0.35–0.70; p<0.0001). However, patients with a mortality risk of 15% or less (low risk, absence of septic shock) had a higher risk of death with combination therapy (OR 1.53; 95% CI, 1.16–2.03; p=0.003) (Kumar 2010). These findings suggest that the impact of combination therapy varies depending on the severity of illness and in turn can have either beneficial or harmful effects on survival.

THERAPY DURATION

The optimal duration of antimicrobial therapy in sepsis and septic shock is often difficult to determine because it depends on several factors, including the patient, the microorganism, and the infection site. Over the past 10 years, there have been considerable efforts to investigate shorter durations of therapy for common infections such as pneumonia, UTIs, and intra-abdominal infections. Most studies have found that shorter durations are just as effective and are associated with fewer adverse effects. These findings have led to guideline updates for several common infections. A meta-analysis by the authors of the 2016 HAP/VAP clinical practice guidelines found no difference in mortality, clinical cure, or recurrence between a 7- to 8-day and a 10- to 15-day antimicrobial course for the treatment of VAP, leading to a recommended duration of 7 days (Kalil 2016). The clinical practice guidelines on the diagnosis and treatment of adults with community-acquired pneumonia recommend no less than 5 days of antibiotic therapy as long as clinical stability has been achieved (e.g., normal vital signs, mentation, ability to eat) (Metlay 2019). These recommendations are also based on several studies that found that longer durations (7 days or more) are not more effective but may increase the risk of adverse effects (Tansarli 2018; Dimopoulos 2008). The STOP-IT trial, which compared outcomes in patients who received antibiotics for either 4 days or 8 days after source control, found no difference in mortality, surgical site infections, or recurrent intra-abdominal infections (Sawyer 2015). Subsequently, this finding also led to an update in guideline recommendations by the Surgical Infection Society (Mazuski 2017).

Similar to these clinical practice guidelines, shorter courses of antimicrobials are also recommended over longer courses by the SSC guidelines, but because most of the studies were not conducted in critically ill patients, this recommendation is rated as weak with very low-quality evidence (Evans 2021). One important caveat is that almost all studies investigating shorter therapy durations excluded patients with an uncontrolled source of infection. Source control interventions such as abscess drainage, necrotic tissue debridement, and removal of infected implants and catheters are key interventions in the management of sepsis and septic shock. These interventions should be implemented as soon as possible after initial resuscitation and are associated with improved

survival (Evans 2021; Busch 2020). As a result, shorter durations should only be applied to patients who have achieved adequate source control. If adequate source control cannot be achieved, therapy duration is typically extended and may need to be individualized. See the interactive case "Is Shorter Better – Duration of Therapy in Critically Ill Patients" for further information on this subject.

When the therapy duration is unclear, PCT concentrations can be used in addition to clinical evaluation to help decide when discontinuation may be appropriate (Evans 2021). Procalcitonin is a prohormone converted into calcitonin by the thyroid cells that is typically present in low serum concentrations (less than 0.02 ng/mL) in healthy individuals. During an acute bacterial infection and sepsis, PCT is produced by other tissues without the ability to be converted into calcitonin, and as a result, its serum concentrations increase. Compared with other traditional inflammatory markers (e.g., CRP, lactate), one significant advantage of PCT is its ability to discriminate bacterial infections from viral infections and autoimmune-mediated inflammation (Maruna 2000). Of interest, fungal infections may increase PCT concentrations as well, but these are still significantly lower than the concentrations observed with bacterial infections (PCT range 0.69–1.23 vs. 4.18–12.9, respectively) at the onset of fever (Dou 2013). Use of PCT has been studied extensively in critically ill patients and is associated with a decreased duration of antibiotics with a range of 1.7–3.8 days (Covington 2018). A meta-analysis showed lower mortality in patients who underwent PCT monitoring than in those who did not (RR 0.89; 95% CI, 0.80–9.99) and no effect on hospital or ICU stay (Evans 2021).

Many PCT algorithms (largely for lower respiratory infections) exist to help clinicians determine whether a bacterial infection is likely and thus whether empiric antibiotics should be continued. In culture-negative patients with sepsis, a PCT concentration less than 0.5 ng/mL or an 80% decrease from peak concentration may warrant antibiotic discontinuation (Schuetz 2019; Covington 2018). In general, it is recommended that PCT concentrations be obtained every 24–48 hours to allow PCT trending. Finally, patients with congestive heart failure and chronic kidney disease (CKD) have higher PCT concentrations. As a result, PCT monitoring may be less accurate and/or may require higher thresholds if these comorbidities are present (Covington 2018).

PK CONSIDERATIONS IN SEPSIS AND SEPTIC SHOCK

The basic elements of PK (i.e., absorption, distribution, metabolism, and elimination) are significantly altered by the presence of critical illness. These changes can further affect the PK of antimicrobials to varying extents and are described in greater detail in the text that follows. The SSC guidelines have a best practice statement that recommends optimized antimicrobial dosing on the basis of PK/PD principles and

Patient Care Scenario

S.Q., a 59-year-old man, is brought to the ED after a motor vehicle crash. The patient's respiratory status worsens in the ED, and he is placed on a ventilator and admitted to the ICU for treatment. S.Q. has no contributory medical history. On ICU day 8, he begins to have increased sputum production, and his vital signs are temperature 102.2°F, blood pressure 95/55 mm Hg, heart rate 112 beats/minute, and respiratory rate 17 breaths/minute. S.Q.'s laboratory test results show the following: K 3.7 mmol/L, SCr 2.1 mg/dL (baseline SCr 0.9 mg/dL), BUN 33 mg/dL, WBC 18 × 10^3 cells/mm^3, Plt 62,000 cells/mm^3, and lactate 4.1 mmol/L. Because of the patient's worsening status, he is initiated on vasopressors to maintain a mean arterial pressure (MAP) greater than 65 mm Hg. Which one of the following is best to recommend as S.Q.'s empiric therapy?

A. Meropenem
B. Linezolid
C. Linezolid and cefepime
D. Vancomycin and cefepime

ANSWER

Based on the patient's current condition, including severity of illness (i.e., septic shock), location of acquisition (i.e., hospital-acquired), and being on a ventilator, S.Q. meets the criteria for risk of drug resistance with MRSA and multidrug-resistant (MDR) gram-negative organisms, and thus should receive broad-spectrum antibiotics (Answer D is correct). According to the SSC guidelines, his MRSA risk factors include presence of invasive devices (i.e., ventilatory support) and severity of illness. His risk factors for MDR gram-negative organisms is a hospital-acquired infection with VAP occurring 7 days after admission. Meropenem does not cover MRSA (Answer A is incorrect). Linezolid does not cover MDR gram-negative organisms and would not be ideal because of the patient's low platelets (Answer B and Answer C are incorrect).

1. Evans L, Rhodes A, Alhazzani W, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med 2021;47:1181-247.
2. 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.

