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Renal Dosing of Antibiotics: Are We Jumping the Gun?

Ryan L. Crass,[1] Keith A. Rodvold,[2] Bruce A. Mueller,[1] Manjunath P. Pai[1]

[1]Department of Clinical Pharmacy, College of Pharmacy, University of Michigan, Ann Arbor; [2]Departments of Pharmacy Practice and Medicine, Colleges of Pharmacy and Medicine, University of Illinois at Chicago

Antibiotic renal dose adjustments are determined in patients with stable chronic kidney disease and may not translate to patients in late-phase trials and practice. Ceftolozane/tazobactam, ceftazidime/avibactam, and telavancin all carry precautionary statements for reduced clinical response in patients with baseline creatinine clearance of 30–50 mL/min, potentially due to unnecessary dose reduction in the setting of acute kidney injury (AKI). In this review, we discuss the regulatory landscape for antibiotics eliminated by the kidney and highlight the importance of the first 48 hours of therapy. Using a clinical database, we identified AKI on admission in a substantial proportion of patients with pneumonia (27.1%), intraabdominal (19.5%), urinary tract (20.0%), or skin and skin structure infections (9.7%) that resolved by 48 hours in 57.2% of cases. We suggest that deferred renal dose reduction of wide therapeutic index antibiotics could improve outcomes in patients with infectious diseases.

Keywords. acute kidney injury; creatinine clearance; kidney function; precision medicine; regulatory science.

The kidney is the major route of elimination for many important classes of antibiotics; correspondingly, patient renal function is the single most important factor used to individualize antibiotic dosing. The goal of renal dosage adjustments is to achieve equivalent exposures in patients with and without renal impairment, thereby minimizing toxicity without compromising efficacy. However, multiple antibiotics recently approved by the US Food and Drug Administration (FDA) demonstrated inferior efficacy relative to comparators in patients with moderate renal impairment [1–3]. Ceftolozane/tazobactam (CTZ), ceftazidime/avibactam (CZA), and telavancin all carry precautionary statements in their labeling for reduced clinical response in patients with creatinine clearance (CrCL) of 30–50 mL/min; yet, the mechanisms that underlie these findings have been incompletely elucidated [4–6].

The current regulatory pathway for compounds eliminated by the kidney is tailored to maintenance therapeutics intended for use in patients with stable chronic kidney disease (CKD). Renal dose adjustments are determined in small, early-phase pharmacokinetic (PK) studies that enroll healthy patients with stable CKD before testing in registry clinical trials. Antibiotics do not fit cleanly into this paradigm due to overwhelmingly episodic, rather than chronic, use. Similarly, renal impairment may be acute, rather than chronic, in a clinically meaningful subset of acutely infected patients, especially those who require hospitalization.

We believe that renal dose adjustment protocols that are based on data from patients with CKD do not accurately reflect renal impairment in patients enrolled in clinical trials for antibiotic approval. Inappropriate empirical dose reduction in the setting of transient acute kidney injury (AKI) may explain the decreased clinical response in patients with moderate renal impairment with the compounds described above. In this review, we discuss the current regulatory pathway for antibiotics eliminated by the kidney, highlight the importance of appropriate empirical therapy as a determinant of outcome, present data on the prevalence of AKI in the infectious syndromes most commonly targeted in antibiotic development, and suggest possible solutions to improve renal dosing of antibiotics in clinical trials and clinical practice.

THE REGULATORY PATHWAY

Following investigational new drug approval, early-phase clinical trials are conducted to evaluate the PK and safety of investigational compounds in healthy individuals. The FDA issued draft guidance in 2010 on the conduct of phase 1 studies in patients with impaired renal function [7]. Under this guidance, renal impairment studies are required for compounds with significant renal elimination (fraction excreted unchanged ≥30%), metabolism or excretion in bile, or intended for chronic use in patients with CKD. Notably, antibiotics are specifically listed as a class of compounds that, although not used chronically, still warrant study in renal impairment due to clinical concerns in this population [7].

Patients enrolled into these studies should have demographics (eg, age, gender, race, weight) similar to those of the target patient population [7]. The guidance recommends

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Correspondence: M. P. Pai, College of Pharmacy, University of Michigan, 428 Church Street, Ann Arbor, MI 48109, USA (amitpai@med.umich.edu).

