Chapter 6
Acute Kidney Injury and Renal Replacement Therapy

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6.1 Definition of Acute Kidney Injury (AKI)

For the purposes of risk stratification, renal failure has been defined functionally, and the term acute kidney injury (AKI) coined to describe progressive grades of functional abnormality. AKI of varying grades, in the presence of sepsis requiring antibacterial therapy is common in critically ill patients. AKI has been defined as a rapid decline in glomerular filtration rate (GFR) that occurs over hours and days. It corresponds with a rapid decrease in renal excretory function and the accumulation of products of nitrogen metabolism such as creatinine and urea, and other unmeasured waste products [1]. The term AKI is a consensus based, graded definition developed by the Acute Dialysis Quality Initiative (ADQI) group in 2004 [2], and the grading classification, under the acronym RIFLE were modified and improved by the Acute Kidney Injury Network (AKIN), which included the ADQI group, in 2007 [3–5]. The RIFLE classification is divided into three levels of renal dysfunction and two levels of clinical outcome: "Loss" and "End-stage kidney disease." The AKIN criteria proposed refinements to the RIFLE criteria by the introduction of a smaller change in serum creatinine (≥26.5 μmol/L) as a threshold to define the presence of AKI and identify patients with Stage 1 AKI (analogous to RIFLE-Risk). In addition, changes in serum creatinine are determined within a time window of 48 h instead of referring to a baseline value. Finally, any patients receiving renal replacement therapy (RRT) are to be classified as Stage 3 AKI (RIFLE-Failure).

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More recently, the Kidney Disease: Improving Global Outcomes (KDIGO) AKI Workgroup proposed a modified definition, harmonizing differences between the RIFLE and AKIN definitions [6]. No individual definition provides a consistently advantageous level of risk stratification. A summary of definitions is provided in Table 6.1.

The presence of renal failure contributes to altered antibacterial PK behavior by a number of mechanisms. Renal protein loss and competition for protein binding sites by unexcreted toxins may result in increased free fraction of antibacterial agents [7]. Reduced creatinine clearance is important for antibiotics substantially excreted via the renal route. Thus, accurate estimations of creatinine clearance and corresponding antibacterial clearance is necessary. Formulae that estimate creatinine clearance from serum creatinine are generally inadequate for this purpose [8]. We recommend direct measurement, for example, 8-h creatinine clearance, as the most viable and accurate method [9].

Table 6.1 Current definitions of renal failure based on function. Criteria are to be applied after an optimal state of hydration is achieved, and criterion that leads to the worst classification should be used

Classification	Definition for AKI	Stage	Serum creatinine	Urine output
RIFLE	An increase in SCr ≥50% within 7 days	Risk	To ≥1.5 times baseline	Less than 0.5 mL/kg/h for more than 6 h
		Injury	To ≥2 times baseline	Less than 0.5 mL/kg/h for more than 12 h
		Failure	To ≥3 times baseline or >0.5 mg/dL (>44 μmol/L) increase to at least 4.0 mg/dL (>354 μmol/L)	Less than 0.3 mL/kg/h for 24 h or anuria for 12 h
AKIN	An increase in SCr within 48 h	I	Increase of ≥0.3 mg/dL (≥26.5 μmol/L) or to 1.5–2 times baseline	Less than 0.5 mL/kg/h for more than 6 h
		II	To >2–3 times baseline	Less than 0.5 mL/kg/h for more than 12 h
		III	To >3 times baseline or ≥0.5 mg/dL (>44 μmol/L) increase to at least 4.0 mg/dL (>354 μmol/L) or initiation of RRT	Less than 0.3 mL/kg/h for 24 h or anuria for 12 h
KDIGO	An increase in SCr within 48 h or ≥50% within 7 days	1	Increase in SCr ≥0.3 mg/dL (≥26.5 μmol/L) within 48 h, or to 1.5–1.9 times baseline	Less than 0.5 mL/kg/h for more than 6 h
		2	To 2.0–2.9 times baseline	Less than 0.5 mL/kg/h for more than 12 h
		3	To 3.0 times baseline or to at least 4.0 mg/dL (>354 μmol/L) or initiation of RRT	Less than 0.3 mL/kg/h for 24 h or anuria for 12 h

AKI acute kidney injury, *Scr* serum creatinine, *RRT* renal replacement therapy

6.2 Epidemiology, Outcome, and Management of Sepsis and AKI

AKI has a hospital prevalence of 1.9% [10] but is more common in critically ill patients, and the prevalence of AKI rises to 40% at the time of admission to the intensive care unit (ICU) if sepsis is present [11]. Of patients in the ICU who develop new AKI, sepsis, and septic shock has been reported to be the likely cause in 11–50% of cases [12–14]. The incidence of AKI increases with increasing severity of sepsis, from approximately 19% in patients with moderate sepsis to 23% and 51% in those with severe sepsis and septic shock, respectively [15]. Conversely, the prevalence of sepsis amongst patients with AKI has been reported by two independent international multicenter studies; sepsis or septic shock occurring in 40.7% and 47.5% of the AKI patients, respectively [16, 17].

Mortality in patients with sepsis-associated AKI appears high. The BEST Kidney investigators reported a 70% overall hospital mortality in patients with septic AKI [12] and prognosis of AKI worsened with increasing age and severity of illness, use of vasoactive drugs, and mechanical ventilation [17]. Moreover, septic AKI patients had a longer duration of stay in both ICU and hospital than non-septic AKI patients [12]. In the same retrospective analysis of 120,000 patients described above, septic AKI was associated with significantly higher covariate adjusted ICU (OR 1.60, 95% CI 1.5–1.7) and hospital mortality (OR 1.53, 95% CI 1.46–1.60), compared with non-septic AKI [11].