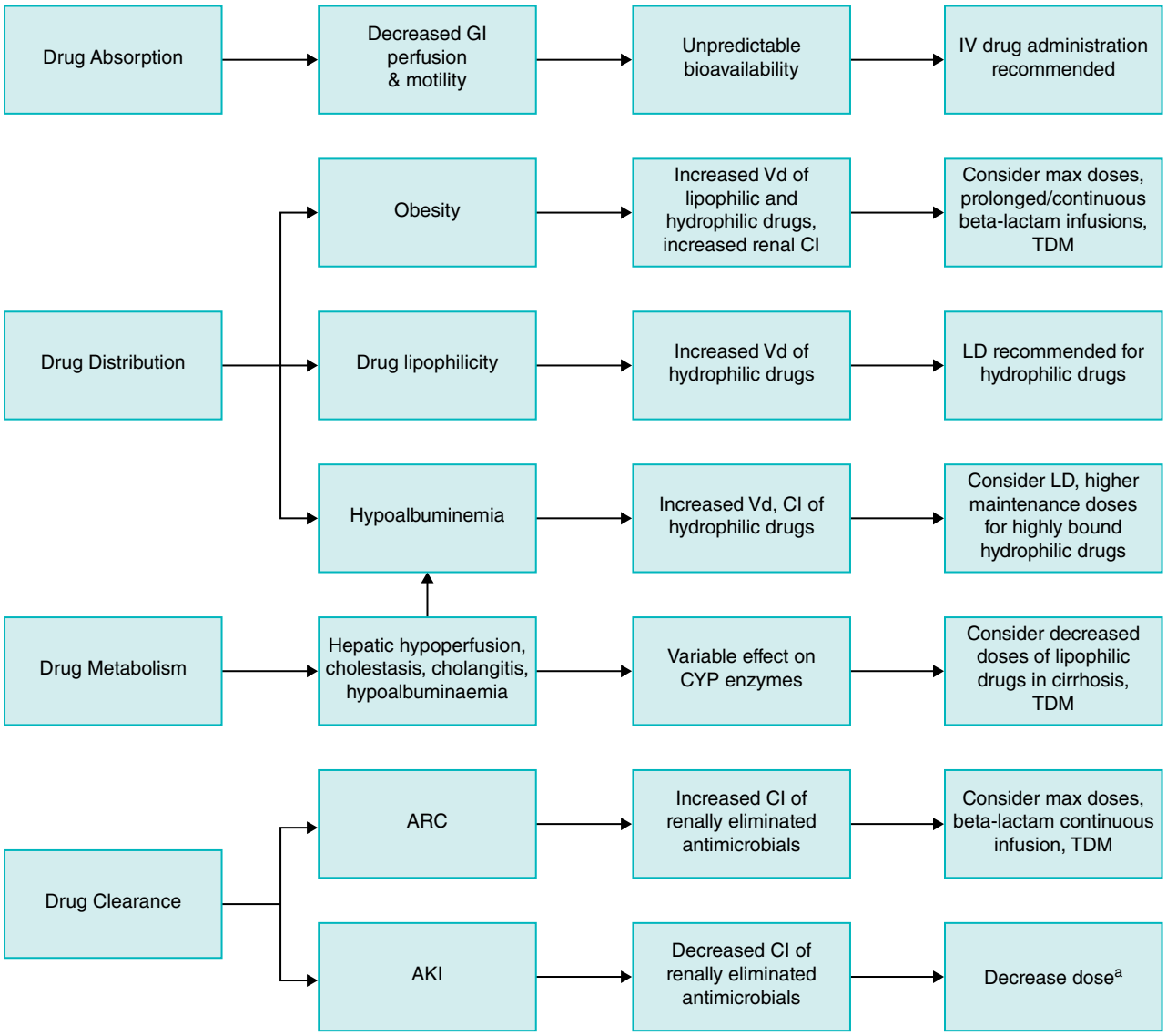

Figure 1. Pharmacokinetic alterations of antimicrobials in sepsis.

[a]Consider waiting 48 hr before decreasing dose.

AKI = acute kidney injury; ARC = augmented renal clearance; Cl = clearance; IV = intravenous(ly); LD = loading dose; TDM = therapeutic drug monitoring; Vd = volume of distribution.

specific drug properties with sepsis or septic shock (Evans 2021). Figure 1 summarizes the PK alterations in critical illness.

Alterations in Drug Absorption

In septic shock, blood flow to the GI tract may be reduced while it is preferentially shunted to vital organs such as the brain and heart. This effect may be compounded by the use of vasopressor agents, which decrease splanchnic blood flow and gut perfusion. Other factors such as concurrent GI conditions (i.e., intestinal ileus, mucosal edema, motility dysfunction), drugs (i.e., opioids), and nutritional support (i.e., continuous feeding regimens) can further affect gastric emptying time and gut peristalsis and adversely affect antimicrobial absorption (Phe 2020; Charlton 2019; Blot 2014). Because antimicrobial availability in critical illness is generally considered unreliable, intravenous administration is preferred, especially during the acute phase of illness.

Alterations in Drug Distribution

Hydrophilic vs. Lipophilic Antimicrobials

Antimicrobials can be classified as either hydrophilic or lipophilic depending on their physiochemical properties. In general, hydrophilic drugs distribute mainly in the systemic circulation (extracellularly), have a smaller volume of distribution (Vd), and lower protein binding and are predominantly renally cleared. However, lipophilic drugs have greater cellular tissue uptake, a larger Vd, and higher protein binding and are predominantly hepatically cleared (Shah 2015; Ulldemolins 2011).

Hydrophilic drugs are more susceptible to PK alterations than lipophilic drugs in patients with sepsis. Vascular endothelial damage and capillary leakage during sepsis result in fluid shifts from the intravascular to the interstitial space. The consequent intravascular hypovolemia and hypotension typically require administration of resuscitation fluids, which further increase interstitial space. These processes significantly increase the Vd for hydrophilic drugs and may in turn delay achieving therapeutic concentrations of antimicrobials. Other processes that can further increase the Vd of hydrophilic drugs include mechanical ventilation, extracorporeal circuits (e.g., renal replacement therapy, extracorporeal membrane oxygenation, plasma exchange), postsurgical drains, and hypoalbuminemia (further described in the text that follows) (Fujii 2020; Phe 2020; Shah 2015; Roberts 2006).

Clinically important hydrophilic antimicrobials include β-lactams, glycopeptides, and aminoglycosides (Table 4). For example, a study of 42 critically ill patients with confirmed gram-negative sepsis found a significantly higher mean Vd of amikacin in these patients than in healthy volunteers (0.41 L/kg vs. 0.25 L/kg, respectively). Furthermore, the study found that the Vd correlated with the severity of disease as determined by the Acute Physiology and Chronic Health Evaluation (APACHE) II score (r=0.7, p=0.001) (Marik 1993).

To account for an increased Vd and avoid underdosing, loading doses for hydrophilic drugs have been suggested during the acute phase of sepsis treatment. Loading doses are not adjusted for renal dysfunction regardless of the patient's CrCl. However, the Vd of lipophilic drugs is not significantly altered by sepsis pathophysiology, and loading doses are generally not needed (Fujii 2020; Shah 2015; Ulldemolins 2011; Roberts 2006).

Effect of Hypoalbuminemia

Albumin is the most prevalent plasma protein and is the main protein responsible for drug-protein binding. Changes in albumin serum concentrations can significantly alter the PK of highly albumin-bound antimicrobials. Hypoalbuminemia, broadly defined as serum albumin concentrations less than 2.5 g/dL, is common in critically ill patients, with an estimated incidence of 40%–50%. Physiologic processes leading to hypoalbuminemia include capillary leakage of albumin from intravascular to extravascular space and decreased hepatic synthesis of albumin. Other risk factors for hypoalbuminemia include the presence of malignancy, advanced age, burns, nephrotic syndrome, and malnutrition (Fujii 2020; Ulldemolins 2011).

Several mechanisms have been described for how hypoalbuminemia can alter the PK of highly bound antimicrobials. Larger concentrations of unbound drug in serum are available to distribute into tissues and extravascular space, which

Table 4. PK Properties of Commonly Used Antimicrobials in Sepsis

Antibiotic	Hydrophilic vs. Lipophilic	Protein Binding[a]
Amikacin	Hydrophilic	Low
Amphotericin B	Lipophilic	High
Azithromycin	Lipophilic	Moderate
Aztreonam	Hydrophilic	Moderate
Caspofungin	Hydrophilic	High
Cefazolin	Hydrophilic	High
Cefepime	Hydrophilic	Low
Ceftazidime	Hydrophilic	Low
Ceftriaxone	Hydrophilic	High
Ciprofloxacin	Lipophilic	Moderate
Clindamycin	Lipophilic	High
Daptomycin	Hydrophilic	High
Doxycycline	Lipophilic	High
Ertapenem	Hydrophilic	High
Fluconazole	Hydrophilic	Low
Gentamicin	Hydrophilic	Low
Levofloxacin	Lipophilic	Moderate
Linezolid	Lipophilic	Moderate
Meropenem	Hydrophilic	Low
Metronidazole	Lipophilic	Low
Micafungin	Hydrophilic	High
Nafcillin	Hydrophilic	High
Piperacillin/ tazobactam	Hydrophilic	Moderate
Tobramycin	Hydrophilic	Low
Vancomycin	Hydrophilic	Moderate

[a]Protein binding defined as high (> 70%), moderate (30%–70%), or low (< 30%).

