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Principles of Antibiotic Adjustment in Renal Failure

Bruno Fraga Dias[1,*], Josefina Santos[1,2,3]

[1] Nephrology Department, Centro Hospitalar Universitário de Santo António, Porto, Portugal.
[2] Nephrology, Dialysis and Transplantation, UMIB - Unit for Multidisciplinary Research in Biomedicine, ICBAS - School of Medicine and Biomedical Sciences, University of Porto, Porto, Portugal.
[3] ITR – Laboratory for Integrative and Translational Research in Population Health, Porto, Portugal.

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ABSTRACT

The incidence and prevalence of patients with acute kidney injury and chronic kidney disease have increased significantly in recent years. Renal failure is associated with profound changes in the pharmacokinetics and pharmacodynamics of antibiotics. It is widely recognized that inadequate adjustment of antibiotics can lead to undertreatment and impair the patient's clinical outcome.

The difficulty of adjusting drugs in renal dysfunction begins with estimating renal function (urinary clearance of inulin is rarely performed, and creatinine/cystatin-based formulas have widely recognized limitations, especially in acute kidney injury). Management becomes more complex, given the frequent changes in the volume of distribution and the introduction of different renal replacement therapies. Efforts must be made to optimize antibiotic targets in this population.

This study aims to review the principal pharmacokinetic and pharmacodynamic modifications that occur with antibiotics in chronic kidney disease and acute kidney injury, with the goal of offering strategies to enhance antibiotic therapy in these scenarios.

Keywords: Acute Kidney Injury; Anti-Bacterial Agents/administration & dosage; Anti-Bacterial Agents/pharmacology; Anti-Bacterial Agents/pharmacokinetics; Dose-Response Relationship, Drug; Drug Dosage Calculations; Kidney Diseases/drug therapy; Renal Insufficiency, Chronic; Renal Replacement Therapy

INTRODUCTION

Acute kidney injury (AKI) and chronic kidney disease (CKD) can affect various systems, and these physiological impacts have been associated with profound changes in the pharmacokinetics and pharmacodynamics of many drugs, namely antibiotics.[1,2] The kidney eliminates most antimicrobials and their metabolites, so acute or chronic renal failure determines important changes in drug metabolism.

The number of patients with AKI and CKD has increased significantly in recent years, following the increasing age of patients and associated comorbidities.[3] The introduction of different renal replacement therapies (RRT) is a challenge that requires a constant reassessment of drug transport across biological membranes (peritoneal dialysis) and artificial membranes (hemodialysis).[4]

The need for dose adjustment of drugs in patients with acute or chronic kidney disease is a real need but a permanent challenge due to the difficulty of accurately estimating the degree of renal dysfunction and balancing the toxicity and the subtherapeutic range.[5]

Patients with kidney disease are known to have worse outcomes, and the inability to optimize antibiotic therapy can determine their clinical course.[1] Recent studies in patients with AKI estimate that suboptimal doses of antibiotics are often used, resulting in treatment failure and increased mortality.[6,7]

This work aims to review the main pharmacokinetic and pharmacodynamic changes of antibiotics in CKD and AKI to provide ways of optimizing antibiotic therapy and dosing.

ASSESSMENT OF KIDNEY FUNCTION

Measured Glomerular Filtration Rate

The glomerular filtration rate (GFR) is the most used measure of renal function and can be more specifically estimated from exogenous substances. Urinary clearance of inulin (the gold standard for this evaluation) is rarely performed except for investigational purposes.[8]

The determination of GFR using an endogenous method is based on creatinine clearance from a 24-hour urine collection; this method,

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in addition to being impractical and limited in anuric patients, has limited clinical value due to the frequency of urine collection errors, analytical interference and delays in obtaining results due to the necessary therapeutic changes.[9,10]

Estimated GFR – Serum Creatinine and Cystatin C-Based Formulae

In usual clinical practice, GFR is predominantly estimated by measuring endogenous substances, such as serum creatinine and serum cystatin, using validated formulas. However, there are several limitations to this approach:

- creatinine concentration is proportional to muscle mass, so it is not a reliable marker in sarcopenic patients or patients with high muscle mass;
- there is variability of evaluation depending on the laboratory;
- the formulas can only be applied in patients with stable serum creatinine, limiting their applicability in AKI.

