

# Acute Dialysis Quality Initiative

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### Workgroup 3

#### Preventing/Minimizing iatrogenic acute kidney injury

*Joseph Dasta*

*Stuart Goldstein*

*Thomas Golper*

*Miet Schetz\**

### Introduction

Iatrogenic acute kidney injury can be defined as acute kidney injury (AKI) that is directly or indirectly due to medical (therapeutic or diagnostic) interventions. This definition does not imply that iatrogenic AKI is always preventable. Indeed, sometimes the need for the medical intervention outweighs the risk of causing kidney dysfunction. On the other hand, in many circumstances iatrogenic renal damage can be prevented or at least minimized. In hospitalized patients reported incidences of iatrogenic AKI vary between 1 and 3% [1,2]. Although therapeutic interventions, such as certain surgical procedures (cardiopulmonary bypass, aortic cross clamping) or intensive care treatments (mechanical ventilation) may also contribute to renal impairment, drug nephrotoxicity is the main cause of iatrogenic kidney dysfunction. 20-60% of all cases of AKI are considered drug-related [3,4]. The exact incidence of nephrotoxicity associated with a particular drug is difficult to determine because of the lack of uniformity in defining the criteria for renal dysfunction and the poor literature that is mostly limited to clinical series and case reports, often restricted to patients with risk factors.

### What are the main factors contributing to iatrogenic kidney injury and how can their impact be minimized?

Iatrogenic AKI is mainly due to insufficient knowledge of and/or attention to: (a) the presence of risk factors for nephrotoxicity, (b) alternative therapies for drugs with potential nephrotoxicity, (c) appropriate drug dosing adapted to altered kinetics, (d) the correct assessment of kidney function before and at appropriate intervals during treatment with the aim of early recognition of kidney injury and (e) preventive measures for nephrotoxicity (general and specific). Education, vigilance and early intervention are therefore the major avenues for prevention of iatrogenic kidney injury.

## *Risk factors*

Whenever possible, risk factors for nephrotoxicity should be corrected prior to prescribing a potentially nephrotoxic drug. The presence of non-modifiable risk factors should prompt a risk-benefit analysis. Risk factors for nephrotoxicity are generally derived from (often small) observational studies with (mostly univariate and seldom multivariate) logistic regression analysis. Unless otherwise stated, the level of evidence for these risk factors is therefore only V. In general, risk factors for nephrotoxicity can be patient-related or drug-related [5,6].

### Patient-related risk factors:

The association between nephrotoxicity and age probably reflects the higher prevalence of other risk factors such as a reduction of glomerular filtration rate (GFR) (often underestimated by serum creatinine concentrations) and concomitant diseases such as degenerative vascular disease or cardiac failure [7,8]. An increased risk of renal toxicity in elderly has been demonstrated for several drugs including aminoglycosides [9-11], vancomycin [12], contrast agents [13-15], cisplatin [16], nonsteroidal anti-inflammatory drugs (NSAID) [17,18] and angiotensin converting enzyme inhibitors (ACEI) [19].

Biologic differences between men and women can result in different responses to drugs [20]. Whether gender is a risk factor for aminoglycoside toxicity remains controversial [10,11,21]. Female gender appears to be a risk factor for cisplatin nephrotoxicity [16] whereas males exhibit an increased risk of amphotericin [22,23] and contrast [13,14,24,25] toxicities.

Chronic kidney disease is a major risk factor for most nephrotoxins as has been demonstrated for crystal-induced nephrotoxicity [26], aminoglycosides [21,27,28], amphotericin [22,29,30], vancomycin [27], contrast agents [14,15,24,25,31-33] and NSAID [18,34]. However, this association may also be related to the definition of acute nephrotoxicity. When the latter is based on a given increase of serum creatinine, the higher incidence in patients with pre-existing renal dysfunction can be explained by the non-linear relationship between serum creatinine and GFR. For the same decrease of GFR, patients with chronic kidney disease will have a more pronounced increase of serum creatinine than patients with higher pretreatment GFR.

Whether, in patients with normal renal function, diabetes is a risk factor for contrast nephropathy remains controversial [14,15,24,25,31-33]. On the other hand diabetes appears to increase the risk for nephrotoxicity induced by aminoglycosides [35], NSAID [17] and ACE inhibitors [19].

