Drug-induced kidney disease in the ICU: mechanisms, susceptibility, diagnosis and management strategies

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Purpose of review
Acute kidney injury (AKI) is a common complication in the critically ill population, is multifactorial and associated with increased mortality. Drug-induced kidney injury is a significant contributor to the development of AKI. The purpose of this review is to provide updates in the epidemiology, susceptibility and management of drug-induced kidney disease (DIKD).

Recent findings
Recent changes in guidelines for the management of serious infections in the critically ill have resulted in an increased frequency of DIKD. Varying definitions employed in clinical trials has complicated the awareness of this adverse event. Causality assessment is often missing from studies as it is complicated by the need to evaluate competing AKI risk factors. This has led to uncertainty in the nephrotoxic risk of commonly used drugs.

Summary
Standard criteria for DIKD should be applied in clinical trials to improve our understanding of the frequency of these events. Adjudication of these events will improve the clinician's ability to evaluate the causal relationship and relative contribution of specific drugs to the AKI event.

Keywords
acute kidney injury, critical illness, drug-induced kidney disease, nephrotoxicity

INTRODUCTION

Acute kidney injury (AKI) is a frequent complication in critically ill patients significantly increasing the risk of morbidity and mortality. A significant number of patients who develop AKI have incomplete recovery, and this is being recognized as a risk factor for progression to chronic kidney disease (CKD). Drug-induced kidney disease (DIKD) is a common cause of AKI in the critically ill population. Often, the cause is multifactorial leading to underestimation of drug-induced causes. A lack of diagnostic markers for DIKD highlights the need for evaluation of all concurrent AKI risk factors and nephrotoxic exposures for causal association. In this review, we will provide an update on the epidemiology, diagnosis, mechanism of injury and management of DIKD.

EPIDEMIOLOGY

Many large observational studies have described the epidemiology of AKI in critical illness and provide information on DIKD [1,2▪]. Most recently, the Acute Kidney Injury-Epidemiologic Prospective Investigation (AKI-EPI), an international cross-sectional study of 1802 critically ill patients, demonstrated that 57.3% of ICU patients developed AKI, and nephrotoxic drugs were reported as the cause for AKI in 14.4% of patients [2▪]. At the time of AKI diagnosis, one-third of patients were treated with diuretics, 11.9% with nonsteroidal anti-inflammatory drugs, aminoglycosides (AMGs) 6.8%, glycopeptides 1.4% and contrast media 2.1% [2▪]. In this study, a large proportion of patients, 47.7%, had residual injury at discharge, as measured by a glomerular filtration rate (GFR) of less than

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KEY POINTS

- DIKD occurs in 14–28% of critically ill patients.
- DIKD can present as AKI, glomerular injury, tubular injury or nephrolithiasis.
- Vancomycin-associated DIKD is a real concern with increased risk when combined with piperacillin/tazobactam.
- Risk factors for DIKD include age, dose, drug concentrations, duration of therapy, concurrent nephrotoxins and history of kidney disease.
- During an episode of DIKD, clinicians should stop the offending drug or reduce the dose, minimize exposure to concurrent nephrotoxins, measure kidney function frequently and assess the need for renal replacement therapy.

60 ml/min/1.73 m^2 [2▪]. The AKI-EPI study along with other studies demonstrates that frequency of DIKD ranges from 14 to 28% in the critically ill population and represents an opportunity for clinicians to mitigate the risk for development of AKI and/or improve injury resolution [1,2▪,3].

MECHANISMS

Adverse drug reactions can be classified as type A or B reactions. Type A reactions are predictable, dose-dependent toxicities based on the known pharmacology of the drug such as acute tubular necrosis secondary to AMG [4]. Type B are unpredictable, dose-independent, idiosyncratic reactions such as acute interstitial nephritis secondary to proton pump inhibitors (PPIs) [4]. DIKD reflects a spectrum of injury to different segments of the nephron and has been historically categorized as hemodynamic, intrinsic and postrenal injury [4]. We convened a panel of international adult and pediatric nephrologists to standardize the definition of DIKD [5▪]. We proposed four phenotypes of DIKD including AKI, glomerular injury, tubular injury and nephrolithiasis [5▪]. We developed primary and secondary criteria for each phenotype based on laboratory or clinical parameters. We will apply these criteria to the discussion of specific causal drugs implicated in DIKD in the critically ill population.