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enrolling patients into 5 groups using the Cockcroft-Gault or modification of diet in renal disease (MDRD) equations: control (≥90 mL/min[/1.73 m^2]), mild impairment (60–89 mL/min[/1.73 m^2]), moderate impairment (30–59 mL/min[/1.73 m^2]), severe impairment (15–29 mL/min[/1.73 m^2]), and end stage renal disease (ESRD; <15 mL/min[/1.73 m^2]) [8–10]. For compounds with wide therapeutic indices, the first 2 categories may be combined to create the control population; this may be especially prudent when using the MDRD equation given the bias associated with this equation at values >60 mL/min/1.73 m^2 [10]. It is worth noting that the European Medicines Agency recommends an exogenous measure of glomerular filtration rate (GFR) with values reported in absolute units, rather than normalized to body surface area [11]. This discordance between the major regulatory agencies adds a layer of complexity to the design of these studies.

In general, only a few patients are enrolled per renal function strata into phase 1 trials. For example, trials for delafloxacin and meropenem/vaborbactam, both FDA approved in 2017, each enrolled 8–10 patients per group in their renal impairment studies [12–14]. These investigations employ rich sampling and noncompartmental analysis to calculate PK parameters. From these data, renal dose adjustments are determined for testing in phase 2 and 3 trials, which generally exclude patients with severe renal impairment (<30 mL/min[/1.73 m^2]) [7]. Further PK information may be obtained in late-phase clinical trials that use sparse sampling and population PK modeling. Data from healthy and infected patients from all phases of the clinical program are pooled for population PK analysis to provide a large dataset for evaluation of covariate effects. If renal function is identified as a covariate that impacts drug clearance in the pooled population model, simulations can be performed to validate the dose adjustments used in phase 2 and 3 trials for inclusion in the final product label.

THE CRITICAL PERIOD

Adequate early antibiotic therapy is a primary driver of outcome in infectious diseases. "Adequate" antibiotic therapy consists of an agent with in vitro activity against target pathogens that is administered at doses sufficient to achieve pharmacodynamic targets in vivo. "Early" defines the empirical treatment period early in the illness when infecting organism and susceptibility profile are generally unknown.

The majority of data that link the timing of adequate antibiotic therapy to patient outcomes are for the critically ill. A retrospective cohort study of patients with septic shock from 14 intensive care units across 10 hospitals found that every hour delay in effective therapy following the onset of hypotension was associated with a 7.6% decrease in survival [15]. A metaanalysis of studies examining empirical therapy in sepsis found that inadequate therapy during the first 48 hours of treatment increased the odds of mortality (odds ratio [OR], 1.60; 95% confidence interval [CI], 1.27–1.86) corresponding to a number needed to treat of 10 (95% CI, 8–15) to prevent 1 death [16].

The first 48 hours has also been identified as a critical period for patients with infections complicated by bacteremia. A single-center study from Israel found that inadequate empirical therapy for bloodstream infection (BSI) was associated with increased mortality (OR, 1.60; 95% CI, 1.3–1.9), with the highest risk in intraabdominal (OR, 3.8; 95% CI, 2.0–7.1) and skin and skin structure (OR, 3.1; 95%, 1.8–5.6) sources [17]. In a study of community-acquired BSI, adequate therapy by 48 hours demonstrated the strongest negative association with 28-day mortality of all time intervals tested (OR, 0.54; 95% CI, 0.43–0.71) [18]. Examining data for specific pathogens, adequate therapy within 48 hours reduced the odds of mortality (OR, 0.21; 95% CI, 0.06–0.80) in patients with enterococcal BSI in 1 study, while administration outside of a classification and regression tree analysis (CART)–derived breakpoint of 48.1 hours increased mortality 3-fold in another [19, 20]. Similarly, a CART-derived breakpoint of 44.75 hours for initiation of adequate therapy was associated with reduced mortality in a study of *Staphylococcus aureus* bacteremia [21].

It is clear from these data that adequate early antibiotic therapy drives patient outcomes in serious infections. Although these studies largely equated in vitro activity with antibiotic activity, dosing and administration have a significant bearing on the ability to achieve pharmacodynamic targets required for efficacy. Given the critical importance of the first 48 hours of therapy, patients who receive reduced doses due to renal impairment may be at risk for poor outcomes if that impairment does not persist throughout this critical period.