True intravascular volume depletion is a generally recognized risk factor for AKI, although the evidence in the literature is limited due to the difficulty in adequately assessing volume status. Not only true but also effective volume depletion, as is noted in patients with congestive heart failure, liver cirrhosis and sepsis, increases the risk of nephrotoxicity [9,10,13,14,21]. Both true and effective volume depletion result in prostaglandin-dependent renal perfusion, explaining the increased risk of NSAID-induced nephrotoxicity [18,36-38], and in reliance on efferent vasoconstriction for the maintenance of glomerular filtration

pressure, explaining the decrease of GFR associated with the use of ACEI and angiotensin receptor blockers (ARB) [39-41]. For the same reason, renal vascular disease is a risk factor for ACEI and ARB-induced kidney injury [42].

Sepsis is a major risk factor for nephrotoxicity, not only because of the associated systemic and renal hemodynamic alterations [43], but also because of the synergistic effect of endotoxin and toxic substances, as has been demonstrated in animal experiments [45,46] Both ischemic and nephrotoxic injuries are induced more readily in sodium-depleted subjects because of impaired renal hemodynamics and activation of the renin-angiotensin system (reviewed in [47]). The association between the use of diuretics and increased nephrotoxicity of several medications can be explained through their effect on circulating volume, through sodium depletion and maybe also by a tendency for physicians to prescribe diuretics in patients developing renal dysfunction. Use of diuretics has been shown to increase the risk of aminoglycoside [48], amphotericin [29], NSAID [17,49], ACEI [19] and vancomycin [12] toxicity. The concomitant use of other nephrotoxic drugs increases the risk for toxic AKI (shown for aminoglycosides [9-11,28,48,50,51], amphotericin [22,23,30,52], vancomycin [9,12], contrast media [33] and NSAID [18]). Patients with multiple myeloma are at increased risk of kidney toxicity, especially when they receive drugs that create conditions favouring intratubular cast formation [53]. Acid/base disturbances may exacerbate intrarenal crystal deposition [26]. Hypoalbuminemia increases the risk for cisplatin- [16,54], aminoglycoside- [10,55] and contrast-induced nephropathy [32].

#### Drug-related risk factors:

The inherent nephrotoxic potential: the drugs or diagnostic agents that are most commonly associated with AKI are the contrast agents, aminoglycosides, amphotericin, NSAID, angiotensin antagonists, anti-viral and anti-cancer drugs. Nephrotoxicity is mostly dose-dependent for drugs inducing crystal deposition, [26,56] and for drugs that act directly on tubular cells or on intrarenal hemodynamics [5]. Dose-dependent toxicity has indeed been demonstrated for contrast agents [13-15,25,32,33,57] and for cisplatin [58]. Nephrotoxicity appears to correlate with the cumulative or daily area under the curve (AUC) of aminoglycosides [51,59], with the cumulative, mean daily or maximal daily dose of amphotericin [22,23,29,52], with the mean daily dose of vancomycin [27] and the serum concentration or AUC of calcineurin inhibitors [60,61]. Prolonged duration of treatment has been shown to increase the nephrotoxicity of aminoglycosides [9-11,28,48,59,62], vancomycin [9,51] and amphotericin [22]. Whether high trough concentrations are a risk factor for aminoglycoside [9-11,59,62] or vancomycin [27,51,63] toxicity remains controversial, since an increased trough concentration may also represent an early manifestation of nephrotoxicity. Extensive literature, including several meta-analysis and reviews [64], suggests that for aminoglycosides the frequency of administration affects nephrotoxicity with most trials showing that once-daily administration is at least as effective and not more toxic than multiple daily doses (Level II). Some studies show an increased efficacy and/or less toxicity, but the differences in nephrotoxicity are small. A retrospective study in children also concluded that once-daily administration of

aminoglycosides is safe and cheaper [65]. For gram-positive infections, such as enterococcal endocarditis, the use of extended-interval dosing remains controversial [66,67].