Information from: Ulldemolins M, Roberts JA, Rello J, et al. The effects of hypoalbuminaemia on optimizing antibacterial dosing in critically ill patients. Clin Pharmacokinet 2011; 50:99-110.

increases the Vd. This effect is compounded in critically ill patients receiving hydrophilic drugs who often already have a larger-than-normal Vd because of sepsis pathophysiology and treatment as described earlier. As a result, increased Vd can lead to subtherapeutic serum concentrations during the drug distribution phase (Ulldemolins 2011).

Hypoalbuminemia can also increase total hepatic and/or renal clearance because only unbound drug can undergo hepatic and renal elimination. This may be of particular relevance for critically ill patients with augmented renal clearance (ARC) (further described in the Augmented Renal Clearance section). In this scenario, a combination of higher glomerular filtration rate (GFR) and higher unbound drug concentrations can lead to increased clearance and decreased serum concentrations during the drug elimination phase (Fujii 2020).

Antimicrobials are typically organized into highly protein bound (greater than 70%), moderately protein bound (30%–70%), and minimally protein bound (less than 30%) (see Table 4). Specific dosing recommendations accounting for hypoalbuminemia are scarce. Investigators have suggested administration of loading doses and higher-than-standard maintenance doses for certain highly bound hydrophilic antimicrobials in critically ill patients (Ulldemolins 2011). For example, authors recommend more frequent dosing of ceftriaxone (1 g intravenously every 8 hours vs. standard frequency of every 24 hours) when higher drug exposure is needed because solely using higher doses can saturate the protein binding sites and result in higher unbound concentration and higher Vd and clearance (Ulldemolins 2011; Joynt 2001). Of note, the authors' dose adjustments for hypoalbuminemia only apply to critically ill individuals with normal renal and hepatic function.

Obesity

Obesity is usually defined as a BMI of 30 kg/m^2 or higher and is associated with an increase in both adipose tissue and lean body mass. The Vd of lipophilic antimicrobials increases in the presence of greater amounts of adipose tissue, whereas the Vd of hydrophilic antimicrobials increases with greater lean mass. Furthermore, increased kidney size and renal blood flow may increase renal clearance (Alobaid 2016; Hanley 2010). The effect of obesity on hepatic drug metabolism is not well studied. Obesity is a risk factor for hepatic steatosis, which can decrease hepatic blood flow (Ijaz 2003). However, the clinical significance of these changes on drug metabolism is unclear.

Several reviews on drug dosing strategies in individuals with obesity have been published (Meng 2017; Alobaid 2016). Obesity-based dosing adjustments for certain antimicrobials are generally widely adopted in clinical practice, such as the use of adjusted body weight in patients with obesity receiving aminoglycosides. The new 2020 consensus guidelines on therapeutic monitoring of vancomycin for serious MRSA infections recommend using actual body weight for vancomycin loading dose calculation with a maximum dose of 3000 mg and using AUC-guided dosing and monitoring for maintenance dosing (Rybak 2020). Nevertheless, it is important to recognize that obesity does not automatically translate to higher dosing. Particularly in critically ill patients, PK alterations are often multifactorial and not solely affected by obesity. Furthermore, patients with obesity are at higher risk of developing dose-dependent drug toxicities such as nephrotoxicity associated with vancomycin and colistin and musculoskeletal toxicity induced by daptomycin (Rybak 2020; Meng 2017). As a result, other PK/PD optimization strategies such as alternative dosing administration (e.g., continuous or prolonged infusions) and maximum dose limits may help minimize toxicities while still achieving adequate plasma concentrations of antimicrobials. In addition, TDM may become particularly important to individualize dosing regimens in this patient population (Meng 2017).

Alterations in Drug Metabolism

The liver is the primary site of drug metabolism, which in turn is largely determined by hepatic blood flow, protein binding, and enzyme activity (Blot 2014). Critical illness affects each of these processes to varying extents. Sepsis can induce the development of different types of liver dysfunction, including hypoxic hepatitis (i.e., shock liver), cholestasis, and secondary sclerosing cholangitis (Strnad 2017). The CYP enzyme system appears to be altered at varying levels, with the activity of some CYP enzymes suppressed, whereas in others, it is elevated. It is postulated that CYP activity is suppressed by the release of proinflammatory mediators because enzymatic abnormalities were most pronounced during the acute phase of sepsis and tended to normalize with clinical improvement (Jacob 2009).

As noted earlier, albumin is produced by the liver, and alterations in Vd and clearance may arise from higher unbound drug concentrations. Presence of edema or ascites in patients with cirrhosis can increase the Vd of hydrophilic drugs. In addition, many drugs (including antimicrobials) inhibit or induce CYP enzymes and necessitate management of drug interactions (Verbeeck 2008).

It is important to distinguish between critically ill patients with acute liver dysfunction (e.g., shock liver) and those with chronic cirrhosis. Almost all published studies on PK changes in liver disease have been in patients with chronic liver disease and varying levels of cirrhosis. Most drug adjustment recommendations use the Child-Pugh score, even though this scoring system was originally developed to predict mortality in patients with cirrhosis and not drug dose adjustment (Pugh 1973; Child 1964). Although pathophysiologic processes indicate that the metabolism of hepatically cleared drugs is likely altered in acute liver dysfunction, data on PK alterations of antimicrobials and need for dose adjustment are poorly studied.

Alterations in Drug Clearance

Augmented Renal Clearance

Augmented renal clearance, defined as a CrCl greater than 130 mL/minute, is estimated to occur in 30%–65% of critically ill patients. Although the exact mechanism of ARC has not been elucidated, ARC is likely the result of increased cardiac output and renal blood flow secondary to systemic inflammatory response syndrome (SIRS). Infection, major surgery or trauma, and burns can all lead to SIRS. Activation of SIRS combined with use of resuscitation fluids and vasopressor support may increase renal blood flow and consequently the GFR, leading to ARC. Another postulated mechanism is the concept of renal functional reserve, where ARC is triggered by physiologic stress and becomes evident in patients with greater physiologic reserves. This hypothesis is supported by the findings that younger patients with fewer comorbidities (and hence greater renal reserves) are at higher risk of ARC. Other risk factors for ARC include male sex, trauma, and lower severity of illness as determined by the APACHE II or sequential organ failure assessment (SOFA) score (Bilbao-Meseguer 2018; Hobbs 2015).

Augmented renal clearance is typically suspected in critically ill individuals with an SCr less than 1.3 mg/dL who have no underlying kidney disease. If a patient meets this criterion, the next step involves assessing the likelihood of ARC using a scoring tool. Two ARC screening tools have been developed that can help assess the likelihood of ARC. The first scoring system was developed in 2013 on the basis of a prospective observational study of 71 critically ill patients with trauma or sepsis. Three risk factors (Table 5) were identified, and specific points were assigned to each according to the results of a multivariate analysis. In general, higher ARC scores were associated with a higher likelihood of ARC. Specifically, 0% of patients who scored 0–3 points had ARC, compared with 36% of patients who scored 4–6 points and 82% of patients who scored 7–10 points (Udy 2013). A separate study using the same scoring system identified that an ARC score cutoff of 7 or higher was associated with a high probability of ARC with 100% sensitivity and 71% specificity (Akers 2014).

The second scoring system is based on a retrospective study of 133 trauma patients and is called the augmented renal clearance in trauma intensive care (ARCTIC) score (Barletta 2017). Similar to the first ARC scoring system, the ARCTIC score comprises three risk factors (age, male sex, and SCr) that are assigned specific points. A score of 6 or higher has been identified as the cutoff for ARC with 84% sensitivity and 68% specificity. The authors further suggested antimicrobial dose individualization for patients with high ARCTIC scores.

Of importance, in critically ill patients with ARC, CrCl should be measured using continuous urine collection. Creatinine clearance estimations using the Cockroft-Gault or Modification of Diet in Renal Disease equation are not recommended because they have only been validated in non-critically ill patients with stable renal function. In fact, studies of critically ill patients show that these estimation formulas consistently underestimate the measured CrCl values (Bilbao-Meseguer 2018). If 24-hour urine collection is not feasible, 8-hour measured CrCl has been proposed instead with acceptable accuracy (Cherry 2002).

