Antibiotic Considerations in the Critically Ill

Empiric Choices and Dosing

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KEYWORDS

• Critical illness • Antibacterial agents • Pharmacokinetics • Drug resistance • Multiple • Bacterial • Sepsis • Drug therapy

KEY POINTS

- Treating infections in critically ill patients is complicated by diverse disease states, high rates of antimicrobial resistance, altered pharmacokinetics/pharmacodynamics, and the narrow margin for error in this high-mortality population.
- Empiric antibiotic selection should integrate local antibiogram data with individual risk factors for multidrug-resistant pathogens, balancing timely coverage with antimicrobial stewardship principles.
- Critical illness often alters drug absorption, distribution, metabolism, and elimination, necessitating tailored dosing strategies, loading doses for hydrophilic agents, and therapeutic drug monitoring when available.
- Pharmacokinetic/pharmacodynamics optimization strategies, such as prolonged beta-lactam infusions, area under the curve-guided vancomycin monitoring, and selective use of alternative agents, can improve target attainment and potentially outcomes in high-risk patients.
- Accurate allergy assessment and consideration of cross-reactivity are essential to avoid unnecessarily broad or suboptimal therapy.

INTRODUCTION

Antibiotic therapy is the cornerstone of managing critically ill patients with suspected or confirmed bacterial infections. In a 2017 international point-prevalence study of over 1150 intensive care units (ICUs) in 88 countries, 54% of patients had a suspected or proven infection; 70% were receiving antibiotics, and hospital mortality among

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Crit Care Clin 42 (2026) 585–609
https://doi.org/10.1016/j.ccc.2026.01.003 **criticalcare.theclinics.com**

Abbreviations	
AKI	acute kidney injury
AUC	area under the curve
AVVH	accelerated veno-venous hemofiltration
BL	beta-lactam
BLI	beta-lactamase inhibitor
CrCl	creatinine clearance
CRE	carbapenem-resistant *Enterobacterales*
CRRT	continuous renal replacement therapy
ECMO	extracorporeal membrane oxygenation
eGFR	estimated glomerular filtration rate
ESBL	extended spectrum beta-lactamase
HIV	human immunodeficiency virus
ICU	intensive care unit
IDSA	Infectious Diseases Society of America
IgE	immunoglobulin E
MBC	minimum bactericidal concentration
MDR	multidrug resistant
MIC	minimum inhibitory concentration
MRSA	methicillin-resistant *Staphylococcus aureus*
NPV	negative predictive value
PCR	polymerase chain reaction
PD	pharmacodynamics
PIRRT	prolonged intermittent renal replacement therapy
PK	pharmacokinetic
PPV	positive predictive value
Scr	serum creatinine
SHEA	Society for Healthcare Epidemiology of America
TDM	therapeutic drug monitoring
TTP	time to positivity
VRE	vancomycin-resistant *Enterococci*

infected patients approached 30%.[1] These findings highlight the global burden of infection in the ICU and the critical importance of timely and effective antimicrobial therapy. However, studies suggest that 30% to 50% of antibiotic prescriptions in hospitalized and critically ill patients may be inappropriate, often because of unnecessary initiation, incorrect dosing, or excessive duration.[2,3]

Although the goals of antibiotic therapy in critically ill patients—rapid pathogen clearance with minimal toxicity—are similar to those in other hospitalized patients, the pathophysiologic derangements of critical illness profoundly alter antibiotic pharmacokinetics (PK), pathogen epidemiology, and treatment response. Septic shock, prior health care exposures, and antimicrobial resistance are common in ICU patients, often necessitating prompt, empiric, broad-spectrum antibiotics. At the same time, clinicians must carefully balance the risks of undertreatment, which can lead to preventable mortality, against the harms of overtreatment, including toxicity, resistance, and superinfection. Furthermore, altered volumes of distribution, fluctuating renal and hepatic function, and extracorporeal therapies commonly complicate dosing strategies. This article will review key principles and practical considerations in selecting empiric antibiotics and optimizing antimicrobial dosing in critically ill patients.

EMPIRIC ANTIBIOTIC CONSIDERATIONS IN CRITICAL ILLNESS

Timing of Empiric and Adequate Antibiotic Therapy

In critical care practice, there is often a reflexive inclination to initiate broad-spectrum antibiotics at the first sign of infection. However, ICU patients with suspected infection

represent a heterogeneous population, ranging from individuals who are critically ill for noninfectious reasons and have no sepsis-related organ dysfunction, to those with sepsis and mild organ dysfunction, to patients in fulminant septic shock with multiorgan failure. Moreover, many ICU patients have noninfectious conditions—such as pancreatitis, drug reactions, postoperative inflammation, or pulmonary embolism—that can mimic infection and trigger unnecessary antimicrobial use.[4,5] The consequences of inappropriate empiric therapy vary accordingly.

Although judicious antibiotic use is generally preferred from a stewardship standpoint, there is little margin for error in patients with septic shock; observational studies have shown that each hour of delay in administering effective antibiotics is associated with a stepwise increase in mortality in this population.[6–11] By contrast, the benefits of immediate broad-spectrum therapy are less well established in patients with sepsis without shock and even more so in infection without sepsis.[10] Practically, this means that not every febrile ICU patient—such as one with isolated fever but no clinical deterioration—warrants immediate empiric broad-spectrum antibiotics.

This distinction is essential, as indiscriminate use of broad-spectrum antibiotics promotes antimicrobial resistance and increases the risk of adverse events, including *Clostridioides difficile* infection, nephrotoxicity, and opportunistic superinfections.[12–14] Excessive empiric therapy has also been associated with higher mortality, likely caused by these complications and disruption of the gut microbiome, which plays a key role in immune regulation.[15–17]

Balancing the risks of undertreatment and overtreatment is therefore a central challenge in critical care. Because microbiologic data typically require 24 to 72 hours to return, empiric regimens must serve as a carefully selected bridge, guided by clinical presentation, severity of illness, local resistance patterns, and patient-specific risk factors for multidrug-resistant organisms.