The management of established severe sepsis and the varying degrees of AKI has important implications for antibacterial dosing. Treatment is based on initial resuscitation, maintenance of hemodynamic parameters, timely administration of antibacterial agents and source control, while supporting the failing organs and restoring the patient's homeostasis. Accordingly, the administrations of an effective intravenous antibacterial agent within the first hour of recognition of severe sepsis with or without shock are Grade 1C and 1B recommendations, respectively [18].

The use of renal replacement therapy (RRT) remains the mainstay of supportive therapy in patients with severe AKI. Timing of initiation of RRT remains controversial [19–22]. Nevertheless, RRT is often commenced when preventive and medical strategies have clearly failed to correct the underlying laboratory abnormalities with the aim to correct metabolic derangements, fluid overload, and to optimize the administration of fluids including medications, blood products, and nutrition.

Three fundamental forms of RRT are available: continuous, intermittent (either as intermittent hemodialysis (IHD) or sustained low-efficiency dialysis (SLED)), and peritoneal dialysis. Except in developing countries, the use of peritoneal dialysis is limited in the intensive care setting. The use of continuous renal replacement therapy (CRRT) for hemodynamically unstable patients is a Grade 2B recommendation according to the KDIGO guideline and is most commonly used worldwide [23]. This approach is supported by a small number of studies suggesting that continuous therapy might provide a greater benefit in terms of renal recovery [24–27].

The use of a hybrid form of RRT—sustained low-efficiency dialysis (SLED), also known as slow low-efficiency dialysis and extended daily dialysis is moderate intensity dialysis, often with a component of filtration, applied over a period of 6–12 h daily. The method is gaining some popularity. It has advantanges over other forms of IHD in terms of achieving comparable hemodynamic stability with CRRT [28], low anticoagulant requirements, lower cost, and improved patient mobility [29, 30]. However, resultant clearance is inconsistent and highly variable over short periods.

Although the options for performing RRT remain numerous, based on the epidemiological data from BEST and AKI-EPI, CRRT still remains the predominant mode of RRT used worldwide [16, 17].

6.3 Sepsis and Inflammatory Response: Effects on Pharmacokinetic Parameters

The inflammatory response associated with sepsis involves a complex interaction that involves cytokine and mediator release, endothelial damage, and changes in capillary permeability. The acute phase response is also associated with a rapid decrease in serum albumin concentration. In addition, systemic pH, heparin, free fatty acids, and drugs such as salicylate and sulfonamide may act as competitive displacers for drug binding [31]. Fluid shifts result in large extravascular, interstitial fluid accumulation [32]. In addition, therapeutic intervention contributes to total body fluid accumulation as a consequence of the infusion of a large volume of resuscitation fluid. Consequently, in the critically ill, hydrophilic antibacterials (e.g., aminoglycosides, beta-lactams, and glycopeptides) demonstrate a large increase in volume of distribution (V_d) [33–38]. By contrast, lipophilic antibacterials (e.g., fluoroquinolones) have an inherently larger V_d that is often not greatly affected by the inflammatory response and therapeutic interventions [39]. Although the V_d is generally expected to increase in the critically ill, this change is consistent only for certain antibacterials in those with AKI. Specifically, the V_d of amikacin is considerably higher in critically patients with severe sepsis and burns who develop AKI requiring the need of CRRT [40, 41]. For the beta-lactam group, the V_d of pipercillin/tazobactam, ceftriaxone, and ceftazidime is increased in patients with AKI with CRRT when compared to the general group of critically ill patients [42–45]. However, the V_d for cefepime is similar in the critically and non-critically ill [44, 46]. For the glycopeptide—vancomycin, despite a V_d in the critically ill that is nearly twice that of the general population (1.68 vs. 0.4–1 L/kg) [47, 48], the V_d in patients with AKI and CRRT is similar if not somewhat lower than expected 0.32–0.74 L/kg [49, 50]. The V_d of ciprofloxacin is unpredictable and is generally high in non-critically ill patients [51], critically ill patients [52, 53], and those with AKI needing CRRT [54–56]. Therefore, when formulating an individualized dosing

regimen, it is important that actual pharmacokinetic data, relevant to the specific antibacterial agent, is used, rather than making assumptions that broad groups of antibacterials behave similarly. The most accurate possible knowledge of V_d is critical for determining the loading dose of the chosen antibacterial with accuracy.

The physiological response of patients with infection is markedly heterogeneous, and organ failure, with an associated increase in mortality, is a common accompaniment of severe sepsis [18]. Until terminal hemodynamic collapse, the cardiac out in sepsis is generally high [57]. Thus in early sepsis, the glomerular filtration rate (GFR) is frequently increased, both by sepsis and by therapeutic interventions. The combination of hemodynamic alterations, together with fluid resuscitation, and the use of vasopressors as part of the management of sepsis leads to an increase in cardiac output [58, 59]. Increased cardiac output leads to increased renal blood flow and has been shown to be associated with increased glomerular filtration pressure and consequently an increased GFR. This augmented renal clearance (ARC) has consequences for antibacterial dosing [60].

However, should the sepsis response persist, progression to septic shock and multiple organ dysfunction syndrome (MODS) will develop. The definitive mechanisms resulting in septic AKI are yet to be elucidated. It is clear that renal dysfunction does not result from systemic hypoperfusion and ischemia alone [61, 62], but is more likely the result of renal inflammation and tubular responses to sepsis mediators [63, 64]. Septic AKI is associated with reduced GFR and elimination of filtered substances, including many antibacterials. Thus, individualized dosing regimes are necessary to ensure adequate therapeutic, but nontoxic antimicrobial exposure in patients with septic AKI.

The changes in the excretory function of the native kidneys are further complicated by the use of RRT to maintain homeostasis. Thus, a thorough understanding of the principles of RRT is also essential to advise dosing during the maintenance phase of the dosing regimen.