Because patients with ARC have increased GFR, the primary concern is increased clearance of renally eliminated antimicrobials resulting in subtherapeutic serum concentrations and failure to achieve PD targets. Several studies evaluating the impact of ARC on the PK/PD of β-lactams have found an increased likelihood of subtherapeutic concentrations and, in some instances, therapeutic failure (Carrie 2018; Jacobs 2018; Udy 2012). Similar findings were reported for vancomycin and daptomycin (Rybak 2020; Villanueva 2019; Soraluce 2018). Strategies that may help counteract this effect are use of maximum approved dosing regimens, administration of β-lactams as prolonged or continuous infusions, and/or use of TDM. Currently, only one antibiotic, cefiderocol, has a dosing recommendation for ARC in its prescribing

Table 5. ARC Scoring Tools

	Variable	Points
ARC scoring system[a]	Age ≤ 50 yr	6
	Trauma	3
	Modified SOFA score ≤ 4	1

	Variable	Points
ARCTIC score[b]	Age < 56 yr	4
	Age 56–75 yr	3
	SCr < 0.7 mg/dL	3
	Male	2

[a]Total score ≥ 7 points is considered high probability of ARC.

[b]Total score ≥ 6 points is considered high probability of ARC.

ARC = augmented renal clearance; ARCTIC = augmented renal clearance in trauma intensive care; SOFA = sequential organ failure assessment.

Information from: Barletta JF, Mangram AJ, Byrne M, et al. Identifying augmented renal clearance in trauma patients: validation of the augmented renal clearance in trauma intensive care scoring system. J Trauma Acute Care Surg 2017;82:665-71; Akers K, Niece KL, Chung KK, et al. Modified augmented renal clearance score predicts rapid piperacillin and tazobactam clearance in critically ill surgery and trauma patients. J Trauma Acute Care Surg 2014;77:S163-70; Udy AA, Roberts JA, Shorr AF, et al. Augmented renal clearance in septic and traumatized patients with normal plasma creatinine concentrations: identifying at-risk patients. Crit Care 2013;17:R35.

information stating that patients with a CrCl of 120 mL/minute or higher should receive a dosage of 2 g intravenously every 6 hours instead of the standard approved regimen of 2 g every 8 hours. If therapeutic and/or PD targets are still unattainable, alternative antimicrobials that are not renally cleared can be considered (Chen 2020).

Although ARC is associated with subtherapeutic concentrations, data on patient outcomes are limited and have provided inconsistent results. One observational prospective study of 128 surgical and medical ICU patients assessed the prevalence of ARC and the risk of therapeutic failure. Augmented renal clearance was present in 52% of patients. Therapeutic failure was defined as impaired clinical response (e.g., persistent fever, purulent bronchial secretions, organ dysfunction) and need for alternative antimicrobial therapy. Therapeutic failure was more common in patients who had ARC than in those who did not (27% vs. 13%, p=0.04) (Claus 2013). A nested cohort substudy of the BLING II randomized placebo-controlled trial explored the relationship between ARC and clinical outcomes in patients receiving β-lactam antibiotics by intermittent or continuous infusion. Of 432 patients, 45 had ARC. The primary outcomes (i.e., ICU-free days at day 28) did not differ between patients with ARC and those without (p=0.89). Furthermore, 90-day mortality did not differ (Udy 2017). Variability in factors such as studied patient population, definitions of ARC, antimicrobial dosing regimens, and MICs of isolated microorganisms may have contributed to some of the conflicting findings between studies. Although additional studies are needed to define the impact of ARC on clinical outcomes, most clinicians generally agree that PK/PD optimization is still in the patient's best interest and may increase treatment success.

Acute Kidney Injury

Acute kidney injury is a common complication of sepsis and septic shock and affects around 50% of critically ill patients. Risk factors for developing AKI include advanced age, presence of underlying CKD or chronic liver disease, cardiovascular disease, and diabetes (Poston 2019). Patients with AKI have higher mortality as well as higher risk of longer ICU stays, progression to CKD, and need for renal replacement therapy. There are several classifications of AKI, all of which use urine output and SCr to classify the patient into stages. Higher stages are associated with more severe renal impairment and greater risk of long-term complications (Thomas 2015).

The longstanding explanation of AKI pathophysiology was renal hypoperfusion, which resulted in renal ischemia and a decreased GFR. However, newer evidence shows that AKI is the result of a complex interplay between several mechanisms, including inflammation, microcirculatory dysfunction, and metabolic reprogramming. Proinflammatory mediators increase oxidative stress, production of reactive oxygen species, and mitochondrial injury in tubular epithelial cells. Endothelial injury and inflammation unevenly distribute blood flow. Metabolic reprogramming refers to the ability of tubular epithelial cells to prioritize energy expenditures to vital functions and minimize the risk of replicating damaged DNA (Peerapornratana 2019; Bellomo 2017; Gomez 2016).

Pharmacokinetic changes in AKI are multifold and complex. Not surprisingly, AKI will increase the half-life of renally cleared drugs. The unbound fraction of drugs is expected to increase because of hypoalbuminemia and displacement of drugs from their binding sites by uremic toxins. Hypoalbuminemia itself is more common in AKI, not only because of capillary leakage and decreased synthesis, as described earlier, but also because of shorter half-life and higher catabolism of albumin. These effects will largely increase the Vd of highly protein bound drugs and hydrophilic drugs. Kidney injury may also influence the hepatic metabolism of drugs by down-regulating the expression of certain CYP enzymes. The exact mechanism is unclear, but it appears to be at least partly driven by the presence of uremia and proinflammatory mediators (Blanco 2019; Lane 2013).

Optimizing antimicrobial therapy in AKI can be challenging for several reasons. On the one hand, patients with AKI clearly do not have "normal" renal function, and clinicians will be inclined to make dose adjustments to avoid toxicity. On the other hand, patients with AKI have fluctuating kidney function, which is relatively unpredictable. The most commonly used marker of kidney function is SCr, whose changes lag around 1 or 2 days before actual changes occurring in the kidneys. Urine output is a generally nonspecific marker that varies with volume status, diuretic administration or omission, and presence of an obstruction.

Another important consideration is that the use of dose adjustment guidelines is based on data from patients with stable CKD. Because CKD dosing assumes a stable renal function, this may not reflect the PK alterations and dynamic changes occurring in critically ill patients and patients with sepsis and AKI. In fact, adjusting doses solely on the basis of the SCr can lead to underdosing because patients with AKI may compensate by increasing nonrenal elimination pathways (e.g., transintestinal, biliary elimination) (Lewis 2016). In the presence of both septic shock and AKI, where morbidity and mortality are high and early administration of antibiotics is critical for improved survival, some clinicians have argued that reductions in antimicrobial dosing should be delayed by 48 hours for selected antibiotics to avoid underdosing. This approach may be particularly reasonable for β-lactams, which have a relatively wide safety margin and low risk of serious adverse effects. However, antimicrobials with narrow therapeutic indexes such as vancomycin, aminoglycosides, and colistin have higher risks of adverse effects and should have doses adjusted without delay in AKI (Crass 2019). In any case, the antimicrobial regimen will need to be individualized, and

the specific PK of the drug and potential for increased risk of an adverse drug event should be considered. Therapeutic drug monitoring should be used, when possible. Finally, frequent monitoring and drug dosing reevaluation are necessary, given the relatively unpredictable nature of kidney function in AKI.

PD CONSIDERATIONS IN SEPSIS AND SEPTIC SHOCK

Overview of PK/PD Targets

Antimicrobial PD describes the relationship between drug concentration and pharmacologic effect on the target microorganism. Antimicrobials have different PK/PD indexes, which describe their optimal efficacy. The three PK/PD indexes are (1) Cmax/MIC ratio; (2) duration of time (T) that the free drug concentration remains above the MIC during a dosing interval (fT>MIC); and (3) $AUC_{0\text{-}24hr}$/MIC. An optimal antimicrobial regimen ensures sufficient drug exposure in relation to the MIC (Gillespie 2005).