CAUSAL DRUGS

Vancomycin

Vancomycin (VAN) is a glycopeptide antimicrobial with activity against Gram-positive bacteria. The Infectious Diseases Society of America recommends the use of VAN, at target trough concentrations of 15–20 mg/L (grade B-II), for treatment of methicillin-resistant *Staphylococcus aureus* bacteremia (grade A-II), endocarditis (grade A-II), pneumonia (grade A-II), complicated skin and soft tissue infection (grade A-I) and osteomyelitis (grade B-II) [6]. Higher target trough concentrations are recommended as a surrogate to achieve an area under the curve to minimum inhibitory concentration ratio more than 400 [7]. Widespread adoption of this recommendation, despite the strength of evidence, has resulted in higher rates of nephrotoxicity. However, the causal relationship between VAN and kidney injury has been questioned. Historically, impurities in the formulation were responsible for nephrotoxicity and improvements in manufacturing resulted in greater purity and lower rates of toxicity. Yet, the incidence of DIKD is reported to be 5–43% (depending on the definition employed, i.e. nephrotoxicity vs. AKI) [8]. The mechanism of injury is not clear, and genomic studies will further elucidate susceptibility [9,10]. Rat models have demonstrated that VAN induces oxidative stress leading to nephrotoxicity which is ameliorated by administration of hexamethylenediamine superoxide dismutase [11] and erdosteine [12]. In addition, VAN may be potentially 'trapped' in proximal tubular cells as it is transported by the organic cation transporter across basolateral membrane, but no active transport has been identified across brush border membrane [13]. VAN presents as an AKI phenotype which is dose dependent for the majority of cases occurring within 4.3–17 days of therapy initiation [8].

To address the causal question, Sinha Ray *et al.* [14▪] conducted a meta-analysis of seven randomized controlled trials (RCT), representing 4033 patients and found an increased risk of AKI with VAN compared with linezolid or ceftaroline, relative risk (RR) 2.45, 95% confidence interval (CI) (1.69, 3.55). In addition, patients with critical illness are twice as likely to experience nephrotoxicity compared with ward patients, odds ratio (OR) 2.57, 95% CI (1.44, 4.58) [8].

The following risk factors have been identified for VAN-associated nephrotoxicity: obesity, kidney disease, severity of illness, concurrent nephrotoxins, trough concentration, total daily dose, duration of therapy and method of administration. A meta-analysis conducted by van Hal *et al.* [8] found target trough concentrations more than 15 mg/L have a 2.67, 95% CI (1.95–3.65) increased risk for nephrotoxicity. In addition, longer duration of therapy (7–14 days) was associated with greater risk [8]. A study of 1430 critically ill patients receiving VAN provides further support for the association between

concentrations and duration of therapy with risk of nephrotoxicity [15]. Intermittent infusions were associated with a greater risk compared with continuous infusions, OR 8.2, $P < 0.001$ [15]. Post-hoc analysis of prospective studies have examined the need for higher targets and demonstrated equivocal or lower cure rates with trough concentrations above 15 mg/L for the treatment of *S. aureus* nosocomial acquired pneumonia [16,17]. In addition, these studies have demonstrated that alternatives such as linezolid or telavancin could be considered [17,18].

Carreno *et al.* conducted a prospective randomized trial of early switch in antibiotic selection to prevent VAN-associated nephrotoxicity. They enrolled adult patients who were prescribed VAN and had two risk factors of the following for AKI: dose more than 4 g/day, weight more than 110 kg, kidney disease as defined by serum creatinine (Scr) more than 1.3 mg/dL or history of AKI and concurrent vasopressors or nephrotoxins. Patients were randomized based on the type of infection to either continue VAN or switch to linezolid, daptomycin or ceftaroline. The authors found no significant impact on the incidence of AKI by Acute Kidney Injury Network (AKIN) criteria (32.7 vs. 31.4%, $P = 0.89$) [19▪]. However, inclusion of only two risk factors and the lack of adjustment for severity of illness may have impacted the selection of an appropriate patient group who would benefit from switching antibiotics. In the majority of cases, VAN-associated AKI is reversible with few patients requiring renal replacement therapy [8].