Obtaining Appropriate Diagnostic Cultures Before Initiating Antibiotics

Obtaining blood cultures before initiating antibiotics doubles the likelihood of pathogen recovery and remains the most critical microbiologic test in patients with suspected sepsis.[18–20] Although there are few data directly linking blood cultures to improved outcomes, they provide essential diagnostic information to guide immediate treatment decisions and support antimicrobial stewardship. Positive blood cultures facilitate targeted therapy with narrow-spectrum agents potentially reducing adverse effects and antimicrobial resistance. New rapid molecular diagnostic tests, such as polymerase chain reaction (PCR) assays, allow for antimicrobial optimization within a matter of hours compared to days with traditional culture and susceptibility testing. In addition, resistance data from bloodstream isolates are crucial for generating hospital antibiograms and informing empiric prescribing guidelines. When feasible, other site-specific cultures (eg, respiratory, urine, wound) should also be obtained to enhance diagnostic yield and tailor therapy.

Clinicians should make every effort to obtain blood and other appropriate cultures before starting antibiotics, provided this does not meaningfully delay treatment. The Surviving Sepsis Campaign recommends obtaining routine microbiologic cultures before antimicrobial therapy in patients with suspected sepsis or septic shock, if this can be done within 45 minutes.[21]

In patients with central venous catheters in whom a catheter-related bloodstream infection is suspected, it is important to obtain paired blood cultures—one drawn from the central line and one from a peripheral vein. This allows for assessment of differential time to positivity (TTP), which can help determine whether the catheter is the likely source of infection. A central line culture with differential TTP greater than 2 hours

(ie, turns positive at least 2 hours before the peripheral culture) has high sensitivity and specificity for diagnosing catheter-related bloodstream infection.[22]

Syndrome-Based Presumptive Diagnosis

Effective empiric therapy begins with a presumptive diagnosis based on the patient's presenting syndrome, informed by clinical features, imaging, laboratory data, and risk factors. A syndromic approach helps narrow the list of likely pathogens and guides empiric antibiotic selection while awaiting culture results.

For example, community-acquired pneumonia is most commonly caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, and atypical organisms such as *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella* species.[23] In contrast, hospital-acquired and ventilator-associated pneumonia are more frequently caused by *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus* (MRSA).[24] Urinary tract infections in hospitalized patients are often caused by gram-negative bacilli such as *Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus* species, with *P aeruginosa* and *Enterococcus* sp. more likely in patients with chronic catheters or recent antibiotic exposure.[25] Intra-abdominal infections are typically polymicrobial, involving a combination of Gram-negative bacilli, anaerobes (eg, *Bacteroides fragilis*), occasionally *Enterococcus* spp., and *Candida* spp., particularly in healthcare-associated cases.[26] Soft tissue infections also vary by context: non-purulent cellulitis is most often due to streptococci, while abscesses or infections in patients with prior colonization or risk factors for resistance may involve MRSA.[27] Catheter-related bloodstream infections are commonly caused by coagulase-negative staphylococci, *S aureus*, enteric gram-negative bacilli, and *Candida* species.[28]

Identifying the likely source is also critical for anticipating antibiotic concentration at the site of infection. For examples, central nervous system infections require agents with reliable blood-brain barrier penetration (eg, ceftriaxone, cefepime, carbapenems), while pneumonia necessitates drugs with high epithelial lining fluid concentrations and excludes use of daptomycin, which is inactivated by pulmonary surfactant. Establishing a focused presumptive diagnosis is therefore the cornerstone of rational empiric antibiotic selection. Common pathogens and recommended empiric regimens for frequently encountered infectious syndromes are summarized in **Table 1**.

Antibiogram

Local antibiograms report the cumulative susceptibility of various antibiotics to different pathogens throughout an institution. Combined with antimicrobial stewardship programs, antibiograms increase appropriate antibiotic use.[29] In the context of critically ill patients, antibiograms can assist clinicians in selecting empiric antibiotics with favorable susceptibility profiles. Although there are minimal data describing optimal susceptibility cut-offs for infections, survey results show clinicians generally consider a minimum of 90% pathogen susceptibility for severe infections.[30] The 2016 Hospital-acquired and Ventilator-associated Pneumonia guidelines recommend dual anti-pseudomonal therapy in units with greater than 10% resistance to monotherapy options, supporting a 90% susceptibility cut-off for severe infections.[24] Antibiograms can be as broad as an entire health care system or as narrow as a single unit in the hospital. For critically ill patients presenting from the community or transferred from another unit, general hospital antibiograms may be appropriate. However, for optimal management of new infections in patients admitted to the ICU, an antibiogram specific to this population should be used, as ICUs generally have higher resistance rates compared with other units. Antibiograms should only include species with at

Table 1
Common pathogens and empiric antibiotic regimens in critically ill patients by presumed infection source

Presumed Source	Community-Acquired/Low Risk for Antibiotic Resistance[a]	Healthcare-Associated/High Risk for Antibiotic Resistance[b]
Pulmonary	*Common pathogens: S pneumoniae, H influenzae*, atypicals (eg, *Legionella*) *Suggested regimens:* • Ceftriaxone + azithromycin • Levofloxacin is an alternative option, but should not be used as monotherapy in septic shock • Add Vancomycin if patient has septic shock, known MRSA colonization, or necrotizing pneumonia/empyema	*Common pathogens:* gram-negative bacilli (including *Pseudomonas*), *S aureus* (including MRSA) *Suggested regimens:* • Cefepime • Piperacillin/tazobactam • Imipenem or meropenem (if known or suspected colonization/infection with ESBL organisms) • Add vancomycin if patient has septic shock, known MRSA colonization, or necrotizing pneumonia/empyema • Add aminoglycoside or levofloxacin if septic shock and very high-risk for MDR gram-negative organisms • Add azithromycin or levofloxacin if suspicion for *Legionella*
Gastrointestinal/ intra-abdominal	*Common pathogens:* polymicrobial gastrointestinal flora including enteric gram-negative organisms, enteric streptococci, and anaerobes *Suggested regimens:* • Ceftriaxone + metronidazole Piperacillin/tazobactam (if patient has septic shock) • Cefepime + metronidazole (if patient has septic shock)	*Common Pathogens:* Polymicrobial GI flora but greater prevalence of resistant *Enterobacterales, Pseudomonas, Enterococci,* and *Candida* • Piperacillin/tazobactam • Cefepime + metronidazole • Imipenem or meropenem (if known or suspected colonization/infection with ESBL organisms) • Add antifungal therapy (echinocandin) if bowel perforation, heavy colonization with *Candida,* or microbiologic evidence of yeast on intra-abdominal specimens
Skin/soft tissue	*Common pathogens: Streptococcus, S aureus* (including MRSA if purulent cellulitis or abscess) Consider unusual organisms (*C perfringens, Vibrio, Aeromonas*) if necrotizing skin/soft tissue infection *Suggested regimens:* • Vancomycin + ceftriaxone • Add metronidazole if infection involves the groin area • If necrotizing infection suspected (eg, septic shock or crepitus), consult surgery and infectious diseases, and use vancomycin + piperacillin/tazobactam + clindamycin	*Common pathogens: Streptococcus, S aureus* (including MRSA), resistant gram-negative bacilli *Suggested regimens:* • Vancomycin + cefepime • Add metronidazole if infection involves the groin area, or use piperacillin/tazobactam instead of cefepime/ceftazidime • If necrotizing infection suspected (eg, septic shock or crepitus), consult surgery and infectious diseases, and use vancomycin + (piperacillin/tazobactam or imipenem or meropenem) + clindamycin

