Published in final edited form as:
Adv Chronic Kidney Dis. 2013 January ; 20(1): . doi:10.1053/j.ackd.2012.10.004.

Antimicrobial Dosing in Acute Renal Replacement

William H. Fissell[1]

William H. Fissell: William.fissell@vanderbilt.edu

[1]Nephrology and Hypertension, Vanderbilt University, Nashville, TN, P435G MRB IV 2213 Garland Avenue, Nashville, TN 37232 ph 615-343-2442

1. Background and Scope of Problem

Acute kidney injury (AKI) is a common problem in hospitalized patients, associated with significant morbidity and mortality (1). Despite numerous clinical trials that have aimed to improve the outcomes of patients with AKI or to prevent AKI, at present, our only intervention for severe AKI is renal replacement therapy (RRT, also known as dialysis), and AKI requiring RRT is associated with mortality rates of at least 40–50% in critically ill patients (2, 3). It has been estimated that the cost associated with AKI in the United States is upwards of 10 billion dollars/year. The public health and clinical importance of AKI has been further underscored recently by studies demonstrating that the incidence of AKI is rising rapidly (~7% per year), independent of potential changes in diagnostic coding (1). Two large trials showed no benefit from increased doses despite prior clinical and preclinical data suggesting that increased clearance from RRT has beneficial effects (2–6).

Since infection is the leading cause of death in AKI, many have hypothesized that the effects of increased RRT dose on antibiotic clearance may create a competing morbidity. Our own data, as well as those of other groups show that many patients are underdosed when routine “one size fits all” antibiotic dosing is used in patients with AKI on continuous RRT (CRRT) (7, 8) Underdosing jeopardizes recovery from infection and drives evolution of resistant bacterial strains (9). Thus, dialysis, the very therapy that we consider “life-saving,” may also increase mortality because it results in antibiotic underdosing. Design of better antibiotic dosing regimens requires insight not only into pharmacokinetics (“PK”), but also pharmacodynamics (“PD”) targets and identification of a high-risk patient population most likely to benefit.

There is a lack of knowledge on how to dose antibiotics in critically ill patients receiving RRT. Although it is clear that dialysis is life-saving because it clears the blood of toxins, including potassium, organic acids and nitrogenous waste products, dialysis may also have deleterious effects through clearance of medications, including antibiotics. Medication dosing for RRT, and in particular continuous forms of RRT, or CRRT, is frequently extrapolated from small case series of patients. Indeed, our own studies suggest that 25–60% of patients receiving CRRT have subtherapeutic antibiotic levels, despite dosing of antibiotics consistent with standard of care(8, 10). While a handful of antibiotics (vancomycin, aminoglycosides) can be dosed according to measured drug concentrations in

Disclosures: Dr. Fissell has received grant support from NxStage Medical, and the American Society of Nephrology, as well as the National Institutes of Health. He has served as a consultant to Gambro Renal Products.

blood (therapeutic drug monitoring, or TDM) because levels are routinely measured by hospital clinical laboratories, it is not feasible to measure drug levels for the vast majority of antibiotics.

2. Brief Review of Pharmacokinetic and Pharmacodynamic Principles

The study of drug effects in animals and man includes “pharmacokinetics”, or the processes by which the body takes in, distributes, and disposes of a drug, and “pharmacodynamics” which refers to the processes by which the drug has its desired effect. For critically ill patients with renal failure, drug disposition is likely to be altered from what is observed in healthy volunteers, and consequently, the ability of a particular dosing regimen to achieve therapeutic goals in an individual patient may vary considerably from what the clinician expects.

Absorption

Enteric drug absorption in the critically ill patient may be quite unpredictable for several reasons: proton-pump inhibitors administered for ulcer prophylaxis may raise gastric pH enough to dissolve pH-dependent coatings on tablets; fluid overload and gut edema, as well as loss of enteric microarchitecture may impair absorption across the enteric mucosa; cholestasis in the setting of shock or sepsis may alter enterohepatic recirculation; disruption of epithelial tight junctions, loss of enteric mucosa or partial denudation of the enteric lumen may lead to increased absorption (11) and first-pass effects may be altered by portosystemic shunts. For these reasons, oral administration of pharmacologic agents frequently is not even discussed in reviews of drug dosing in critical illness (12, 13). Parenteral administration generally means intravenous infusion, although intraperitoneal and intrathecal administration may be preferred in certain settings (14, 15).

Distribution

After an agent is administered – either orally or parenterally – it will be transported to a greater or lesser extent from its original location – blood, CSF, ascites – throughout the rest of the body. For this discussion, we will assume intravenous administration. As a result of this active and passive transport, the measured concentration of drug in the plasma will be less than just the administered dose divided by the estimated plasma volume. The dose administered divided by the final concentration yields a number with units of volume, called the “volume of distribution”. It can be helpful in dose calculation to frame drug distribution in this way, even though the volume of distribution does not correspond to any particular anatomic space in the body. Once the drug has distributed throughout the body, it will have some final concentration that then gradually decreases as the body eliminates the drug. It may be challenging to distinguish drug excretion or metabolism from delayed distribution.

Unfortunately, the nomenclature is not entirely consistent in describing volume of distribution, and so it is worth some discussion here. Almost all drugs will exist in equilibrium between free drug – the active form of the drug – and drug that is specifically and nonspecifically bound to plasma and tissue proteins. Some drugs also partition into lipids. Often, descriptions of drug concentration and volume of distribution are not clear whether they are referring to both free and bound forms (“total drug”), or the active, free form alone. An example familiar to most practicing nephrologists illustrates the point. Phenytoin, a commonly used antiepileptic, is highly protein bound to albumin (>90%) and the total drug has a relatively small volume of distribution – about 0.7L/kg in adults. The free, pharmacologically active form of the drug is thus only about 10% of the total drug and circulates at a therapeutic concentration of 1–2 mcg/ml. The volume of distribution for the free, active form of the drug is quite different (7L/kg vs 0.7L/kg) from the volume of

distribution for the total drug, and the exact concentration of free drug is exquisitely sensitive to plasma protein concentrations and also, relevant for CKD and AKI, uremic toxins (16). For this discussion, volume of distribution will refer to the free drug, not protein or tissue bound forms. A few other examples of drug distribution familiar to the practitioner from everyday experience may be helpful in anchoring the discussion. At one end of the spectrum, monoclonal antibodies, such as infliximab, are large molecules that are almost entirely retained in plasma and have very low volumes of distribution (17). In contrast, antimetabolites used in cancer chemotherapy are small molecules that bind extensively and nearly instantly to tissues, and have volumes of distribution in the hundreds of liters (18–28).