Piperacillin/tazobactam

Piperacillin/tazobactam (TZP) is a semisynthetic penicillin and beta-lactamase inhibitor combination antibiotic used in the treatment of Gram-negative bacterial infections. Historically, TZP was not considered nephrotoxic but given its coadministration with VAN, it is now associated with AKI. The mechanism for nephrotoxicity is unclear but thought to be acute interstitial nephritis. TZP is eliminated largely as unchanged drug by glomerular filtration and tubular secretion via the organic anion transport system [20].

Burgess *et al.* examined the impact of combination therapy with TZP and VAN (TZP–VAN) compared with VAN alone in 191 hospitalized patients. Patients receiving combination therapy had a higher incidence of nephrotoxicity (8.1 vs.16.3%, $P = 0.041$) with an adjusted OR 2.48, $P = 0.032$ [21].

Several retrospective studies have examined the impact of beta lactam choice, using cefepime (FEP) as the comparator beta lactam, with VAN combination therapy on AKI events. Hammond *et al.* [22] found no significant effect of the choice of beta lactam on the incidence of AKI (32.7 vs. 28.8%, $P = 0.647$). Choice of beta lactam had no significant effect on ICU or hospital length of stay, AKI duration or need for renal replacement therapy [22]. Rutter *et al.* [23,24] found the incidence of AKI was higher in patients receiving TZP–VAN compared with FEP–VAN (21.4 vs. 12.5%, $P < 0.0001$) with an adjusted OR 2.18, 95% CI (1.64, 2.94). A meta-analysis of 15 observational studies on AKI found an increased risk for TZP–VAN combination compared with VAN + beta lactam, OR 4.6, $P < 0.001$, 95% CI (2.9, 7.2) and TZP–VAN compared with VAN alone, OR 4, $P < 0.001$, 95% CI (2.8, 5.8) [25▪]. The question of whether extended infusion beta lactam increases the risk of nephrotoxicity has been evaluated in a few retrospective studies. McCormick *et al.* [26] evaluated the effect of extended (4 hour infusion) vs. standard infusion of TZP–VAN and found no difference in the rate of nephrotoxicity; however, they did not use criteria from AKIN or Kidney Disease Improving Global Outcomes (KDIGO), rather employing stage 2 AKI or 0.5 mg/dl increase in Scr over 24 h. Mousavi *et al.* [27] also studied the impact of extended vs. standard infusion and found no difference in the rate of AKI between infusion strategies (32.9 vs. 29.3%, $P = 0.596$). Cotner *et al.* evaluated the effect of extended infusion strategies for TZP–VAN, FEP–VAN and meropenem/VAN combinations on AKI. They found no impact of extended infusion strategies on the development of AKI across the three beta lactams/VAN combinations [28].

Polymixins

Colistin and polymixin B (PMB) are two drugs in this class with similar antimicrobical spectrum but different pharmacokinetic and dynamic profiles. Colistin is administrated as a prodrug, colistimethate sodium, which is converted to colistin and can accumulate in kidney disease. Colistin nephrotoxicity is a type A reaction, presenting as the AKI phenotype. In a meta-analysis conducted by Vardakas and Falagas [29], the rate of nephrotoxicity across included studies was 24–74% for colistin and 21–46% for PMB with unadjusted nephrotoxicity occurring more commonly with colistin, RR 1.55, 95% CI (1.36–1.78). However, the majority of events were classified as risk or injury by the Risk, Injury, Failure, Loss of kidney function, End stage kidney disease criteria, and there was no difference in mortality between treatments. Predictors of nephrotoxicity in this meta-analysis included older age, larger doses, longer treatment duration,

baseline Scr less than 1.5 mg/dL, larger weight, ICU admission, bacteremia and intra-abdominal infections [29]. As nephrotoxicity is dose dependent, and direct comparison of doses between the two drugs is challenging, this may account for differences in the incidence of nephrotoxicity between these agents.