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Presumed Source	Community-Acquired/Low Risk for Antibiotic Resistance[a]	Healthcare-Associated/High Risk for Antibiotic Resistance[b]
Urinary	*Common pathogens:* gram-negative bacilli *Suggested regimens:* • Ceftriaxone • Cefepime or ceftazidime (if patient has septic shock) • Fluoroquinolones alone should not be used as first-line treatment	*Common pathogens:* resistant gram-negative bacilli including *Pseudomonas, Enterococci, Staphylococci* (with urinary catheters) *Suggested regimens:* • Cefepime (or ceftazidime) • Imipenem or meropenem (if known or suspected colonization/infection with ESBL organisms) • Add vancomycin if patient has septic shock, history of MRSA colonization in the urine, recent instrumentation, or indwelling urinary catheter
Unknown	*Suggested regimens:* • Vancomycin + ceftriaxone • Vancomycin + (ceftazidime, cefepime, or piperacillin/tazobactam) (if patient has septic shock) • Add azithromycin or levofloxacin if atypical pneumonia is possible • Add metronidazole if intra-abdominal sepsis is possible and no other anaerobic coverage	*Suggested regimens:* • Vancomycin + (cefepime or ceftazidime) ± Metronidazole • Vancomycin + piperacillin/tazobactam • Vancomycin + (imipenem or meropenem)* • Add azithromycin or levofloxacin if atypical pneumonia is possible • Consider adding antifungal therapy (echinocandin) if central line-associated bloodstream infection is possible

Underlined antibiotic choices indicate preferred regimens in most scenarios.

[a] Community-acquired/low risk for antibiotic resistance - consider low-risk if none of the following are present: intravenous antibiotic exposure in past 90 days, hospitalization (5 or more days) in past 90 days, currently hospitalized greater than 5 days, residence in a chronic care facility, chronic hemodialysis, or immunocompromised state.

[b] Healthcare-associated/high risk for antibiotic resistance - consider at risk if any of the following are present: intravenous antibiotic exposure in past 90 days, hospitalization (5 or more days) in past 90 days, currently hospitalized greater than 5 days, residence in a chronic care facility, chronic hemodialysis, or immunocompromised state.

least 30 isolates available, which may limit usefulness for uncommon pathogens or smaller institutions.[31]

Risk Factors for Multidrug-Resistant Organisms

Although antibiograms provide a valuable population-level snapshot of local resistance patterns, they cannot capture patient-specific variables that influence the risk of resistant infections. To select the most appropriate empiric regimen—especially in critically ill patients—it is essential to combine antibiogram data with an assessment of individual risk factors for multidrug-resistant (MDR) organisms. Numerous studies have evaluated risk factors for MDR organisms across different infection syndromes.[32–37] Although the specific predictors may vary by site of infection—for example, risk factors for MDR pneumonia may differ from those for urinary tract or bloodstream infections—several clinical features have been consistently associated with increased risk of MDR pathogens across settings. The following factors are among the most robust and commonly identified risk factors.

- Recent health care exposure, including hospitalization or residence in a long-term care facility within the past 90 days
- Hospital-acquired (vs community-acquired) infection
- Recent antibiotic use, particularly broad-spectrum and intravenous agents, within the past 90 days
- Prior colonization or infection with MDR organisms (eg, MRSA, vancomycin-resistant *Enterococci* [VRE], extended spectrum beta-lactamase [ESBL]-producing *Enterobacterales*, carbapenem-resistant *Enterobacterales* [CRE], MDR *Pseudomonas*)
- Presence of indwelling medical devices, such as central venous catheters, urinary catheters, or tracheostomies
- Immunosuppression, including receipt of chemotherapy, chronic systemic corticosteroids, or solid organ/stem cell transplant
- Septic shock, which independently increases the risk of MDR infection and adverse outcomes
- Mechanical ventilation, which increases the risk of MDR pathogens in pneumonia
- Hemodialysis or other chronic organ support therapies

These risk factors should prompt clinicians to broaden empiric coverage to include resistant pathogens such as MRSA and *P aeruginosa*, depending on the suspected source of infection.