The time course for transport of a drug depends on its chemical characteristics, especially size and protein binding, as well as the nature of the tissues into which it distributes. This matters not only in optimizing dosing strategies for the site of infection, but half-lives are affected by distribution, as reservoirs of drug in tissues may refill the plasma compartment as the kidney or liver removes the drug. Blood flow distributions to splanchnic, skeletal muscle and fat are altered in acute kidney injury and critical illness, so the apparent volume of distribution may change over the dosing cycle as well over the course of the illness. This effect may be modeled as early, nearly instant drug distribution into a “central” compartment and then slower distribution into one or more peripheral compartments. It is tempting but inaccurate to assign the identities of the modeled peripheral compartments to a particular organ or fluid. Drugs do not distribute into the entire body, and there are certainly anatomic compartments in the body to which some antibiotics have poor access, such as abscesses, bone, and CSF. Many antibiotics administered intravenously penetrate the blood brain barrier slowly or not at all (14). This is a major challenge in therapeutic drug monitoring as antibiotic concentrations for therapeutic drug monitoring are usually measured in blood samples and almost certainly overestimate concentrations at the site of infection (29–31).

Volumes of distribution in acute kidney injury may be severely deranged from published population estimates derived from healthy subjects. First, hospitalized inpatients may have been obese and far above ideal body weight at time of admission, leading to overestimation of total body water if weight-based nomograms are used. Subsequent fluid overload and extracellular fluid volume expansion in turn increase volumes of distribution for hydrophilic drugs, such as aminoglycosides. Acutely ill subjects frequently have decreased plasma protein concentrations, and, additionally, uremic solutes such as hippurate and indoxyl sulfate alter drug binding to albumin in chronic renal failure, and might do so in acute renal failure, although this has not been tested (32, 33). The free fraction of many drugs – phenytoin, digoxin, and others is increased in renal failure, even though the volume of distribution for total drug may increase due to movement of unbound drug into interstitial or total body water (34, 35). Failure to adjust drug doses to account for these changes can result in unexpected toxicity as total drug remains the same, but the free concentration is higher than expected.

Clearance, Metabolism and Excretion

Clearance is a concept familiar to most nephrologists which needs but little further discussion in the context of pharmacokinetics. Creatinine clearance, commonly used as an easily calculated surrogate for glomerular filtration rate, includes creatinine removed from blood by glomerular filtration and tubular secretion, although in individual patients the relative contributions of each are generally not known. The same is true for drugs which may be filtered and either reabsorbed or secreted by the tubule. In renal failure, filtration and secretion are reduced, and it is usually assumed that reduced renal drug clearance occurs in proportion to reductions in glomerular filtration rate.

In consideration of drug clearance, metabolism of the drug is usually significant and sometimes dominates disappearance of drug from plasma. Metabolism may take the form of chemical modification of the drug by catalysis or hydrolysis, or addition of groups (e.g. glucuronidation) that enhance excretion of the drug by modifying its solubility. The drug may also be secreted in bile and then eliminated unchanged in stool. Non-renal drug disposition is not independent of renal failure, however. Uremia and or azotemia change hepatobiliary drug metabolism, possibly via product inhibition by accumulated metabolites (36). Hepatic cytochrome P450 expression are reduced in chronic uremia, and in vitro studies of rodent hepatocytes suggest that a dialyzable factor contributes to the suppression (37).

Extracorporeal clearance by the dialysis circuit occurs in parallel with endogenous clearance. Only the unbound or free drug is removed by the dialysis circuit, as the plasma proteins (albumin) to which the drug is bound are too large to pass through the pores of the dialysis membrane. Continuous renal replacement (CRRT) has dialysate/effluent flow limited small solute clearance (Blood flow “Qb” ≫ dialysate flow “Qd”), and CRRT urea clearance is generally close to the effluent flow rate, typically 2–3L/hour or 33–50 ml/min. Sustained low-efficiency dialysis (SLED) (Qd > Qb, Qb 100 ~ ml/min) and hemodialysis (Qd > Qb; Qb ~ 350–400 ml/min) have blood-flow limited small solute clearance, and barring significant recirculation or clotting in the fiber bundle, urea clearance is close to the blood flow rate. Peritoneal dialysis (PD) is only rarely used in acute renal failure and drug kinetics in acute PD are not well studied. In CRRT, SLED, and conventional hemodialysis, middle molecule clearance is appreciably less than urea clearance and may be negligible(38) (39).

Typical antibiotic dosing adjustments in CRRT involve estimating ongoing extracorporeal clearance (e.g. 15 ml/min) and dosing the antibiotic according to the guidelines for the equivalent creatinine clearance. Typical adjustments to dose in intermittent dialysis involve estimating drug removal in the course of a single session, frequently from the published literature rather than individualized data, and then supplementing the regular antibiotic dosing schedule with additional doses after each dialysis session. Anecdotal evidence suggests individual institutions vary widely in their adherence to supplemental dosing.

