CHAPTER 92

Principles of Antimicrobial Prescription in Intensive Care Unit Patients With Acute Kidney Injury

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OBJECTIVE

This chapter will:

1. Identify antimicrobial- and patient-specific factors that may influence antimicrobial dosing in critically ill patients.

DESCRIPTION OF ANTIMICROBIAL PRESCRIBING PRACTICES IN THE INTENSIVE CARE UNIT

Antimicrobials are listed consistently in the top 10 drugs prescribed annually in the intensive care unit (ICU), with 70% of patients receiving at least one antimicrobial agent during their stay.[1,2] Approximately one third of patients receive antimicrobials as combination therapy empirically before de-escalation occurs.[3] Hospital expenditures for systemic antimicrobials in the United States was approximately $3.1 billion dollars in 2010.[4] Vancomycin, piperacillin-tazobactam, levofloxacin, ceftriaxone, and gentamicin accounted for the five most frequently prescribed antimicrobials in the ICU in a study of 183 hospitals in 2011.[2]

There is a difficult balance between over- and underdosing antimicrobials in critically ill patients. The concern for toxicity associated with prescribing too much of an antimicrobial is real, especially for drugs with narrow therapeutic indexes such as aminoglycosides and vancomycin. For both of these antibiotic drug classes, a supratherapeutic trough can result in nephrotoxicity. Prescribing too much of an antimicrobial often occurs because of a decreased clearance, as in the case of acute kidney injury (AKI). Approximately 19% to 67% of drugs are prescribed excessively in kidney disease.[5] Specifically, antimicrobials are dosed higher than recommended in elderly patients with chronic kidney disease and are common causes for AKI as well.[6] A decline in drug clearance forces the clinician to determine the need

for a change in dose, frequency, or both to avoid potential toxicity.

The adverse consequences of underdosing antimicrobials is amplified in critically ill patients because of the severity of their illness. An inadequate dose can be the result of improvement in clearance when a patient's renal function recovers and dose adjustment is overlooked.[7] Often we focus on the concern for toxicity and decreasing antimicrobial doses, but when the acute scenario resolves, we may increase the possibility of therapeutic failure resulting from inadequate dose readjustment. Another reason for inadequate dosing is that population-based data providing recommendations for standard dosing do not typically include a critically ill population. Therefore doses may be insufficient for this specialized patient population.[8,9]

Current studies are gaining better insight into inadequate dosing of antimicrobials in critically ill patients. For example, in the case of β-lactams, an assessment of current dosing indicated that only 16% of patients had antibiotic concentrations above the minimum inhibitory concentration (MIC) of the pathogen for 50% of the dosing interval and were less likely to have a positive outcome.[10] These inadequate concentrations may be due to increases in volume of distribution resulting from capillary leak and fluid resuscitation during the systemic inflammatory response syndrome (SIRS).[11] Patients with SIRS undergo a hyperdynamic effect from the activation of inflammatory mediators that could result in increased drug clearance. Last, the concept of augmented renal clearance (ARC) may explain the inadequate concentrations of antimicrobials.[12] ARC is defined as a creatinine clearance (CrCl) greater than 120 mL/min and has been associated with subtherapeutic concentrations and worsened patient outcomes.[13–15] ARC is hypothesized to be a natural response to critical illness in patients with a greater physiologic reserve.[16] Risk factors for ARC include age 50 years or younger, admission for trauma, and a modified Sequential Organ Function Assessment score of 4 or less.[12] Therefore patients with a low estimated CrCl and a high CrCl complicate antibiotic dosing because of the limited available data. This chapter discusses the relevant pharmacokinetic (PK) and pharmacodynamic (PD) concepts that must be considered for appropriate antibiotic prescribing in critically ill patients with an emphasis on those with AKI.

CONSIDERATIONS REGARDING ANTMICROBIAL THERAPY AND ACUTE KIDNEY INJURY

Appropriate Antimicrobial Selection

Selection of antimicrobials is dependent on factors such as the likely microorganisms causing the suspected infection, local resistance patterns to antimicrobials (i.e., institution and ICU-specific antibiograms), likelihood for multidrug-resistant pathogens, a patient's medication allergies, and the potential toxicities of therapy.[17] Antimicrobial therapy should also be (1) initiated as soon as possible after cultures are drawn, especially in sepsis where data has shown an increased risk of mortality by approximately 7% per hour of delay of appropriate antimicrobials and (2) adequate dosing to achieve adequate PK parameters, specific to the antimicrobial chosen. Inadequate therapy has been shown to be an independent risk factor for hospital mortality.[18,19]