The time of administration may be important for aminoglycoside toxicity and appears to be minimal if the aminoglycosides are administered during the active period of the day, possibly related to food intake [48,68]. The rate of administration appears to be important for drugs causing crystal-induced nephropathy [26,69] and for cisplatin [70]. Amphotericin infusion over 45 min did not induce more nephrotoxicity than an infusion over 4h (Level II) [71]. On the other hand a continuous infusion appears to be safer than a 4h infusion (Level II) [72]. The route of administration may also be a risk factor. The intra-arterial administration of contrast will increase the risk of contrast nephropathy [73] and intravenous administration of calcineurin inhibitors is more toxic than the enteral route [74].

Several level I and II studies have shown decreased nephrotoxicity with lipid formulations of amphotericin (reviewed in [75,76]). The risk of nephrotoxicity appears to be lower with liposomal amphotericin than for amphotericin lipid complex [77] (level I). Lipid formulations of cisplatin are also under development [78]. A level I trial [25] and a meta-analysis [79] have shown the superiority of low versus high osmolar contrast agents in patients with pre-existing renal dysfunction. Iso-osmolar contrast agents appear to be even better than low-osmolar [80] (level I). Specific drug combinations may result in synergistic nephrotoxicity, such as certain cephalosporins and aminoglycosides [50,81], the combination of vancomycin and aminoglycosides [10,51] or the combination of cephalosporin and acyclovir [82].

### *Alternative therapies for drugs with potential nephrotoxicity*

The best way to avoid nephrotoxicity is of course to avoid the use of nephrotoxic drugs. Whether aminoglycosides are appropriate empirical therapy in patients with sepsis is increasingly being questioned [83-85]. Other antifungal drugs belonging to the classes of azoles (voriconazole) or echinocandines (casprofungin) have been shown to be equally effective or even superior to amphotericin [86-88] in certain indications. At this time the (limited) potential nephrotoxicity of vancomycin cannot be used as the sole reason to choose an alternative. Other analgesics than NSAID are preferred in patients with compromised hemodynamic status or volume depletion. It is important to emphasize that COX-2 inhibitors have similar effects on the kidney as nonselective NSAID [37,89] (level II).

### *The appropriate drug dosing adapted to altered kinetics.*

Excessive dosing for patients with impaired renal or hepatic function appears to be one of the leading types of errors causing adverse drug events [90,91]. Correct drug dosing, based on organ function, habitus and edema assessment is further discussed below as is the role of therapeutic drug monitoring.

### *Correct assessment of kidney function*

Correct assessment of kidney function is important both for dosage adjustment of renally excreted drugs and for early detection of drug nephrotoxicity, that mostly is reversible if the offending agent is

discontinued. Biomarkers of ARF are discussed by the ADQI IV working group on primary prevention of ARF. Not taking into account the non-linear relationship between serum creatinine and GFR (with large reductions in GFR initially producing only small increases in serum creatinine) may be one of the most common causes of drug overdose [92,93]. Creatinine clearance or GFR should therefore be determined by timed urine collection or from prediction equations such as Cockcroft-Gault [94], MDRD [95] or Schwarz [96] (for children). It should also be remembered that a correct assessment of kidney function is difficult when serum creatinine concentrations change rapidly [97]. Early signs of renal injury can be subtle e.g. minor changes in electrolyte excretion or excretion of tubular enzymes or microproteins [98]. Biomarkers such as KIM-1 may also be early markers of toxic renal injury [99,100]. These subtle changes are particularly important, since they can be useful predictors of serious nephrotoxicity, allowing timely prevention and/or discontinuation of the offending drug.

### *Preventive measures for nephrotoxicity (general and specific)*

General preventive measures for nephrotoxicity include addressing all the previously mentioned risk factors that can be corrected or modified. Besides correct dosing and reassessment of concomitant medications, assuring adequate hydration is of utmost importance before the administration of nephrotoxic drugs. However, no consensus exists on the optimal type of solution, volume or timing. The available evidence for preventive hydration is level IV at most but it is questionable whether higher-level studies will ever be conducted. The importance of hydration has been shown for amphotericin [101,102], contrast [103], cisplatin [70,104], foscarnet [105] and for drugs causing crystal-induced nephropathy [26], tumor lysis [106] and rhabdomyolysis [107]. Intravenous hydration might be better than oral fluid intake, as has been shown for foscarnet and contrast agents [108,109] (level II). For the same reason discontinuation of diuretics has been advocated before the start of ACEI or ARB [40, 110] or NSAID [49].