THE PROBLEM

We posit that renal impairment is acute, rather than chronic, in a clinically meaningful proportion of patients admitted with infectious diseases and that this impairment resolves within 48 hours in a substantial portion of cases. To test this hypothesis, we retrospectively reviewed records for patients admitted to Michigan Medicine with infectious diagnoses between January 2006 and April 2018. A waiver of Health Insurance Portability and Accountability Act authorization was obtained from the institutional review board prior to data acquisition and analysis. The database was queried to identify adult patients with International Classification of Diseases, Ninth Edition, and Tenth Edition, codes consistent with the most common regulatory pathways for antibiotics used in hospitalized populations: complicated urinary tract (cUTI), complicated intraabdominal (cIAI), bacterial pneumonia (PNA), and acute bacterial skin and skin structure infections (ABSSSI). Diagnoses coded as admitting, primary, or present on admission were eligible for

inclusion, while encounters with codes for more than 1 infection type were ineligible. Female patients with cUTI had to be aged ≥56 years in order to meet the complicated definition [22]. Patients with stage 4 or greater CKD, incomplete or inaccurate records, or fewer than 3 serum creatinine (Scr) levels were excluded. Only the first encounter per patient was eligible for inclusion.

The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines were used to impute baseline Scr and define AKI [23]. A minimum absolute Scr increase of 0.3 mg/dL, in addition to the proportional increases that define each individual KDIGO stage, was required in order to restrict the analysis to clinically meaningful AKI. Baseline Scr was imputed as the mean value from 365 to 7 days prior to the index admission or the minimum value obtained during the admission if no prior data were available. Renal function was assessed as CrCL using the Cockcroft-Gault equation and estimated GFR using the MDRD ($eGFR_{MDRD}$) and CKD Epidemiology Collaboration ($eGFR_{CKDEPI}$) equations [8, 10, 24]. Moderate renal impairment was defined as a CrCL or eGFR of 30–50 mL/min[/1.73 m^2]. AKI was classified as transient if there was resolution of KDIGO criteria by 48 hours [25]. Descriptive statistics were calculated in total and for each individual infection type; however, no statistical comparisons were made between groups. All analyses were performed in the R environment [26].

More than 18 500 unique patient encounters were identified (Table 1). cUTI (41.0%) and ABSSSI (31.7%) contributed the majority of cases followed by cIAI (15.9%) and PNA (11.4%). In general, demographics were similar across the 4 infection types (Table 1). The mean (± standard deviation) baseline Scr was 0.88 ± 0.36 mg/dL across all infection types, with higher values in cUTI (0.94 ± 0.38 mg/dL) and ABSSSI (0.87 ± 0.34 mg/dL) than PNA (0.81 ± 0.38 mg/dL) and cIAI (0.80 ± 0.32 mg/dL). The prevalence of moderate renal impairment on admission was 14.3% to 16.4% depending on the equation used.

The overall rate of AKI on admission was 17.5% (Table 2). AKI on admission was most common in PNA (27.1%) followed by cUTI (20.0%) and cIAI (19.5%). Kidney injury was comparatively less common in patients with ABSSSI (9.7%). Restricting analysis to patients with admission renal impairment likely to warrant dose adjustment (<60 mL/min[/1.73 m^2]), AKI was present in 36.7% to 38.0% of cases. Kidney injury resolved in 57.2% of patients by 48 hours, although rates varied among the individual infection types (Table 2). In patients with moderate renal impairment on admission, 42.8% to 45.9% had improvement of renal function greater than 50 mL/min[/1.73 m^2] by 48 hours. Figure 1 depicts the fractional change in Scr relative to baseline over the first 4 days of hospitalization. As illustrated, there is higher probability that patients with AKI on admission will have recovery of renal function (Figure 1*B* and *C*) than persistence of renal impairment (Figure 1*D*).

THE IMPLICATIONS

These data highlight the dynamic nature of renal function in patients with acute infectious diseases. AKI occurred in nearly

Table 1. Baseline Characteristics of Patients Admitted With Common Infectious Syndromes