Pharmacodynamics

Antimicrobial antibiotics fall into several broad classes of agent (Table 1) which exert their selective effect on microbes by targeting enzymes that are not shared with their mammalian host. Each class of agent is thought to have a particular preferred concentration-time profile that optimizes microbial killing while minimizing side effects. Drugs are usually classed as time-dependent, meaning that time – or percentage of the dosing interval - above some threshold concentration influences kill rates to a greater extent than does the magnitude of the peak concentration observed; conversely, concentration-dependent agents show more dependence on the magnitude of the peak concentration than how long the concentration exceeded some multiple of the microbial minimum inhibitory concentration. Several agents exhibit a potent post-antibiotic or post-antifungal effect caused by the irreversible binding of the drug to bacterial or fungal cellular machinery. The pharmacokinetic processes (distribution and clearance) described above cause the concentration-time profile at the site of infection to differ from the concentration-time curve in plasma, so that plasma concentrations may or may not be close to concentrations at the site of infection. Optimization of the plasma concentration profile to achieve a desired tissue concentration-time profile is an active area of research.

3. Antibiotic dosing in Acute Kidney Injury

Unlike cancer chemotherapy agents or antiepileptic drugs, most antibiotics have large therapeutic indices- that is, toxic doses far exceed therapeutic doses and dose-limiting toxicities are rare. For example, vancomycin toxicity is frequently reported at concentrations in tenfold excess of the therapeutic concentration (52, 53). Commonly encountered exceptions include aminoglycosides and amphotericin B which concentrate in the renal cortex, causing acute kidney injury. Several azoles and macrolides are CYP3A4 inhibitors and accumulation in renal failure may cause elevations in other drugs, especially immunosuppressants and antiarrythmics, such as amiodarone, that are metabolized via CYP3A4. Beta-lactam antibiotics, especially carbapenems, have epileptogenic neurotoxicity that may be exacerbated by renal failure (54). Because of these direct and indirect toxicities, practitioners have been keen to avoid overdose when prescribing antibiotics for patients with renal failure.

Dose adjustment in renal failure is usually based on the present level of renal function; however, estimation of renal function in acute renal failure is a challenging proposition that is becoming its own field of study (55–59). GFR estimates that are based on creatinine or urea levels, such as the Modification of Diet in Renal Disease estimating equation, are confounded by several factors (60). First, not all subjects generate wastes at the same rate. Second, measurements of serum levels always assess renal function “in arrears” as they reflect accumulation of the solute in the hours and days after the change in GFR occurred. Third, in acute kidney injury, the volume of distribution of these solutes is likely to also be changing rapidly, so that changes in plasma levels arise not just from changes in generation and in clearance, but also changes in total body water. Several tools have been developed to quantify acute kidney injury in a repeatable fashion, and most well known are the RIFLE and AKIN criteria (61, 62). These tools were developed to standardize definitions and stages of acute kidney injury for research purposes, as previous studies of acute kidney injury were difficult to compare side-by-side due to widely varying definitions of acute kidney injury. These scoring systems are relatively blunt instruments with limited utility in bedside medical decision-making, although they are extremely helpful to the clinician’s sense of risk stratification and anticipatory guidance to family and friends of the patient. In this background context of extraordinary difficulty in estimating renal function in the critically ill patient, rapid-turnaround use of existing laboratory assays can be immensely useful. Four-hour creatinine clearance, for example, can give insight into a patients renal function during the interval between administration of a loading dose and the first maintenance dose (63). These real-time assessments of actual creatinine clearance may prove helpful in estimating GFR when the patients clinical condition is evolving (63).

4. Antibiotic dosing in Extracorporeal Renal Replacement

In this section, we will discuss the literature on antibiotic dosing in renal failure requiring support, and focus exclusively on continuous therapies. For intermittent dialysis, several published guides suggest supplemental doses to replace dialytic losses (64). Sustained low-efficiency dialysis (SLED) has had limited penetration in the US despite the highly attractive financial implications of using low-cost disposables in the ICU setting. Out of over 10,000 RRT treatments in the ATN study, less than 300 were SLED; in the RENAL study, all subjects received post-dilution venovenous hemodiafiltration (2, 3). That said, the majority of the literature in SLED in AKI has been published in the last 3–4 years, so drug dosing guidelines in sustained, low-efficiency treatments is likely to be increasingly important and will require extensive research efforts to develop optimal dosing strategies for SLED (65).

The primary difficulty in applying the published literature on antibiotic dosing in CRRT to bedside clinical decision making stems from ongoing evolution of the standard of care in CRRT and significant heterogeneity in CRRT prescribing patterns. Here, we will focus on one very commonly used antibiotic, piperacillin-tazobactam, and review the prior literature as an example of the difficulties encountered by the practitioner attempting to devise a rational dosing scheme for an individual patient. Many if not all of the challenges discussed are applicable to other antimicrobial agents in acute kidney injury. The literature spans nearly two decades, involves relatively small numbers of subjects, and reports very different CRRT prescriptions.

As discussed by Trotman in his excellent review article on antibiotic dosing in CRRT, mode and dose of CRRT vary quite widely from center to center and from report to report, making it very difficult to create generally applicable dosing guidelines (72).

Pharmacokinetic parameters for piperacillin in our study resembled those reported by Seyler et al (8), and notably differ from those published in a commonly used prescribing guide ("The Green Book")(73). Protein binding was lower, volume of distribution was higher, and half-life longer than described in this prescribing guide (73). Half-lives measured in our study resembled those measured by Valtonen for 2L/hour of CVVHDF effluent, but were shorter than those reported by Arzuaga et al (69, 74). Total and extracorporeal clearance was higher in our study (74 ml/min vs 50 ml/min; 30.8 ml/min vs 11.45 ml/min respectively) than reported by Arzuaga for patients with severe renal failure on CVVH (74). Arzuaga used similar equipment, but in predilution continuous hemofiltration with much lower effluent rates than in the patients reported here. In comparison to Mueller's measurements, our patients had slightly longer half-lives and lower elimination rate constants for both piperacillin and tazobactam (70). At this point, a side note regarding β-lactam/β-lactamase inhibitor combinations is warranted in that the pharmacokinetics of the two components may be quite different; in our hand, tazobactam had a larger volume of distribution and a longer half life than piperacillin (10). Our pharmacodynamic data resembled those of others suggesting that the proportion with target attainment (PTA, or proportion reaching >50%T>MIC64 mcg/mL) was not 100% (8, 75, 76). Measurements of tissue levels for beta-lactams are generally at best half to a quarter of plasma levels, and in septic patients, possibly much lower (29, 75, 77, 78). The relatively low PTA raises significant concerns regarding response to infections and development of antimicrobial resistance.