The CKD-EPI 2021 equation was developed recently to estimate the GFR without the variable "race".[11,12]

Cystatin C has been increasingly used in clinical practice to determine GFR. Cystatin C is a low molecular weight protein filtered in the glomeruli without being reabsorbed in the tubules. Serum cystatin does not depend on muscle mass, so it is more sensitive in diagnosing kidney disease in elderly patients with low muscle mass. There are several determinants of serum cystatin C in addition to GFR. Higher levels of cystatin C are associated with male sex, greater height and weight, greater lean and fat mass, diabetes, inflammation, hyperthyroidism, hypothyroidism, and glucocorticoid use.

The most accurate GFR estimates result from equations that contain both markers (creatinine and cystatin).[13] There is debate about which formula is preferred for drug dosing because neither is a perfect representation of the true value of the GFR. Table 1 points to the advantages and disadvantages of each formula.

ANTIBIOTIC ADJUSTMENT IN CHRONIC KIDNEY DISEASE

Chronic kidney disease is defined by kidney damage or a GFR <60 mL/min/1.73m^2 over more than three months. Chronic kidney disease is increasingly prevalent and a public health problem worldwide.[14]

In patients with CKD, the stage of the disease should be determined based on the level of renal function, irrespective of the diagnosis, and classified according to the KDIGO.[15]

For some drugs with a more complex pharmacokinetic profile and/or with a narrow therapeutic margin, the dose adjustment can be difficult and must be based on the measurement of plasma levels (e.g. vancomycin and aminoglycosides); for many others, the individualization of the pharmacological therapy in patients with renal insufficiency may imply only a simple dose adjustment (dose reduction and/or prolongation of the administration interval), based on the degree of reduction in renal function (estimated by GFR).

Several therapeutic guidelines for patients with reduced renal function have been published. However, in many cases, there is little quality evidence to guide therapeutic decisions. The volume of distribution (VD) of many drugs is increased in patients with CKD due to decreased protein binding, increased tissue binding, or changes in body composition (e.g. volume overload).[1]

Considerable variability exists between dosing recommendations.[16] Limited pharmacokinetic studies in the past may explain the vague and conflicting renal dosing recommendations encountered with older compounds. Given the limitations, the decision to dose-adjust and the dose to prescribe requires careful consideration of patient and antibiotic-related factors.[17]

The most important antibiotic-related factor to consider when adjusting doses for renal function in CKD is whether the antibiotic demonstrates concentration or time-dependent pharmacodynamic activity. Administration of lower doses maintains more stable drug concentrations and is therefore preferred for time-dependent antibiotics. Prolonging the time between antibiotic doses maintains high peak concentrations, and is therefore preferable for concentration-dependent antibiotics.[17]

Table 1

Relationship between patient characteristics and formula accuracy.

Relationship between patient characteristics and formula accuracy		
	Cockroft-Gault formula	CKD-EPI formula
Reduced GFR	Less accurate	More accurate
Body surface area >1.73 m^2	Depends on body weight	Underestimates GFR in weighty and tall patients
Older age	Acceptable	Acceptable
Younger age	Less accurate	More accurate
Obesity	Overestimates GFR	Underestimates GFR
Body mass index <18.5 kg/m^2	Acceptable	Overestimates GFR (use eGFR (mL/min/1.73 m^2) x patient's body surface area ÷ 1.73

Some antibiotics have their action dependent on urinary excretion. Nitrofurantoin, fosfomycin, and trimethoprim are primarily eliminated through renal excretion, leading to elevated concentrations within the urinary tract; reduced urinary concentrations have been documented for all three antibiotics in patients with compromised renal function. The concern arises from the potential decline in therapeutic efficacy when drug concentrations in the urine fall below a certain threshold. Nevertheless, robust pharmacokinetic-based evidence supporting this concern is currently lacking.[18-20]

■ Loading Dose

The loading dose is not changed in patients with chronic kidney disease unless the patient has a very low or very high volume of distribution. The following formula allows adjusting the loading dose in these cases: patient's loading dose = usual loading dose x (patient's VD/ normal VD).[1]

■ Maintenance Dose

The maintenance dose should be guided by current guidelines and based on the stage of renal dysfunction calculated by the formulas discussed above.

