CHAPTER 203

Drug Dosing in Pediatric Acute Kidney Insufficiency and Renal Replacement Therapy

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OBJECTIVES

This chapter will:

1. Describe the pharmacokinetic alterations that occur in critically ill children with acute kidney insufficiency that may affect drug dosing.
2. Review the limitations of the various methods used to calculate drug doses in children receiving continuous renal replacement therapy.
3. Identify the factors that influence drug removal through continuous renal replacement therapy.
4. Identify the factors that influence drug removal through intermittent hemodialysis.
5. Present a standard approach for crafting an appropriate dosing regimen for critically ill children on continuous renal replacement therapy.

Drug dosing in the pediatric population can be a challenging task and is particularly problematic in patients with acute kidney insufficiency (AKI) or those receiving renal replacement therapy (RRT). Dosing studies with RRT are sparse, especially for methods such as continuous renal replacement therapy (CRRT) and newer hybrid forms of dialysis such as slow low-efficiency dialysis and extended daily dialysis. In fact, less than 20% of currently used medications have dosing recommendations for CRRT, and less than 1% have recommendations for new hybrid therapies.[1] There are even fewer recommendations specific to pediatric patients. Therefore drug doses often are extrapolated from either the adult literature or clinical experience.

Several limitations exist with extrapolating drug doses for the pediatric population from the adult literature. First is the physiologic changes that occur during maturation that affect drug pharmacokinetics. For example, bioavailability is variable owing to changes in gastric acidity, motility, and enzymatic activity. Volume of distribution (V_d), which is the mathematic concept representing the nonphysiologic compartment in which a drug disperses, is higher in children, particularly for drugs that are highly water soluble (e.g., aminoglycosides). Protein binding is reduced, thereby increasing the free fraction or pharmacologically active portion of the drug at the site of action. Drug metabolism (phase I and phase II reactions) and elimination pathways are immature at birth but generally reach adult levels within 1 year.[2,3] Another limitation pertains to the methodology used in the adult literature. Many drug doses for CRRT are extrapolated from pharmacokinetic studies conducted in patients with chronic kidney disease on intermittent hemodialysis (IHD). They fail to account for the differences in nonrenal clearance that are observed in patients with AKI. Even studies that are specific to CRRT frequently use outdated CRRT technology and substandard dialysis doses, which can lead to dosing errors when applied to current practices. Furthermore, differences in drug removal may exist based on the method of clearance used because the efficiency of each mode can vary with each medication and its physical or chemical properties (i.e., molecular weight, water vs. lipid solubility). Finally, the dialysis prescription used in pediatric patients can provide greater clearance than that achievable with the same prescription used in adults. Because the dialysis prescription typically is measured by urea kinetic modeling (i.e., Kt/V where k = dialyzer clearance of urea, t = time of dialysis, and V = total body water) and V naturally is smaller in pediatric patients, greater clearance (and increased drug removal) can be obtained, in case K and t do not vary.

This chapter reviews principles of drug dosing in critically ill pediatric patients with AKI requiring RRT. The primary focus is to provide a framework for making dosing decisions rather than providing individual recommendations for specific agents given the lack of primary literature in this area and the variability that exists with local practices. Hopefully initiatives such as the Kidney Health Initiative, a partnership between the Food and Drug Administration and the American Society of Nephrology, will increase awareness for the importance of dosing studies in this realm.[4,5]

ESTIMATION OF CREATININE CLEARANCE

Quantification of kidney function is important in critically ill children to properly adjust the dosage of medications that are eliminated by the kidneys. The glomerular filtration rate (GFR) represents a direct overall measure of kidney

BOX 203.1

Common Equations to Assess Renal Function in Pediatric Patients

Timed Urine Specimen Creatine Clearance

CrCl = [Ucr × (Vur/SCr)] × [1.73/BSA]

CrCl, creatinine clearance (mL/min/1.73 m^2); Ucr, urine creatinine (mg/dL); Vur, total urine volume (mL) divided by the duration of the collection (min); SCr, serum creatinine (mg/dL), (when midpoint values are not available, use average serum creatinine values from start and end of collection period); BSA, body surface area (m^2)

Serum Creatinine-Based Formulas

Schwartz (updated)

Estimated GFR = 0.413 × (L/SCr)

GFR, glomerular filtration rate (mL/min/1.73 m^2); *L,* length (cm); *SCr,* serum creatinine (mg/dL)

Flanders Metadata

Estimated GFR = (0.0414 × ln(age) + 0.3018) × L/SCr

GFR, glomerular filtration rate (mL/min/1.73 m^2); L, length (cm); SCr, serum creatinine (mg/dL).