There are a few caveats when studying PD relationships. Only unbound antimicrobial concentration is active against microorganisms, so attention needs to be paid to whether total drug concentration or free fraction is being measured and reported. Furthermore, the antimicrobial needs to be able to reach its site of action. Plasma concentrations are commonly used as surrogate markers of antimicrobial exposure at the infected site. Ideally, antimicrobial concentrations at the site of action would provide the most accurate measurements; however, they may not be clinically feasible or safe to obtain (Fratoni 2021; Gillespie 2005).

Minimum inhibitory concentration testing is another critical element for interpreting achievable drug exposure, especially for gram-negative microorganisms where the MIC values of an antibiotic can vary widely. However, MIC testing may not be as accurate as clinicians often assume. Even though MIC is reported as a single value, the accuracy of that measurement is affected by strain-to-strain differences within a species, variations in assays (i.e., inoculum preparation, media, incubation time and temperature), and variation between laboratories (i.e., facilities, technician skills and training) (Mouton 2018). As a result, instead of focusing on the reported MIC value as the "true" value, it may be more appropriate to recognize the MIC value as a range that is one or two dilutions away from the measured MIC (Fratoni 2021; Abdul-Aziz 2020; Mouton 2018).

Another challenge associated with MIC measurement is that many clinical laboratories use automated antimicrobial susceptibility testing systems. Although these systems are efficient and reduce the cost of labor, they typically do not perform full-range MIC testing but instead may test a few dilutions above and below the breakpoint. If a specific MIC value is needed for PK/PD optimization, close collaboration with a clinical microbiology laboratory is needed to determine which microorganisms should undergo additional testing beyond automated antimicrobial susceptibility testing. The Etest (i.e., gradient MIC strips) can be used to determine the MIC and guide the treatment of critically ill patients (Fratoni 2021).

Because clinical PK/PD targets for efficacy need an MIC value for calculation, measures of MIC distribution such as the epidemiologic cutoff (ECOFF) value have been proposed for antimicrobial dosing. This approach separates the bacteria into populations with no phenotypically detectable resistance (also called "wild type"), low resistance, or high resistance. The ECOFF is defined as the highest MIC for isolates without phenotypically detectable resistance. If the measured MIC equals the ECOFF value or is below it, the ECOFF value should be used for PK/PD target attainment calculation. If the measured MIC is immediately above the ECOFF, a 2-fold dilution should be added to the MIC for faster target attainment. If the measured MIC is far above the clinical breakpoint, the PK/PD target is likely unattainable (Mouton 2018). The ECOFF values often match the clinical breakpoint and can be found online at the European Committee on Antimicrobial Susceptibility Testing website.

Given the significant variation in PK among critically ill patients, several dosing strategies have been studied to optimize the PK/PD of antimicrobials. The strategies most commonly used in clinical practice are extended/continuous infusions of β-lactams and TDM.

Altered Administration Technique

Intravenous β-lactams can be administered by three basic strategies: intermittent schedule, where the dose is infused over a relatively short (60 minutes or less) time; extended or prolonged schedule, where the dose is infused over 3–4 hours; and continuous infusion, where the dose is administered continuously over 24 hours. Probability of target attainment (PTA) decreases at higher MICs and higher renal function. Because β-lactams have time-dependent killing, extended/continuous infusions have been studied as a way to increase the PTA. The fT>MIC value required for bactericidal activity varies by β-lactam class. Penicillins require a % fT>MIC of 50%–60%, cephalosporins 60%–70%, and carbapenems 40%–50% (Chen 2020). However, emerging clinical data suggest that a more aggressive PK/PD target of up to 100% fT>4×MIC improves clinical efficacy and may suppress the emergence of resistance. Extended/continuous infusions have usually been studied for piperacillin/tazobactam, cefepime, ceftazidime, and meropenem (Table 6). The findings among studies can be difficult to compare because they vary by their specific PK/PD target, renal function, dosing regimen, and infusion time. Although prolonging the infusion time is an effective way to increase the fT>MIC, whether the increase is sufficient ultimately depends on the patient's renal function and the MIC of the pathogen. For example, a population PK study of critically ill patients compared a 3-hour extended infusion

Table 6. Suggested Extended- and Continuous-Infusion Dosing Regimens for β-Lactams

Drug	Loading Dose (g)	Extended-Infusion Regimens (duration of each infusion)	Continuous-Infusion Regimens
Cefepime	2	2 g IV q8hr (3–4 hr)	6 g over 24 hr
Ceftazidime	2	2 g IV q8hr (3–4 hr)	6 g over 24 hr
Meropenem	1–2	1–2 g IV q8hr (3–4 hr)	2 g over 8 hr, or 3 g over 12 hr
Piperacillin/tazobactam	3.375–4.5	3.375–4.5 g IV q8hr (4 hr)	13.5–18 g over 24 hr

IV = intravenous(ly); q = every.

Information from: Marguigan KL, Al-Shaer MH, Peloquin CA. β-lactams dosing in critically ill patients with gram-negative bacterial infections: a PK/PD approach. Antibiotics (Basel) 2021;10:1154; Lexicomp Online [internet database]. Lexicomp. Updated periodically.

with a ½-hour infusion of meropenem 2 g intravenously every 8 hours in those with a CrCl of 50–120 mL/minute. The PTAs in the extended-infusion group were 99.6%, 95.9%, and 73.0% at MICs of 4, 8, and 16 mg/L, respectively. However, the PTAs for a ½-hour infusion at the same MICs were 89.2%, 74.8%, and 40.7%. The investigators also analyzed doses for lower CrCl ranges. In patients with a CrCl of 30–49 mL/minute who received meropenem 1 g intravenously every 8 hours by either a 3-hour or a ½-hour infusion, only the extended infusion provided adequate exposure for an MIC of 8 mg/L, with PTAs of 89.6% and 65.4%, respectively (Crandon 2011).

Finally, it is important to recognize that, in some cases, the PK/PD target may not be reachable despite high doses and continuous infusion. A prospective observational study of 79 critically ill patients with sepsis evaluated six β-lactam antibiotics, all of which were administered at maximum doses and by continuous infusion (including a loading dose). Despite the optimized regimen, the investigators reported that 20% of patients did not reach the PK/PD target of fT>4×MIC. Patients with a CrCl of 170 mL/minute or higher had a significantly higher chance of subexposure (OR 10.1; 95% CI, 2.4–41.6; p=0.001) (Carrie 2018). Further studies are warranted to explore whether further dose increases are safe and effective.

Clinical outcomes associated with extended and continuous infusions have been studied with inconsistent results, with some showing improved mortality and clinical cure rates while others did not. Some of the more rigorously designed studies on this topic are the β-lactam infusion group (BLING) studies, which are two multicenter double-blind randomized controlled trials. The BLING I study compared continuous infusion with intermittent dosing of piperacillin/tazobactam, meropenem, and ticarcillin/clavulanate in 60 patients with severe sepsis. Eighty-two percent of patients in the continuous arm achieved antibiotic concentrations exceeding the MIC compared with 29% in the intermittent arm (p=0.001). Clinical cure was higher in the continuous group (70% vs. 43%, p=0.037). Survival to hospital discharge was higher in the continuous group than in the intermittent group, but it was not statistically significant (90% vs. 80%, p=0.47) (Dulhunty 2013). The BLING II studied the same antibiotic regimens among 432 patients with severe sepsis. The BLING II found no difference between the continuous and intermittent arms in 90-day survival (74.3% vs. 72.5%, respectively; HR 0.91; 95% CI, 0.63–1.31; p=0.61) or clinical cure (52.4% vs. 49.5%, respectively; OR 1.12; 95% CI, 0.77–1.63; p=0.56) (Dulhunty 2015).

Subsequently, several systematic reviews and meta-analyses have analyzed the findings and produced different results on the basis of their specific inclusion criteria. Some reviews focused on specific microorganisms (i.e., *Pseudomonas* spp.), infection site (i.e., HAP/VAP), or β-lactams. The types of infusions included also differ, with some studies grouping extended and continuous infusions together and comparing this with intermittent infusion and others focusing on one infusion type (i.e., continuous infusion only). One notable meta-analysis of randomized trials compared mortality and clinical efficacy of extended/continuous with intermittent infusion of antipseudomonal β-lactams. Although the study found no difference in clinical improvement (RR 1.06; 95% CI, 0.96–1.17), a significant decrease in mortality was associated with prolonged/continuous infusions (RR 0.70; 95% CI, 0.56–0.87). Furthermore, there was no difference between reported adverse effects and development of resistance between groups, though only a few trials reported these data (Vardakas 2018).