Specific measures for the prevention of contrast nephropathy are discussed by the ADQI IV working group on primary prevention. Sodium administration is suggested to prevent amphotericin nephrotoxicity in one level II [111] and several level V studies [112-114]. A higher sodium content in the hydration solution also seems to increase the elimination of methotrexate, although a reduction of side effects was not demonstrated in this level II study [115]. The protection against cisplatin-induced nephrotoxicity by its administration in hypertonic saline, suggested by a level V study [116], was not confirmed by a subsequent level II study [117]. Probenecid, a competitive inhibitor of organic anion transport that decreases the cellular content of toxins using this transporter, has been administered to decrease the nephrotoxicity of cisplatin [118] (level V), sevoflurane [119] (level V) and cidofovir [120] (level III). Amifostine, an organic thiophosphate that chelates cisplatin, has recently been demonstrated to be nephroprotective [121] (level II)

Urinary alkalization, together with the establishment of high urine flow rates, is mostly suggested for crystal-induced nephrotoxicity and for kidney injury associated with tumor lysis syndrome or rhabdomyolysis. The evidence for the preventive effect of urinary alkalization is, however, limited to case series (reviewed in [26,122,106,107]). In addition, two level III studies did not find a protective effect

of bicarbonate, combined with mannitol, in traumatic rhabdomyolysis [123,124]. In tumor lysis syndrome, urinary alkalinization may result in precipitation of calcium phosphate. Since indinavir is more water soluble at acidic pH, alkalinization is not recommended for this drug [125].

Allopurinol, a competitive inhibitor of xanthine oxydase that reduces uric acid generation, is part of common prophylactic regimens of tumor lysis syndrome. The evidence for its nephroprotective effect is limited to uncontrolled studies ([126]. In addition, high doses may result in xanthine nephropathy [127,128]. In tumor lysis syndrome, uric acid oxidase converts uric acid into a more soluble form, which has been shown to result in a lower uric acid level compared with allopurinol, however without significant effect on serum creatinine [129] (level II). An effect on renal function is only shown in level IV [130] or level V studies [131,132]. Its use has recently been reviewed [133]. The evidence for a prophylactic effect of CRRT on tumor lysis syndrome remains limited to a few case reports [134,135]. Despite their theoretical benefit and positive results in some animal studies, there is no evidence from clinical trials that oxygen scavengers [136,137], diuretics [104,138,139] or vasodilators [140-142] are protective against drug nephrotoxicity.

### *Classification of Mechanism of Kidney Injury by Drug or Drug Class*

Drugs may damage the kidney by several mechanisms. The most prevalent mechanisms of nephrotoxicity are summarized below.

**Vasoconstriction** is the main mechanism of nephrotoxicity for calcineurin inhibitors and vasopressors and contributes to the nephrotoxicity of amphotericin and contrast agents.

**Altered intra-glomerular hemodynamics** are responsible for the decline in renal function seen with NSAID and ACEI and ARB. In patients with hemodynamic instability and volume depletion, renal perfusion becomes prostaglandin-dependent, thus explaining the nephrotoxic effect of NSAID. Renal dysfunction that accompanies antihypertensive therapy is a result of excessively lowering of blood pressure. ACEI and ARB are more commonly associated with this complication, since any decline in intraglomerular pressure due to blood pressure lowering will be exaggerated by concomitant vasodilation of the efferent arteriole. And even without a decline in blood pressure, the decrease of efferent resistance may result in a lower GFR in patients where constriction of the efferent arteriole serves to minimize the decline in GFR such as in patients with absolute or effective reduction in circulating volume, in patients with obstructive renal vascular disease or in patients receiving drugs associated with afferent vasoconstriction [110].

**Tubular cell toxicity** is the cause of kidney injury associated with aminoglycosides, amphotericin, calcineurin inhibitors, cisplatin, methotrexate, antivirals such as foscarnet, cidofovir and antiretrovirals, pentamidine and contrast agents.

**Interstitial nephritis** has been associated with antibiotics (beta-lactams, quinolones (especially ciprofloxacin), rifampin, macrolides, sulphonamides, tetracyclines), most NSAID, diuretics (thiazides,

loop diuretics and triamterene), anti-convulsants (phenytoin), cimetidine and ranitidine, allopurinol, acyclovir (reviewed in [144]).