Counahan-Barratt

Estimated GFR = (0.43 × L)/SCr

GFR, glomerular filtration rate (mL/min/1.73 m^2); L, length (cm); SCr, serum creatinine (mg/dL)

Cystatin C-Based Formulas

Hoek

Estimated GFR = −4.32 + 80.35 / CysC

GFR, glomerular filtration rate (mL/min/1.73 m^2); CysC, cystatin C (mg/L)

LeBricon

Estimated GFR = (78 / CysC) + 4

GFR, glomerular filtration rate (mL/min/1.73 m^2); CysC, cystatin C (mg/L)

Larsson

Estimated GFR = $77.24 \times CysC^{-1.2623}$

GFR, glomerular filtration rate (mL/min); CysC, cystatin C (mg/L)

Rule

Native Chronic Kidney Disease: Estimated GFR = $66.8 \times CysC^{-1.3}$

Transplant recipient: Estimated GFR = $77.6 \times CysC^{-1.16}$

GFR, glomerular filtration rate (mL/min/1.73 m^2); CysC, cystatin C (mg/L)

Filler and Lepage

Estimated GFR = $91.62 \times CysC^{-1.123}$

GFR, glomerular filtration rate (mL/min/1.73 m^2); CysC, cystatin C (mg/L)

Zappitelli

Estimated GFR = $75.94 \times CysC^{-1.17}$

GFR, glomerular filtration rate (mL/min/1.73 m^2); CysC, cystatin C (mg/L)

Combined SCr-Cystatin C-Based Formulas

Zappitelli

Estimated GFR = $(43.82 \times e^{(0.003 \times Ht)}) / (CysC^{0.635} \times SCr^{0.547})$ [× 1.165 if renal transplant] [× $1.57 \times SCr^{0.925}$ if spina bifida]

GFR, glomerular filtration rate (mL/min/1.73 m^2); CysC, cystatin C (mg/L); SCr, serum creatinine (mg/dL); Ht, height

Chehade

Estimated GFR = $0.42 \times (Ht/SCr) - 0.04 \times (Ht/SCr)^2 - 14.5 \times CysC + 0.69 \times Age + (18.25$ if female or 21.88 if male)

GFR, glomerular filtration rate (mL/min/1.73 m^2); CysC, cystatin C (mg/L); SCr, serum creatinine (mg/dL); Ht, height (cm); Age (yrs)

Chronic Kidney Disease in Children (CKiD) Study

Estimated GFR = $39.8 \times (Ht/SCr)^{0.456} \times (1.8 / CysC)^{0.418} \times (30 / BUN)^{0.079} \times 1.076^{male} \times (Ht / 1.4)^{0.179}$

GFR, glomerular filtration rate (mL/min/1.73 m^2); CysC, cystatin C (mg/L); SCr, serum creatinine (mg/dL); Ht, height (m); BUN, blood urea nitrogen (mg/dL)

Bouvet

Estimated GFR = $63.2 \times (SCr / 96)^{-0.35} \times (CysC / 1.2)^{-0.56} \times (Wt / 45)^{0.30} \times (Age / 14)^{0.40}$

GFR, glomerular filtration rate (mL/min); CysC, cystatin C (mg/L); SCr, serum creatinine (μmol/L); Age (yr)

Data from references 18–29.

function and may be diminished significantly before the onset of overt signs or symptoms of kidney failure.[6,7] GFR is a measure of the renal clearance of a substance from plasma and is expressed as the volume of plasma that is cleared of that substance over 1 minute—in absolute values (mL/min) or in relative values (mL/min/1.73 m^2), after correction for body surface area.[6–8] Glomerular filtration must be monitored closely in the setting of acute kidney injury, especially in those children receiving potentially nephrotoxic agents that are eliminated by the kidneys. GFR is measured most accurately by evaluating the urinary or plasma clearance of exogenous filtration markers such as inulin, iohexol (^{99m}Tc-diethylenetriaminepentaacetic acid),[9] Cr-ethylenediaminetetraacetic acid (EDTA), or iothalamate.[6,7,10,11] However, these infusion techniques are impractical in clinical situations in which merely a reliable approximation of GFR is required to adjust medication dosages or to evaluate a trend in variable kidney function. As an alternative, equations that use serum creatinine levels are implemented routinely by clinicians to estimate GFR.[12]