Measuring drug concentrations is one way to optimize therapeutic regimens when available (namely aminoglycosides and vancomycin) and should be performed routinely. Therapeutic drug monitoring requires the availability of rapid, specific, and reliable assays and known correlations of drug concentration to therapeutic and adverse outcomes. Hypoalbuminemia may influence the interpretation of drug concentrations (the total concentration may be reduced even when the active unbound drug concentration is normal).

■ Peritoneal Dialysis

Access to the peritoneal cavity allows for local and systemic antibiotic administration in patients on peritoneal dialysis. In these patients, intraperitoneal antibiotic administration is preferred, namely for the treatment of acute peritonitis in the absence of sepsis.[17] There is long experience with the intermittent administration of glycopeptides (vancomycin and teicoplanin), which can be given at intervals of 5 to 7 days, as well as for aminoglycosides and cephalosporins (which are suitable for daily administration).[1]

The magnitude of the gradient depends on several factors: the volume of dialysate in which the drug is diluted, the concentration gradient from dialysate to plasma, molecular size and electrochemical properties of the drug, exposure time, and rate of peritoneal infusion.[21]

In continuous ambulatory peritoneal dialysis (CAPD) antibiotics can be administered every intraperitoneal dwell or with the long dwell. Administration during long dwell is more convenient, more economical, and more suitable for concentration-dependent antibiotics. The administration of antibiotics on each stay allows continuous exposure to the drug, which is why it is more suitable for antibiotics whose pharmacokinetics are time-dependent.[17]

The use of automated peritoneal dialysis (APD) is increasing, which brings challenges in the management of antibiotics.[22] In general, drug clearance during APD is greater than during CAPD, so drug dosing recommendations for CAPD may not be appropriate for APD.[23] Since there are few pharmacokinetic studies in APD, most centers temporarily transit patients to CAPD.

Residual renal function is a factor to consider in the antibiotic treatment of patients on peritoneal dialysis, although studies are very contradictory, and there are no consistent options in this scenario.[24,25]

With regard to drugs administered systemically, the clearance of a drug through peritoneal dialysis is at most 10 mL/min; since most drugs are higher than urea, clearance is even lower (probably between 5 and 7.5 mL/min).[1]. Many studies conducted in the past show that drug clearance by peritoneal dialysis does not increase drug removal to the extent that a dose modification is required.[21,26]

■ Hemodialysis

The adjustment of antibiotic treatment in patients on intermittent hemodialysis (HD) depends primarily on the availability of information from well-designed pharmacokinetic studies. Patients receiving intermittent HD critically depend on the availability of reliable information from well-designed pharmacokinetic studies. Doses recommended by studies conducted before 2000 probably need to be empirically increased by 25%-50%, as these studies underestimate the impact of hemodialysis on drug clearance.[1]

The most essential drug-related factors are molecular weight or size, degree of protein binding, and volume of distribution. The main factors related to the dialytic technique are the type of dialyzer, the surface area of the filter, the blood flow, the technique performed (diffusion/convection), the dialysate rate, and the ultrafiltration. High flux dialysis membranes have larger pores, allowing most solutes to pass through, including drugs with a molecular weight of 20 000 Daltons.[27,28]

Additionally, the impact of the dialytic technique may be even wider. There is evidence that certain drugs stick to the dialyzer membrane, and recent information suggests that dialysis modifies liver clearance, presumably by altering CYP450 3A4 secondary to removing uremic toxins.[29]

■ ANTIBIOTIC ADJUSTMENT IN ACUTE KIDNEY INJURY

Acute kidney injury is common in hospitalized patients and is associated with increased hospital mortality. Frequently, patients with AKI have infectious complications. On the other hand, sepsis is a frequent cause of AKI[5,30,31] and often develops in the context of multiple organ dysfunction.[4] Mortality rates in critically ill patients with sepsis range from 20% to 60%.[32]