6.4 Goal of Antibacterial Administration

The goal of antibacterial administration is to rapidly attain therapeutic blood concentrations, based on an in vitro minimum inhibitory concentration (MIC), sufficient to kill the offending pathogen(s) [65–68]. Underdosing may result in decreased bacterial killing, failure of clinical resolution and increased resistance, while overdosing may result in toxicity [69].

In addition, understanding the relationship between the pharmacokinetic and pharmacodynamic properties of a chosen antibacterial is important to determine the optimal dosing regimen. Important pharmacodynamic parameters to consider are time above MIC, peak concentration (C_{max}), and the area under the serum concentration-time curve (AUC).

6.5 Achieving an Optimal Pharmacokinetic (PK)–Pharmacodynamics (PD) Relationships

For antibacterial agents that exhibit time-dependent killing (e.g., beta-lactams), maximal bacterial eradication is related to the time for which the serum concentration is above a threshold concentration: MIC ($\%T >$ MIC). Recommended concentrations range from 1 to 5 times MIC [70] for 40–100% of the dosing interval [71]. Using extended or continuous infusions should be superior to maximize time above the threshold concentration without unnecessarily high peak concentrations [72–76].

For concentration-dependent antibacterials (e.g., aminoglycosides), maximizing the C_{max}, between 8 and 10 times higher than the minimum inhibitory concentration (MIC) of the causative pathogen (C_{max}/MIC 8–10) [70, 77], is likely to result in maximal bacterial killing. Clinically, maintaining a fixed dosage with a prolonged dosing interval not only increases the efficacy of the treatment but also minimizes toxicity [77–79].

For antibacterials with both time and concentration-dependent killing characteristics (e.g., vancomycin and fluoroquinolones), achieving a sufficient ratio of the area under the concentration-time curve during a 24 h period (AUC24) to MIC (AUC 24/MIC) is required to optimize killing activity [80–82].

6.6 Basic Principles of Continuous Renal Replacement Therapy (CRRT)

In the critically ill, CRRT is the most common modality of RRT [16, 17]. Rapid fluid and electrolyte shifts in hemodynamically unstable patients are avoided and control of patient fluid balance is more precise than with traditional intermittent hemodialysis (IHD). CRRT is usually performed through a double lumen venous catheter situated in a large (usually femoral or internal jugular) vein, either as continuous venovenous hemofiltration (CVVH), continuous venovenous hemodialysis (CVVHD), or a combination of the two, continuous venovenous hemodiafiltration (CVVHDF) [83–85].

CVVH uses a predominantly hydrostatic pressure gradient to drag solute along with water across a filter membrane to achieve clearance by the principle of convection. Replacement fluid can be added to the circuit either before blood reaches the membrane (predilution) or after passage over the filter membrane (postdilution). Similarly to traditional IHD, CVVHD uses the principle of diffusion across a membrane to provide clearance of solute. This is achieved by generating a continuous concentration gradient using counter-current flow of blood and dialysate fluid, between which equilibration occurs. A combination of the two above techniques at the same time is known as CVVHDF.

6.6.1 Hemofiltration

Most commonly used antibacterials, including larger molecules such as vancomycin (1448 Da) and teicoplanin (1878 Da), are small enough that convective transport across commonly used modern membranes (pore sized 10,000–30,000 Da) is unimpeded [86, 87]. The ability of a solute (including antibacterials) to pass through the membrane is expressed as the sieving coefficient (S_c): the ratio of drug concentration in the ultrafiltrate to plasma.

In general, the S_c ranges from 0 to 1. The relatively small size of antibacterial agents means that protein binding (PB) is the main determinant of S_c. It has been suggested that the S_c can be estimated from published values of PB, such that $S_c = 1 - \text{PB}$, and measured S_c and S_c estimated from published values of protein binding are correlated [88]. However, because protein binding in the critically ill is variable, the S_c can vary widely for the same antimicrobial agent [54, 89–91]. Furthermore, the S_c may also be affected by membrane material and flux properties [92].

Replacement fluid can be added to the circuit either before the filter (predilution) or after (postdilution). In postdilution mode, solute clearance simply depends on ultrafiltration rate and S_c such that:

$$\text{Cl}_{\text{CVVH}}\left(\text{post}\right) = Q_f \times S_c$$

In predilution mode, the plasma entering the hemofilter is diluted by replacement fluid and antimicrobial clearance will be lowered by a correction factor (CF) determined by blood flow rate (Q_b) and predilution replacement rate (Q_{rep}). Thus,

$$\text{Cl}_{\text{CVVH}}\left(\text{pre}\right) = Q_f \times S_c \times \text{CF}, \quad \text{where CF} = Q_b / Q_b + Q_{rep}$$

The point of dilution is only likely to be significant if the rate of fluid replacement is high. The proportion of predilution may influence the S_c. For example, the S_c for vancomycin steadily decreases as the proportion of predilution increases, with higher clearances observed at a predilution:postdilution ratio of 1:2 when compared to the predilution mode [93].