In addition to appropriate initial selection, de-escalation of antimicrobials upon receipt of clinical data is also of importance. Prompt de-escalation of broad-spectrum antimicrobials (i.e., 48 to 72 hours of initiation) has shown to reduce broad-spectrum antimicrobial use and total duration of antimicrobial therapy, without an increase in mortality or recurrent infection.[20] Despite the limitations of rapid diagnostics (e.g., matrix-assisted laser desorption ionization – time of flight [MALDI-TOF], peptide nucleic acid fluorescent in situ hybridization [PNA-FISH]) and surveillance tools (e.g., Methicillin-resistant *Staphylococcus aureus* polymerase chain reaction, procalcitonin, respiratory cultures), these methods may be helpful in aiding with de-escalation, although limited data exist regarding clinical efficacy.[21,22]

Antimicrobial-Specific Factors

Dosage and dose frequency of antimicrobials are determined by their PK and PD characteristics. Antimicrobials can be characterized into three categories based on PD parameters: concentration-dependent, time-dependent, or a combination of both. The effect of concentration-dependent antimicrobials (e.g., aminoglycosides) depends on the relationship between the peak concentration obtained during a dosing interval and the MIC of the microorganism. These antimicrobials also tend to have a postantibiotic effect, allowing for continued suppression of antimicrobial growth after exposure. Time-dependent antimicrobials (e.g., β-lactams) are dependent on the amount of time that the unbound antimicrobial concentration exceeds the MIC during the dosing interval. Antimicrobials that are dependent on concentration and time (e.g., vancomycin) rely on a combination of both of the aforementioned characteristics. In general, for patients with AKI, retaining the dose is recommended to maximize PD for concentration-dependent agents, while decreasing the frequency of dosing for renally excreted agents for dose adjustment. The opposite is true for time-dependent antimicrobials, with the frequency largely being maintained, while the dose is decreased. To maximize the PD for time-dependent antimicrobials, recent data have evaluated the possibility of extending the infusion or administering a continuous infusion of these agents. Data support extended-infusion (e.g., 3 to 4 hours) in regard to an increased chance of PK target attainment, clinical cure, and a shorter hospital length of stay.[23] Two recent randomized controlled trials (BLISS and BLING II) evaluating continuous infusion of β-lactams, however, found no difference in mortality, when compared to standard administration.[24,25]

Antimicrobials and Concern for Acute Kidney Injury: Monotherapy and Combinations

In addition to finding the balance in dosing antimicrobials appropriately, clinicians also must consider antimicrobials as a nephrotoxin. Antimicrobials can be a significant contributor to the development of AKI with an antimicrobial-associated AKI prevalence up to 36%.[26] Forty-one drugs out of 182 (22.5%) representing the top 100 drugs in each of the six adult ICUs at a large academic medical center were determined to have nephrotoxic potential.[27] A total of 18,180 orders (22% of all orders) were made for these nephrotoxic drugs. Antimicrobials accounted for 37% (n = 6723) of the nephrotoxic drug orders. Aminoglycosides, amphotericin B, β-lactam antimicrobials used alone or in combination, and vancomycin are major contributors to antimicrobial-associated AKI.[3] In at least one third of these AKI cases, the antimicrobial was administered concomitantly with another nonantimicrobial nephrotoxin, with 50% of patients having dehydration at the time of admission.

The story of vancomycin-induced nephrotoxicity has seen an interesting evolution through the years. Vancomycin initially was considered to be highly nephrotoxic, and this toxicity was eventually correlated with the impurities in its formulation, leading to the name "Mississippi Mud."[28] After the product was purified, the concern for nephrotoxicity declined when used at appropriate doses.[29,30] The need for therapeutic drug monitoring came into question as the belief of vancomycin-induced nephrotoxicity was low when given alone.[31–34] Vancomycin given concomitantly with other nephrotoxins does appear to pose additional risk for nephrotoxicity (e.g., vancomycin and aminoglycosides or vancomycin and piperacillin/tazobactam).[35–37] Although there are opposing viewpoints to this, there is a lack of nephrotoxicity reported with these combinations.[38–40] In about one third of reported antimicrobial-associated AKI cases, patients received more than one possible antimicrobial-related nephrotoxin.[3] Other antibiotic combinations are suggested to increase risk as well, including amphotericin B and β-lactams. Administration of nephrotoxins is a modifiable risk factor for the development of AKI, so coprescribing of nephrotoxins including antimicrobials should be considered carefully.