Given the high mortality rate of sepsis, adequate antibiotic therapy is essential for humanistic and economic reasons. Actions with the greatest impact on patient survival include early administration of antibiotics, choice of antibiotic based on the patient's history, and maintaining an adequate antibiotic dose (which is key to preventing bacterial resistance, infection by opportunistic bacteria, overdosing-related toxicity, and higher mortality).[4,33,34]

Antibiotic prescription in AKI is challenging for physicians; pharmacokinetic studies to guide the clinician through the complexities of drug dosing in patients with AKI have only been conducted for a limited number of antibiotics.[34,35] Growing evidence supports aggressive dosing of β-lactam antimicrobials in sepsis induced AKI for the first 48 hours of therapy.[36,37]

Some factors are responsible for the complexity of antibiotic management in AKI:

- AKI is a dynamic clinical situation, in which conventional GFR formulas have limited applicability.
- The evolution of renal function requires constant and sometimes unpredictable therapeutic adjustments.
- Acute kidney injury is associated with pharmacokinetic and pharmacodynamic changes.
- The severity of kidney injury may require renal replacement therapy, making the management of antibiotic therapy even more complex. Knowledge of the main principles that regulate the transport of solutes through dialysis membranes may allow for a better antibiotic prescription. [38]

Adequate antibiotic therapy requires a dose high enough to achieve pharmacodynamic goals and should consider antibiotic clearance, antibiotic resistance and concerns about toxicity, adverse effects and cost of antibiotics.[39,40]

PHARMACOKINETIC ALTERATIONS

Critically ill patients with AKI are heterogeneous and often have different pharmacokinetic profiles in response to antibiotic treatment than those without kidney disease.[34,38,41] Generally, pharmacokinetic changes can be categorized as absorption, distribution, metabolism, and elimination changes.

Absorption

Oral drug absorption may be altered by gastrointestinal dysmotility in critically ill patients with AKI; however, with rare exceptions, critically ill patients with AKI do not receive oral antibiotics.

Gastrointestinal dysmotility (up to 60% of ICU patients), with decreased oral absorption, can occur due to multiple factors: sepsis, postoperative ileus, use of opioids, ventilation, treatment with vasopressors and trauma.[42,43] The decrease in absorption can also be conditioned by other factors: adherence of antibiotics to feeding tubes, interaction with enteral nutrition (namely fluoroquinolones and tetracyclines), and reduced bioavailability related to gastric suppressant treatment (decreased absorption of weak bases such as ketoconazole).[44,45]

Additionally, calcium carbonate (phosphate binder used in patients with kidney disease) can modify the absorption of several drugs, so antibiotics should be administered 2 hours before or 4-6 hours after the binder. Lanthanum carbonate is associated with a very significant reduction in the absorption of ciprofloxacin.[46,47]

Absorption of subcutaneous drugs may be affected by edema, sepsis, and vasopressors, but antibiotics are not administered by this route.[48]

To ensure the appropriate dose of antibiotics in critically ill patients, they should be given intravenously whenever possible. Subsequently, if favorable evolution, they can be administered orally to preserve venous capital and for economic reasons.[40]

Distribution

The volume of distribution is an estimate of the extent to which an antibiotic will migrate into extravascular tissues. It is a major source of pharmacokinetic variability in AKI patients. The pathogenesis of sepsis involves endothelial dysfunction and damage, increased capillary permeability and fluid accumulation into the interstitial space, and increased antibiotic volume of distribution.[41] The increase in the interstitial fluid can be substantially elevated in oliguric AKI, especially in the presence of high-volume delivery in resuscitation, intravenous medication, and parenteral nutrition.