6.6.2 Hemodialysis

Equilibration across the filter membrane is dependent on the interaction between drug molecular weight, blood flow, and dialysate flow. As the dialysate flow rate in CVVHD and CVVHDF is relatively low compared with blood flow rate [94], neither blood flow nor molecular size (for the same reasons as above) are important factors in clearance of most commonly used antibacterial agents. The ability of a solute to diffuse through the filter membrane is expressed as the saturation coefficient (S_d):

$$S_d = \frac{\left[\text{Drug}\right]\text{dialysate}}{\left[\text{Drug}\right]\text{plasma}}$$

Similarly to S_c, protein binding is the main determinant of S_d. It is membrane specific and ranges in value from 0 to 1. In usual practice, as blood flow rate is so much greater than dialysate flow, complete saturation is likely to occur and antibacterial clearance is effectively dependent on dialysate flow rate (Q_d) and S_d:

$$\mathrm{Cl}_{\mathrm{CVVHD}} = Q_d \times S_d$$

6.6.3 Hemodiafiltration

Hemodiafiltration combines both convection and diffusion clearance to eliminate solutes. In general, drug clearance in CVVHDF may be estimated as:

$$\mathrm{Cl}_{\mathrm{CVVHDF}} = \left(Q_f + Q_d\right) \times S_d$$

Although the two processes interact and simple addition of each component potentially leads to an overestimation of total clearance, the clinical relevance is unclear [86]. Interestingly, CVVHDF has shown to provide greater clearance than predilution CVVH with equivalent effluent (ultrafiltrate plus dialysate) flow [95]. For both CVVHD and CVVHDF, the estimation of S_d may be affected by protein binding, membrane material, and flux properties.

From these equations it can be seen that the main determinants of elimination by CRRT are sieving or saturation coefficient and effluent flow rate (ultrafiltration rate, dialysate flow rate, or the two combined). Antimicrobial S_c and S_d are closely related to the unbound protein fraction and acute phase changes in plasma protein concentrations are common in critical illness, affecting both S_c and S_d. Therefore, it is essential that the S_c and S_d used for antibacterial dosing estimation should be based from actual studies with substantially similar categories of critically ill patients. In addition, operating parameters (i.e., filter membrane type) should be similar. A summary of the different modes of CRRT and clearance calculations are outlined in Table 6.2.

Table 6.2 Calculated clearance based on the different CRRT modalities

Mode of CRRT	Calculation of CRRT clearance
CVVH (post)	$\mathrm{Cl}_{\mathrm{CVVH}}$ (post) = $Q_f \times S_c$
CVVH (pre)	$\mathrm{Cl}_{\mathrm{CVVH}}$ (pre) = $Q_f \times S_c \times (Q_b/Q_b + Q_{rep})$
CVVHD	$\mathrm{Cl}_{\mathrm{CVVHD}} = Q_d \times S_d$
CVVHDF	$\mathrm{Cl}_{\mathrm{CVVHDF}} = (Q_f + Q_d) \times S_d$

$\mathrm{CL}_{\mathrm{CVVH}}$ (post), clearance from continuous venovenous hemofiltration using postfilter hemodilution; Q_f, ultrafiltrate rate; S_c, sieving coefficient; $\mathrm{CL}_{\mathrm{CVVH}}$ (pre), clearance from continuous venovenous hemofiltration using prefilter hemodilution; Q_b, blood flow rate; Q_{rep}, predilution replacement rate; $\mathrm{CL}_{\mathrm{CVVHD}}$, dialysate flow rate; S_d, saturation coefficient; $\mathrm{CL}_{\mathrm{CVVHDF}}$, clearance from continuous venovenous hemodiafiltration

Unfortunately, CRRT is not a single modality applied in a uniform way. Variations in type of filter material, blood flow rate, pre- or postdilution fluid replacement, and effluent flow rate settings could result in substantially different antibacterial pharmacokinetics [96–98]. Furthermore, CRRT is frequently not continuous but is interrupted for technical reasons and to transport patients for imaging or surgery and delivered clearance may be considerably lower than prescribed. Thus, dosing of antibacterials should take these variables into account.

6.7 Individualized Dosing Based on First Principles (in Patients Receiving CRRT)

A number of factors contribute to altered antibiotic efficacy in this patient population, such as changes in V_d, the killing characteristics of the antibiotic, the MIC of the target organism, changes in non-CRRT clearance, the effluent rate (depending on the different CRRT modality), and saturation or sieving coefficient, as well as the fact that these coefficients may change with acute phase changes in plasma protein concentrations [23]. As a result, it is not surprising that rigid, protocol-based dosing results in a large proportion of patients being either under or overdosed [99–101]. Even adjustments based only on estimated or measured renal clearance are likely to be inadequate and there have been several calls for the development of methods of individualized dosing [101–104].

We, therefore, recommend a method of individualized antibacterial dosing based on first principles.

Following administration of a drug, the initial fall in concentration is due to the distribution of the drug through the various body compartments. The extent of this distribution is reflected by the V_d. The antibacterial loading dose should therefore be based on the *appropriate* V_d for critically ill patients. Thereafter falls in concentration are predominantly dependent on *total* clearance—total clearance being the sum of CRRT clearance, residual renal clearance, and non-renal non-CRRT clearance in a critically ill patient.

Our recommendation is to base the initial dose on the published V_d of each specific antibiotic in critically ill patients, and the target concentration of that antibacterial (Fig. 6.1) as dosing that does not take into account changes in V_d will frequently lead to low initial serum concentrations [44]. The target blood concentration is based on the MIC of the suspected organism, indicative local MIC data, or published breakpoint data for the organism published by international bodies such as European Committee on Antimicrobial Susceptibility Testing—EUCAST (www.eucast.org).

