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Review Article

Individualising Antibiotic Dosing in Critically Ill Patients with Acute Kidney Injury: Pharmacokinetic and Pharmacodynamic Challenges

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ABSTRACT

Acute kidney injury (AKI) is common in critically ill patients and alters the handling of renally cleared antibiotics, while sepsis adds unpredictable changes in volume of distribution, protein binding and organ perfusion. Renal dosing recommendations derived from stable chronic kidney disease can leave patients underexposed early in infection, whereas later drug accumulation drives neurotoxicity and nephrotoxicity. This review examines the pharmacokinetic and pharmacodynamic basis for individualised antibiotic dosing in AKI, compares loading with maintenance strategies, and considers the limits of creatinine-based estimates, renal replacement therapy, therapeutic drug monitoring and toxicity. Much of the supporting evidence is pharmacokinetic or observational, and randomised trials of dose adjustment in AKI are lacking. We therefore propose a stepwise framework for clinical judgement: full loading doses, prolonged β-lactam infusion, reassessment of maintenance doses at 24 to 48 hours, and concentration monitoring where available. Practical implications for Indian intensive care units and for clinical pharmacists are discussed.

INTRODUCTION

Sepsis is a leading reason for intensive care admission, and early effective antibiotic therapy is among the few measures with a proven survival benefit[1,2]. The drug must also reach infected tissue at a level that is effective yet safe. Acute kidney injury (AKI), a common complication of critical illness[3], makes that balance difficult to maintain. Most antibiotics are cleared by the kidney, so falling filtration lets drug accumulate. Sepsis acts in the opposite direction: capillary leak enlarges the volume of distribution, albumin falls, and in some patients clearance rises[4].

In the Defining Antibiotic Levels in Intensive care unit patients (DALI) study of 384 patients, many on standard β-lactam doses missed conservative pharmacodynamic targets, and lower exposure was associated with worse outcome[5]. The Sampling Antibiotics in Renal Replacement Therapy (SMARRT) study of patients on renal replacement therapy (RRT) found regimens

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differing several-fold and widely scattered drug levels[6]. This review asks how dosing can be individualised in critically ill patients with AKI, with attention to Indian intensive care units (ICUs).

PHARMACOKINETIC AND PHARMACODYNAMIC BASIS

AKI is defined by the kidney disease: Improving Global Outcomes (KDIGO) criteria using a rise in serum creatinine, a fall in urine output, or both[7]. In sepsis it is rarely static: filtration can fall within hours and recover just as fast, and recovery may overshoot into augmented renal clearance, with the opposite danger of underdosing[8]. Tubular secretion, an important route for many β-lactams, can also be impaired independently of filtration[4].

Antibiotic effect is usually tied to one of three pharmacodynamic (PD) indices[4]: for β-lactams, the fraction of the dosing interval that free drug exceeds the minimum inhibitory concentration (MIC), denoted fT>MIC; for aminoglycosides, the peak-to-MIC ratio (Cmax/MIC); and for vancomycin, linezolid and polymyxins, the area under the concentration–time curve relative to MIC (AUC/MIC). In severe infection many experts aim to keep free β-lactam levels above MIC throughout the interval[9]

Fluid resuscitation and capillary leak enlarge the volume of distribution (Vd) of water-soluble drugs, so the first dose gives a lower peak than expected; in one multicentre study, first-dose concentrations of most β-lactams studied fell short of a stringent target[10]. Early concentrations are set by Vd, whereas clearance governs how quickly drug disappears. Reduced clearance in AKI therefore changes the maintenance requirement far more than the first dose, and AKI is rarely a reason to cut the initial dose.

ESTIMATING RENAL FUNCTION

Creatinine-based estimates of clearance assume a steady state that AKI destroys. When filtration drops suddenly, creatinine rises slowly and the estimate overstates function; in recovery the error reverses[4,7]. A timed urine collection over four to eight hours gives a measured creatinine clearance and can be repeated[4]. Drug levels, where available, reflect true clearance better than any equation[9].