Our group has developed similar data for carbapenems to that reported by Seyler suggesting that not all subjects reach pharmacodynamic targets in plasma, let alone in tissue (8).

The literature is presented for piperacillin-tazobactam as it is among the most widely used antibiotics in the critical care environment, and it highlights the challenges confronting the practitioner who seeks evidence-based dosing guidelines. Piperacillin-tazobactam is a mainstay in treatment of gram-negative sepsis, and as such it is amongst the best studied in acute kidney injury. As is evident, even for this extensively used drug, the literature supporting dosing recommendations is based on remarkably few subjects and heterogeneous RRT prescriptions. The same is evident for other renal dose adjustments.

Given that the CRRT prescriptions in the literature vary widely and practice patterns evolve, it seems unwise to dose-adjust antibiotics according to a set recommendation for "Dialysis" and "CRRT". Instead, in the last section of the manuscript, a generally applicable strategy for dose adjustment in renal failure and dialysis will be developed.

5. Practice Recommendations for Inpatient Acute kidney Injury

What dose adjustment recommendations can be provided to the practitioner today? First, if prescribed CRRT doses are similar to those of the ATN or RENAL studies; that is, between 25–35 ml/kg/hr, there is a very real possibility that antibiotics will be underdosed if older dose adjustments are followed. This is reflected in Aronoff's reference, which increased piperacillin dose recommendations between the 4th and 5th editions of the book (64, 79). Except in cases where a particular dose-related side effect is a known concern, practitioners may prefer to err on the side of higher, not lower doses. Trotman's reference is an excellent source of information for volumes of distribution and protein binding which will guide initial and subsequent doses (72). There is little if any data to support reduction of the initial antibiotic dose solely on the basis of renal failure; the most obvious influences on the volume of distribution of the free drug tend to cancel each other: hypoalbuminemia tends to increase the free fraction of drug, while extracellular fluid volume expansion dilutes that free fraction more than in a normovolemic patient. Aminoglycosides and vancomycin will continue to require weight based dosing and therapeutic drug monitoring wherever possible. The more complicated aspect of dosing lies in scheduling subsequent doses. Concentration-dependent agents, such as fluoroquinolones, aminoglycosides, daptomycin, and amphotericin, generally are adjusted by altering the length of the dosing interval, whereas for time-dependent agents such as beta-lactams and triazoles, the dosing interval is kept constant or nearly so, and the dose is reduced. Individual hospitals' prescribing practices often combine both approaches.

Although some references categorize drugs as having either renal or hepatic clearance (72), the reality is that nearly all drugs undergo a combination of major, minor, and co-dominant elimination pathways. Micromedex, Lexi-Comp, Epocrates, and other online or mobile databases offer extensively referenced continuously updated and easily available data on an extensive library of drugs. A quick look at the pharmacokinetic or ADME (absorption, distribution, metabolism, elimination) sections of a drug monograph can help the practitioner quickly decide if renal dose adjustment is necessary. Highly similar drugs in the same class cannot be assumed to share common pharmacokinetics and elimination. An example familiar to nephrologists is the difference between atenolol and metoprolol. Atenolol is excreted 85% unchanged in urine, while metoprolol is hepatically metabolized and undergoes negligible renal clearance. Once the practitioner has identified that renal clearance is a dominant or codominant mechanism of elimination, he or she needs to estimate the aggregate renal and extracorporeal drug elimination in his or her individual patient. Typical dose adjustments categorize renal function roughly into < 10 ml/min, 10–20 ml/min, 30–60 ml/min, or > 60 ml/min; many variations on this theme exist but the concept is uniform. Renal clearance can be assumed to be nearly zero in anuric patients, and in patients with some urine output, a rapid assessment of function with a four-hour creatinine clearance can broadly assign a patient's renal function to one of the categories in the dosing guide. CRRT drug clearance for most antibiotics can be estimated as the unbound fraction (derived from a drug reference such as Micromedex or other) or from Trotman's review (72) multiplied by the effluent rate (that is, dialysate plus ultrafiltrate).

Thus, for piperacillin in a 100 kg anuric patient receiving 25 ml/kg/hour CVVHD, our own data measured a free fraction as 81% (10). CRRT clearance could be estimated as 0.81 * 100 kg * 25 ml/(kg*hr) * 1 hr/60 min or about 35 ml/min. Looking in any of several references for dose adjustments for a creatinine clearance of 35 ml/min, we find 3 grams IV every eight hours (Micromedex), 2.25 grams piperacillin-tazobactam IV every 6 hours (Lexi-comp) which are very similar, either 8 or 9 grams of piperacillin over a 24 hour period. These also correspond exactly to the dosing at the two sites in our study (10). By aggregating measured renal and calculated extracorporeal clearance into a single number, the practitioner has a

surrogate for creatinine clearance that allows application of the more commonly available dose adjustments for chronic kidney disease to patients with acute kidney injury with or without residual renal function and any renal replacement strategy, bearing in mind that most drugs undergo multiple clearance mechanisms, and this approach only accounts for the renal component of clearance.