**Crystal deposition** (reviewed in [26]) explains the nephrotoxicity occurring with acyclovir, sulfonamide, methotrexate, indinavir and triamterene. Uric acid and calcium phosphate crystals occur in tumor lysis syndrome, most commonly observed following chemotherapy for high-grade lymphoproliferative malignancies [106].

**Drug-induced thrombotic microangiopathy** has been reported with mitomycin, cyclosporin, tacrolimus, OKT3, interferon, ticlopidine, clopidogrel and quinine and has recently been reviewed [145].

**Hyperoncotic solutions** may decrease GFR due to their effect on glomerular filtration pressure or due to osmotically-induced tubular damage (vacuolization and swelling of tubular cells termed osmotic nephrosis) [146,147]. Stimulation of the tubuloglomerular feedback due to the high distal solute delivery may also contribute. This is the mechanism of nephrotoxicity associated with high doses of mannitol [148,149], immunoglobulins (due to the direct effect of the immunoglobulin or to the stabilizing agent sucrose) [150,151], dextrans [152] and starches [153,154].

The development of **rhabdomyolysis** with resulting kidney injury has recently been described with statins [155] but may also occur with other drugs [107].

### *Pediatric considerations*

Very little study has been performed over the last 20 years to delineate the causes of acute kidney injury in pediatric patients. Most reports since 1995 are comprised of review articles [156-161], most of which continue to cite haemolytic uremic syndrome and burns as the most common causes of pediatric acute kidney injury. Some recent single-center reports assessing outcome for children who receive renal replacement therapy and one study that evaluated the epidemiology of acute kidney injury demonstrates that the kidney often becomes injured as a result of, or by a nephrotoxic medication required in the treatment of some other systemic illness [162,163]. This broadened scope of acute kidney injury in children results from the application of solid organ and stem cell transplantation [164-168] therapies to the pediatric population, as well as improvements in corrective repair of congenital cardiac lesions, which require the same sort of cardio-pulmonary bypass procedures utilized in adults receiving open heart surgery [169-172]. Thus, the spectrum of clinical situations leading to pediatric acute kidney injury is similar to adults. In terms of pre-disposing factors for iatrogenic kidney injury, children differ from adults in terms of the relative lack of co-morbid condition prevalence such as chronic hypertension, diabetes mellitus and CKD. Premature neonates and infants with congenital heart disease often exhibit predisposing conditions such as ineffective volume contraction from either immature tubular development leading to polyuria or diminished cardiac output resulting from congenital anatomic cardiac lesions.

Consensus Statement: Iatrogenic AKI can be reduced by taking into account the risk factors for nephrotoxicity (patient- and drug-related), by considering alternative therapies, by correct drug dosing, adequate assessment of kidney function and general and specific preventive measures, in particular adequate hydration. The main mechanisms of nephrotoxicity are vasoconstriction, altered intraglomerular hemodynamics, tubular cell toxicity, interstitial nephritis, crystal deposition, thrombotic microangiopathy and osmotic nephrosis.

Recommendations for Clinical Practice: Before prescribing a potentially nephrotoxic drug, the risk to benefit ratio should be considered. Alternative drugs are preferred especially in patients with risk factors. Modifiable risk factors such as volume or sodium depletion, use of diuretics or the administration of other nephrotoxic drugs should be corrected. The correct drug dosage adjusted for changes in organ function, body habitus and edema status should be applied. Patients should be prehydrated and GFR should be frequently monitored during the administration of a potentially nephrotoxic drug (Grade E).

Recommendations for Future Research: Future research should evaluate whether the use of early markers of tubular damage can reduce the incidence of nephrotoxicity. The optimal fluid and regimen for prehydration, the role of sodium and urinary alkalization should be evaluated in higher-level trials. Studies are needed to elucidate the mechanisms of nephrotoxicity in order to design more rational prevention and treatment strategies (e.g. [143]).

## What are the considerations required for drug dosing in patients with impaired kidney function?

Patients with impaired kidney function or those at high risk for AKI, (acute kidney injury) should have careful attention to appropriate drug dosing and utilization. To accomplish this, key pharmacokinetic principles must be considered.