	All Patients	Pneumonia	Complicated Intraabdominal Infection	Complicated Urinary Tract Infection	Acute Bacterial Skin and Skin Structure Infection
Demographics					
N (%)	18 650 (100)	2130 (11.4)	2965 (15.9)	7650 (41.0)	5905 (31.7)
Age (years)	61 (17)	57 (18)	53 (16)	69 (14)	55 (17)
Total body weight (kg)	84.5 (25.8)	80.4 (24.3)	82.1 (22.8)	80.5 (23.8)	92.4 (28.3)
Height (cm)	169.4 (11.4)	170.5 (11.3)	170.6 (10.8)	167.5 (11.4)	171.0 (11.3)
Body mass index (kg/m^2)	29.4 (8.4)	27.5 (7.7)	28.1 (7.3)	28.6 (7.8)	31.6 (9.2)
Body surface area (m^2)	1.98 (0.33)	1.93 (0.32)	1.96 (0.30)	1.92 (0.31)	2.07 (0.34)
Male sex	9585 (51.4%)	1347 (63.2%)	1626 (54.8%)	3395 (44.4%)	3217 (54.5%)
Race					
Caucasian	15 897 (85.2%)	1773 (83.2%)	2530 (85.3%)	6549 (85.6%)	5045 (85.4%)
Black	1763 (9.5%)	218 (10.2%)	226 (7.6%)	724 (9.5%)	595 (10.1%)
Other/not available	990 (5.3%)	139 (6.5%)	209 (7.0%)	377 (4.9%)	265 (4.5%)
Admission renal function[a]					
Serum creatinine (mg/dL)	1.12 (0.79)	1.10 (0.76)	1.03 (0.69)	1.24 (0.94)	1.00 (0.58)
Creatinine clearance[b]	100 (64)	105 (70)	111 (61)	78 (53)	121 (66)
$eGFR_{MDRD}$	83 (55)	94 (80)	91 (50)	72 (52)	88 (46)
$eGFR_{CKDEPI}$	78 (33)	83 (37)	86 (32)	67 (31)	85 (31)

Data presented as mean (standard deviation) or number (percentage).

Abbreviations: $eGFR_{MDRD}$, estimated glomerular filtration rate using the modification of diet in renal disease equation; $eGFR_{CKDEPI}$, estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaborative equation.

[a]Creatinine clearance is expressed in absolute units (mL/min) while the $eGFR_{MDRD}$ and $eGFR_{CKDEPI}$ are normalized to body surface area (mL/min/1.73 m^2) [8, 10, 24].

[b]Creatinine clearance calculated using the Cockcroft-Gault equation.

Table 2. Acute Kidney Injury on Admission in Patients With Common Infections

AKI Categories	All Patients (N = 18650)	Pneumonia (n = 2130)	Complicated Intraabdominal Infection (n = 2965)	Complicated Urinary Tract Infection (n = 7650)	Acute Bacterial Skin and Skin Structure Infection (n = 5905)
Any AKI[a]	3256 (17.5%)	578 (27.1%)	577 (19.5%)	1531 (20.0%)	570 (9.7%)
KDIGO stage[a]					
0	15394 (82.5%)	1552 (72.9%)	2388 (80.5%)	6119 (80.0%)	5335 (90.3%)
1	1697 (9.1%)	276 (13.0%)	279 (9.4%)	806 (10.5%)	336 (5.7%)
2	971 (5.2%)	188 (8.8%)	180 (6.1%)	445 (5.8%)	158 (2.7%)
3	588 (3.2%)	114 (5.4%)	118 (4.0%)	280 (3.7%)	76 (1.3%)
Transient AKI[b]	1862/3256 (57.2%)	267/578 (46.2%)	308/577 (53.4%)	923/1531 (60.3%)	364/570 (63.9%)

Abbreviations: AKI, acute kidney injury; KDIGO, Kidney Disease: Improving Global Outcomes.

[a]AKI was defined using the KDIGO criteria with the added requirement of an absolute increase in serum creatinine of at least 0.3 mg/dL [23].

[b]Transient AKI was defined as the absence of KDIGO criteria at 48 hours in patients who met KDIGO criteria for AKI on admission [23, 25].

1 in 5 patients admitted with common infectious diagnoses targeted in antibiotic development, and this rate of AKI was approximately 2-fold higher in patients with admission CrCL or eGFR <60 mL/min[/1.73 m^2]. Additionally, more than 50% of patients with AKI on admission had resolution of renal injury by 48 hours, highlighting the potential for rapid recovery in a substantial subset of patients. However, it should be noted that neither antibiotic dosing nor patient outcomes were evaluated. A prospective study is required to definitively establish causal links between antibiotic dose, transient AKI, and patient outcomes.