References

1. Hsu, C-y; Vittinghoff, E.; Lin, F.; Shlipak, MG. The incidence of end-stage renal disease is increasing faster than the prevalence of chronic renal insufficiency.[see comment]. Annals of Internal Medicine. 2004; 141(2):95–101. [PubMed: 15262664]
2. Network VNARFT. Intensity of renal support in critically ill patients with acute kidney injury. New England Journal of Medicine. 2008; 359(1):7–20. [PubMed: 18492867]
3. Bellomo R, Cass A, Cole L, Finfer S, Gallagher M, et al. Renal Replacement Therapy Study I. Intensity of continuous renal-replacement therapy in critically ill patients. New England Journal of Medicine. 2009; 361(17):1627–38. [PubMed: 19846848]
4. Ronco C, Bellomo R, Homel P, Brendolan A, Dan M, Piccinni P, et al. Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomised trial.[see comment]. Lancet. 2000; 356(9223):26–30. [PubMed: 10892761]
5. Bouman CS, Oudemans-Van Straaten HM, Tijssen JG, Zandstra DF, Kesecioglu J, Bouman CSC, et al. Effects of early high-volume continuous venovenous hemofiltration on survival and recovery of renal function in intensive care patients with acute renal failure: a prospective, randomized trial. Critical Care Medicine. 2002; 30(10):2205–11. [PubMed: 12394945]
6. Cornejo R, Downey P, Castro R, Romero C, Regueira T, Vega J, et al. High-volume hemofiltration as salvage therapy in severe hyperdynamic septic shock. Intensive Care Medicine. 2006; 32(5):713–22. [PubMed: 16550372]
7. Lorenzen JM, Broll M, Kaever V, Burhenne H, Hafer C, Clajus C, et al. Pharmacokinetics of Ampicillin/Sulbactam in Critically Ill Patients with Acute Kidney Injury undergoing Extended Dialysis. Clinical Journal of the American Society of Nephrology. 2012; 7(3):385–90. [PubMed: 22223613]
8. Seyler L, Cotton F, Taccone FS, Backer DD, Macours P, Vincent J-L, et al. Recommended beta-lactam regimens are inadequate in septic patients treated with continuous renal replacement therapy. Critical Care. 2011; 15:R137. [PubMed: 21649882]
9. Roberts JA, Kruger P, Paterson DL, Lipman J. Antibiotic resistance--what's dosing got to do with it? Crit Care Med. 2008; 36(8):2433–40. Epub 2008/07/04. [PubMed: 18596628]
10. Bauer SR, Salem CA, Connor MJ Jr, Groszek JJ, Taylor ME, Wei P, et al. Pharmacokinetics and pharmacodynamics of piperacillin-tazobactam in 42 patients treated with concomitant CRRT. CJASN. 2012; 7:452–7. [PubMed: 22282479]
11. Clark JA, Coopersmith CM. Intestinal crosstalk: a new paradigm for understanding the gut as the "motor" of critical illness. Shock. 2007; 28(4):384–93. Epub 2007/06/20. [PubMed: 17577136]
12. McKenzie C. Antibiotic dosing in critical illness. Journal of Antimicrobial Chemotherapy. 2011; 66(suppl 2):ii25–ii31. [PubMed: 21398304]
13. Goncalves-Pereira J, Povoa P. Antibiotics in critically ill patients: a systematic review of the pharmacokinetics of beta-lactams. Crit Care. 2011; 15(5):R206. Epub 2011/09/15. [PubMed: 21914174]
14. Neuner EA, Ahrens CL, Groszek JJ, Isada C, Vogelbaum MA, Fissell WH, et al. Use of therapeutic drug monitoring to treat Elizabethkingia meningoseptica meningitis and bacteraemia in an adult. The Journal of antimicrobial chemotherapy. 2012; 67(6):1558–60. Epub 2012/02/24. [PubMed: 22357803]
15. Swartz RD, Messana JM. Simultaneous catheter removal and replacement in peritoneal dialysis infections: update and current recommendations. Advances in peritoneal dialysis Conference on Peritoneal Dialysis. 1999; 15:205–8. Epub 2000/02/22. [PubMed: 10682103]
16. von Winckelmann SL, Spriet I, Willems L. Therapeutic Drug Monitoring of Phenytoin in Critically Ill Patients. Pharmacotherapy. 2008; 28(11):1391–400. [PubMed: 18956999]