Creatinine is an endogenous metabolic product derived primarily from the metabolism of creatine and phosphocreatine in muscle. Creatinine typically is present at relatively stable serum levels and reflects overall muscle mass. Creatinine is filtered freely by glomeruli; however, it also is secreted into urine by renal proximal tubular cells. Because creatinine is filtered primarily through the glomerular capillary wall, a common approach to estimating GFR in pediatric and adult patients is to measure the 24-hour urinary creatinine clearance (CrCl). A measured CrCl is calculated by analyzing creatinine levels obtained from serum and from a 24-hour urine sample (Box 203.1).[11,13] In the critical care setting, however, medical decision making and institution of therapy typically occur before completion of such prolonged evaluations. As such, some clinicians have investigated the accuracy of shorter collection periods.[14–16] One study of critically ill pediatric patients demonstrated that a 12-hour CrCl was as accurate as the standard 24-hour CrCl.[15] A second study of critically ill adult patients recommended a minimum collection period of at least 8 hours for clinical decision making.[14] Regardless of the urine collection period used, measured CrCl estimates can overestimate GFR by roughly 10% to 40% in healthy persons, owing to the renal tubular secretion of creatinine.[7,11,17] This can be particularly relevant when estimated CrCl is low.

To overcome the need to perform timed urine collections, several equations have been developed to provide a rapid

estimation of GFR or CrCl (see Box 203.1). Such equations typically incorporate patient weight, height, age, gender, and race. In addition, they assume that renal function is stable, with steady-state serum creatinine kinetics. In the pediatric population, the *Schwartz equation* has been evaluated broadly and used as eGFR.[6,8,15,30] The Schwartz equation originally was derived in 1976 from data obtained in 186 non–critically ill pediatric patients using factors such as patient height (as a measure of muscle mass) and plasma creatinine.[8] Subsequently, the Schwartz equation underwent several revisions for estimating GFR using patient height, serum creatinine level (using Jaffe creatinine methodology), and a constant based on the age and gender of the patient.[6,8,31,32] This formula has demonstrated adequate correlation with measured CrCl, along with sufficient accuracy for clinical use in pediatric patients without acute critical illness. However, several studies have demonstrated that the Schwartz equation was not an accurate indicator of kidney function in critically ill pediatric patients.[15,33,34]

Much of the precision of estimating GFR when using creatinine-based equations is dependent upon the creatinine assay. Creatinine values determined by enzymatic creatinine assays differ and are more accurate than the Jaffe method. Particularly at low levels (as is the case in the pediatric population), enzymatic creatinine values tend to run lower than those obtained with the Jaffe method, thereby resulting in an overestimation of GFR if used with the same constant "k" values recommended by the original Schwartz formula.[35,36] This prompted the development of updated values for constant "k" values to estimate GFR when obtaining serum creatinine levels with the enzymatic assay/analyzer. Using data obtained from the Chronic Kidney Disease in Children (CKiD) study, the largest prospective cohort study of chronic kidney disease (CKD) in children in North America, a new estimated growth factor receptor (GFR) Schwartz formula was generated, based on the enzymatic creatinine method. This new formula provided the best correlation with measured GFR in children with CKD: eGFR = k L/S_{CR}.[18] In his formula k = 0.413 and L is the patient height (see Box 203.1).

Another equation that uses plasma creatinine to estimate GFR is the Counahan-Barratt equation.[19] The Counahan-Barratt equation uses the plasma creatinine and patient length to estimate body surface area-adjusted GFR (mL/min/1.73 m^2). The Schwartz and the Counahan-Barratt equations are simple techniques to estimate GFR and remain the standard for rapid assessment of GFR in non–critically ill pediatric patients.

The evaluation of kidney function in critically ill pediatric patients represents an exceptional challenge owing to the significant variability in kidney function, altered body composition or muscle mass, inconsistent or poor nutritional status, irregular volume status, and hemodynamic instability seen in this population. As a result of such wide inconsistency, steady-state serum creatinine kinetics cannot be achieved readily, limiting the accuracy particularly of creatinine-based equations for evaluation of kidney function. In addition, such formulas do not account for obligate renal tubular secretion of creatinine, which may represent a greater overall proportion of total observed clearance at lower GFR.[37] Furthermore, an increase in serum creatinine typically is delayed behind the actual decrease in overall kidney function, so equations that estimate CrCl may not detect declining kidney function until a significant proportion of that function is lost.