The frequency of AKI across these infections and the rapidity with which it resolved in the majority of cases has significant implications for empirical dose reductions for renal

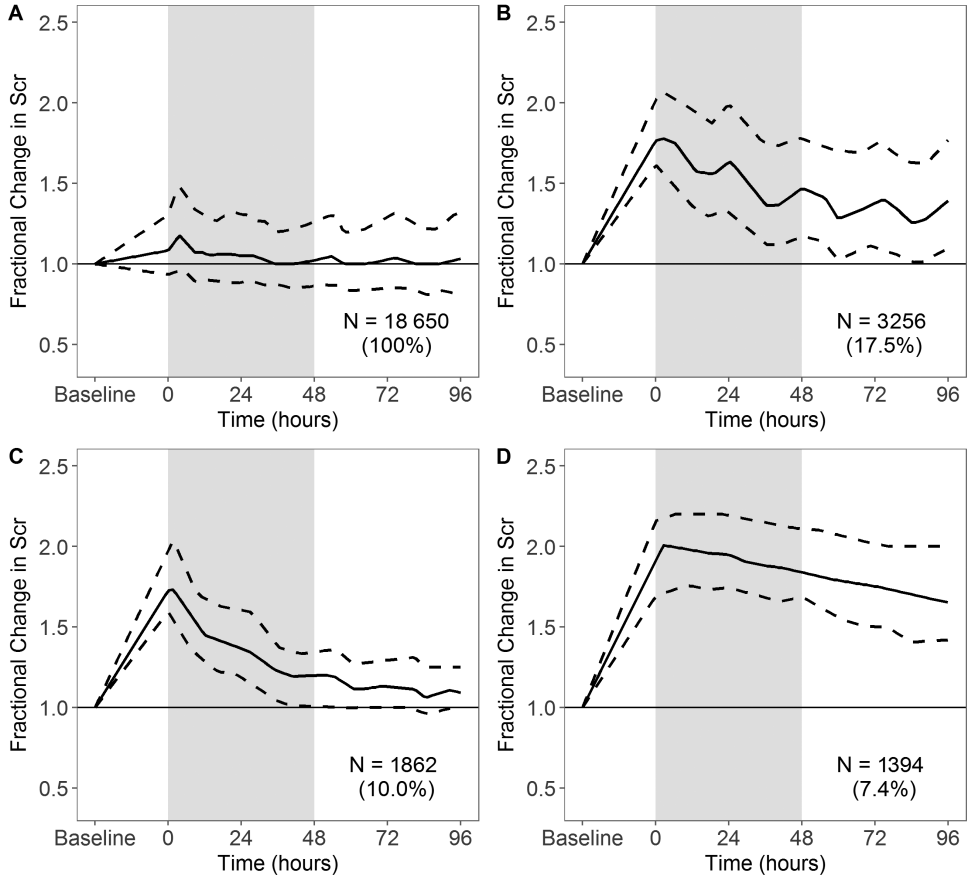

Figure 1. Fractional change in serum creatinine relative to baseline through the first 4 days of admission. The median trend is depicted by the solid black line, and the interquartile range is bounded by dashed lines. The shaded region contains the first 48 hours after admission; resolution of acute kidney injury (AKI) within this time period was used to define transient AKI. Each plot represents a different patient subpopulation with the corresponding number and percentage of the total population included in the bottom right: *A*, all patients; *B*, patients with AKI on admission; *C*, patients with transient AKI; *D*, patients with persistent AKI.

impairment. All standard creatinine-based equations used to estimate renal function are based upon the assumption of steady-state conditions; therefore, they are unable to accurately estimate renal function in the dynamic setting of AKI. Multiple "kinetic eGFR" equations have been developed to improve the assessment of GFR in dynamic renal states, all of which rely on multiple Scr measurements and the mathematics of creatinine mass balance [27–31]. However, these equations are all based on constant rate assumptions of creatinine production and volume of distribution that may not be accurate, especially in acutely ill patients [32, 33]. Perhaps more important to antibiotic posology is the lag time between changes in GFR and the corresponding change in Scr. The rate of change in Scr is proportional to both the degree of change in GFR and the patient's baseline renal function [34]. Considering the kinetics of creatinine, it is likely that patients with resolution of AKI by 48 hours actually had recovery of GFR much earlier in their hospitalization. Thus, antibiotic dosing based on CrCL or eGFR in AKI is akin to driving a car while looking out the rearview mirror.

These data support the view that inappropriate dose reductions in the setting of transient AKI may have played a role in the decreased clinical response seen in patients with moderate renal impairment in antibiotic clinical trials. Such studies include a small number of patients in this renal function category; therefore, small absolute differences can have a large impact on outcome rates. In its registry trial for cIAI, CZA with metronidazole cured 14/31 (45.2%) patients with CrCL 30–50 mL/min compared to 26/35 (74.3%) with meropenem (absolute difference, −29.1%; 95% CI, −50.05% to −5.36%) [3, 5]. Similarly, CTZ with metronidazole cured 11/23 (47.8%) patients with cIAI and moderate renal impairment compared to 9/13 (69.2%) treated with meropenem [2, 35]. Clinical cure rates across trials and treatment arms were greater in patients with CrCL >50 mL/min (85%–88%). Proportional dose reductions for moderate renal impairment in these studies were 50% for CTZ (1.5 g every 8 hours to 0.75 g every 8 hours), 66% for CZA (2.5 g every 8 hours to 1.25 g every 12 hours), and 33% for meropenem (1 g every 8 hours to 1 g every 12 hours). Notably, the recommended dose of CZA in moderate renal impairment was increased to 1.25 g every 8 hours in the final product label [3].