There are several theories regarding why extended/continuous infusion has not consistently shown more favorable outcomes. If there is a predominance of pathogens with low MICs, both the intermittent and prolonged infusions would be expected to provide adequate fT>MIC. Other reasons include concomitant use of other non–β-lactam antibiotics, comparison of dosing regimens, inconsistent use of loading doses, and heterogeneous patient populations. Finally, there is currently no evidence that extended/continuous infusions are inferior to intermittent infusions (Grupper 2016). To further elucidate this matter, a third BLING trial (BLING III) is currently

under way to compare continuous infusion with intermittent infusion of β-lactam antibiotics and measure 90-mortality in 7000 critically ill patients with sepsis (Lipman 2019).

Most of the novel β-lactams are administered as extended infusions because they have mainly been studied to target MDR gram-negative bacteria. Both cefiderocol and meropenem/vaborbactam are infused over 3 hours. A ceftolozane/tazobactam 4-hour infusion was associated with improved PTAs compared with an intermittent infusion for MDR *P. aeruginosa* isolates (Natesan 2017). A retrospective observational study found that extending the ceftazidime/avibactam infusion from 2 hours to 3 hours was associated with survival benefit for the treatment for a carbapenemase-producing *Klebsiella pneumoniae* infection (Tumbarello 2021). Overall, extended/continuous infusion is an important strategy for treating MDR pathogens when limited treatment options are available.

In addition to clinical outcomes, some logistical barriers may need to be overcome when extended/continuous infusions are used. Compatibility issues can arise when other intravenous medications need to be administered through the same line as the extended/continuous infusion. Sometimes, rescheduling medication administration times can resolve this issue. However, when several concurrent intravenous medications with compatibility issues are required, it may be more feasible to change back to intermittent infusions. Another concern is the stability of β-lactams because the drug degrades over time and can lead to loss of therapeutic efficacy. Stability varies among β-lactams, with carbapenems generally having the greatest instability.

Overall, extended/continuous infusions of β-lactams are reasonable in patients with sepsis despite inconsistent outcome findings. This approach increases the chance of PK/PD optimization and probable outcome benefits without harmful effects on safety or efficacy. This rationale is also noted in the SSC guidelines, which suggest using extended over intermittent infusion (weak recommendation, moderate level of evidence) because of possible mortality benefit (Evans 2021). Finally, a loading dose administered right before the extended infusion is recommended to achieve therapeutic concentrations faster and may increase clinical cure rates (Wu 2021).

Therapeutic Drug Monitoring

As described in the PK section of this chapter, many factors can affect the probability of attaining PK/PD targets during critical illness. Several studies have shown that standard dosing regimens are often suboptimal and may increase the risk of clinical failure. The DALI study was a prospective multinational PK study that measured β-lactam concentrations among 384 critically ill patients and then calculated PK/PD targets to describe the effect of antibiotic exposure on patient outcomes (Roberts 2014). The investigators evaluated four PK/PD targets among eight β-lactams, including the 50% fT>MIC and 100% fT>MIC achieved. The investigators found that 16% of patients did not achieve 50% fT>MIC and that these patients were 32% less likely to have a positive clinical outcome (OR 0.68; 95% CI, 0.52–0.91; p=0.009), which was defined as completion of a treatment course without a change in antibiotic therapy. Almost 40% of patients did not achieve the 100% fT>MIC PK/PD target. The multivariate regression model showed that, in addition to lower organ dysfunction scores (APACHE II and SOFA scores), higher 50% fT>MIC and 100% fT>MIC were significantly associated with positive clinical outcomes ($p<0.05$). Finally, the authors noted significant variability in antibiotic concentrations across all antibiotics as well as across PK/PD ratios.

Significant variability in antimicrobial PK/PD as well as lack of a consensus on how to apply TDM in clinical practice led to the publication of a position paper by an international group of critical care and infectious disease experts (Abdul-Aziz 2020). The position paper recommends specific PK/PD targets for efficacy and toxicity monitoring and suggests sampling strategies and timing. Furthermore, the panel recommends routine TDM of six antimicrobials/antimicrobial classes in critically ill patients: aminoglycosides, β-lactams, linezolid, teicoplanin, vancomycin, and voriconazole (Table 7). The most significant change brought on by these recommendations is TDM of β-lactams, which are one of the most commonly used antimicrobial classes but have not historically been managed through TDM.

As more scientific studies and experts increasingly support β-lactam TDM in critically ill patients, several barriers to its implementation in clinical practice remain. This was shown by several studies that found that β-lactam TDM is rarely used because of a combination of lacking resources and clinician knowledge (Abdullah 2022; Lui 2021; Tabah 2015). In 2015, the European Society of Intensive Care Medicine surveyed ICU clinicians from 53 (mainly European) countries on practices in dosing, administration, and monitoring of commonly used antibiotics. Although 79.6% of respondents reported availability of TDM for vancomycin, piperacillin, and carbapenems, TDM was performed in 3.3% and 6.2%, respectively (Tabah 2015). The study also found wide variability in antibiotic dosing and monitoring practices and exposed potential barriers such as access to evidence-based guidelines, assay availability, and cost in resource-limited areas. An ongoing study is evaluating ICU practitioners' perspectives and factors that influence implementation of β-lactam TDM and will include U.S. institutions (Barreto 2021).

With respect to resources, β-lactam measurements require validated in-house assays using chromatographic equipment with either UV or mass spectrometry methods. This laboratory equipment is costly and requires personnel expertise; hence, it may not be widely available at institutions. Institutions that cannot measure β-lactam concentrations can send out samples to independent diagnostic laboratories, but this can delay turnaround time, which may be problematic in critically ill individuals. In addition to assay availability, clinician knowledge

Table 7. Recommendations for PK/PD Targets and Sampling

Antibacterial	TDM Parameter	Sample Type and Sampling Time	Target
Aminoglycosides	AUC/MIC	Cmax (30 min after infusion) AND C_1 (6–22 hr after the infusion)[a]	AUC/MIC 80–100 mg hr/L
	Cmax/MIC	Cmax (30 min after infusion)	Cmax ≥ 8–10 mg/L
β-Lactams	Intermittent/prolonged infusion: Cmin	Cmin (24–48 hr after therapy initiation)	100% fT>MIC
	Continuous infusion: C_{ss}	One sample during infusion	C_{ss} > MIC
Linezolid	Cmin	Cmin (48 hr after therapy initiation)	Cmin 2–7 mg/L
Vancomycin	AUC/MIC	Cmax (1–2 hr after infusion) AND Cmin[a]	AUC/MIC ≥ 400 mg hr/L
	Continuous infusion: C_{ss}	One sample during infusion	C_{ss} 20–25 mg/L
Voriconazole	Cmin	Cmin (2–5 days after therapy initiation)	Cmin 2–6 mg/L

[a]One sample may be sufficient with use of Bayesian software programs.

C_{ss} = steady state drug concentration; fT>MIC = duration of time that the free drug concentration remains above the MIC during a dosing interval; TDM = therapeutic drug monitoring.

Information from: Abdul-Aziz MH, Alffenaar JWC, Bassetti M, et al. Antimicrobial therapeutic drug monitoring in critically ill adult patients: a position paper. Intensive Care Med 2020;46:1127-53.

on how to interpret β-lactam concentrations and adjust the regimen when needed presents a challenge. Population PK software and Bayesian modeling are generally preferred because they provide an accurate PK profile, calculate the fT>MIC, and offer dose suggestions to reach the PD target. As a result, familiarity with or training on how to use the software and interpret the results is necessary. The software programs vary in cost, subscription options, ability to integrate into the electronic health record, and number of β-lactams they support. Therefore, institutions need to evaluate the options carefully to find the best fit for their needs.

Infectious disease pharmacists are well positioned to provide support by educating other pharmacists and critical care staff on TDM and collaborating with stakeholders (e.g., microbiology laboratory, ICU clinicians, pharmacy staff) to establish processes and guidelines for TDM implementation. In fact, a recent survey of over 3000 ICU specialists in China found that 89% of respondents agreed that interpretation of TDM results by clinical pharmacists is better and more rational for providing individualized antimicrobial regimens (Liu 2021). As a result, this presents a unique opportunity for pharmacists to fill a need in the critical care setting and improve patient outcomes.