While V_d determines the initial or loading dose, subsequent dosing is determined by total drug clearance. In patients with oliguric AKI, total drug clearance is the sum of CRRT clearance, residual renal clearance, and non-renal non-CRRT clearance (e.g., hepatic clearance). In general, drugs with a high V_d (>1 L/kg) and high

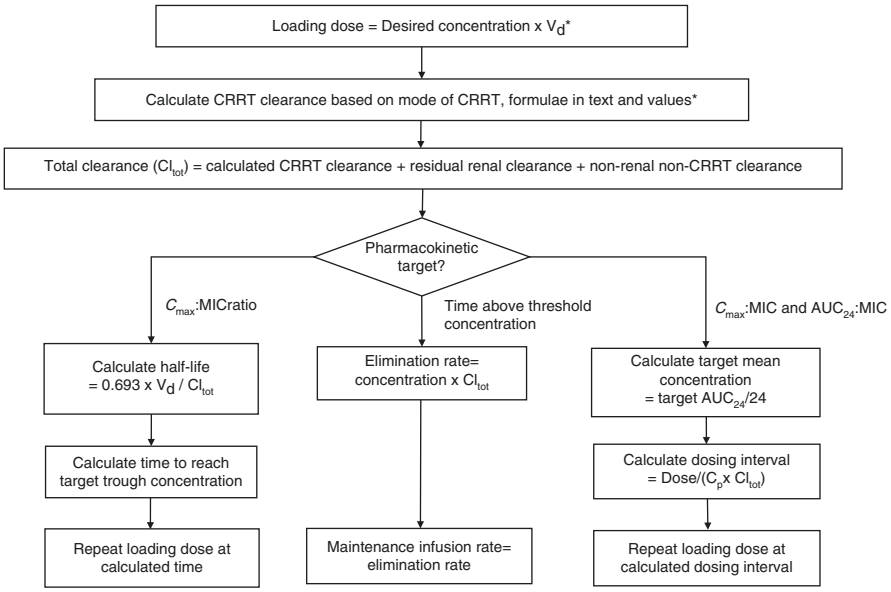

Fig. 6.1 Calculation of intravenous antibacterial doses based on first principles. CRRT, continuous renal replacement therapy; C_{max}, maximum postdistribution plasma concentration; MIC, minimum inhibitory concentration; AUC24, area under concentration-time curve over 24 h; V_d, volume of distribution; C_p, target plasma concentration. (*Asterisk*) Data obtained from website: http://www.aic.cuhk.edu.hk/web8/PK_data.htm

protein binding (>80%) are poorly eliminated by CRRT as the plasma concentration of drug available for filtration is low relative to the amount of antibacterial in the body [105]. This has led to the recommendation of reduced supplemental dosing of these drugs [106]. Nevertheless, this recommendation should be considered with caution. For example, for the lipophilic fluoroquinolones, such as ciprofloxacin and levofloxacin, V_ds are large (>1.5 L/kg), but renal clearance still accounts for ≥70% of total clearance [107, 108]. As V_d does not change, elimination half-life of both drugs will approach that of normal healthy volunteers when ultrafiltration and/or dialysate flow rates are high, obviating the need for reduced dosing [89]. For different reasons, some antibacterials with high protein binding will have an increased V_d as a result of reduced protein concentrations in the critically ill. This also leads to increased elimination by CRRT (and native kidneys) because of the increase in the free fraction of the drug. Appropriately adjusted CRRT clearance can be determined from the equations given above, assuming appropriate S_d and S_c are chosen.

For residual renal clearance, creatinine clearance should be measured. There is a risk of underdosing for agents with important tubular secretion or overdosing for drugs with tubular reabsorption although this is likely to be of limited clinical relevance [78].

Non-renal, non-CRRT clearance, for example, hepatic clearance may be variable depending on the degree of underlying organ failure and severity of illness [109, 110]. Dosing should also take into account the effect of hepatic failure. For example, the half-life of ciprofloxacin was increased in renal failure, but this was greatly exacerbated by additional hepatic failure [56]. Alternative elimination pathways such as transintestinal excretion (e.g., for ciprofloxacin) may represent compensatory mechanisms that also prevent accumulation in patients with renal failure [56]. Quantitative or at least qualitative evaluation of hepatic function should therefore be considered prior to formulating an antibacterial dosing regimen, in particular for agents with multiple routes of clearance (e.g., ciprofloxacin and meropenem).

Further examples of antibacterial dosing utilizing the principles outlined above are illustrated in Figs. 6.2 and 6.3.