17. Klotz U, Teml A, Schwab M. Clinical Pharmacokinetics and Use of Infliximab. Clinical Pharmacokinetics. 2007; 46(8):645–60. [PubMed: 17655372]
18. Calvert AH, Newell DR, Gumbrell LA, O'Reilly S, Burnell M, Boxall FE, et al. Carboplatin dosage: prospective evaluation of a simple formula based on renal function. Journal of Clinical Oncology. 1989; 7(11):1748–56. [PubMed: 2681557]
19. Baxter Healthcare C. Cyclophosphamide for Injection, USP. Deerfield, IL: Baxter Healthcare Corporation; 2007.
20. Bedford, L. VinBLAStine Sulfate for Injection USP. Bedford, Ohio: Bedford Laboratories; 2001.
21. Ben Venue Laboratories I. Daunorubicin Prescribign Information. Bedford, OH: Bedford Laboratories; 1999.
22. den Hartigh J, McVie JG, van Oort WJ, Pinedo HM. Pharmacokinetics of mitomycin C in humans. Cancer Research. 1983; 43(10):5017–21. [PubMed: 6411336]
23. Hassan M, Öberg G, Ehrsson H, Ehrnebo M, Wallin I, Smedmyr B, et al. Pharmacokinetic and metabolic studies of high-dose busulphan in adults. European Journal of Clinical Pharmacology. 1989; 36(5):525–30. [PubMed: 2753072]
24. Pinguet F, Culine S, Bressolle F, Astre C, Serre MP, Chevillard C, et al. A phase I and pharmacokinetic study of melphalan using a 24-hour continuous infusion in patients with advanced malignancies. Clinical Cancer Research. 2000; 6(1):57–63. [PubMed: 10656432]
25. Rengelshausen J, Hull WE, Schwenger V, Goggelmann C, Walter-Sack I, Bommer J. Pharmacokinetics of 5-fluorouracil and its catabolites determined by 19F nuclear magnetic resonance spectroscopy for a patient on chronic hemodialysis. American Journal of Kidney Diseases. 2002; 39(2):E10. [PubMed: 11840401]
26. Stewart CF. Use of etoposide in patients with organ dysfunction: pharmacokinetic and pharmacodynamic considerations. Cancer Chemotherapy & Pharmacology. 1994; 34 (Suppl):S76–83. [PubMed: 8070032]
27. Takeuchi M, Yamauchi T, Yoshida I, Soda R, Ueda T, Takahashi K, et al. Pharmacokinetics of a standard dose of cytarabine in a patient with acute promyelocytic leukemia undergoing continuous ambulatory peritoneal dialysis. International Journal of Hematology. 2003; 77(2):196–8. [PubMed: 12627859]
28. Yoshida H, Goto M, Honda A, Nabeshima T, Kumazawa T, Inagaki J, et al. Pharmacokinetics of doxorubicin and its active metabolite in patients with normal renal function and in patients on hemodialysis. Cancer Chemotherapy & Pharmacology. 1994; 33(6):450–4. [PubMed: 8137454]
29. Roberts JA, Roberts MS, Robertson TA, Dalley AJ, Lipman J. Piperacillin penetration into tissue of critically ill patients with sepsis—Bolus versus continuous administration? Crit Care Med. 2009; 37:926–33. [PubMed: 19237898]
30. van Zanten AR, Polderman KH, van Geijlswijk IM, van der Meer GY, Schouten MA, Girbes AR, et al. Ciprofloxacin pharmacokinetics in critically ill patients: a prospective cohort study. Journal of Critical Care. 2008; 23(3):422–30. [PubMed: 18725050]
31. Zeitlinger MA, Erovic BM, Sauermann R, Georgopoulos A, Muller M, Joukhadar C. Plasma concentrations might lead to overestimation of target site activity of piperacillin in patients with sepsis. Journal of Antimicrobial Chemotherapy. 2005; 56(4):703–8. [PubMed: 16120628]
32. Gulyassy PF, Jarrard E, Stanfel LA. Contributions of hippurate, indoxyl sulfate, and o-hydroxyhippurate to impaired ligand binding by plasma in azotemic humans. Biochem Pharmacol. 1987; 36(24):4215–20. Epub 1987/12/15. [PubMed: 3120733]
33. Igarashi P, Gulyassy P, Stanfel L, Depner T. Plasma hippurate in renal failure: high-performance liquid chromatography method and clinical application. Nephron. 1987; 47(4):290–4. Epub 1987/01/01. [PubMed: 3696332]
34. Butterfield JM, Patel N, Pai MP, Rosano TG, Drusano GL, Lodise TP. Refining vancomycin protein binding estimates: identification of clinical factors that influence protein binding. Antimicrobial agents and chemotherapy. 2011; 55(9):4277–82. Epub 2011/06/15. [PubMed: 21670191]
35. Roberts JA, Taccone FS, Udy AA, Vincent JL, Jacobs F, Lipman J. Vancomycin dosing in critically ill patients: robust methods for improved continuous-infusion regimens. Antimicrobial agents and chemotherapy. 2011; 55(6):2704–9. Epub 2011/03/16. [PubMed: 21402850]

36. Vilay AM, Churchwell MD, Mueller BA. Clinical review: Drug metabolism and nonrenal clearance in acute kidney injury. Critical Care. 2008; 12:235–44. [PubMed: 19040780]
37. Michaud J, Nolin TD, Naud J, Dani M, Lafrance JP, Leblond FA, et al. Effect of hemodialysis on hepatic cytochrome P450 functional expression. Journal of pharmacological sciences. 2008; 108(2):157–63. Epub 2008/10/11. [PubMed: 18845914]
38. Tiranathanagul K, Yossundharakul C, Techawathanawanna N, Katavetin P, Hanvivatvong O, Praditpornsilp K, et al. Comparison of middle-molecule clearance between convective control double high-flux hemodiafiltration and on-line hemodiafiltration. Int J Artif Organs. 2007; 30(12): 1090–7. Epub 2008/01/19. [PubMed: 18203071]
39. Messer J, Mulcahy B, Fissell WH. Middle-molecule clearance in CRRT: In-Vitro Convection, Diffusion, and Dialyzer Area. ASAIO Journal. 2009; 55(3):224–6. [PubMed: 19282753]
40. Sauermann R, Zeitlinger M, Erovic BM, Marsik C, Georgopoulos A, Muller M, et al. Pharmacodynamics of piperacillin in severely ill patients evaluated by using a PK/PD model. International Journal of Antimicrobial Agents. 2003; 22(6):574–8. [PubMed: 14659654]
41. Shea KM, Cheatham SC, Wack MF, Smith DW, Sowinski KM, Kays MB, et al. Steady-state pharmacokinetics and pharmacodynamics of piperacillin/tazobactam administered by prolonged infusion in hospitalised patients. International Journal of Antimicrobial Agents. 2009; 34(5):429–33. [PubMed: 19726163]
42. Van Bambeke F, Tulkens PM. Macrolides: pharmacokinetics and pharmacodynamics. International Journal of Antimicrobial Agents. 2001; 18(Supplement 10):17–23.
43. Decker BS, Mohamed AN, Chambers M, Kraus MA, Moe SM, Sowinski KM. Gentamicin Pharmacokinetics and Pharmacodynamics during Short-Daily Hemodialysis. Am J Nephrol. 2012; 36(2):144–50. Epub 2012/07/21. [PubMed: 22813936]
44. Wright DH, Brown GH, Peterson ML, Rotschafer JC. Application of fluoroquinolone pharmacodynamics. Journal of Antimicrobial Chemotherapy. 2000; 46(5):669–83. [PubMed: 11062185]
45. Agwuh KN, MacGowan A. Pharmacokinetics and pharmacodynamics of the tetracyclines including glycylcyclines. Journal of Antimicrobial Chemotherapy. 2006; 58(2):256–65. [PubMed: 16816396]
46. Rybak MJ. The Pharmacokinetic and Pharmacodynamic Properties of Vancomycin. Clinical Infectious Diseases. 2006; 42(Supplement 1):S35–S9. [PubMed: 16323118]
47. Begic D, von Eiff C, Tsuji BT. Daptomycin pharmacodynamics against Staphylococcus aureus hemB mutants displaying the small colony variant phenotype. The Journal of antimicrobial chemotherapy. 2009; 63(5):977–81. Epub 2009/03/24. [PubMed: 19304733]
48. Groll AH, Piscitelli SC, Walsh TJ. Antifungal pharmacodynamics: concentration-effect relationships in vitro and in vivo. Pharmacotherapy. 2001; 21(8 Pt 2):133S–48S. Epub 2001/08/15. [PubMed: 11501987]
49. Baddley JW, Patel M, Bhavnani SM, Moser SA, Andes DR. Association of fluconazole pharmacodynamics with mortality in patients with candidemia. Antimicrobial agents and chemotherapy. 2008; 52(9):3022–8. Epub 2008/07/02. [PubMed: 18591269]
50. Andes D, Marchillo K, Conklin R, Krishna G, Ezzet F, Cacciapuoti A, et al. Pharmacodynamics of a New Triazole, Posaconazole, in a Murine Model of Disseminated Candidiasis. Antimicrobial agents and chemotherapy. 2004; 48(1):137–42. [PubMed: 14693531]
51. Antachopoulos C, Meletiadis J, Sein T, Roilides E, Walsh TJ. Comparative in vitro pharmacodynamics of caspofungin, micafungin, and anidulafungin against germinated and nongerminated Aspergillus conidia. Antimicrobial agents and chemotherapy. 2008; 52(1):321–8. Epub 2007/10/17. [PubMed: 17938191]
52. Bunchman TE, Valentini RP, Gardner J, Mottes T, Kudelka T, Maxvold NJ. Treatment of vancomycin overdose using high-efficiency dialysis membranes. Pediatric Nephrology. 1999; 13(9):773–4. [PubMed: 10603118]
53. Lemaire M, Connolly B, Harvey E, Licht C. Treatment of paediatric vancomycin intoxication: a case report and review of the literature. NDT Plus. 2010; 3(3):260–4.