The expanded volume of distribution can differ substantially from that reported in pharmacokinetic studies of healthy individuals. It may be especially relevant with hydrophilic antibiotics such as aminoglycosides, β-lactams, glycopeptides, and daptomycin, suggesting higher doses to maintain serum concentrations.[49-52] Excessive increase in body volume can also dilute plasma creatinine leading to a delay in the diagnosis and treatment of AKI.[53]

A prospective multicenter study that evaluated serum concentrations of β-lactam antibiotics in patients with sepsis after initial administration showed that concentrations after the first dose were acceptable only for meropenem. Standard doses of piperacillin-tazobactam, ceftazidime, and cefepime were insufficient for the empirical treatment of these patients.[54] Significantly elevated volume of distribution is also observed in critically ill patients with AKI treated with daptomycin and gentamicin.[55,56]

The high volume of distribution at the beginning of therapy tends to decrease progressively over time if the patient progresses favorably, with correction of water overload by medical treatment or through renal replacement technique. The dose of hydrophilic antibiotics must necessarily accompany the decrease in the volume of distribution to prevent toxicity. Some early studies show evident changes in the volume of distribution of aminoglycosides throughout the in-hospital course in septic patients: the volume of distribution of gentamicin decreased from 0.43 to 0.29 L/kg and the required gentamicin dosage

decreased from 5.14 mg/kg per 24 hour to 3.98 mg/kg per 24 hour, despite stable renal function.[57]

Obesity may have significant effects on the pharmacokinetics of antimicrobials sufficient to require altered dosing schemes; obese patients experience an increase in the distribution volume due to increased adipose and lean muscle mass.[58] Fluoroquinolones and other lipophilic antibiotics tend to have a larger total volume of distribution. Although less pronounced, obese patients also have an increased volume of distribution of hydrophilic antibiotics.[59]

In obese patients, it is not clear which is the best way to adjust the antibiotic: total body weight, adjusted weight or lean body mass. The surrogate marker of choice is total weight for vancomycin and daptomycin, and adjusted body weight for aminoglycosides.[59] For drugs for which there is no recommended dose for obese patients, higher doses within the prescribed range should be used.[34]

The volume of distribution of antibiotics in acute kidney injury may be altered by their binding to plasma proteins but the extent of decreased protein binding in critically ill AKI patients is challenging to predict.[60]

Hypoalbuminemia is reported in 40% to 50% of critically ill patients and is associated with AKI in hospitalized patients.[61,62] Hypoalbuminemia decreases the amount of drug binding to protein, resulting in an increased unbound fraction of the drug, the fraction responsible for its pharmacological effects.[63] Unbound drugs will be distributed into tissues, increasing the volume of distribution, and will be cleared by kidneys and/ or RRT, thereby increasing drug clearance. One common example is ceftriaxone: the volume of distribution and clearance of this drug (85%–95% protein binding) in critically ill patients with hypoalbuminemia were increased 2-fold.[64]

Antibiotic therapy in elderly patients with AKI necessitates a comprehensive approach, encompassing strategies to enhance appropriate antibiotic prescribing, restrict their use for uncomplicated infections, and ensure the attainment of an optimal pharmacokinetic/pharmacodynamic target. To this end, further studies involving the elderly are required to better understand antibiotic pharmacokinetics.

■ Elimination

Non-RRT Elimination

Renal clearance is a continuous and dynamic process involving glomerular filtration, tubular secretion, and reabsorption. In AKI, the compromise in glomerular filtration and impaired tubular secretion can cause the accumulation of antibiotics eliminated by kidneys.[65]

Antibiotic dosages and frequency may need to be reduced to avoid accumulation and toxicity. This is particularly important with antibiotics with a narrow therapeutic index, such as aminoglycosides and vancomycin.

The evaluation of the residual renal function is very important since these patients will require higher doses of antibiotics than their anuric patients. A patient with renal dysfunction consistently displaying sub-therapeutic levels of vancomycin/aminoglycosides should alert to a probable recovery of renal function.[66]

RRT Elimination

RRT can markedly increase drug clearance, adding another layer to the complexity of antibiotic dosing; physicochemical properties of drugs (molecular weight, protein binding, and volume of distribution) will influence drug clearance with RRT; however, determining the exact drug clearance can be challenging given the heterogeneity in modalities of RRT.[40]

■ RRT Clearance is Affected by Protein Binding, Adsorption, and Gibbs-Donnan Effect:

1. Protein binding

Decreased binding to plasma proteins increases the ability to pass through the membrane (sieving coefficient) and the ability of a drug to diffuse through the filter membrane (saturation coefficient). The unbound fraction of ceftriaxone is increased in patients with critical illness and further increased by renal failure. As a result, RRT clearance is likely to be higher than expected.[38] In general, drugs with a high volume of distribution (>1 L/kg) and high protein binding (>80%) are poorly eliminated by RRT.