### *Clearance (Cl)*

Cl measures the intrinsic ability of the body to eliminate the drug from the blood or plasma and is defined as the volume of blood or plasma in which the solute is completely eliminated (cleared) in that unit of time (Volume / Time) [173,174]. It is important for the calculation of the maintenance dose at steady state:

$$\text{Maintenance dose} = Cl \times C_p \times t \text{ where}$$

$$C_p = \text{desired plasma concentration (average steady state)}$$

$$t = \text{dosing interval}$$

and the units are L/minute  $\times$  mg/L  $\times$  minutes = mg.

Total body Cl is the sum of all regional clearances, e.g. renal, hepatic, other metabolic pathways, extracorporeal devices, etc. Renal excretion is glomerular filtration plus tubular secretion minus tubular reabsorption. Hepatic clearance depends on hepatic blood flow, age, hormones, stress conditions, fever,

protein binding, presence of drugs competing for metabolism, and hepatocellular injury resulting in impaired enzymatic activity, i.e. health of the liver [175]. Most importantly, regional clearances are not particularly independent of each other. The impaired function of a clearing organ may stimulate another regional clearance to increase, such as retained solutes in uremia may enhance hepatic metabolism (compensatory detoxification). For most drugs generally, a regional clearance of 30% or greater of the total body clearance is considered substantial enough to appreciate clinically [176,177].

### *Volume of Distribution (Vd)*

Vd is a mathematical construct of the conceptual volume the drug would occupy if the body were a single homogeneous reservoir whose concentration is equal to the plasma concentration. It relates the amount in the body to the plasma concentration and is a function of protein and tissue binding [173,174]. A drug highly bound to certain tissues (e.g. digoxin, tricyclic antidepressants, metoclopramide) will frequently have a large Vd while drugs highly bound to circulating proteins (e.g. oxacillin, phenytoin) will be restricted primarily to the vascular space, and thus will have a small Vd. Certain disease states (such as uremia) change the Vd. This assumes clinical relevance especially when the Vd is small. Although the Vd is a mathematical construct, for occasional drugs it may approximate a particular actual space, such as aminoglycoside antibiotics in the extracellular fluid space. Vd is used to calculate the loading dose required to reach a target concentration such that

$$\text{Loading dose} = \text{Vd} \times \text{target concentration} \times \text{Body Weight.}$$

Alterations of Vd occur in the critically ill. However, this will have clinical relevance only when Vd is “small” as defined, for example, by the water space (< 0.6L/kg). To follow the aminoglycoside example further, edema, ascites and effusion fluid all add to their Vd. A standard per kg. loading dose would be inadequate in this circumstance [178,179]. It would be appropriate to estimate the amount of excess extracellular fluid and increase the dose accordingly (see below, level IV evidence, grade E recommendation). Alternatively, extracellular volume depletion will reduce aminoglycoside Vd. A standard per kg. of total body weight loading dose would be excessive in this circumstance. This may explain the increased incidence of aminoglycoside nephrotoxicity in the obese [180] (Corcoran 88), who have a reduced fraction of total body weight that is extracellular water [181]. To address this predicament, estimate the deficit in extracellular fluid and correct it prior to aminoglycoside administration (level V evidence, grade E recommendation). If this delay risks the success of the antibiotic therapy, then the loading dose should be decreased by 20 mg per kg. of the extracellular fluid volume deficit (see below) (level V evidence, grade E recommendation).

For drugs that bind to tissue proteins circulatory failure may result in delayed delivery to the binding sites (distribution) and serum levels may be higher than expected for longer than anticipated. Uremia per se can alter the binding of opiates to central nervous system receptors and digitalis to cardiac receptors such that both agents must be administered in lower doses from the outset, i.e. both the loading dose and maintenance doses should be reduced (level IV evidence, grade E recommendation).