LOADING VERSUS MAINTENANCE DOSING

Because the loading dose depends on Vd and not clearance, a full loading dose is appropriate in AKI for most antibiotics[4]. The vancomycin consensus guideline supports 20 to 35 mg/kg of actual body weight in critically ill patients, up to roughly 3 g, without reduction for AKI[11]; polymyxin guidance likewise advises a loading dose whatever the renal function[12]. Prolonged β-lactam infusions also begin with a bolus, as in the Beta-Lactam Infusion Group (BLING) III trial[13].

Maintenance is where renal function matters. Crass and colleagues noted that most label adjustments derive from stable chronic kidney disease, and that in the first 24 to 48 hours of AKI, trimming wide-margin β-lactams may cause underexposure more often than it prevents toxicity[14]. This rests on pharmacological reasoning and observational data; no trials have compared early full with adjusted dosing. We favour a time-based compromise: wide-margin β-lactams stay at full dose for 24 to 48 hours, then follow the renal trajectory and measured levels. Narrow-margin drugs (aminoglycosides, vancomycin, polymyxins) should be individualised from the start.

COMMONLY USED ICU ANTIBIOTICS

Table 1 summarises the main PD targets and AKI-specific considerations for the antibiotics discussed below.

Because β-lactam activity is time-dependent, prolonged infusion makes pharmacological sense. BLING III randomised 7,031 septic patients to continuous or intermittent infusion of piperacillin–tazobactam or meropenem; 90-day mortality was 24.9% versus 26.8% (not statistically significant), while clinical cure was higher with continuous infusion (55.7% versus 50.0%) [13]. A meta-analysis pooling this trial with earlier ones found lower mortality with prolonged infusion[15]. The contrast between a neutral primary result and a pooled benefit suggests that the effect is modest and that the evidence is not yet definitive. Meropenem is unstable at room temperature, so in warm climates 3- to 4-hour extended infusions are often more realistic than 24-hour ones. Cefepime accumulates in AKI and can cause encephalopathy and non-convulsive status epilepticus[16].

Vancomycin guidance has moved from troughs to AUC-guided dosing, targeting an AUC24/MIC of 400 to 600 mg·h/L[11]; in AKI, repeated levels or Bayesian software are needed rather than a fixed schedule. Vancomycin plus piperacillin–tazobactam carried higher odds of AKI than vancomycin alone (odds ratio 3.40) [17]. For aminoglycosides, the interval is lengthened in AKI, later doses follow measured levels and courses are kept shor[9]. Colistimethate is a prodrug of colistin, so renal impairment lowers the maintenance need, whereas polymyxin B is cleared mainly non-renally and usually needs no renal adjustment, though a loading dose is advised[12].

Table 1: Key Pharmacodynamic Targets and Implications in AKI for Commonly Used ICU Antibiotics

Antibiotic	Main PD index	Implication in AKI	Ref.
Piperacillin–tazobactam, meropenem	fT>MIC	Full dose for 24–48 h, then adjust; extended infusion after loading	4,13,14
Cefepime	fT>MIC	Accumulates; watch for encephalopathy and seizures	16
Vancomycin	AUC24/MIC 400–600 mg·h/L	Load in full; maintenance by levels or Bayesian estimate	11
Aminoglycosides	Cmax/MIC	Full first dose; later doses by levels; short course	4,9
Colistimethate sodium	AUC/MIC	Load in full; reduce maintenance with renal function	12
Polymyxin B	AUC/MIC	Load in full; no renal dose reduction	12
Linezolid	AUC/MIC	No label adjustment; monitor platelets	4

AKI, acute kidney injury; AUC, area under the concentration–time curve; AUC24, area under the concentration–time curve over 24 hours; Cmax, peak concentration; fT>MIC, time for which free drug concentration exceeds the minimum inhibitory concentration; ICU, intensive care unit; PD, pharmacodynamic. Table 1 is an orientation and does not replace local formularies or specialist advice.

DOSING DURING RENAL REPLACEMENT THERAPY

RRT adds an extracorporeal route of clearance depending on modality, effluent flow, membrane, and drug properties such as protein binding and Vd. Total clearance can be treated as residual native function plus extracorporeal clearance; at a delivered effluent rate near 2 L/h, extracorporeal clearance of an unbound small molecule is about 30 mL/min[6]. Doses should follow the dose delivered, not the dose prescribed. In SMARRT (381 patients, 29 ICUs), higher estimated total renal clearance was associated with lower trough concentrations for every drug studied, and troughs fell below the optimal lower limit in 4%, 4% and 55% of patients for meropenem, piperacillin and vancomycin respectively[6]. For intermittent haemodialysis, dosing after the session avoids early removal. Many patients with AKI never receive RRT and need dosing based on residual function and close monitoring.