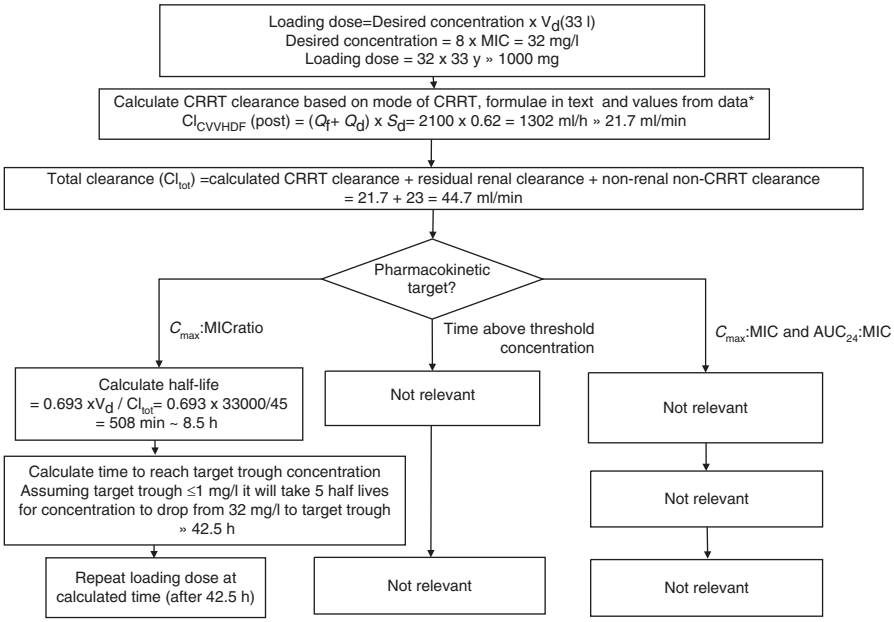

Fig. 6.2 Calculation of amikacin dose for empirical non-enterobacteriaceae (with MIC of 4 mg/L) nosocomial sepsis for a 70-kg patient with anuric acute renal failure on continuous venovenous hemodiafiltration using an AN69 filter and with targeted total effluent of 30 mL/kg/h. Note that figures are included for illustrative purposes. Dose prescribed should also take into account the risk of toxicity and may need to be reduced to comply with dose range approved by regulatory authorities. A formula for dose calculation for bolus dosing is given in the text. Cl_{tot}, total clearance; C_{max}, maximum postdistribution plasma concentration; MIC, minimum inhibitory concentration; AUC24, area under concentration-time curve over 24 h; CRRT, continuous renal replacement therapy; Q_f, ultrafiltrate flow rate; Q_d, dialysate flow rate; S_d, saturation coefficient; Cl_{CVVH}, clearance by continuous venovenous hemofiltration; V_d, volume of distribution; Cl_{CVVHDF}, clearance by continuous venovenous hemodiafiltration. (*Asterisk*) Data obtained from website: http://www.aic.cuhk.edu.hk/web8/PK_data.htm

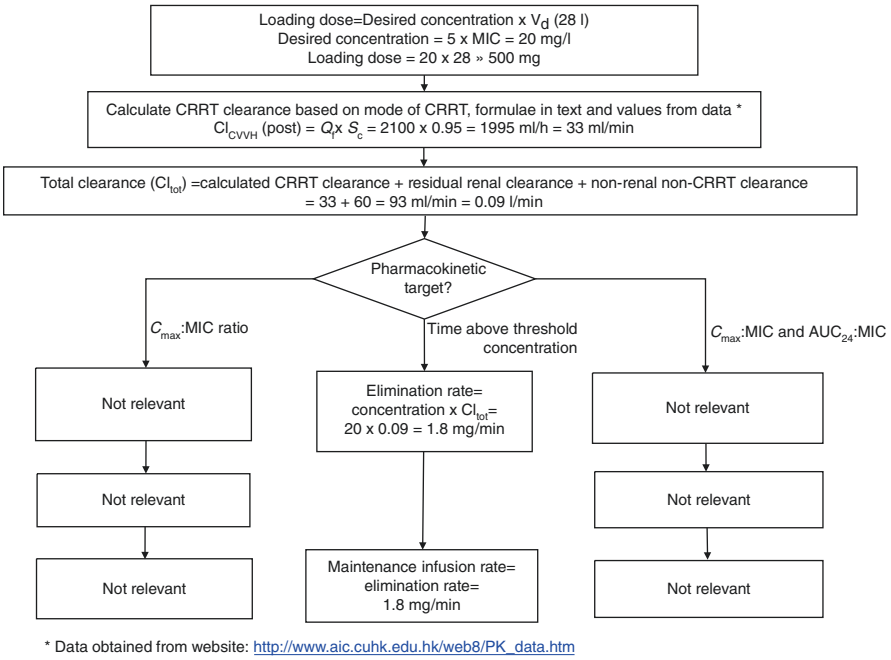

Fig. 6.3 Calculation of dose of meropenem for empirical non-enterobacteriaceae/enterobacteriaceae (with MIC of 4 mg/L) nosocomial sepsis for a 70-kg patient with anuric acute renal failure on continuous venovenous hemofiltration (postdilution) using AN69 0.9 m^2 filter with a targeted ultrafiltration rate of 30 mL kg h. Note that figures are included for illustrative purposes. Note that figures are included for illustrative purposes. Dose prescribed should also take into account the risk of toxicity and may need to be reduced to comply with dose range approved by regulatory authorities. A formula for dose calculation for bolus dosing is given in the text. Cl_{tot}, total clearance; C_{max}, maximum postdistribution plasma concentration; MIC, minimum inhibitory concentration; AUC24, area under concentration-time curve over 24 h; CRRT, continuous renal replacement therapy; Q_f, ultrafiltrate flow rate; Q_d, dialysate flow rate; S_d, saturation coefficient; Cl_{CVVH}, clearance by continuous venovenous hemofiltration; V_d, volume of distribution; Cl_{CVVHDF}, clearance by continuous venovenous hemodiafiltration. (*Asterisk*) Data obtained from website: http://www.aic.cuhk.edu.hk/web8/PK_data.htm

6.8 Critique of Currently Available Dosage Regimes in AKI

Details of published recommendations (Table 6.3) and their limitations for antibacterial dosing in critically ill patients have been previously summarized [112]. In brief, dosing regimes derived from either downward adjustment from healthy individuals or upward titration from chronic renal failure with adjustments based primarily on creatinine clearance are unlikely to result in consistently appropriate blood concentrations of antimicrobial agents in the critically ill [31, 111]. Doses recommended for anuric patients may also not achieve the appropriate PK-PD targets as a result of the changes in PK parameters expected in the critically ill. In addition, the optimal PK-PD target requires knowledge of the usual MIC of the

Table 6.3 Alternative equations to calculate dosing based on the modality of CRRT

Methods	Authors	Formula	Mode of CRRT
1	Schetz et al. [111]	$D = \dfrac{D_{\text{anuria}}}{1-\left(\dfrac{\text{Cl}_{\text{EC}}}{\text{Cl}_{\text{EC}}+\text{Cl}_{\text{NR}}+\text{Cl}_{\text{R}}}\right)}$	All modes
2	Bugge [31]	$D = D_{\text{N}} \times \left(P_{\text{x}} + \left(1-P_{\text{x}}\right)\right)\dfrac{\text{Cl}_{\text{CRtot}}}{\text{Cl}_{\text{CRn}}}$	CVVHDF
3	Schetz et al. [111]	$D = D_{\text{N}}\left(\dfrac{\text{Cl}_{\text{NR}}+\left(\text{UFR}\times S_{\text{c}}\right)}{\text{Cl}_{\text{N}}}\right)$	CVVH
4	Golper and Marx [88]	$D = C_{\text{SS}} \times \text{UBF} \times \text{UFR} \times I$	CVVH