ESBL-producing Enterobacterales warrant special consideration given controversial efficacy from common first-line antipseudomonal β-lactams (eg, cefepime and piperacillin-tazobactam), necessitating empiric carbapenem therapy when infection is suspected. Key risk factors for ESBL infection include prior colonization or infection with ESBL organisms, recent exposure to later-generation cephalosporins (particularly when sepsis develops while on third- or fourth-generation cephalosporins), recent hospitalization or residence in a long-term care facility, indwelling urinary catheters, and recent travel to regions with high ESBL prevalence.[38,39] ESBL organisms most commonly cause urinary tract infections, but can also contribute to intra-abdominal infections, bacteremia, and pneumonia in critically ill patients.[40]

Geographic and Local Epidemiology Considerations

Empiric antibiotic selection must also be informed by local and regional resistance patterns, which can vary widely by geography, care setting, and health care infrastructure. For example, resistant gram-negative organisms such as ESBL-producing

Enterobacterales, CRE, and *Acinetobacter baumannii* are relatively uncommon in North America and Northern Europe but are endemic in parts of South Asia and Southeast Asia, Latin America, and the Middle East, where broader empiric coverage—including carbapenems or novel agents—may be warranted, particularly in patients with recent health care exposure.[41–44] MRSA prevalence also varies globally, influencing the need for empiric coverage in pneumonia or skin/soft tissue infections. Within hospitals, resistance rates tend to be highest in ICUs, making ICU-specific or source-specific antibiograms more useful than hospital-wide data. In resource-limited settings, broader empiric therapy may be necessary because of limited diagnostics or surveillance, while institutions with strong stewardship programs may support narrower initial therapy. Ultimately, general guidelines must be adapted to local epidemiology to ensure effective and judicious empiric antibiotic use.

Beta-Lactams as the Backbone of Empiric Therapy

Beta-lactams (BLs) are the backbone of empiric therapy in hospitalized and critically ill patients because of their broad-spectrum activity, favorable safety profile, and bactericidal properties. Anti-pseudomonal BLs such as piperacillin-tazobactam, cefepime, and carbapenems (imipenem/cilastin, meropenem) are commonly used for serious infections like sepsis, pneumonia, and intra-abdominal infections, as they provide reliable coverage against a wide range of gram-negative pathogens, including *P aeruginosa* and many gram-positive organisms. It is important to note that while ceftazidime is also anti-pseudomonal, it lacks clinically meaningful gram-positive coverage, making it unsuitable for empiric monotherapy when gram-positive pathogens are a concern. The broad-spectrum efficacy and clinical familiarity of most anti-pseudomonal BLs make them essential components of initial empiric regimens in acutely ill patients.

Piperacillin-Tazobactam versus Cefepime: Controversies

The choice between piperacillin-tazobactam and cefepime for empiric therapy—particularly in combination with vancomycin—has been the focus of ongoing debate. Early observational studies suggested that vancomycin plus piperacillin-tazobactam was associated with a higher risk of acute kidney injury (AKI) compared with vancomycin plus cefepime, likely because of synergistic nephrotoxicity.[45,46] However, the recent ACORN randomized controlled trial, which enrolled 2511 hospitalized patients started on anti-pseudomonal antibiotics (77% also receiving vancomycin) within 12 hours of presentation, found no significant difference in kidney outcomes between the 2 regimens, challenging prior observational findings.[47] Notably, the median duration of vancomycin therapy in ACORN was only 2 days, leaving uncertainty about nephrotoxic risks with longer courses. Additionally, an updated nationwide analysis of 8427 patients with septic shock also showed no difference in AKI rates with piperacillin-tazobactam or cefepime.[48] A subsequent large observational study using instrumental variable analysis reported higher mortality in sepsis patients treated with piperacillin-tazobactam versus cefepime, potentially because of the adverse effects of unnecessary anti-anaerobic therapy.[49] Yet these findings have been questioned by an analysis attributing the results to collider bias.[50] Balancing this, cefepime is associated with a risk of neurotoxicity—including encephalopathy and seizures—particularly when dosed inappropriately and in older adults, those with renal dysfunction, and critically ill patients.[51] Notably, the ACORN trial reported higher rates of delirium with cefepime compared to piperacillin-tazobactam, although other outcomes of neurotoxicity (such as seizures) were not assessed.[47] Given the totality of evidence, the authors generally consider piperacillin-tazobactam safe for empiric use with vancomycin,

particularly when anaerobic coverage is needed or when patients are at higher risk for cefepime-associated neurotoxicity.

Sequence of Administration of Vancomycin and Beta-Lactam

Empiric combination therapy with vancomycin and a broad-spectrum BL is commonly prescribed for patients with suspected sepsis. However, MRSA accounts for only a small proportion of sepsis cases, making vancomycin retrospectively unnecessary in most instances. When vancomycin is administered first in patients with limited intravenous access, it can delay BL initiation because of its prolonged infusion time (typically at least 60 minutes to reduce infusion reactions). Two retrospective studies suggest that administering BLs before vancomycin may improve outcomes.[52,53] Although these findings may be influenced by residual confounding, prioritizing BL administration remains appealing given that these agents are rapidly infused, well tolerated, rapidly bactericidal, and provide coverage against most sepsis pathogens.

Need for Double Coverage of Pseudomonas

Double coverage for *P aeruginosa*—typically with 2 agents from different antibiotic classes, such as an antipseudomonal BL combined with a fluoroquinolone or an aminoglycoside—is often recommended for patients with septic shock at high risk of multidrug-resistant gram-negative infection.[21] The aim is not synergy but to maximize the chance that at least 1 agent will be active when susceptibility is uncertain, as inappropriate initial therapy is linked to increased mortality, especially in sepsis or septic shock.[54–56] In patients with gram-negative bacteremia and sepsis, empiric double coverage has been associated with higher rates of appropriate empiric therapy and improved survival compared with monotherapy.[57]

However, there is little evidence of benefit to continuing double coverage beyond the empiric period, and prolonged use of combination therapy increases the risk of toxicity—particularly nephrotoxicity with aminoglycosides—and contributes to antimicrobial resistance. As such, once susceptibilities are known, definitive therapy should be narrowed to a single active agent.

Double coverage is generally not necessary in patients at low risk for resistant organisms or in those who are clinically stable. Moreover, certain agents commonly used for empiric double coverage (eg, aminoglycosides) have poor tissue penetration for specific infections (eg, pneumonia), which limits their efficacy as monotherapy and emphasizes their role as a temporary supplement during the empiric phase. Ultimately, double coverage should be used selectively and discontinued once culture results and clinical stability allow for de-escalation.