Given the limitations associated with serum creatinine-based estimates of GFR in children (particularly in those with reduced muscle mass), recent studies have advocated for measuring other endogenous markers, such as serum cystatin C to estimate GFR.[20,21,38,39] Cystatin C is a nonglycosylated protein produced by all nucleated cells at a relatively constant rate.[40] Cystatin C is freely filtered, reabsorbed, and completely metabolized in renal tubular cells with little excreted in the urine; therefore it cannot be used to measure GFR by urinary clearance techniques. Production of cystatin C is independent of inflammatory conditions, muscle mass, gender, and age (>1 year).[41,42] However, serum cystatin C levels can be influenced by non-GFR determinants such as thyroid disease, corticosteroid use, and degree of adipose tissue.[36]

One study using a cystatin C–based GFR equation provided an improved estimate of GFR in non–critically ill children compared with that obtained with the Schwartz equation.[20] However, this equation has not been evaluated in critically ill children with AKI. Several additional cystatin C formulas have been derived and have not been proven superior to creatinine-based equations and are often much less practical.[43] However, in specific situations, reduced muscle mass equations using cystatin C may be more accurate than creatinine-based equations, particularly in children less than 2 years of age.[44]

Equations for estimated GFR (eGFR) have been developed that combine serum creatinine and cystatin C with demographic variables (height, weight, age, gender). Several combined creatinine and cystatin C equations have been shown to improve GFR estimations.[21–24] However, such equations become much more complex and less practical to use at the bedside, particularly in patients with evolving kidney injury.

PHARMACOKINETIC ALTERATIONS WITH ACUTE KIDNEY INSUFFICIENCY

The typical pharmacokinetic parameters that are evaluated in making drug dosing decisions are bioavailability, volume of distribution (V_d), elimination half-life, and clearance. Renal failure can have a profound effect on many of these parameters, and failure to recognize these changes can lead to inappropriate dosing regimens and possibly treatment failure.

The V_d can be altered significantly in critically ill children with renal failure.[45] Such alterations most commonly are due to increased extracellular volume, intravascular fluid shifts, and decreased protein binding. An increase in fluid volume from either fluid resuscitation or oliguria can increase the V_d, particularly for hydrophilic drugs such as the aminoglycosides. Accordingly, larger loading doses would be necessary to achieve similar peak serum concentrations. Conversely, the V_d of digoxin is known to be lower in patients with renal disease as a result of competitive inhibition of tissue binding.[45] Loading doses therefore should be reduced.

Plasma protein concentrations can change in patients with renal failure, influencing V_d by altering the free or unbound portion of drug available at the site of action.[46] The three major plasma proteins that influence protein binding are albumin, α_1-acid glycoprotein (AAG), and lipoproteins. Acidic drugs such as furosemide, theophylline, and phenytoin are bound primarily to albumin, whereas basic drugs such as lidocaine and morphine are bound to AAG.[45] Albumin concentrations typically are reduced in children with AKI, so the unbound fraction of drug

is increased. AAG, on the other hand, often is increased in AKI, so unbound drugs may be lower and the clinical effects are reduced.

Although renal failure naturally affects the clearance of drugs that are eliminated primarily by the kidney, it also can affect the clearance of drugs that are not. Hepatic metabolism can be reduced significantly in patients with end-stage or chronic kidney disease, but in patients with AKI, it can be highly variable.[47] In fact, some studies have demonstrated higher nonrenal clearance values for drugs in patients with AKI than in those with chronic kidney disease who have similar CrCl values.[48] For example, the nonrenal clearance of imipenem has been reported to be 90 to 95 mL/min in adult patients with AKI, compared with 50 mL/min for those with end-stage kidney disease ($p < .02$).[48] Meropenem has a nonrenal clearance of 40 to 60 mL/min in patients with AKI versus 30 to 35 mL/min with end-stage kidney disease. Extrapolating drug doses recommended for patients with chronic kidney disease to those with AKI therefore should be done with caution because of the associated risk for underdosing. Additional studies that are specific to pediatric patients are needed to address this concern.