CONCLUSION

Early antimicrobial therapy is a key intervention that may decrease mortality and improve clinical outcomes in patients with sepsis and septic shock. Selection of appropriate antimicrobial therapy requires a careful patient evaluation and should consider illness severity, infection site, and risk factors for certain microorganisms such as MRSA, MDR gram-negative organisms, fungal pathogens, and/or viral pathogens. Antimicrobial dosing may present another

Practice Points

- **It is important to quickly recognize sepsis and septic shock so that antimicrobials can be administered as soon as possible to improve patient outcomes.**
- **Broad-spectrum antibiotics covering MDR gram-negative organisms and MRSA are no longer recommended and should only be initiated in the presence of organism-specific risk factors.**
- **When choosing an empiric regimen for a patient with sepsis, clinicians should consider individual patient factors, severity of illness, suspected source of infection, risk factors for drug-resistant organisms, and local prevalence of resistance patterns.**
- **Combination therapy for definitive treatment of gram-negative bacilli is generally not supported by the guidelines unless an MDR organism is present.**
- **Shorter courses of antimicrobials are generally recommended over longer courses because of similar efficacy. However, patients without adequate source control may require longer therapy durations and an individualized plan. PCT trending may help in deciding when to discontinue antimicrobials.**
- **Absorption, distribution, metabolism, and elimination of antimicrobials are significantly altered in patients with sepsis or septic shock. The extent of these alterations depends on the PK of the antimicrobial.**
- **The two strategies most commonly used in clinical practice to optimize the PK/PD of antimicrobials are extended/continuous infusions of β-lactams and TDM.**

challenge because critical illness may alter drug absorption, distribution, metabolism, and clearance. The resulting variability in PK among critically ill patients has led to the need to optimize the PK/PD of antimicrobials. Depending on the PK/PD index of the antimicrobial, infectious disease clinicians can use strategies such as loading doses, extended/continuous infusions, and TDM to achieve optimal efficacy and improve patient outcomes.

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Self-Assessment Questions

Questions 1—3 pertain to the following case.

P.T. is a 76-year-old man (height 70 inches, weight 130 kg) whose medical history includes poorly controlled diabetes, peripheral neuropathy, hypertension, and obstructive sleep apnea. He is admitted from a skilled nursing facility to the ICU with increased shortness of breath, fevers, and confusion. A chest CT confirms a diagnosis of pneumonia, and P.T. is empirically initiated on intravenous cefepime and vancomycin. At presentation, his temperature is 101.2°F, with blood pressure 90/58 mm Hg, heart rate 110 beats/minute, respiratory rate 20 breaths/minute, lactate 0.6 mmol/L, and Glasgow Coma Scale score 14. P.T.'s CBC shows WBC 14.2 × 10^3 cells/mm^3, Hgb 8.2 mg/dL, and Plt 180,000 cells/mm^3. P.T.'s chemistry panel is as follows: sodium 140 mEq/L, potassium 4.7 mEq/L, Cl 110 mEq/L, BUN 18 mg/dL, and SCr 1.2 mg/dL. His liver function tests return as AST 35 U/L, ALT 44 U/L, albumin 4.0 g/dL, and INR 1.1.

1. Which one of the following best evaluates the pharmacokinetic (PK) properties of the antibiotics cefepime and vancomycin for P.T.?

   A. Both cefepime and vancomycin are hydrophilic and not highly protein bound.
   B. Cefepime is hydrophilic and highly protein bound, whereas vancomycin is lipophilic and not highly protein bound.
   C. Both cefepime and vancomycin are hydrophilic and highly protein bound.
   D. Cefepime is lipophilic and not highly protein bound, whereas vancomycin is hydrophilic and not highly protein bound.

2. Which one of the following, in addition to being critically ill, is P.T.'s greatest risk factor for altered PK/pharmacodynamics (PD) of antibiotics?

   A. Obesity
   B. Hypoalbuminemia
   C. Augmented renal clearance (ARC)
   D. Acute kidney injury (AKI)

3. Which one of the following cefepime dosing strategies is best to recommend for P.T.?

   A. 2 g intravenously infused over 30 minutes every 8 hours
   B. 2 g intravenously once over 30 minutes, then 2 g intravenously infused over 3 hours every 8 hours
   C. 2 g intravenously once over 30 minutes, then 1 g intravenously infused over 3 hours every 8 hours
   D. 2 g intravenously infused over 60 minutes every 8 hours

4. A 69-year-old man (height 68 inches, weight 85 kg) with a medical history of stage 5 chronic kidney disease (CKD) (baseline SCr 2.1 mg/dL) and systolic congestive heart failure is admitted to the ICU for septic shock secondary to an intra-abdominal infection. A CT of the abdomen reveals an intra-abdominal abscess secondary to GI perforation. The patient has an ultrasound-guided percutaneous needle aspiration with subsequent catheter drainage and is empirically initiated on intravenous ceftriaxone and metronidazole. Four days later, a repeat CT reveals that the abscess is still present but has decreased in size, and the surgical team is assessing the need for a surgical intervention. The patient's vital signs have significantly improved since admission, and he is hemodynamically stable. His temperature is 99°F, with blood pressure 110/74 mm Hg, heart rate 82 beats/minute, and respiratory rate 15 breaths/minute on room air. Which one of the following is best to recommend regarding continuation of this patient's antibiotic therapy?

   A. Discontinue ceftriaxone and metronidazole because the patient has completed a 4-day course of empiric antibiotics and is stable.
   B. Discontinue metronidazole but continue ceftriaxone because the patient has clinically improved.
   C. Continue both ceftriaxone and metronidazole because the source of the infection has not been eliminated.
   D. Continue both ceftriaxone and metronidazole and order procalcitonin (PCT) to help guide therapy duration.

Questions 5 and 6 pertain to the following case.

B.B., a 29-year-old man (height 71 inches, weight 79 kg) with an unknown medical history, is admitted to the neurosurgical ICU with a subdural hematoma after a motorcycle crash. Five days later, he spikes a fever, and imaging reveals new lung infiltrates of concern for ventilator-associated pneumonia (VAP). B.B. is initiated on meropenem 500 mg intravenously every 6 hours (infused over 30 minutes) and vancomycin 1 g intravenously every 8 hours (infused over 60 minutes). He continues to be intubated and sedated. His vital signs are as follows: temperature 101°F, blood pressure 105/77 mm Hg, heart rate 98 beats/minute, and respiratory rate 16 breaths/minute on a ventilator. The patient's CBC shows WBC 20.2 × 10^3 cells/mm^3, Hgb 7.9 mg/dL, and Plt 170,000 cells/mm^3. B.B.'s chemistry panel is as follows: sodium 140 mEq/L, potassium 4.0 mEq/L, Cl 101 mEq/L, BUN 12 mg/dL, and SCr 0.6 mg/dL. His liver function test results are AST 42 U/L, ALT 39 U/L, and albumin 3.3 g/dL.

5. Which one of the following best evaluates B.B.'s augmented renal clearance in trauma intensive care (ARCTIC) score?

   A. 4
   B. 6
   C. 9
   D. 12

6. Two days after antibiotics are initiated, B.B.'s respiratory cultures return, growing *P. aeruginosa* with MICs as follows:

Drug	Minimum Inhibitory Concentration
Amikacin	< 16 (S)
Aztreonam	16 (I)
Ceftazidime	16 (I)
Cefepime	16 (I)
Levofloxacin	>8 (R)
Meropenem	2 (S)
Piperacillin/tazobactam	16/4 (S)
Tobramycin	< 2 (S)

A meropenem trough is 2.11 mg/L, and vancomycin is discontinued. Which one of the following is best to recommend for B.B. to optimize the PK/PD of meropenem?

A. Change meropenem to 2 g intravenously every 8 hours infused over 30 minutes.
B. Change meropenem to 6 g intravenously infused over 24 hours.
C. Change meropenem to 2 g intravenously every 8 hours infused over 3 hours.
D. Change meropenem to 1 g intravenously every 12 hours infused over 3 hours.