54. Schliamser SE, Cars O, Norrby SR. Neurotoxicity of beta-lactam antibiotics: predisposing factors and pathogenesis. The Journal of antimicrobial chemotherapy. 1991; 27(4):405–25. Epub 1991/04/01. [PubMed: 1856121]
55. Ferguson MA, Waikar SS. Established and emerging markers of kidney function. Clin Chem. 2012; 58(4):680–9. Epub 2012/02/09. [PubMed: 22311920]
56. Wang E, Sandoval RM, Campos SB, Molitoris BA. Rapid diagnosis and quantification of acute kidney injury using fluorescent ratio-metric determination of glomerular filtration rate in the rat. American journal of physiology Renal physiology. 2010; 299(5):F1048–55. Epub 2010/08/06. [PubMed: 20685826]
57. Cruz DN, Ricci Z, Ronco C. Clinical review: RIFLE and AKIN--time for reappraisal. Crit Care. 2009; 13(3):211. Epub 2009/07/30. [PubMed: 19638179]
58. Bouchard J, Macedo E, Soroko S, Chertow GM, Himmelfarb J, Ikizler TA, et al. Comparison of methods for estimating glomerular filtration rate in critically ill patients with acute kidney injury. Nephrol Dial Transplant. 2010; 25(1):102–7. Epub 2009/08/15. [PubMed: 19679558]
59. Demirjian S, Poggio ED. Critical care: estimating renal function in the ICU: even more challenging. Nat Rev Nephrol. 2011; 7(10):549–50. Epub 2011/09/07. [PubMed: 21894185]
60. Matsushita K, Mahmoodi BK, Woodward M, Emberson JR, Jafar TH, Jee SH, et al. Comparison of risk prediction using the CKD-EPI equation and the MDRD study equation for estimated glomerular filtration rate. JAMA. 2012; 307(18):1941–51. Epub 2012/05/10. [PubMed: 22570462]
61. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P, atAw. Acute renal failure – definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Critical Care. 2004; 8:R204–R12. [PubMed: 15312219]
62. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007; 11(2):R31. Epub 2007/03/03. [PubMed: 17331245]
63. Pickering JW, Frampton CM, Walker RJ, Shaw GM, Endre ZH. Four hour creatinine clearance is better than plasma creatinine for monitoring renal function in critically ill patients. Crit Care. 2012; 16(3):R107. Epub 2012/06/21. [PubMed: 22713519]
64. Aronoff, GR.; Bennett, WM.; Berns, JS.; Brier, ME.; Kasbekar, N.; Mueller, BA., et al. Drug Prescribing in Renal Failure. 5. Philadelphia: American College of Physicians; 2007.
65. Bogard KN, Peterson NT, Plumb TJ, Erwin MW, Fuller PD, Olsen KM. Antibiotic dosing during sustained low-efficiency dialysis: special considerations in adult critically ill patients. Crit Care Med. 2011; 39(3):560–70. Epub 2011/01/12. [PubMed: 21221000]
66. Joos B, Schmidli M, Keusch G. Pharmacokinetics of antimicrobial agents in anuric patients during continuous venovenous haemofiltration. Nephrol Dial Transplant. 1996; 11(8):1582–5. Epub 1996/08/01. [PubMed: 8856215]
67. van der Werf TS, Mulder PO, Zijlstra JG, Uges DR, Stegeman CA. Pharmacokinetics of piperacillin and tazobactam in critically ill patients with renal failure, treated with continuous veno-venous hemofiltration (CVVH). Intensive Care Med. 1997; 23(8):873–7. Epub 1997/08/01. [PubMed: 9310805]
68. Capellier GMD, Cornette CP, Boillot AMD, Guinchard CP, Jacques TMD, Blasco GMD, et al. Removal of piperacillin in critically ill patients undergoing continuous venovenous hemofiltration. Critical Care Medicine. 1998; 26(1):88–91. [PubMed: 9428548]
69. Valtonen M, Tiula E, Takkunen O, Backman JT, Neuvonen PJ. Elimination of the piperacillin/tazobactam combination during continuous venovenous haemofiltration and haemodiafiltration in patients with acute renal failure. J Antimicrob Chemother. 2001; 48(6):881–5. [PubMed: 11733473]
70. Mueller SC, Majcher-Peszynska J, Hickstein H, Francke A, Pertschy A, Schulz M, et al. Pharmacokinetics of Piperacillin-Tazobactam in Anuric Intensive Care Patients during Continuous Venovenous Hemodialysis. Antimicrob Agents Chemother. 2002; 46(5):1557–60. [PubMed: 11959598]
71. Arzuaga A, Maynar J, Gascon AR, Isla A, Corral E, Fonseca F, et al. Influence of renal function on the pharmacokinetics of piperacillin/tazobactam in intensive care unit patients during continuous

venovenous hemofiltration. Journal of Clinical Pharmacology. 2005; 45(2):168–76. [PubMed: 15647409]