Acute kidney injury increases not only the half-life of the parent compound (for renally eliminated medications) but also its active metabolites. This is of particular concern with drugs that have a narrow therapeutic window. For example, the active metabolite of midazolam, 1-OH-midazolam-glucuronide, has been shown to accumulate in patients with renal failure, leading to prolonged sedation.[49] In fact, one study noted levels of 1-OH-midazolam-glucuronide in a child with renal failure that were twice that of the population mean.[50] 1-OH-midazolam-glucuronide is removed effectively with continuous venovenous hemofiltration (CVVH) and continuous venovenous hemodialysis (CVVHD), whereas midazolam (the parent drug) is not.[51,52]

DOSING CONSIDERATIONS WITH RENAL FAILURE

Several key principles must be considered in establishing a dosing regimen for a critically ill child with renal failure (Box 203.2). One factor is the proportion of renal clearance for a given medication in relation to total body clearance. Generally, when renal clearance accounts for less than 30% of total body clearance, AKI will have minimal impact on drug removal.[53] Dosing adjustments therefore are not required. A second consideration, which is extremely important in the critically ill, addresses the balance between a need for aggressive therapy with the adverse effect profile of the individual agent. Depending on the severity of disease, it may not always be appropriate to choose drug doses that are at the lower end of the dosing range, particularly for medications that generally are considered safe (e.g., β-lactam antibiotics). A third consideration is the ability to reach the patient-specific pharmacodynamic goal after considering the pharmacokinetic alterations that exist with AKI (Table 203.1). Pharmacodynamics refers to the relationship between the concentration of a drug and the response that is obtained in the patient. For example, higher vancomycin concentrations may be necessary in a patient with an infection caused by methicillin-resistant *Staphylococcus aureus* in which the minimum inhibitory concentration (MIC) is 2 mcg/mL compared to a similar infection in which the MIC is 0.5 mcg/mL. Finally is the potential accumulation of active metabolites or the presence of toxic excipients found in IV formulations (e.g., benzyl alcohol, propylene glycol). In such instances, a safer alternative may exist (e.g., hydromorphone instead of morphine because of active metabolites with morphine that can accumulate in AKI and are not dialyzable).

BOX 203.2

Principles of Drug Dosing in Acute Kidney Injury

- The proportion of renal clearance in relation to total body clearance must be assessed. Drugs that are cleared predominantly by nonrenal mechanisms do not require dosing adjustments for AKI.
- The degree of renal insufficiency should be determined as the thresholds for dosing adjustments vary by medication.
- Accumulation of active metabolites and toxic excipients must be considered when selecting a medication in AKI. In some cases, a safer alternative may exist (e.g., hydromorphone instead of morphine).
- Dosing adjustments in the critically ill should balance the need for aggressive therapy because of high disease severity with the adverse effect profile of the medication. Clinicians should be careful to not underdose safe medications in the critically ill.
- Clinicians should consider the starting medication dose if renal function were normal and adjust downward rather than using a fixed dose from a tertiary reference. In some instances (e.g., meningitis), higher doses are required.
- Clinicians should recognize the limitations of creatinine clearance (CrCl) estimates particularly when CrCl is in the range of a dosing adjustment (e.g., an estimated CrCl of 28 mL/min when a dosing adjustment is recommended for CrCl < 30 mL/min).
- Drug doses should factor in pharmacokinetic alterations encountered with AKI and patient specific pharmacodynamics.

TABLE 203.1

Pharmacodynamic Goals of Commonly Used Antimicrobial Medications

ANTIMICROBIAL	PHARMACODYNAMIC PARAMETER THAT BEST DESCRIBES ACTIVITY	THRESHOLD FOR EFFICACY
Penicillins	fT > MIC	Greater than 50%
Cephalosporins	fT > MIC	Greater than 50%–70%
Carbapenems	fT > MIC	Greater than 40%
Aminoglycosides	fC_{max}:MIC	Greater than 8–10:1
Fluoroquinolones	AUC:MIC	Gram-negative: Greater than 125:1 Gram-positive: Greater than 30:1
Vancomycin	AUC:MIC	Greater than 400:1
Linezolid	fT > MIC AUC:MIC	Greater than 40%–80% Greater than 80–120:1

AUC:MIC, Ratio of area under the curve (AUC) to MIC; *fC_{max}:MIC,* ratio of maximum free concentration (fCmax) to MIC; *fT > MIC,* percentage of time the free concentration (fT) is above the minimum inhibitory concentration (MIC).
Data from references 54–56.