Empiric Use of Novel Beta-Lactam/Beta-Lactamase Inhibitor Antibiotics

Rising rates of highly resistant gram-negative pathogens over the past decade—including CRE and MDR *P aeruginosa*—have posed increasing challenges for empiric therapy in critically ill patients.[44] Fortunately, this period has also seen the development of safer and more effective BL/beta-lactamase inhibitor (BLI) combinations, such as ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-relebactam, reducing reliance on older, more toxic agents like colistin or polymyxin B.

Routine empiric use of these novel BL/BLI agents is generally discouraged because of their broad spectrum, high cost, and potential to promote resistance—particularly given the relative rarity of CRE and other multidrug-resistant gram-negative pathogens.[58] However, empiric use may be warranted in select high-risk patients, particularly those with prior colonization or infection with CRE or difficult-to-treat *Pseudomonas*, recent health care exposure in regions with a high prevalence of

resistant organisms, or recent receipt of multiple broad-spectrum antibiotics. In these situations, initiating therapy with a novel BL/BLI may be appropriate while awaiting culture and susceptibility data. When available, rapid diagnostic testing and early infectious diseases consultation should inform prompt de-escalation based on pathogen identification and susceptibility results.

Empiric Methicillin-Resistant Staphylococcus Aureus Coverage and Role of Methicillin-Resistant Staphylococcus Aureus Nasal Swab Testing

Although most patients treated for suspected sepsis do not have MRSA infections, the high morbidity and mortality associated with MRSA justify empiric coverage in select critically ill patients.[59] Vancomycin is often appropriate in those with known colonization, risk factors for MRSA, suspected pneumonia, severe skin and soft tissue infections (particularly with purulence), or suspected central line-associated bloodstream infections. Empiric therapy should be narrowed promptly once culture and susceptibility results are available.

Nasal swab testing for MRSA has emerged as a valuable tool to guide antibiotic therapy. A recent negative MRSA nasal swab has a high negative predictive value (NPV) for MRSA pneumonia—exceeding 95% in many studies—and can safely support withholding or discontinuing empiric vancomycin in patients with suspected pneumonia.[60] However, the NPV is lower for other infections (eg, bloodstream or soft tissue), and the positive predictive value (PPV) is limited in all contexts. As such, MRSA nasal swabs are best used to rule out MRSA rather than confirm its presence. Several studies have demonstrated that using MRSA swabs in this context can reduce unnecessary vancomycin use in critically ill populations with suspected pneumonia.[61,62] A negative MRSA nasal PCR result generally remains valid for at least 14 days, which can extend its utility in guiding antibiotic decisions across an episode of care.[63,64]

Empiric Vancomycin-Resistant Enterococcus Coverage and Role of Vancomycin-Resistant Enterococcus Rectal Swab Testing

Compared with MRSA nasal swabs, VRE rectal swabs are less well-studied for guiding empiric therapy. Known colonization does increase the risk of invasive VRE infection, particularly in immunocompromised patients, those with prolonged hospital stays, or recent broad-spectrum antibiotic use.[65,66] In these high-risk settings, empiric treatment with linezolid or daptomycin may be appropriate in patients with positive VRE swabs when *Enterococcus* is a likely pathogen (eg, intra-abdominal or catheter-related infections) and the patient is severely ill. However, most colonized patients do not develop invasive disease, and a positive swab lacks the specificity to justify routine empiric coverage. Furthermore, unlike MRSA, VRE infections often cause more indolent bacteremia, giving clinicians more time to assess the need for targeted therapy. In this context, a prior negative VRE swab can help support the decision to withhold empiric VRE coverage.[67]

Empiric Use of Linezolid for Necrotizing Infections

While vancomycin is generally used for empiric gram-positive coverage in severe necrotizing skin/soft tissue infections, linezolid is gaining popularity because of its ability to inhibit protein synthesis and suppress endotoxin expression.[68] Compared with clindamycin, which is commonly used for its antitoxin effect, linezolid exhibits higher susceptibility rates for MRSA and *Streptococcus* species.[68,69] In a large retrospective target trial emulation study of patients with invasive group A streptococcal infections, linezolid was non-inferior to clindamycin for in-hospital mortality when combined with

BL therapy, with no significant differences in length of stay or *C difficile* infection, supporting its use, particularly amid rising clindamycin resistance.[70] Linezolid may also be given as monotherapy rather than in combination with another agent. A recent quasi-experimental study comparing outcomes before and after updating internal guidelines for necrotizing soft tissue infections from vancomycin plus clindamycin to linezolid found similar efficacy but lower rates of AKI in the linezolid group, likely because of reduced vancomycin use.[71] This benefit may apply to necrotizing pneumonia also, although robust studies are lacking.[72,73] Outside of necrotizing infections, linezolid has shown similar efficacy compared with vancomycin for other severe MRSA infections, mainly complicated soft-tissue and pulmonary infections.[74,75]

Empiric Antifungal Therapy

Candida species are among the most common causes of nosocomial bloodstream infections in the ICU and are associated with very high crude and attributable mortality rates.[28,76] Empiric antifungal therapy is therefore an important consideration in critically ill patients with risk factors for *Candida* bloodstream infections, which include recent broad-spectrum antibiotic exposure, central venous catheter use, total parenteral nutrition, abdominal surgery (especially with gastrointestinal perforation or anastomotic leak), prolonged ICU stay, blood transfusion, and immunosuppression.[77] Colonization with *Candida* at multiple sites may also increase risk, although it is neither sensitive nor specific. Clinical clues such as persistent fever despite broad-spectrum antibacterial therapy or new signs of sepsis without an identified source should raise suspicion. However, several randomized controlled trials of empiric antifungal therapy in non-neutropenic critically ill patients at high risk for invasive candidiasis have not demonstrated improved clinical outcomes, highlighting the importance of careful patient selection.[78–80] In cases where empiric antifungal therapy is pursued, an echinocandin is typically preferred for empiric coverage because of its broad activity against most *Candida* species, including *C glabrata* and *C krusei*, and favorable safety profile. Early de-escalation or discontinuation based on culture data and clinical trajectory is essential to avoid overtreatment and minimize antifungal resistance.