Patient-Specific Factors

Volume of Distribution

Volume of distribution (V_D) may be altered in critically ill patients, with either an increase or decrease in total body water and intravascular volume. For example, in patients with septic shock, patients initially have a large V_D as a result of cytokine release, which only increases with volume resuscitation. V_D is the largest factor in drug dosing during the initial stages of septic shock, and therefore loading doses are necessary to obtain therapeutic levels quickly (e.g., vancomycin 25–30 mg/kg). So, larger doses of drugs with a large V_D are necessary until septic shock resolves or fluid is removed. Patients then may require lower doses of drugs as they approach their usual weight. In addition, patients who are obese with AKI may require increased doses of drugs to account for an increased V_D, although these data are limited given this specific patient population. These doses may approach that of patients who have preserved renal function. The presence of extracorporeal membrane oxygenation also may increase V_D, adding another factor to complicate drug dosing. Additional pathologies that may affect V_D include advanced liver disease and major burn injury. Hydrophilic antimicrobials (e.g., aminoglycosides, β-lactams, vancomycin) therefore may require higher doses than what is recommended because of this increased V_D.

Protein Binding

Critically ill patients may be affected by several variables, including acid-base disturbances and alterations in protein concentrations. Studies performed in the critically ill (e.g., sepsis) show that a decrease in the concentration of albumin or an increase in the concentration of alpha-1-acid glycoprotein may occur.[41] This decrease in albumin occurs because of increased vascular permeability (i.e., capillary leak) and decreased production, which typically does not recover until the recovery phase of critical illness.[42] Implications of these changes in proteins include increased active drug resulting from decreased protein binding (e.g., phenytoin and albumin) and changes in V_D.[43] Shifts in protein concentrations or acid-base status can affect the amount of unbound drug (i.e., active drug) available in the body. These changes ultimately can affect the amount of drug available for removal by the body (e.g., renal clearance).

Metabolism

Assessment of other organ function is essential to determine the potential for accumulation of active metabolites as well as parent compounds. Drug metabolism may be altered in renal failure, leading to altered hepatic metabolism and resulting in altered systemic clearance. One plausible explanation is the presence of uremic toxins that influence the change of cytochrome (CYP) activity.[44] Although data are limited, the use of renal replacement therapy (RRT) has been shown to increase the metabolism of certain medications that are metabolized via CYP.[45]

Elimination

Because of AKI, clearance of renally eliminated antimicrobials is decreased. Calculation of a patient's clearance of medications is also difficult, because commonly used methods such as Cockcroft-Gault or the Modification of Diet in Renal Disease (MDRD) formula have inherent limitations.[46] Neither of these methods is validated in patients with AKI and therefore have limited utility in estimation of CrCl. Further complicating antimicrobial dosing is the estimation equation used in the package insert for estimating CrCl. The application of RRT also complicates dosing recommendations. Studies have indicated that nonrenal clearance of drugs may increase when AKI initially occurs but decreases as continuous RRT (CRRT) is initiated. Nonrenal clearance is dominated by hepatic clearance but includes other organs as well. Antimicrobials exhibiting altered clearance include imipenem, meropenem, and vancomycin. Alterations to drug elimination include altered cytochrome P450 and P-glycoprotein systems, which may result in the accumulation of active metabolites. The existence of residual renal function also must be considered because this may further enhance drug clearance in a patient undergoing CRRT. The addition of residual renal function to CRRT clearance should be considered to ensure adequate dosing of drugs, especially antimicrobials. Furthermore, fluid removal by CRRT may result in changes in drug elimination by other organs.

Other Factors

Dosing may be required to be higher in patients based on the suspected severity of infection, in patients who have an impaired immune system, and in patients with deep-seated infection. In addition, antibiotic dosing may require higher dosing in patients with a hypermetabolic state, including burn injury patients. Finally, transdermal, subcutaneous, and oral administration drug absorption also can be affected significantly by volume overload and by peripheral and intestinal edema. Because edema is reduced with CRRT, enteral drug absorption may increase.

Renal Replacement Therapy

Modes of RRT include intermittent hemodialysis (IHD) and CRRT. RRT is used in approximately 6% of the ICU population that develops AKI. CRRT offers the potential advantage of continuous removal of fluid and solutes, reducing the

TABLE 92.1

Maintenance Dosing Recommendations for Select Antimicrobials Based on Renal Function or Renal Replacement Therapy