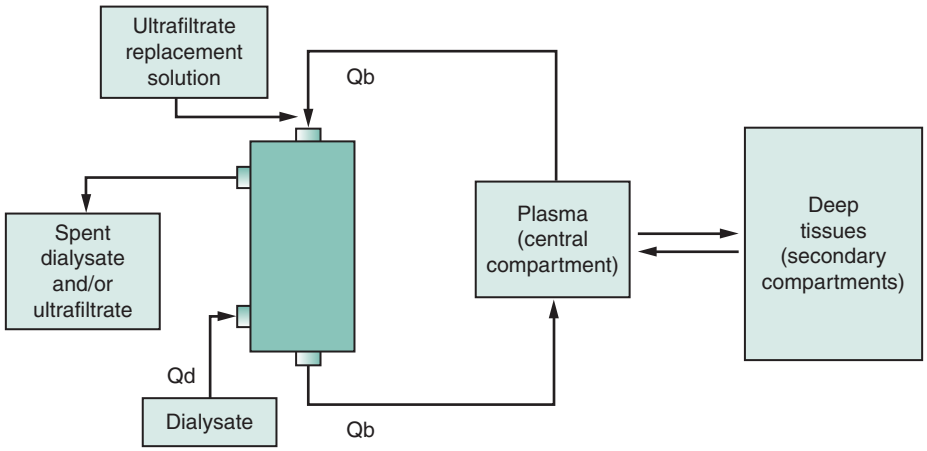

FIGURE 203.1 Pharmacokinetics of drug removal through continuous renal replacement therapy. Q_b, Blood flow rate; Q_d, dialysate flow rate.

DOSING CONSIDERATIONS WITH RENAL REPLACEMENT THERAPY

Continuous Renal Replacement Therapy

Continuous renal replacement therapy (CRRT) is becoming the most popular modality for dialysis in the critically ill patient with AKI.[57] When crafting a dosing regimen for CRRT, the clinician must evaluate several factors, which can be categorized as either drug related or dialysis related.[58]

The major drug-related factors that influence extracorporeal clearance are volume of distribution, protein binding, and molecular weight. Drugs that have a smaller V_d (i.e., less than 0.6 L/kg) are removed more effectively than drugs with a larger V_d. This is because drugs with a smaller V_d generally are confined to the plasma (which in pharmacokinetic terms is known as the central compartment), and only solutes present in the plasma are removed by CRRT (Fig. 203.1). Drugs with a larger V_d distribute within deeper tissues and are less affected by the dialysis prescription. Instead, as drug is cleared from the central compartment during CRRT, an equilibration ultimately will occur as the drug is transferred back into the central compartment from the deeper tissues. The primary factor affecting drug removal in this case is not the rate at which the drug can be eliminated by means of CRRT, but the rate at which the drug can transfer from the auxiliary compartments into the central compartment. Another important point pertaining to V_d is that many patients with AKI will be fluid-overloaded secondary to oliguria, which will increase the V_d, particularly for water-soluble drugs (e.g., aminoglycosides). Removal of this fluid using CRRT therefore will lower the V_d and increase drug removal.

Another drug-related factor that can influence extracorporeal clearance is protein binding. Drugs that are highly protein bound (i.e., greater than 80%) are less likely to be removed via CRRT. In fact, protein binding often is used as a surrogate for sieving coefficients (applicable for hemofiltration) and saturation coefficients (applicable for hemodialysis). Clinicians should use caution, though, when estimating protein binding using tertiary references because they are not reflective of the variability that may exist secondary to critical illness.