2. Adsorption

Adsorption of antibiotics by the filter is also documented (especially with polyacrylonitrile filters), although it is difficult to predict. Tian *et al* studied the adsorption of vancomycin on polyacrylonitrile, polyamide, and polysulfone filters and documented its occurrence. A study shows that a significant amount of amikacin binds irreversibly to sulfonated polyacrylonitrile membranes *in vitro*. However, this effect will likely have little clinical relevance.[67,68]

3.Gibbs-Donnan effect

Gibbs-Donnan effect refers to the retained anionic protein on the blood side of the membrane. This effect leads to consequent retention of cationic drugs (such as aminoglycosides and levofloxacin) and great excretion of anionic drugs (such as ceftazidime and cefotaxime). The clinical significance of this effect is not well determined.[69]

The water-soluble antibiotics (e.g. β-lactams and aminoglycosides) are poorly transported across cell membranes, and they are removed efficiently by RRT with a consequent need for dose adjustment. Lipophilic antibiotics (e.g., macrolides, tetracyclines, and linezolid) are easily transported across cellular membranes; they usually have a predominant hepatic elimination, with a few exceptions, such as quinolones, which show a variable fraction of renal elimination. Extracorporeal removal of lipophilic antibiotics is often negligible, and dose adjustments are not required.[4,70]

Convective techniques, namely continuous venovenous hemofiltration, are more effective in removing high molecular weight solutes, but are comparable to diffusive techniques in removing lower molecular weight solutes.

Drug clearance can be affected by several other variables, namely filter material, surface area, porosity, water permeability, and the efficiency in removing low and medium molecular weight molecules.[71] High-flux filters have increased permeability to mid-molecular-weight molecules and remove considerably more drugs than low-flux filters.[72]

In general, drugs with low plasma protein binding have a high volume of distribution and are easily removed by RRT.[73,74]

The essential RRT-related factors that affect drug removal is the effluent volume (which is determined by flow rate and therapy duration), extraction coefficient, and the type of fluid replacement in convective techniques (pre-dilution or post-dilution).[38] The effluent rate is determined from dialysate rate (Qd) and ultrafiltration rate (Quf) (effluent rate= Qd+Quf)[34]; the effluent rate depends on the experience of each center but is overall higher than previously practiced[75] who should lead to a critical reflection on the published antibiotic doses, taking into account old studies carried out with lower effluent rates. Prescribing RRT at high effluent rates implied higher antibiotic doses than those recommended in guidelines developed for low flow rates.[34]

Sustained low-efficiency dialysis (SLED) uses lower flow rates than IHD but the duration of SLED often results in higher clearance rates and thus has a potentially greater impact on drug clearance, increasing the risk of subtherapeutic antibiotic concentrations, which is potentiated by possible dose administration while dialysis is running. When this is not possible, antibiotics should be administered at the end of the technique.

According to several recent studies, patients with AKI and RRT often do not reach the pharmacokinetic goals of antibiotic treatment. Several recommendations suggest using higher doses than traditionally recommended to obtain therapeutic concentrations.[76-78]

RRT may have a role in providing the best treatment and preventing toxicity in concentration-dependent drugs. In patients undergoing intermittent dialysis therapy, some investigators suggest pre-dialysis administration of higher dosage because it can allow a higher peak concentration and maximize antibacterial pharmacodynamic goals with subsequently rapid dialytic clearance to minimize toxicity. Several studies document that the scheme for gentamicin administration[79-82] and Veinstein *et al* and Roberts *et al* presented good results.[80,83] This treatment method is not without risks: delay in dialysis schedule, unexpected dialysis discontinuation secondary to clotting, or intolerance to the treatment can put the patient at risk of antibiotic toxicity, due to inadequate drug clearance.[34,40,83]

PHARMACODYNAMIC ALTERATIONS

Pharmacodynamics integrates the pharmacokinetic characteristics of the drug with its antibacterial effect. The complex relationship between pharmacokinetics and pharmacodynamics was explained by the characterization of antibiotics in concentration-dependent and exposure time-dependent activity.