Durante-Mangoni evaluated the incidence of nephrotoxicity in 166 critically ill patients receiving colistin 2 million units three times daily for life threatening extensively drug-resistant *Acinetobacter baumannii*. This was a secondary analysis of data from a multicenter RCT; however, plasma concentrations were not monitored in this trial. AKI was observed in 50.6% of patients with the 40.4% developing stage 1 and 10.2% developing stages 2 and 3 [30]. Age, presence of diabetes, CKD and malignancy were significant risk factors for the development of colistin associated AKI [30]. The authors demonstrated that the cumulative incidence of AKI doubled when the duration of therapy went from 7 to 14 days [30]. Horcajada *et al.* [31] found the rate of nephrotoxicity to be significantly higher (71.4 vs. 19.3%, $P = 0.001$) when using a colistin plasma concentration breakpoint of 2.42 mg/l in 64 patients with multidrug-resistant Gram-negative bacteria infection. Careful attention should be given to older patients or those with diabetes or CKD to monitor drug exposure and limit the duration of therapy when applicable.

Prediction models have been developed to assess the risk of nephrotoxicity from colistin using risk factors such as age, dose, duration of therapy, concomitant nephrotoxins [32,33▪,34,35]. These models may aide in reducing the incidence of nephrotoxicity; however, studies on implementation of risk prediction to guide clinical care are lacking.

Aminoglycosides

AMG antibiotics are used in the treatment of enterococcal, mycobacterial and Gram-negative infections in the critically ill population. AMGs have several advantages including concentration-dependent bactericidal activity, prolonged postantibiotic effect, synergy with beta lactam antibiotics, low resistance rates and cost [36]. However, their use has been on the decline as extended spectrum carbapenems and fluoroquinolones have a greater safety profile [36]. AMGs undergo glomerular filtration with reabsorption in the proximal tubules and accumulation in the renal cortex.

AMGs induce apoptosis and necrosis of tubular epithelial cells, alter water and solute transport, reduce renal blood flow and GFR [37]. All AMGs are considered to be nephrotoxic; however, some studies have documented lower rates of nephrotoxicity with tobramycin [38,39]. Nephrotoxicity usually occurs after 7 days of treatment and presents as nonoliguric AKI phenotype that is typically reversible [36]. The risk of nephrotoxicity is increased with advanced age, trough concentrations >2 mg/L, multiple doses per day, prolonged duration of therapy and concomittant nephrotoxin exposures.

The incidence of nephrotoxicity varies between 12 and 25% depending on definition of nephrotoxicity used and the population studied [40–42]. Paquette *et al.* [43▪] conducted a retrospective study of 562 patients and found the incidence of AKI was 12% with the majority developing stage 1 AKI. Independent risk factors for AKI included VAN cotherapy, OR 5.19, 95% CI (2.24–12.01), heart failure, OR 3.25, 95% CI (1.08–9.76) and trough concentration more than 2 mg/l, OR 3.44, 95% CI (1.57–7.54) [43▪]. This study highlights that injury is not always reversible as 51% of patients had renal recovery within 21 days of discontinuing the AMG [43▪].

Proton pump inhibitors

PPI use has been associated with a small but significantly increased risk of AKI and CKD in noncritically ill populations [44–46]. PPIs are thought to cause acute interstitial nephritis leading to AKI [47]. Lee *et al.* [48▪] examined the association between prior to admission use of a PPI, histamine 2 receptor antagonist (H2RA) or no acid suppression therapy with the development of AKI in a cohort of 15 063 critically ill patients. Using the KDIGO criteria guidelines, AKI occurred in 20.0 and 18.0% of PPI and H2RA users, respectively, compared with 16.2% of those not taking acid suppressive medications [48▪]. After adjusting for demographics, illness severity and treatment indication, PPI use prior to admission was not associated with critical illness AKI, OR 1.02, 95% CI (0.91–1.13) [48▪].