Drug removal also can be influenced by molecular weight. However, this has become less relevant with the advancements in filter technology. High-flux hemofilters have increased permeability to mid-molecular weight molecules, such as vancomycin, and will remove more drug than low-flux filters. High-flux filters are used in almost all CRRT machines.[59]

The major dialysis-related factors that influence clearance are CRRT mode, CRRT dose (or effluent rate), and filter type. Drug removal through CVVH occurs by convection, whereas drug removal through CVVHD occurs by diffusion. Convective clearance is more efficient with removal of mid-molecular weight molecules versus diffusion, particularly with higher flow rates.[58] Clearance for drugs such as vancomycin therefore may be greater with CVVH than CVVHD. Many institutions use a combination of diffusive and convective mechanisms (e.g., continuous venovenous hemodiafiltration (CVVHDF)), which presents the most challenging scenario for optimizing drug dosing. This is not only because of the lack of pharmacokinetic literature specific to pediatric patients but also the pharmacokinetic variability related to the mode of dialysis. Unfortunately, combining the two methods does not always yield solute removal equivalent to the sum of the clearances for both methods used alone. In one study, clearance of smaller particles by CVVHDF using an M-60 filter was reduced moderately compared with the sum of the individual clearances.[9] Clearance values using an M-100 filter, on the other hand, were similar to the sum of convective clearance and diffusive clearance measured separately. By contrast, clearance of larger particles was markedly lower with both filters. In fact, the addition of diffusion did not increase clearance beyond that achieved with convection alone. This limitation can have considerable impact in use of medications with a larger molecular weight.

One of the most important dialysis-related factors influencing clearance is the CRRT dose or effluent rate. The relationship between drug clearance and CRRT dose has been established clearly.[60–62] Unfortunately, there is great variability in flow rates used in practice today that may not be consistent with that reported in drug-dosing studies. This led to concerns with underdosing of medications in CRRT.[63] In fact, several manuscripts have described the potential for underdosing in CRRT in pediatric and adult populations. One study described a pediatric pharmacokinetic model for meropenem and reported only 29% of patients younger than 1 year of age and 70% of patients between the ages of 1 and 5 achieved target attainment of

BOX 203.3

Stepwise Approach for Crafting Drug Dosing Regimens in Continuous Renal Replacement Therapy

- Use doses derived from clinical studies conducted in pediatric patients in whom the dialysis prescription (e.g., CRRT dose, mode, filter type) is similar to local practices.
- Extrapolate data from clinical studies conducted in adult patients in whom the dialysis prescription is similar to local practices. It is important to recognize the dissimilarities that exist between adult and pediatric patients.
- Use doses derived from in vitro pharmacokinetic studies in which the dialysis prescription is similar to local practices.
- Calculate the dose using pharmacokinetic principles and the estimated degree of clearance.
  - Dosage adjustment factor = $(Cl_{CRRT} + Cl_{Nonrenal} + Cl_{Residual}) / Cl_{Normal}$
  - Cl_{CRRT} = (1 − % protein bound) × Q, where Q = ultrafiltration rate or dialysate rate as indicated by mode
  - Use pharmacodynamics principles to determine if dose should be lowered or frequency prolonged.
  - Always consider patient-specific factors, such as the severity of infection, location of infection, and organism MIC.

40% time above the MIC with a 20 mg/kg dose every 12 hours.[64] This increased to only 56% and 86%, respectively, with a dosage of 20 mg/kg every 8 hours. Total effluent rate was significantly higher in younger children. A second study described β-lactam regimens in adult intensive care unit (ICU) patients with severe sepsis and septic shock.[65] Pharmacodynamic goals (i.e., 4 times the MIC) were achieved with doses recommended in CRRT[66] for meropenem in 81%, piperacillin-tazobactam in 71%, ceftazidime in 53%, and cefepime in 0. The preferred method for developing dosing regimens in critically ill children on CRRT is to use an individualized approach using data from published pharmacokinetic studies specific to the pediatric population. It is important that the dialysis filter type, CRRT modality, and effluent rates used in the study be similar to that used in the clinician's individual practice. Unfortunately, this literature is limited, and extrapolations from adult-based recommendations often must be made. In such instances, the pharmacokinetic alterations specific to children and the shortcomings of these studies themselves (regarding filter type, dialysis fluid rates, residual clearance, and so on) must be considered. A stepwise approach for crafting drug dosages in CRRT is presented in Box 203.3.

Intermittent Hemodialysis

The predominant mechanism for drug removal by hemodialysis is diffusion. Drug characteristics that favor elimination through hemodialysis are a small V_d, a low degree of protein binding, high water solubility, and a low molecular weight.[45,53] As with CRRT, the impact of molecular weight has changed substantially with the availability of newer, high-flux dialysis filters. These filters have larger pore sizes, allowing for passage of molecules up to 20,000 daltons. Conventional filters typically are impermeable to molecules larger than 1000 daltons. Vancomycin, which generally is considered a larger medication, has a molecular weight of approximately 1450 daltons.