For concentration-dependent antibiotics (aminoglycosides, fluoroquinolones and daptomycin), the therapeutic effect is maximum when a high peak serum concentration (Cmax) is reached in relation to the minimum inhibitory concentration (MIC).[2] With time-dependent antibiotics, the therapeutic effect is maximized with increasing time with serum concentration above the MIC (time%>MIC).[2] Some drugs need both characteristics to optimize the antimicrobial effect (e.g. vancomycin and linezolid).[40]

In addition to the pattern of antibiotic activity, there are other parameters to be considered to optimize the effects of the drugs, namely the presence and duration of the post-antibiotic effect (the period between exposure to the antibiotic and the moment when the surviving microorganisms begin to multiply).[40]

Concentration Dependent Antibiotics

In AKI the desirable pharmacodynamic characteristics may be difficult to obtain with standard antibiotic doses. With the use of aminoglycoside antibiotics, MICs of 10-12 ng/mL are associated with a greater effect and bacterial mortality but prolonged treatment with these antibiotics is limited by their renal, vestibular, and hearing toxicity.[84] In order to optimize the pharmacodynamic profile with amikacin treatment in patients with sepsis, higher starting doses may be required.[85] Initial aggressive treatment is particularly important in the presence of microorganisms with high MICs, in patients with severe infections and with a high volume of distribution.[34]

Time-Dependent Antibiotics

In time-dependent antibiotics (e.g. β-lactams, clindamycin, macrolides and oxazolidinones), maintaining serum concentrations above the MIC optimizes therapeutic efficacy and prevents resistance.[2] The time %>MIC of at least 40% to 60% of the dosing interval has been known to be desirable to yield an appropriate effect of β-lactams.[86]

In patients with AKI the decreased renal clearance reduces the likelihood of infratherapeutic concentrations but RRT can remove large amounts of antibiotics.[34]

Valtonem *et al* compared three methods of renal replacement therapy (continuous venovenous hemofiltration, continuous venovenous hemodiafiltration 1 L/h and continuous venovenous hemodiafiltration 2 L/h) on the elimination of piperacillin/tazobactam; increased dialysis fluid flow increased the mean elimination of piperacillin and tazobactam and treatment with continuous venovenous hemodiafiltration nearly equaled renal elimination of piperacillin and tazobactam in healthy patients.[87] Therefore, initiation of RRT should be followed by the consideration of increased antibiotic doses or alternative administration strategies to prolong T%>MIC with β-lactams.[40]

Methods of Administration

Various methods of administration have been developed to optimize bactericidal activity in time-dependent antibiotics: prolonged intermittent infusions, low dose regimens with short intervals administrations, and continuous infusions.[34,88]

Extended antibiotic infusion time can increase T%> MIC; however, outcomes of more prolonged infusions continue to be debated. Continuous infusions are of special interest in patients on RRT as they allow drug administration at a rate similar to the withdrawal rate. This strategy has already been tested with meropenem (loading dose of 500 mg followed by an infusion of 2 g meropenem over 24 hour) and ceftazidime (loading dose of 2 g and an infusion of 3 g over 24 hours) with good results.[89] The importance of T%>MIC is even greater in treating bacterial strains with intermediate sensitivity.

Prolonged infusion is a compromise between a typical 30-minute antibiotic infusion and continuous infusion; there are few data on prolonged administration in patients with acute kidney injury and the need for RRT.[40]

Continuous or prolonged infusions can be particularly useful in treating agents with decreased susceptibility to drugs and patients with high volumes of distribution.[40] Prolonged infusions can be more challenging to manage due to the complexity of administration and the need to occupy venous access for long periods.