THERAPEUTIC DRUG MONITORING

Therapeutic drug monitoring (TDM) is long established for aminoglycosides and vancomycin, and an international position paper supports extending it to β-lactams in critically ill adults, especially with AKI or RRT[9]. Clinical evidence is thinner: TARGET randomised 254 patients and found no reduction in organ dysfunction with TDM-guided piperacillin–tazobactam (mean Sequential Organ Failure Assessment [SOFA] score 7.9 versus 8.2), though most infections involved low-MIC organisms[18]. TDM is likely to help most in selected patients, such as those with unstable renal function, on RRT, or with higher-MIC pathogens. In many Indian centres β-lactam assays are unavailable; vancomycin and aminoglycoside levels give the best return, and even a single trough can reveal accumulation. Bayesian model-informed dosing is increasingly used for vancomycin[11].

ANTIBIOTIC-ASSOCIATED TOXICITY

Nephrotoxicity is most closely linked to aminoglycosides, polymyxins and vancomycin, with risk rising in sepsis, hypovolaemia and combinations such as vancomycin with piperacillin–tazobactam[12,17]. When

creatinine rises on these drugs, doses and levels should be reviewed and unnecessary nephrotoxins stopped. β-Lactam neurotoxicity is easily missed because confusion and myoclonus are blamed on sepsis or uraemia; renal impairment is a prominent risk factor for cefepime neurotoxicity[16], so unexplained confusion, myoclonus or seizures in AKI should prompt dose review and, if possible, a drug level. Linezolid-related thrombocytopenia also warrants monitoring.

STEWARDSHIP AND THE INDIAN CONTEXT

Dose optimisation is part of stewardship: guidelines list prospective audit with feedback, early de-escalation and optimisation of dose and duration as core elements[19]. A structured review at 48 to 72 hours, once cultures return, is a natural point to stop drugs and adjust doses. Gram-negative resistance in Indian ICUs is high[20], increasing reliance on carbapenems and polymyxins, where dosing errors have the greatest consequences. Limited assay access, cost and uneven pharmacy involvement are real obstacles. Realistic responses include clinical pharmacist review, order sets with built-in loading doses and a 48-hour reassessment prompt, and regional laboratories offering vancomycin, aminoglycoside and ideally β-lactam assays.

A PRACTICAL STEPWISE APPROACH

This sequence is a framework for clinical judgement, not a protocol.

1. Give a full, weight-based loading dose without delay, whatever the renal function.
2. Use extended β-lactam infusion after loading where stability and logistics allow.
3. Estimate renal function from creatinine, urine output and, if feasible, a timed urine collection; treat every estimate as provisional.
4. Keep wide-margin β-lactams at full dose for 24 to 48 hours, then adjust; individualise vancomycin, aminoglycosides and polymyxins from the outset.
5. On RRT, base doses on total clearance and the delivered modality.
6. Use TDM where available, review daily and de-escalate as soon as microbiology allows.

CONCLUSION

Much of this guidance rests on pharmacokinetic and observational studies rather than randomised trials in AKI, and patient-centred outcomes are seldom reported. Pragmatic trials of early full versus adjusted dosing, TDM studies in high-variability populations and data from low- and middle-income countries are the clearest needs. Dosing antibiotics in a critically ill patient with AKI means managing two risks at once: too little drug early and too much later. Full loading doses, prolonged β-lactam infusion, repeated reassessment of renal function, allowance for extracorporeal clearance and concentration monitoring where feasible offer a reasonable course between them. Individualisation is not a luxury of well-resourced centres; stewardship-linked dose review and pharmacist involvement can deliver much of the benefit in any ICU.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Abinash K: Conceptualisation, literature search, manuscript preparation and drafting.

Monica K: Literature review, critical evaluation and manuscript revision.

Manisha M: Scientific supervision, critical review and final approval

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