DRUG	CrCl < 30 mL/min	CRRT	HD
Acyclovir[a]	5–10 mg/kg q24h	5–10 mg/kg q12–24h	2.5–5 mg/kg q24h or 10 mg/kg after HD on HD days
Aminoglycosides	Dosing based on levels and adequate to achieve goal C_{max}/MIC: peak for efficacy and trough for safety; goal levels dependent on individual aminoglycoside		
Ampicillin-sulbactam	1.5–3 g q12h	3 g q8–12h	1.5–3 g q24h
Aztreonam	1–2 g q12h	1–2 g q12h	0.5–1 g q12h
Cefazolin	1–2 g q12–24h	1–2 g q12h	1–2 g q24h or 2 g qHD if HD in 2 days; 3 g if HD in 3 days
Cefepime	1–2 g q12–24h	1–2 g q12h	1 g q24h
Ceftazidime	1–2 g q12–24h	1–2 g q12h	1–2 g q24h
Ciprofloxacin	400 mg q12–24h	200–400 mg q12h	400 mg q24h
Colistin	2.5 × ([1.5 × CrCl] + 30), divided into two doses (q12h dosing)	160 mg q8h	100 mg daily on HD days, 75 mg daily on non-HD days
Daptomycin	4–10 mg/kg q48h	4–10 mg/kg q48h	4–10 mg/kg q48h
Doripenem	250–500 mg q12h	250–500 mg q8h	500 mg q24h
Fluconazole	200–400 mg q24h	200–800 mg q24h	50% of normal dose after HD
Levofloxacin	250–500 mg q24h or 500–750 mg q48h	250–750 mg q24h	250–500 mg q48h
Meropenem	0.5–1g q12–24h	0.5–1g q8–12h	0.5–1g q24h
Piperacillin–tazobactam	2.25–3.375 g q6–8h; 4.5 g q8–12h	2.25–3.375 g q6–8h; 4.5 g q8-12h	4.5 g q12h
Sulfamethoxazole/trimethoprim[b]	5–10 mg/kg q12–24h	2.5–7.5 mg/kg q8–12h	5–10 mg/kg q24h
Vancomycin	10–20 mg/kg q24h Alternative: dosing based on vancomycin levels		

[a]Dosing weight is ideal body weight in obese patients.
[b]Dosing based on trimethoprim content.
C_{max}, Peak serum concentration; *CrCl,* creatinine clearance calculated via Cockroft-Gault equation; *CRRT,* continuous renal replacement therapy; *HD,* hemodialysis; *MIC,* minimum inhibitory concentration; *q,* every.

potential fluctuations in electrolytes, fluid balance, and hemodynamic stability, compared with IHD. Although there is ongoing debate regarding the optimal use and application of RRT in the ICU, its frequent use necessitates drug dosing considerations. CRRT techniques include continuous venovenous hemofiltration (CVVH), continuous venovenous hemodialysis (CVVHD), and continuous venovenous hemodiafiltration (CVVHDF). Drug clearance follows the following pattern: CVVHDF>CVVHD>CVVH, because of the presence of replacement fluids in CVVHDF and CVVHD. This leads to different dosing recommendations dependent on the CRRT technique used. Drug dosing in IHD is expected to be less overall than CRRT, with dosing of antimicrobials generally recommended to occur after IHD has finished. Data support the potential administration of high-dose aminoglycosides before IHD in regard to goal pharmacodynamics goal attainment, but given the potential for delayed or interrupted IHD, risk of toxicity may not outweigh the potential benefit.[46a]

THERAPEUTIC DRUG MONITORING

There is a need for improved prescribing of antimicrobials in the ICU as we learn more about factors that influence the PK and possible toxicities or therapeutic failures. The focus on personalized dosing is attractive. Traditionally, clinicians are familiar with personalized dosing for drugs such as aminoglycosides and vancomycin. Recent data exist for therapeutic drug monitoring of β-lactams, colistin, daptomycin, fluoroquinolones, and linezolid, with dose selection based on PK and PD properties.[47] The concern for additional costs associated with personalized monitoring must be offset by clinical data demonstrating improved patient outcomes before widespread adoption.

ANTIMICROBIAL DOSING RECOMMENDATIONS

Table 92.1 provides maintenance dosing recommendations for some commonly used intravenous antimicrobial agents in the ICU. Dose ranges are provided to account for patient factors such as body weight, estimated creatinine clearance, severity of infection, and for CRRT as solute removal varies by the mode of CRRT. Dosing recommendations are based on available literature and expert opinion. Dosing in CRRT is based on limited, heterogeneous data. The dosing recommendations provided in Table 92.1 should serve as general guidelines and should not supersede clinical judgment. Initial loading doses do not have to be adjusted and should be considered strongly to achieve rapid therapeutic levels in serious infections.

SUMMARY

Optimal antimicrobial prescribing in critically ill patients requires consideration of PK and PD parameters. Despite the longevity of antimicrobial use, we still need to gain a better understanding of dosing in clinical scenarios such as ARC, increased Vd, and obesity. Antimicrobial prescribing

in patients with AKI adds to the complexity of dose selection. In addition, antimicrobial use alone can contribute to the development of AKI.

Key Points

1. Appropriate dosing of antimicrobials requires understanding of antimicrobial and patient-specific factors.
2. Antimicrobial-induced acute kidney injury is understudied, especially with combination therapy, in the critically ill patient.
3. Future studies are needed to optimize dosing strategies and to prevent adverse outcomes.

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A complete reference list can be found online at ExpertConsult.com.

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