Antibiotic Allergy Considerations

Selection of empiric therapy can be complicated by reported allergies. Up to 35% of patients self-report an antimicrobial allergy, although true rates are much lower.[81] Penicillin allergy is documented in up to 25% of US medical records, yet immunoglobulin E (IgE)-mediated reactions are confirmed in only about 5% of cases; true prevalence in the general population is approximately 1% to 3%.[82,83] Overdocumentation often stems from childhood hypersensitivity reactions, and up to 80% of previously positive patients lose sensitivity within 10 years.[84] Inaccurate allergy labels can lead to suboptimal antibiotic choices, increasing risks of *C difficile* infection, treatment failure, longer hospital stays, repeat therapy, and mortality.[85–88]

Clinicians should review reported allergies carefully, distinguishing non–immune-mediated effects (eg, diarrhea) or subsequent tolerance after a reported reaction from true hypersensitivity. For confirmed IgE-mediated reactions, cross-reactivity should be considered. In BLs, this is driven mainly by similarities in the R1 side chain: early generation cephalosporins share side chains with aminopenicillins, whereas later generations have minimal overlap.[89] Skin testing shows up to 25% of confirmed penicillin-allergic patients react to first-generation cephalosporins, but only about 2.4% react to third-generation cephalosporins, similar to the background rate.[90] Carbapenem hypersensitivity occurs in fewer than 1% of penicillin-allergic patients.[91,92] Given these low rates, later-generation cephalosporins should be considered as

carbapenem-sparing options in IgE-mediated penicillin allergy. Although test doses, allergy consultation, or desensitization may be appropriate, their utility is limited in the urgent empiric setting.

ANTIBIOTIC DOSING CONSIDERATIONS IN CRITICAL ILLNESS

Overview of Pharmacokinetics and Pharmacodynamics in the Critically Ill

Optimizing drug dosing in critically ill patients requires an understanding of pharmacokinetics (PK) and pharmacodynamics (PD). PK describes how the body absorbs, distributes, metabolizes, and eliminates the drug, or what the body does to the medication; PD is the relationship between the drug concentration at the site of effect and the resulting effect, or what the drug does to the body.[93,94] The interaction between PK and PD determines the drug's effect over time.

Critical illness often causes profound PK alterations, leading to increased or decreased plasma concentrations (Fig. 1). Contributing factors include changes in cardiac output, protein binding, hepatic or renal function, volume status, capillary leak, and drug absorption/distribution.

Absorption is the rate and extent of drug entry into systemic circulation. Intravenous administration ensures 100% bioavailability, whereas enteral absorption in the critically ill is unpredictable and often reduced by surgery, opioids, vasopressors, or gut edema; in such cases (excluding *C difficile* infections), intravenous therapy is preferred.

Distribution describes drug movement from circulation into tissues. In critical illness, volume of distribution frequently increases early (eg, from resuscitation, heart failure, malnutrition), lowering serum concentrations. Studies show BL distribution volumes up to twice those in healthy volunteers, supporting aggressive early dosing in sepsis.[95,96]

Metabolism, the biotransformation of a drug to facilitate excretion, is primarily hepatic and may be altered by changes in hepatic blood flow, enzyme activity, and protein binding. Phase 1 (oxidation, reduction, hydrolysis) is typically more impaired than

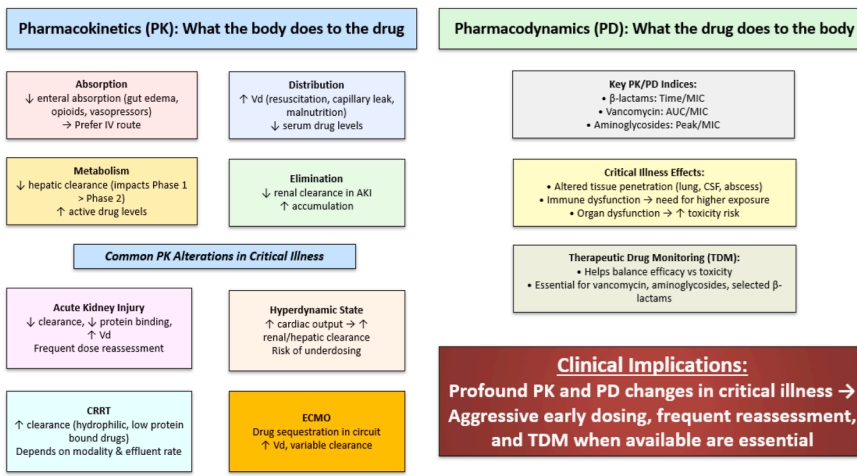

Fig. 1. Pharmacokinetic/pharmacodynamic changes in critical illness. AKI, acute kidney injury; AUC, area under the curve over 24 hours; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; MIC, minimum inhibitory concentration; TDM, therapeutic drug monitoring; Vd, volume of distribution.

phase 2 (eg, glucuronidation, sulfation) in acute liver injury, potentially increasing active drug levels.

Elimination, or drug removal from the body, is usually by means of renal excretion. AKI can markedly reduce clearance resulting in accumulation of drug.

Pharmacokinetics/Pharmacodynamics in Acute Kidney Injury

AKI is common in critical illness and presents substantial dosing challenges because of rapidly changing renal function, with AKI resolution sometimes seen within 24 to 48 hours. Key variables to assess include urine output, serum creatinine (Scr), and cystatin C. Urine output typically declines first, followed by rises in cystatin C, while Scr may lag up to 48 hours.[97]

Cystatin C is a low molecular weight protein that is constantly produced by all nucleated cells and eliminated by glomerular filtration.[98] It is less affected by muscle mass than SCr and is emerging as a valuable biomarker of kidney function, although it can still be impacted by some nonglomerular filtration determinants. Conditions that falsely elevate cystatin C include hyperthyroidism, obesity, inflammation, corticosteroid use, malignancy, human immunodeficiency virus (HIV), and smoking; conversely, hypothyroidism can falsely decrease levels.[98]

Most drug dosing adjustments are based on estimated kidney function using creatinine clearance (CrCl) or estimated glomerular filtration rate (eGFR), which assume steady state conditions. In critical illness, steady state is rare, making these estimates less reliable. For example, in anuric patients, true renal clearance is absent, rendering calculated CrCl or eGFR negligible. In early septic shock, however, the risk of underdosing antibiotics may outweigh the risk of accumulation, so clinicians must balance urgency with safety.