### *Elimination Half-life (T<sub>1/2</sub>).*

The T<sub>1/2</sub> is the time it takes for the plasma concentration of a drug, after distribution equilibrium, to diminish by 50%. Since the plasma and tissue compartments are in equilibrium, the body drug burden has also declined by 50% [173,174]. The T<sub>1/2</sub> is used to predict how long it takes for a dosing regimen to achieve a steady-state concentration, i.e. after four to five half lives, if no loading dose has been administered. It is a dependent variable that can be derived by the following equation

$$T_{1/2} = 0.693 \times V_d / Cl.$$

### *Protein Binding (PB)*

PB refers to binding to serum proteins, hence circulating proteins. Acidic drugs bind to albumin. Basic drugs bind to alpha1-acid glycoprotein. Only the unbound fraction of drug is pharmacologically active, metabolized and excreted [173,174]. With the exception of certain sorbents which can compete with binding proteins for drug affinity, the protein-bound drug fraction is unavailable for removal by renal replacement therapies. Drug concentrations measured in serum, blood or plasma are almost always totals of the bound and free fractions, thus are potentially misleading, and certainly do not always reflect the active drug concentration.

Many factors affect the degree of drug protein binding including uremia, acidosis, the presence of elevated free fatty acids (FFA), the molar ratios of drug to protein, temperature, inflammation (alpha1-acid glycoprotein is an acute phase reactant), the presence of displacing substances such as organic acids, bilirubin, and drugs, for example heparin [173,174,182]. The clinical significance of drug-protein binding will vary from drug to drug, patient to patient and for varying clinical conditions. As a result protein binding alterations in uremia are not necessarily predictable [183]. Alterations of PB in the critically ill are only clinically relevant if PB is high and there is a small V<sub>d</sub> and narrow therapeutic index.

### *Aminoglycoside dosing using the principles above.*

When one considers the use of an aminoglycoside, two initial questions have to be addressed. First, is this patient a high risk patient for AKI (risk)? Secondly, is the aminoglycoside the preferred antibiotic (benefit)? Then the nature of the infection must be considered (location, medical vs. surgical therapy, life threatening vs. less serious). What is the suspected organism and what generally is its MIC? Pseudomonas has an MIC for gentamicin or tobramycin that is usually <2mg/L. For the purposes of this exercise, pseudomonas will be used as the organism requiring the highest aminoglycoside level. If a ratio of 10 times the MIC is desired for efficient pseudomonal killing, a peak concentration of 10 to 20 mg/L will be required [184,185]. The efficacy and safety of extended interval dosing (EID) is discussed below. It should however be noted that almost all the available studies have been carried out in patients without or with limited degree of renal insufficiency. In patients with severe renal dysfunction EID of aminoglycosides will

lead to prolonged exposure to high drug concentrations which is opposite to the rationale of this dosing regimen.

Aminoglycosides distribute into extracellular water and, consequently, inadequate doses are often administered to fluid overloaded patients. Thus, a reasonable rule of thumb is:

- If at ideal body weight (IBW) gentamicin or tobramycin EID dose is 5-7mg/kg
- IBW in kg is calculated as follows:

$$\text{IBW male} = 50 + 2.3 (\text{H}-60) (\text{height in inches}) = 0.9H - 88 (\text{height in cm})$$

$$\text{IBW female} = 45.5 + 2.3 (\text{H}-60) (\text{height in inches}) = 0.9H - 97 (\text{height in cm})$$

- For each kg of edema, ascites or effusion fluid, add 20 additional mg of aminoglycoside (level V evidence, grade E recommendation).
- For aminoglycoside dosing in the morbidly obese, a similar strategy applies where the dosing weight is the ideal body weight plus 0.4 times (total body weight – ideal body weight) [186] (level V evidence, grade E recommendation).
- The next dose should occur when the serum concentration is  $\leq 1$ mg/L. The extended dose interval should probably not exceed 48 hours, because of the increased risk of bacterial regrowth. So with a low endogenous clearance as seen with a low GFR, this interval will be (too?) long. In this setting one should reassess whether alternative antibiotics would be equally efficacious, because they probably will be less nephrotoxic (level IV evidence, grade E recommendation).