C_{ss}, measured blood concentration at steady state; Cl_{ANUR}, drug clearance in anuric patient; Cl_{CRn}, normal creatinine clearance; Cl_{CRtot}, sum of renal and extracorporeal creatinine clearance; Cl_{EC}, extracorporeal clearance; Cl_N, normal total drug clearance; Cl_{NR}, non-renal clearance; Cl_R, renal clearance; D_{anuria}, recommended dose for anuric patients, D_N, dose recommended for patients with normal renal function; I, dosing interval; P_x, extrarenal clearance fraction (=Cl_{ANUR}/Cl_N); *UBF* unbound fraction, *UFR* ultrafiltration rate

suspected pathogen in the prescribing clinician's locality, and no previous dosing recommendation adjusts for this parameter. Furthermore, the assumption that S_d or S_c can be accurately estimated from data on protein binding [88] obtained from non-critically ill patients is likely to be inaccurate as these coefficients change with changes in plasma protein concentrations and binding capacity in the critically ill.

6.9 A Proposed Individualized Dosing Regime for Patients Receiving CRRT, Based on First Principles

We recommend individualized antibacterial dosing should be based on a dataset derived from published data in the critically ill receiving CRRT. The patient's dose should thus be derived from a dataset chosen by matching as far as possible the severity of illness, organ failure, and modes of support used. A selection of datasets from which to choose relevant PK data is available from our website (http://www.aic.cuhk.edu.hk/web8/PK_data.htm). This section is best understood if read with reference to the examples in Figs. 6.1, 6.2, and 6.3.

The loading dose is calculated using the published V_d of the specific antibacterial agent derived from a population of critically ill patients receiving CRRT. The desired blood concentration of the antibiotic is dependent on the MIC of the target organism(s). This information is sourced from the laboratory reported MIC, local MIC data accumulated within the ICU, or appropriate published clinical break-points, such as those published by EUCAST.

The maintenance dose is based on an estimate of total clearance, which is the sum of CRRT clearance, residual renal clearance, and non-renal non-CRRT clearance. Data selected (i.e., S_c and S_d) used to determine CRRT clearance should be from published data, where the operational characteristics such as blood flow rate, point of dilution of replacement fluid, and membrane material are as close to the individual patient's therapy as possible. Residual renal clearance should be determined by timed creatinine clearance, rather than formula-based estimation, and non-renal non-CRRT clearance should also be based on published data derived from critically ill patients receiving CRRT.

There are limitations to these recommendations. Firstly, for simplicity, the formula recommended for the calculation of the half-life is based on a single compartment and is therefore not strictly accurate. Second, continuous intravenous infusion of antibacterials with time-dependent killing characteristics is recommended because dose estimation is much simpler and evidence demonstrates better PK-PD target attainment in critically ill patients with [44, 45] and without RRT [113]. Thirdly, both residual renal clearance and non-renal non-CRRT clearance need to be accounted for. Thus, measurement of timed creatinine clearance is preferentially required, as estimations based on serum creatinine are inaccurate in critically ill patients [8]. This is of particular importance if CRRT is being employed early, before anuria, or during the recovery phase of oliguric/anuric AKI, for indications other than for AKI, such as maintenance of fluid control in massive blood transfusion, dysnatremia, temperature dysregulation, and toxin removal. Dosing should also take into account the effect of concomitant renal and hepatic failure. This is of particular importance for antibacterials with multiple routes of elimination, such as ciprofloxacin and meropenem. Actual values for non-renal non-CRRT clearance in critically ill patients are available [55, 56, 97, 114] and should be utilized as part of determination of total clearance. S_c and S_d may be derived for the individual patient from measured blood and effluent antimicrobial concentrations, but this capability is often not available for many commonly used agents or information is delayed. Reliance on published values from the critical care literature is a reasonable alternative.

Maintenance antibacterial doses are required to be amended whenever CRRT doses are altered (resulting in a change in effluent flow rate), or when the delivered dose of CRRT differs substantially from the prescribed dose. Lastly, the calculated dose may result in administration of very large doses, depending on the exact pharmacokinetic target chosen (e.g., C_{max}/MIC or %T >MIC) and the MIC. It is important that these doses are prescribed with due consideration of the risks of toxicity and may require consideration of the possibility that using another agent with a more favorable risk: benefit ratio as a preferable clinical choice. Where no suitable alternative exists it may be prudent to restrict doses to those approved by regulatory authorities. It is interesting to note that other authors have used a more aggressive regimen of dosing with antibacterials such as daptomycin in the healthy individual [115] and colistin in the critically ill [116], without apparently increasing the risk of toxicity.

The approach to individualized dosing described above, like all other dose adjustments for CRRT, has not been formally validated. Nevertheless, other authors

have advocated similar approaches, and recent data provide some supportive evidence [117–119] for this, by demonstrating a strong association between blood concentrations and effluent rate. In an in vitro model, Yamamoto et al. found that the ratio of predicted clearance (based on measurement of unbound fraction and effluent rate) to actual clearance ranged from 0.67 to 1.5 [119]. Beumier et al. found that serum concentrations of meropenem, ceftazidime, cefepime, and piperacillin-tazobactam were correlated with effluent rate when an unadjusted dosing regimen for patients were given to a group of septic patients requiring CRRT [99]. Similarly, effluent rate has been shown to be associated with doripenem clearance [120], piperacillin clearance [121] and vancomycin serum concentration [122]. Jamal et al. systematically reviewed the literature and demonstrated that CRRT clearance of meropenem, piperacillin-tazobactam, and vancomycin is associated with the effluent rate [123]. In some cases quoted above, CRRT clearance was derived from the equations given above and therefore CRRT clearance and effluent rate would have been mathematically coupled. However, not all current data supports the relationship between effluent rate and clearance. Roberts et al. found that trough concentrations of meropenem, piperacillin-tazobactam, vancomycin, and ciprofloxacin were not associated with effluent rate [100]. However, in this investigation, the dose of antibacterial given was at the discretion of the treating clinicians who may have taken the effluent rate into account, thus directly influencing the trough concentration despite the different effluent rates reported in the study. Udy et al. also found there was no relationship between vancomycin clearance and CRRT effluent rate, based on population pharmacokinetic analysis, suggesting the presence of multiple confounders influencing antibacterial prescription [124].