AKI also alters many pharmacokinetic processes. For example, enteral absorption may be reduced because of volume overload and gut edema.[99] Volume expansion increases volume of distribution and leads to hypoalbuminemia, which reduces protein binding. Renal metabolism and clearance may be markedly reduced.[99]

In patients with unstable renal function, drug dosing should be frequently reassessed – often multiple times per day – and individualized based on therapeutic drug monitoring when available, rather than relying on fixed levels. Cystatin C-based nomograms for multiple antimicrobials have shown promise in improving target attainment and reducing toxicities, although further validation in critically ill populations is needed.[100,101] Ultimately, optimal dosing in AKI requires integrating urine output, biomarker trends, hemodynamics, and pharmacologic properties of the drug.

Pharmacokinetics/Pharmacodynamics in Continuous Renal Replacement Therapy

Initiation of continuous renal replacement therapy (CRRT) introduces additional pharmacokinetic changes. Absorption is generally unaffected except for potential improvements in pH, which may enhance activity of drugs that rely on a less acidic environment.[99] CRRT increases circulating blood volume, altering the volume of distribution, while metabolism is typically unchanged, and elimination is greatly increased.

The type of CRRT will also impact drug removal. Solute removal occurs by means of convection (ultrafiltration driven by replacement fluid rate, effective for medium-sized molecules) and diffusion (passive movement across a semipermeable membrane driven by dialysis rate, effective for small-medium molecules such as electrolytes and BLs).[102]

The likelihood of drug removal by RRT is influenced by molecular size, protein binding, and volume of distribution.[103] Medications that are hydrophilic (volume of

distribution <1.5 L/kg) and those with limited protein binding (<80%) may be removed by RRT. Another important factor is the fluid replacement rate: higher rates lead to increased clearance of renally eliminated antimicrobials, often necessitating higher or more frequent dosing.

A stepwise approach to evaluating whether a medication will be removed by RRT is as follows. First, review drug properties (molecular size, protein binding, and volume of distribution) to determine if it is capable of being removed by CRRT. Second, identify the CRRT modality and replacement/dialysate rates. Third, consult the literature search for drug-specific CRRT clearance data.

Accelerated veno-venous hemofiltration (AVVH) or prolonged intermittent RRT (PIRRT) uses high filtration rates over shorter sessions (often overnight), allowing breaks for rehabilitation and other activities. Limited dosing guidance exists; key considerations include session duration, filtration rate, residual urine output, drug properties, and infection severity. A practical starting point is to give a dose after each session, with supplemental dosing during the session if clearance is high. For example, cefepime may be given a few hours into a 12-hour high-rate AVVH session, followed by a single dose after the session is completed to maintain time above MIC.

Pharmacokinetics/Pharmacodynamics in Extracorporeal Membrane Oxygenation

Extracorporeal membrane oxygenation (ECMO) can significantly impact drug pharmacokinetics, particularly for antimicrobials, leading to increased or decreased plasma concentrations.[104] A key mechanism is drug sequestration within the circuit, which is influenced by surface area of the tubing and membrane, type and age of the circuit, priming fluid, and coated versus noncoated tubing.[105] Sequestration lowers plasma concentrations and may cause therapeutic failure, while unpredictable release can prolong drug effects.

Lipophilic and highly protein-bound drugs are most susceptible to sequestration, although hydrophilic agents such as BLs and aminoglycosides still may be impacted. Drug properties such as molecular size, degree of ionization, lipophilicity, and plasma protein binding may all influence the extent of binding to the circuit components. ECMO also increases the volume of distribution, warranting aggressive initial dosing of hydrophilic antimicrobials, followed by adjustments as clearance declines.[106] Lipophilic medications (fluoroquinolones, sulfamethoxazole-trimethoprim) may also require higher early doses to offset sequestration.[106]

Membranes become saturated after subsequent doses, causing a sudden increase in free drug concentrations requiring dose adjustment. However, circuit changes or membrane replacements reset the saturation process, causing the drug to become sequestered again, making it essential to reassess dosing and obtain therapeutic drug monitoring.

Pharmacokinetic/Pharmacodynamic Targets of Antibiotics

Optimizing antibiotic therapy requires understanding both the PK and PD relationship between the drug and patient, and between the drug and pathogen. This latter relationship is defined by PK/PD parameters, which vary by the combination of antibiotic and bacteria. The 2 main categories are time dependent and concentration dependent.[107] Both depend on drug exposure relative to the pathogen minimum inhibitory concentration (MIC), the lowest concentration of an antimicrobial that will inhibit pathogen growth.[108] MICs can be interpreted broadly as susceptible versus nonsusceptible or in more nuanced ways such as susceptible dose-dependent or elevated, which may require dose optimization to reach optimal effect. To be labeled susceptible, an isolate needs to be at or below the MIC breakpoint for that agent.

Breakpoints consider PK/PD parameters and toxicity for agents and pathogens. An MIC that would require toxic concentrations to reach the target PK/PD parameter in the body would not be safe and thus classified as resistant or nonsusceptible. Importantly, breakpoints across different agents should not be compared. For example, an *E coli* isolate may have a ciprofloxacin MIC of 0.25 and a ceftriaxone MIC of 1. While the ciprofloxacin MIC may be lower, this does not necessarily correlate with increased clinical effectiveness, as both these MICs are susceptible.

Another commonly misunderstood principle is bacteriostatic and bactericidal antibiotics. Many infer this as antibiotics that kill bacteria versus do not kill bacteria. However, at physiologic concentrations, many bacteriostatic agents do cause bacterial death. These are in vitro microbiologic definitions, with bacteriostatic agents defined as a ratio of the minimum bactericidal concentration (MBC) to MIC of greater than 4.[109] In vivo, the MBC may be reached by the antibiotic, calling into question the bacteriostatic definition. Studies have failed to show clinical differences when using bactericidal versus bacteriostatic antibiotics.[110] Rather than use these definitions to decide on empiric therapy, clinicians should instead reference clinical literature comparing agents or clinical guidelines where appropriate.