72. Trotman RL, Williamson JC, Shoemaker DM, Salzer WL. Antibiotic Dosing in Critically Ill Adult Patients Receiving Continuous Renal Replacement Therapy. Clinical Infectious Diseases. 2005; 41(8):1159–66. [PubMed: 16163635]
73. Aronoff, G.; Bennett, W.; Berns, J.; Brier, M.; Kasbekar, N.; Mueller, BA., et al. Drug Prescribing in renal Failure. 5. Philadelphia: American College of Physicians; 2007.
74. Arzuaga A, Maynar J, Gascon AR, Isla A, Corral E, Fonseca F, et al. Influence of renal function on the pharmacokinetics of piperacillin/tazobactam in intensive care unit patients during continuous venovenous hemofiltration. Journal of Clinical Pharmacology. 2005; 45(2):168–76. [PubMed: 15647409]
75. Joukhadar CMD, Frossard MMD, Mayer BXP, Brunner MMD, Klein NMD, Siostrzonek PMD, et al. Impaired target site penetration of [beta]-lactams may account for therapeutic failure in patients with septic shock. Critical Care Medicine. 2001; 29(2):385–91. [PubMed: 11246321]
76. Sadaba B, Azanza JR, Campanero MA, Garcia-Quetglas E. Relationship between pharmacokinetics and pharmacodynamics of beta-lactams and outcome. Clinical Microbiology & Infection. 2004; 10(11):990–8. [PubMed: 15522002]
77. Boselli E, Breilh D, Rimmelé T, Guillaume C, Xuereb F, Saux M-C, et al. Alveolar concentrations of piperacillin/tazobactam administered in continuous infusion to patients with ventilator-associated pneumonia. Crit Care Med. 2008; 36:1500–6. [PubMed: 18434883]
78. Varghese JM, Roberts JA, Lipman J. Pharmacokinetics and pharmacodynamics in critically ill patients. Current Opinion in Anaesthesiology. 2010; 23:472–8. [PubMed: 20489605]
79. Aronoff, GR.; Berns, JS.; Brier, ME.; Golper, TA.; Morrison, G.; Singer, I., et al. Drug Prescribing in Renal Failure. 4. Philadelphia: American College of Physicians; 1999.

6. Take-away messages

- Adult patients treated with continuous renal therapies in the ICU are probably at risk for antibiotic underdosing and therapeutic failures. One-size-fits-all dosing is likely inappropriate.
- Estimation of renal function in acute injury is very challenging, but recently short-interval creatinine clearance measurements have been demonstrated.
- Widely available drug databases support individualized decision-making.
- There is little literature to support adjusting the loading dose of antibiotic in AKI
- The sum of renal creatinine clearance and CRRT effluent rate normalized for drug protein binding provides a starting point for renally-based dose adjustment for subsequent doses of antibiotic.
- When available, therapeutic drug monitoring should be used, especially for drugs with low therapeutic index.

Table 1

Antimicrobial Properties

Class	Example	Mechanism of Action	Microbial Killing Profile
Beta-lactams	Penicillin, ceftriaxone, meropenem	Irreversible binding to enzymes necessary for peptidoglycan synthesis in the bacterial cell wall	Time-dependent (40, 41)
Macrolides	erythromycin	Bind 50S subunit of ribosome and block peptide chain elongation and protein synthesis	Time-dependent (42)
Aminoglycosides	gentamicin	Bind 30S ribosome and interfere with peptide chain elongation, but individual agents may have additional effects	Concentration-dependent (43)
Fluoroquinolones	ciprofloxacin	Inhibits DNA gyrase and blocks protein synthesis	Concentration-dependent (44)
Tetracyclines	doxycycline	Bind 30S ribosome and prevent transfer RNA from binding, thus preventing peptide chain elongation and blocking protein synthesis.	Understudied. Concentration-dependent (45)
Glycopeptides	Vancomycin	Inhibits cell wall synthesis	Time-dependent (46)
Lipopeptides	Daptomycin	Depolarizes cell membrane	Concentration- dependent(47)
Polyenes	Nystatin, Amphotericin B	Binds to ergosterol component of fungal cell membrane and increases membrane permeability	Concentration-dependent (48)
Triazoles	Fluconazole	Blocks synthesis of ergosterol component of fungal cell membrane	Time-dependent (49, 50)
Echinocandins	caspofungin	Inhibits B(1,3) glucan synthase and interrupts fungal cell wall synthesis	Concentration- dependent(51)

Table 2

PK/PD Studies of Piperacillin-tazobactam in CRRT

Author	N	CRRT Prescription
Joos (66)	8	CVVH 13 ml/min
van der Werf (67)	9	CVVH 26 ml/min
Capellier (68)	10	CVVH 840 ml/hr
Valtonen (69)	6	CVVH 1L/hr or CVVHDF 2L/hr
Mueller (70)	8	CVVHD 1.5L/hr
Arzuaga (71)	14	CVVH 20–30ml/min
Seyler (8)	16	CVVH and CVVHDF 45 ml/kg/hr
Bauer (10)	42	CVVHD and CVVHDF 26 ml/kg/hr