6.10 Intermittent Hemodialysis Techniques and Antibacterial Dosing

Several factors make antimicrobial dose optimization in patients requiring IHD difficult. These include the intermittent nature of dialysis, the high clearance rate for very short periods (2–5 h), rapid fluid removal, and the interaction of the timing of antibacterial dosing and the dialysis period [125]. While guidelines for the adjustment of antimicrobial dosage in patients requiring IHD are ubiquitous, the optimization of antimicrobial dosing *in critically ill patients* receiving IHD has received less attention than dosing associated with the use of continuous modes. Guidelines for IHD dose adjustments generally assume a thrice weekly HD exposure of 3–4 h duration as typically utilized in non-critically ill, chronic renal failure patients [126]. It is thus necessary to make intuitive adjustments to account for expected PK changes induced by critical illness. Recommendations also inconsistently stipulate that additional doses, or dose timing be adjusted to coincide with the end of dialysis sessions. The authors recommend that whenever possible, therapeutic drug monitoring (TDM) should be considered when IHD is utilized in critically ill patients.

In particular, there is an increased risk of antibacterial underdosage during SLED, especially during the second half of the extended dialysis session [127]. Dosing during SLED is likely to be more difficult than in continuous forms of RRT because of the large variation in clearance on and off SLED [125], with a period of high antimicrobial clearance (around 75 mL/min) alternating with no dialysis. It has therefore been recommended that institutions who utilize SLED should establish their own dosing guidelines to ensure delivery of antibacterials at adequate concentrations [128]. Antibacterials that are likely to require adjusted dosing are those that have a small molecular size, high water solubility, low protein binding, and are substantially dependent on renal clearance. The clinical use of SLED has, until now, been limited to only a relatively small number of centers, and consequently pharmacokinetic data to guide the establishment of guidelines in critically ill patients receiving SLED is limited. More data to guide dosing of antimicrobial agents is urgently needed to allow optimization of dosage when SLED is utilized, and once again, point of care TDM may offer the best solution for optimized dosage.

6.11 Therapeutic Drug Monitoring

The individualized antibacterial dosing regimes proposed in this chapter are based on first principles taking into account the optimal PK-PD goals. While it is possible to use published data in critically ill patients and calculations of CRRT clearance to improve dosing, considerable risk of inaccuracy remains. For example, the V_d of many antibacterials may vary considerably between individual patients, as may sieving and saturation coefficients. The magnitude of change is dependent on illness severity that fluctuates with time. Furthermore, changes in hepatic or gastrointestinal function, which are difficult to monitor clinically, may result in changes in non-renal non-CRRT clearance.

The use of therapeutic drug monitoring may be useful to adjust dosing regimes and adjust for individual patient variation. Currently, TDM is focused on a few antibacterials with emphasis on the prevention of toxicity (e.g., aminoglycoside trough concentration monitoring), with empirical adjustment by the clinician. To be successful from a therapeutic perspective, patient selection, sampling time, assay methods, and dose adjustment strategies need to be individualized for different classes of antibacterials [129]. To overcome the inherent inaccuracy in empirical clinician adjustments, future use should combine therapeutic drug monitoring with sophisticated population-based pharmacokinetic models, which take into account critical illness and the variability described above to generate more appropriate individualized antibacterial dosing regimes [130]. Studies to develop population PK models based on data from critically ill patients with AKI are currently underway [131]. Presently, only a limited number of ICUs utilize TDM routinely as a comprehensive therapeutic strategy [132].

6.12 Conclusion

Both AKI and sepsis are common in the critically ill, with the prevalence of AKI increasing in association with increasing severity of sepsis; the combination resulting in a high mortality rate. Recent agreed consensus definitions of AKI will facilitate the standardization of epidemiological and outcome studies to delineate optimal therapies in this special group of critically ill patients. While the pathophysiological mechanism of sepsis-induced AKI is yet to be completely elucidated, it is now thought that inflammation, microcirculatory dysfunction, and tubular cell adaptation to injury are the more common pathways involved. Recognition of AKI is important as it must be accompanied by measurement of creatinine clearance to facilitate appropriate antibacterial dosing. Similarly, awareness of the increased incidence of augmented renal clearance in subgroups of patients (e.g., resuscitated trauma, major surgical and burns patients) should lead to appropriate measurement of creatinine clearance and dose adjustment.

Timely administration of appropriately chosen antibacterial agents and optimal dosage combine to improve patient outcomes. In the critically ill, sepsis and/or AKI are associated with marked physiological alterations that are often associated with unrecognized pharmacokinetic changes. A thorough understanding of pharmacokinetic principles and organ function in the critically ill is required to guide appropriate dosing.

Although controversy exists regarding the optimal timing and mode of renal replacement therapy, continuous modes of renal replacement therapy are predominantly employed worldwide. However, CRRT is not a single modality and variability in practice leading to markedly different clearance may exist between and within the same institution and even the same patient.

The use of TDM informed by population-based PK data in critically ill patients offers further promise for the optimization of antibacterial dosing. Future directions should include the conduct of large-scale studies of AKI patients receiving CRRT with the development of pharmacokinetic models that can be used to generate optimized dosing applications.

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