After a hemodialysis session, occurrence of a "rebound" effect is not uncommon when the transfer rate of drug from blood to dialysate exceeds the transfer rate from the tissues to blood. For example, one study in adult patients demonstrated an increase in gentamicin serum concentration of approximately 27% within 1½ hours after dialysis.[67] Clinicians must be cautious when interpreting postdialysis drug concentrations that are drawn immediately after dialysis because the effectiveness of clearance can be overestimated. This error can lead to supratherapeutic doses and potentially increased toxicity.

In establishing drug regimens in the critically ill patient on hemodialysis, doses typically begin with the appropriate dose based on the estimated degree of residual renal function. Supplemental doses therefore are administered for medications that are eliminated adequately through hemodialysis. If doses are extrapolated from adult guidelines, a greater degree of drug removal for the pediatric patient should be considered.[68] Careful coordination of drug administration and the dialysis schedule is necessary to ensure that optimal drug concentrations are maintained. For example, administration of medications for which a high degree of clearance occurs through hemodialysis should be scheduled after the dialysis session has been completed. Greater clearance has been noted even for drugs that have a large V_d (and therefore minimal expected clearance) if they are administered immediately before or during dialysis, before distribution to the deeper tissues has been completed.

THERAPEUTIC DRUG MONITORING

Therapeutic drug monitoring can be particularly useful in optimizing dosing regimens for drugs that have a narrow therapeutic index. However, some important considerations arise in evaluating serum concentrations in patients with AKI. First is whether or not the serum concentration represents a steady-state level. Typically, it takes approximately 4 to 5 half-lives to reach steady state, but in the patient with AKI, half-life is prolonged significantly. Second is the timing of the level in relation to the dose. The most appropriate time for assessment (e.g., peak versus trough) will vary for each individual drug. It is essential to confirm that the blood sample actually was drawn at the time intended. For peak levels, adequate time for distribution must be allowed; otherwise, artificially high levels will be recorded. Samples for trough levels should be drawn within 1 hour before the next dose. A third factor is the timing of sampling in relation to dialysis and the potential for drug rebound. Finally, the severity of disease and specific pharmacodynamic principles (e.g., peak to MIC ratio for antibiotics) must be considered in determining the necessary therapeutic range.

CONCLUSION

A multitude of factors may affect drug dosing in critically ill children with renal failure who are undergoing renal replacement therapy. These factors can be drug specific, practitioner specific, or patient specific. Failure to appreciate this variability can lead to suboptimal drug dosing, potentially increasing the risk for treatment failure or drug toxicity. Unfortunately, the literature evaluating drug dosing in renal failure that is specific to pediatric patients is limited. Extrapolations from the adult literature, clinical guidelines,

and published references (electronic and print) must be made with caution, in view of the shortcomings of these recommendations and the advances in dialysis therapy since their publication. An individualized approach should be sought, with consideration of the clinician's personal preferences and practices. Therapeutic drug monitoring should be used when applicable.

Key Points

1. Pharmacokinetic alterations that occur in critically ill children with renal failure can be the source of significant error in dosing extrapolations from pharmacokinetic studies in healthy volunteers (and the adult literature), leading to inappropriate drug dosages in these patients.
2. Key considerations in establishing a dosing regimen in critically ill children with renal failure include the proportion of renal clearance in relation to total body clearance, balance between a need for aggressive therapy and the adverse effect profile for the medication, and the pharmacodynamic properties of the drug.
3. Factors that affect drug removal during continuous renal replacement therapy are the characteristics of the drug (e.g., volume of distribution, degree of protein binding, molecular weight), the mode of dialysis used (i.e., continuous venovenous hemofiltration, continuous venovenous hemodialysis, or continuous venovenous hemodiafiltration), and the dialysis prescription within each mode.
4. Dialysis prescriptions that use convective and diffusive mechanisms represent the most difficult scenarios for drug dosing, because combining the two methods may not always yield solute removal equivalent to the sum of removal with each method alone.
5. The availability of newer, high-flux dialysis filters has allowed for removal of drugs with much larger molecular weights, such as vancomycin.
6. Therapeutic drug monitoring should be used to optimize dosing regimens for drugs that have a narrow therapeutic index.

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