In our analysis, 9.0% of patients admitted with cIAI had moderate renal impairment on admission by CrCL. This is consistent with the phase 3 trial for CZA (8.0%) but higher than the trial for CTZ (4.5%) [5, 35]. We found that 47.9% with moderate impairment on admission had improvement of CrCL above 50 mL/min by 48 hours, which is consistent with the results of the phase 3 study of CZA where 67.2% of patients with moderate renal impairment at baseline had improvement above 50 mL/min by 48–72 hours [5]. Given the inaccuracy of renal function estimates in AKI and the frequency of transient impairment, alternative renal dosing strategies should be identified for clinical trials and practice.

THE POTENTIAL SOLUTIONS

The problem, both in clinical trials and clinical practice, is the inability to differentiate acute from chronic renal impairment and transient from persistent injury when selecting antibiotic doses based on Scr. We have highlighted the critical importance of adequate early antimicrobial therapy in determining outcomes for patients with infectious diseases. Therefore, it is paramount that renal dose adjustments for complicated infectious syndromes, such as PNA and cIAI, ensure adequate drug exposure during the first 48 hours of therapy.

The beta-lactams are the most commonly used antibiotic class for the management of infections in hospitalized patients. Correspondingly, beta-lactams and beta-lactam/beta-lactamase inhibitor combinations represent a major share of the systemic antimicrobials in drug development. These compounds are eliminated primarily by the kidney and have wide therapeutic indices with relatively few safety concerns compared to other antimicrobial classes. Furthermore, nonrenal mechanisms play a role in the clearance of clinically relevant antibiotics, including carbapenems and vancomycin, and existing data suggest that these pathways are not compromised to the same degree in AKI as in CKD [36]. For antibiotics with wide safety margins, dose adjustment could in theory be deferred until 48 hours after initiation of therapy when the trajectory of patient renal function is better characterized. The potential for toxicity is low but non-zero; therefore, the risk-to-benefit ratio is minimized by standard dosing in the first 48 hours with subsequent dose reduction if renal impairment persists [37, 38]. Such a deferred dose adjustment strategy could be used in clinical trials and practice to ensure pharmacodynamic targets are met during this critical period in therapy. This strategy is pragmatic and more easily implemented into clinical trial protocols and care pathways than complex calculations of kinetic eGFR or predictive models of AKI and recovery.

For narrow therapeutic index antibiotics, such as aminoglycosides, vancomycin, and polymyxins, deferred renal adjustment carries an unacceptable risk of treatment-related toxicity. Clinical trials of antibiotics with narrow therapeutic indices, especially those with the potential for nephrotoxicity, require empirical dose adjustment for acute or chronic renal impairment. Blood samples should be obtained in patients with renal impairment enrolled in late-phase clinical trials in order to critically evaluate drug exposure in this at-risk patient subgroup. Sparse sampling strategies are likely sufficient in this case since

PK models can be enriched using data obtained in early-phase studies. In clinical practice, these compounds require early therapeutic drug monitoring to ensure that safe exposures are achieved in individual patients.

CONCLUSIONS

AKI is a dynamic perturbation of renal steady-state where accurate characterization of patient kidney function is challenging. The current regulatory environment relies on very small studies in patients with stable CKD to determine dose adjustments for registry trials and ultimately clinical practice. This paradigm is appropriate for maintenance therapeutics, which are administered chronically to patients with CKD; however, it may overestimate dose reductions for patients with AKI. We identified AKI on admission in approximately 1 in 5 patients with 4 common infectious syndromes and demonstrated resolution of this injury within 48 hours in more than 50% of cases. It is well documented that the provision of adequate antibiotic therapy within the first 48 hours is a significant determinant of outcome in infectious diseases; therefore, unnecessary dose reduction in this window may contribute to increased clinical failure of antibiotics. We suggest that deferred renal dose adjustment during this critical period with wide therapeutic index antibiotics may improve outcomes for patients with infectious diseases.

Notes

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