ALTERED NON-RENAL METABOLISM IN ACUTE KIDNEY INJURY

Changes in extrarenal metabolism and drug clearance in AKI have been poorly studied. Hepatic metabolism depends on hepatic blood flow, enzymatic activity, and protein binding. In sepsis, hepatic metabolism is reduced by decreased hepatic perfusion secondary to hemodynamic changes and vasoconstrictor drugs.[34,42]

Accumulated uremic toxins, inflammatory cytokines, and parathyroid hormones may modulate the expression of intestinal and hepatic drug metabolism enzymes and change uptake and efflux transporters.[90]

Kirwan *et al* documented impaired activation of CYP3A in patients with AKI, although the exact mechanism remains unclear.[91] The decrease in CYP3 activity leads to an increase in the activity of drugs whose degradation is mediated by these enzymes and a reduction in the activity of drugs that require activation. Jones *et al* documented that the "standard" dose of ciprofloxacin did not result in significantly different serum concentrations in patients with sepsis and severe acute kidney injury (<20 mL/min) and patients with clearance greater than 20 mL/min; increased transintestinal and biliary elimination may explain these findings.[92] Similar changes are seen with other antibiotics, namely imipenem, and vancomycin.

TOXICITY

Antibiotic toxicity is a genuine concern in critically ill patients with AKI, despite many arguments favoring more aggressive antibiotic therapy in this context. Patients with multiorgan dysfunction generally receive multiple possible toxic drugs. Several studies point to an increased risk of drug toxicity in patients with AKI, especially related to antibiotic treatment.[93-95]

Vancomycin and aminoglycosides are drugs of recognized nephrotoxicity but are crucial in treating critically ill infections.[96,97] The risk-benefit analysis is essential in the use of these drugs.

In addition, β-lactams antibiotics have been associated with hypersensitivity reactions, blood dyscrasias, and neurotoxicity; carbapenem and cefepime-induced seizures have been well documented in the literature in patients with renal impairment.[98,99] Prolonged or continuous administration may lead to lower peaks reducing the risk of β-lactam toxicity.[40]

Antibiotic-induced toxicities are often transient and reversible, but the long-term effect is still unclear and needs further studies. Antibiotic toxicity is also associated with a substantial increase in healthcare costs, although this cost may be lower than the cost associated with treatment failure. In an economic assessment of aminoglycoside nephrotoxicity, total hospital costs were 2-fold higher in patients with nephrotoxicity compared to those without nephrotoxicity.[100]

PRACTICAL APPROACH

Loading doses are used to achieve adequate early antibiotic concentrations or high initial peak concentrations (that are strongly related to the clinical response in antibiotics with concentration-dependent activity). Loading doses are necessary even when drugs are administered as a continuous infusion.[40] In patients with residual renal function and a significant increase in the distribution volume, a higher dosage is warranted.

In RRT, the best time for drug administration should be highlighted in relation to the course of the technique to avoid undertreatment by increasing drug clearance. Monitoring should include the rebound effect, remembering that drug concentrations may increase after completion of the technique as the drug sequestered in the tissues returns to the bloodstream.[4]

The best way to maintain adequate monitoring is to consult the literature (if the patient's conditions and the RRT technique are comparable). Currently, most institutions employ higher dialysate flow rates than in the past; as a result, we tend to use higher antibiotic doses than recommended in some of these published sources.[34]

Recently, a study was published reviewing several calculation techniques and individualization of antibiotic therapy in patients with RRT, estimating extracorporeal creatinine clearance. This method, used individually, does not include the estimation of renal secretion and reabsorption, so it can lead to subtherapeutic and supratherapeutic concentrations.[38]

CONCLUSION

Appropriate antibiotic therapy is a challenge in acute and chronic kidney disease.

Clinicians are limited in determining the severity of renal dysfunction, measuring other physiological mechanisms that may compromise drug availability, and identifying extrarenal clearance.

RRT makes antibiotic management even more complex, and more recent pharmacokinetic and pharmacodynamic studies are needed in this setting. Determination of drug concentrations is essential to ensure the therapeutic range, but it is still exceptional from the list of drugs used in clinical practice.

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Corresponding Author:
Bruno José Fraga Dias
Nephrology Department, Centro Hospitalar Universitário de Santo António, Largo do Prof. Abel Salazar, 4099-001 Porto, Portugal
Email: brunodias.nefrologia@chporto.min-saude.pt