Pharmacokinetic/Pharmacodynamic Considerations with Beta-lactams

BLs are time-dependent antibiotics, requiring free drug concentrations to remain above the MIC(fT>MIC) for optimal effect—traditionally at least 50% for penicillins, at least 50% to 70% for cephalosporins, and at least 40% for carbapenems.[111,112] In critically ill patients, higher targets may be beneficial: a recent meta-analysis found that 100% fT greater than 4 × MIC was associated with higher cure rates and lower resistance.[113]

Dose optimization often involves prolonged infusions for select agents, as recommended in the 2016 Society for Healthcare Epidemiology of America (SHEA)/Infectious Diseases Society of America (IDSA) stewardship guidelines.[114] Although benefits are not universal, studies in patients with elevated MICs or altered PK, including those with sepsis or septic shock, have shown improved outcomes.[115,116] A meta-analysis in adults with sepsis or septic shock found lower 90-day mortality with prolonged versus intermittent infusion, particularly for anti-pseudomonal BLs.[117] Most studies investigated anti-pseudomonas BLs, so benefit may not be seen with other agents. A loading dose over 30 minutes is recommended to rapidly achieve therapeutic levels. Barriers to prolonged infusions—drug stability, line availability, and compatibility with other infusions—can usually be mitigated through collaboration with nursing and pharmacy teams.

Prolonged infusion may be given as extended infusion (eg, cefepime 2 g over 3 hours every 8 hours) or continuous infusion. There are no clinical studies comparing prolonged infusion methods, although many experts consider the different strategies equivalent based on pharmacokinetic data. Implementation will depend on institution resources and needs.

BL therapeutic drug monitoring (TDM) is emerging as a tool for individualized dosing in critically ill patients, improving target attainment and cure rates, although a consistent mortality benefit has not been shown.[118] Its use may be most valuable in high-risk scenarios (eg, ECMO, high MICs, suspected toxicity, CRRT).[119,120]

An emerging strategy is delaying dose adjustment in AKI. Given BLs' favorable safety profile and frequent rapid AKI recovery, maintaining high initial dosing for 24 hours may improve outcomes. One observational study in ICU sepsis patients found lower mortality with delayed adjustment, although another failed to confirm this finding.[121,122]

Pharmacokinetic/Pharmacodynamic Considerations with Vancomycin

Vancomycin remains one of the most prescribed antibiotics in US hospitals.[123] Although newer agents such as daptomycin and linezolid are increasingly used for invasive MRSA infections, advances in monitoring have sustained vancomycin's role. As a concentration-dependent antibiotic, an AUC/MIC of 400 to 600 is recommended for severe MRSA infections.[124] This is based on data showing optimal efficacy at AUC/MIC of at least 400 and optimal safety at AUC no more than 600 mg*h/L, assuming MRSA MIC of no more than 1.[124] An MIC of 2—though technically susceptible—would require an AUC of at least 800, risking toxicity; in such cases, alternative therapy or infectious diseases consultation is advised.

AUC/MIC monitoring is safer than trough-only monitoring and feasible in general hospital settings.[125,126] In the ICU, however, rapidly changing PK complicates monitoring. Two-level AUC calculations are cumbersome and must be repeated after each dose change, while Bayesian modeling assumes steady state, which may be inaccurate early in critical illness.[127] For unstable patients, trough monitoring may be the only practical approach; AUC/MIC monitoring should be implemented once PK stabilizes to minimize toxicity risk.

SUMMARY

Effective antibiotic management in critically ill patients requires balancing the urgency of early, appropriate therapy with the risks of overtreatment, resistance, and toxicity. Clinicians must integrate knowledge of pathogen epidemiology, patient-specific risk factors, and local resistance patterns with an understanding of altered PK and PDs in critical illness, including the impact of organ dysfunction and extracorporeal therapies. Empiric regimens should be carefully selected, promptly reassessed as diagnostic data become available, and optimized through strategies such as dose adjustments, prolonged BL infusions, and therapeutic drug monitoring. These principles can help clinicians maximize therapeutic efficacy while minimizing harm, ultimately improving outcomes for this vulnerable population.

CLINICS CARE POINTS

- Do not delay antibiotics in septic shock. Each hour of delay in administering effective therapy increases mortality risk. In sepsis without shock or infection without sepsis, the urgency is lower, and time should be taken to confirm diagnosis before initiating broad-spectrum therapy.
- Obtain appropriate cultures before antibiotics whenever feasible, but do not delay treatment in unstable patients.
- Use syndrome-based empiric therapy guided by likely pathogens, local resistance patterns, and site-specific penetration.
- Incorporate ICU-specific antibiograms when available; general hospital data may underestimate resistance risk in ICU-acquired infections.
- Identify MDR risk factors early (eg, recent health care exposure, prior colonization, recent antibiotics, indwelling devices) to guide empiric coverage.
- Avoid unnecessary double coverage for *Pseudomonas*; limit to high-risk septic shock patients and de-escalate when susceptibilities return.
- Be cautious with allergy labels. Verify history to avoid unnecessary avoidance of preferred BL agents.

- Initiate loading doses of hydrophilic antibiotics (eg, BLs, aminoglycosides, vancomycin) in critically ill patients to rapidly reach therapeutic concentrations.
- Adjust dosing dynamically in AKI, CRRT, and ECMO; standard dosing may underexpose or overexpose patients.
- Use prolonged or continuous infusions for antipseudomonal BLs (after an initial loading dose) in critically ill patients with sepsis to optimize fT>MIC.
- Interpret MICs within drug context; lower MIC values across different agents are not interchangeable indicators of efficacy.
- Apply TDM for vancomycin, aminoglycosides, and selected BLs when available, particularly in unstable PK states.

DISCLOSURES

Dr Rhee reports grant funding from the Centers for Disease Control and Prevention and Agency for Healthcare Research and Quality to conduct research related to sepsis; royalties from UpToDate, Inc. for chapters related to procalcitonin use; and payments from DynaMed for his role as a sepsis topic editor. No disclosures for the other authors.

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