DIAGNOSIS

The diagnosis of DIKD should be made on the basis of defined biomarker criteria (e.g. KDIGO Scr criteria), clinical phenotype, concurrent risk factors and causality assessment [5▪]. We have adapted the Bradford-Hill criteria [5▪,49] for causal associations with causality assessment in DIKD:

(1) The duration of drug exposure must be at least 24 h and must precede the event.
(2) There should be biological plausibility for the suspected drug to cause kidney injury.

(3) An assessment of the relative contribution of the suspected drug vs. concomitant risks and exposures to other nephrotoxic agents should be employed.
(4) The strength of the relationship between the suspected drug and injury should be based on drug exposure, duration of therapy and the temporal relationship.

The Naranjo scale is a causality assessment tool, which aids the clinician in evaluating the causal relationship between a suspected drug and an adverse event [50]. This tool has been modified to improve sensitivity for organ-specific adverse reactions such as drug-induced liver injury or skin and hypersensitivity reactions [51,52]. Causality assessment tools for DIKD have not been developed or reported. Challenges in causality assessment of DIKD include multidrug exposures and evaluation of concurrent AKI risks. For example, consider a patient with sepsis and hypotension who is receiving multiple antibiotics known to cause kidney injury and requires contrast exposure for imaging. The risk of each drug should be evaluated individually with respect to its possible contribution to the phenotype and the underlying risk factors should be evaluated for their relative contribution [5▪]. With multidrug exposure, each causal agent should be classified in rank order based on the temporality, known mechanism of injury and severity [5▪]. Causality assessment of DIKD is subjective, centering on the clinician's knowledge with few diagnostic markers to guide the evaluation. Novel urinary biomarkers have improved prediction, detection and prognostication of AKI.

Novel urinary biomarkers such as kidney injury molecule 1 have shown good correlation with kidney injury secondary to VAN in rat models but human studies are lacking [53,54]. Urinary biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL) and *N*-acetyl-β-D-glucosaminidase were shown to be early markers of gentamicin injury in neonates with peak concentrations occurring prior to an increase in Scr [55]. In the setting of colistin treatment for urinary tract infections in geriatrics, there was limited use for NGAL measurement as urinary tract infections were found to impact NGAL concentrations [56]. Further research is needed on the utility of novel urinary biomarkers for the enhanced detection of DIKD.

MANAGEMENT

Electronic surveillance systems have been successfully used to detect patients at risk for DIKD, alert clinicians to re-evaluate nephrotoxin exposures and reduce the rate of DIKD [57]. Management of DIKD includes reducing the dose of the offending agent in the case of type A reactions or discontinuing the drug in the case of type B reactions with the consideration of alternative treatments. Guideline based care of AKI should be applied to the management of DIKD. Exposure to concurrent nephrotoxins should be reduced if possible. Assessment of kidney function during AKI is challenging as Scr is not in steady state and most estimating equations overestimate kidney function in the critically ill patient [58,59]. Devices to measure real-time GFR are in clinical trials and will greatly enhance our ability to detect kidney function changes and appropriately adjust doses of critical medications [60,61]. Until these devices reach the commercial marketplace, clinicians should employ timed urine collection for measurement of creatinine clearance or iohexol-based GFR measurements, where available, to quantify kidney function during AKI [62,63▪▪]. Most cases of DIKD are reversible with few patients requiring renal replacement therapy. However, adequate documentation of the event is necessary to prevent repeat exposures and subsequent injuries during future hospitalizations.

CONCLUSION

The epidemiology of DIKD is challenging to study without phenotype standardization. Association of changes in Scr or GFR measures in relation to a drug does not imply causation. Causality assessment including careful review of concurrent risk factors is essential in DIKD as the cause of AKI is often multifactorial. Novel urinary biomarkers are an important area for research in the early detection of DIKD with the aim of reducing injury severity and hastening renal recovery. Most cases of DIKD are reversible, yet a substantial number of patients have residual injury, and care must be taken to avoid repeated exposures.

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Conflicts of interest

There are no conflicts of interest.

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