Questions 7 and 8 pertain to the following case.

J.S., a 68-year-old woman (height 67 inches, weight 79 kg), has a medical history that includes diabetes, chronic bronchiectasis, chronic obstructive pulmonary disease, and *Pseudomonas* pneumonia. She is admitted to the ICU with shortness of breath and altered mental status. Chest radiography reveals bilateral lower lobe infiltrates of concern for an infectious process. J.S. is subsequently intubated and initiated on empiric vancomycin, a piperacillin/tazobactam continuous infusion, and tobramycin. On hospital day 2, J.S.'s MRSA nasal swab returns negative, and vancomycin is discontinued. On hospital day 3, her respiratory cultures return as *P. aeruginosa* with the following MICs:

Drug	MIC
Amikacin	< 16 (S)
Aztreonam	2 (S)
Ceftazidime	8 (S)
Cefepime	8 (S)
Levofloxacin	4 (I)
Meropenem	2 (S)
Piperacillin/tazobactam	16/4 (S)
Tobramycin	< 2 (S)

7. J.S.'s care team asks your advice about whether to continue to "double-cover" *P. aeruginosa* with piperacillin/tazobactam and tobramycin. Which one of the following is best to recommend regarding J.S.'s combination therapy?

A. Continue piperacillin/tazobactam and tobramycin because they will act synergistically to eradicate the patient's infection.
B. Continue piperacillin/tazobactam and tobramycin because they will increase the patient's probability of target attainment (PTA).
C. Continue piperacillin/tazobactam and discontinue tobramycin because combination therapy will likely not improve the patient's clinical outcomes.
D. Continue piperacillin/tazobactam and discontinue tobramycin because combination therapy increases the risk of antibiotic resistance.

8. J.S.'s care team asks whether piperacillin and tazobactam concentrations should be ordered. According to the current evidence, which one of the following is best to recommend for J.S.?

A. Order because the patient is critically ill.
B. Order because the patient has several chronic comorbidities.
C. Do not order because *P. aeruginosa* is susceptible to the drug.
D. Do not order because the patient has no PK/PD alterations.

9. Which one of the following best justifies the use of epidemiologic cutoff (ECOFF) values for the PK/PD optimization of antimicrobials?

A. Account for MIC variability in assay, laboratory, and microorganism testing.
B. Measure how many wild-type microorganisms are resistant to an antibiotic.
C. Can be used as a substitute to the MIC measurement.
D. Represent the highest MIC for microorganisms without phenotypically detectable resistance.

Questions 10 and 11 pertain to the following case.

D.R., a 55-year-old man, presents to the ED by ambulance from the community after being struck by an automobile and having a subdural hemorrhage, left six to nine rib fractures, and a left hemothorax. The patient's Glasgow Coma Scale score worsens in the ED, and he is placed on a ventilator and admitted to the ICU for treatment. D.R.'s medical history is significant for chronic low back pain. On ICU day 7, he begins to have increased sputum production, and his vital signs are temperature 101.2°F, blood pressure 97/55 mm Hg, heart rate 117 beats/minute, and respiratory rate 16 breaths/minute. D.R.'s laboratory test results show the following: potassium 3.6 mmol/L, SCr 1.9 mg/dL (baseline SCr 0.9 mg/dL), BUN 33 mg/dL, WBC 17 × 10^3 cells/mm^3, Plt 67,000

cells/mm^3, and lactate 4.1 mmol/L. Because of the patient's worsening status, he is initiated on norepinephrine to maintain a mean arterial pressure greater than 65 mm Hg.

10. Which one of the following is best to recommend to help identify D.R.'s source of infection?
    A. Blood cultures
    B. Respiratory cultures
    C. Blood and respiratory cultures
    D. Respiratory and urinary cultures
11. According to the criteria for sepsis, which one of the following best evaluates D.R.'s condition and plausibility of infection?
    A. Probable septic shock
    B. Definite septic shock
    C. Probable sepsis without shock
    D. Possible sepsis without shock

Questions 12 and 13 pertain to the following case.

J.T. is a 35-year-old man admitted to the ICU for concern of possible sepsis because of meningitis versus seizure. Three days ago, he started having frequent nausea and vomiting and severe headaches, resulting in poor oral intake. J.T. has a medical history of depression and was diagnosed with a benign brain tumor 2 weeks ago. He denies intravenous drug use. His blood samples are obtained, and a lumbar puncture is performed. Initial laboratory and culture data show the following: sodium 144 mEq/L, potassium 4.1 mEq/L, Cl 98 mEq/L, HCO_3 22 mEq/L, BUN 18 mg/dL, SCr 1.3 mg/dL, glucose 126 mg/dL, and WBC 9.7 × 10^3 cells/mm^3. J.T.'s vital signs are temperature 102°F, blood pressure 172/68 mm Hg, heart rate 112 beats/minute, and respiratory rate 18 breaths/minute.

12. Which one of the following is best to recommend for J.T.?
    A. Broad-spectrum antibiotics with multidrug-resistant (MDR) gram-negative organism and MRSA coverage
    B. Narrow-spectrum antibiotics specific to meningitis
    C. Broad-spectrum antibiotics plus an antiviral agent and an antifungal agent
    D. Narrow-spectrum antibiotics specific to meningitis plus an antifungal agent
13. J.T. is initiated on intravenous vancomycin and ceftriaxone for empiric coverage of meningitis. On day 2, his laboratory test results are as follows: sodium 146 mEq/L, potassium 4.2 mEq/L, Cl 101 mEq/L, HCO_3 22 mEq/L, BUN 16 mg/dL, SCr 0.9 mg/dL, glucose 113 mg/dL, and WBC 5.8 × 10^3 cells/mm^3. The initial CSF analysis results show glucose 55 mg/dL, protein 20 mg/dL, no WBCs or RBCs, and appearance – clear, and the CSF culture returns with no organisms seen. J.T.'s vital signs are temperature 98°F, blood pressure 137/68 mm Hg, heart rate 87 beats/minute, and respiratory rate 18 breaths/minute. Which one of the following is best to recommend for J.T.?
    A. Continue current antimicrobial regimen.
    B. Discontinue antimicrobial regimen.
    C. Broaden antimicrobial regimen.
    D. Add antiviral coverage to current regimen.

Questions 14 and 15 pertain to the following case.

G.H. is a 74-year-old woman brought to the ED by ambulance from her long-term care facility. On presentation, emergency medical services conveys that G.H. has been more confused and has been incontinent for the past 4 days, which is not normal for her. The patient's medical history includes dementia, hypertension, depression, and hospital admission (2 months ago) for septic shock secondary to pneumonia treated with piperacillin/tazobactam. G.H.'s vital signs in the ED are temperature 100.4°F, blood pressure, 99/68 mm Hg, heart rate 97 beats/minute, and respiratory rate 16 breaths/minute. A urinary catheter is placed, and a urinalysis results in large leukocyte esterase, positive nitrite, 0–5 RBCs per high-power field (HPF), 21–50 WBCs/HPF, few squamous epithelial cells/HPF, and many bacteria. Her other laboratory values include SCr 1.2 mg/dL, WBC 16.2 × 10^3 cells/mm^3, and albumin 2.1 g/dL. The primary care provider is concerned for urosepsis and possible bacteremia and wants to initiate broad-spectrum antibiotics with vancomycin, ceftazidime, and amikacin.

14. The nurse caring for G.H. reports that she has only one peripheral intravenous site available and asks you how she should time each antibiotic. Which one of the following is best to recommend for G.H.?
    A. Administer vancomycin first.
    B. Administer ceftazidime first.
    C. Administer amikacin first.
    D. Infuse vancomycin and amikacin together first.
15. Which one of the following best evaluates the effect of G.H.'s hypoalbuminemia on the PK of her antimicrobial regimen?
    A. No effect on amikacin; increased volume of distribution (Vd) and clearance of vancomycin and ceftazidime
    B. No effect on ceftazidime; increased Vd and clearance of vancomycin and amikacin
    C. No effect on vancomycin; increased Vd and clearance of amikacin and ceftazidime
    D. No effect on amikacin, vancomycin, or ceftazidime