### ***Rationale for extended interval dosing (EID)***

Many investigators have shown either no significant difference in either efficacy or safety or a benefit toward lower toxicity with EID. Importantly, no reports have shown less efficacy or greater toxicity [64]. The bactericidal effect of aminoglycosides is concentration-dependent, hence the desire for a C<sub>peak</sub>/MIC ratio of 10. The high peak concentrations kill all susceptible organisms reducing the emergence of resistance. Aminoglycosides exhibit a post-antibiotic effect (PAE) wherein there is continued suppression of bacterial growth despite a low or absent serum concentration. The duration of the PAE may be extended by beta-lactams. Aminoglycoside uptake into the cells where they exhibit toxicity (renal tubular cells, inner ear cells) appears to become saturable at relatively low serum levels, suggesting that higher peak concentrations may not necessarily be more toxic. By allowing a trough concentration to get very low, it may allow disposition away from the vulnerable cells. Therefore, because of the reduced complexity, equal efficacy and probably reduced toxicity of EID, this is the recommended approach to aminoglycoside administration (level II evidence, grade C recommendation). Therapeutic drug monitoring (TDM) during EID includes measuring a peak concentration after the first dose and ensuring a trough concentration below 1 mg/L.

### *Pediatric considerations*

Pharmacokinetic principles do not differ for children versus adults, but the age-dependent variability of total body water, metabolic rates, renal tubular function and protein binding issues require specific attention. Infants and young children have a greater total body water to weight ratio of 700 to 800 ml per kg compared to older children and adults [187-190]. In addition, younger children demonstrate greater metabolic rates [191] and often require more frequent dosing of certain medications than older children. Premature infants and some term newborns exhibit immature proximal tubular function [192-194], so drugs that depend upon significant renal secretion may require dose adjustment. For premature neonates and infants, one must consider the potential for a drug to displace bilirubin from protein binding sites, as newborn are at risk for hyperbilirubinemia-induced kernicterus [65,195,196].

The discussion of extended interval dosing is relevant to the pediatric population as well. Assessment of single daily dosing (SDD) versus standard twice or three times daily dosing has been shown SDD to be equally efficacious across all ages ranges, from infants to young adults, and to confer no more risk of nephrotoxicity or ototoxicity [198-200]. Careful monitoring of serum aminoglycoside concentrations remains warranted for extended therapeutic courses.

Consensus Statement: An understanding of pharmacokinetic principles has the potential to both enhance drug efficacy and to reduce drug toxicity in patients with compromised kidney function.

Recommendations for Clinical Practice: An accurate estimation of lean body weight and dry weight will enhance dosing accuracy for most drugs and may reduce both the incidence and severity of dosing errors (Grade E). The use of extended interval dosing for aminoglycoside antibiotics in patients with normal or minimally impaired kidney function will not jeopardize efficacy and may decrease toxicity (Grade C).

Recommendations for Future Research: A multicentered randomized controlled trial of dosing aminoglycosides according to dry weight and ideal (lean) body weight that demonstrated decreased toxicity and equal or superior efficacy would convince physicians to use this approach based on pharmacokinetics.

### **Self-correcting systems and processes of care minimize medication errors and adverse drug events. How can such systems and processes be applied to minimize kidney injury?**

The Harvard Medical Practice Study reported an injury rate of 3.7 per 100 hospitalized patients and that injuries were most often related to medications [201]. Injury resulting from drug use is termed an adverse drug event (ADE). These ADEs are common, clinically significant, and costly [202]. As such, there is increasing emphasis in the medical literature and lay press regarding patient safety and medication use as important issues of public policy. However, the MEDWATCH form used to report ADEs can be cumbersome to use. The kidney is susceptible to and responsible for a variety of systemic effects, both direct and indirect. For example, AKI patients have reduced clearance of renally cleared drugs. As such,

patients with ARF are at high risk for errors in drug dosing and subsequent ADEs. In one study, 45% of sixty hospitalized patients with renal dysfunction who were prescribed renally eliminated drugs were prescribed dosages in excess of those recommended [203].

Various agencies have emphasized ways to avoid medication errors and optimize therapy in hospitalized patients. The Institute of Medicine, for example, has issued several reports that not only document the scope of the medication errors but propose systems-based solutions. Their most recent publication extends their scope of influence to recommend that all health care organizations establish comprehensive patient safety systems that provide complete patient information and clinical decision support tools [204]. The Joint Commission of Accreditation of Healthcare Organizations [205] has adopted a series of national patient safety goals, including ways to improve the effectiveness of communication among caregivers by developing a list of abbreviations, acronyms and symbols to avoid. A coalition of over 150 public and private Fortune 500 organizations called the Leapfrog group that provides health care benefits have taken a proactive stance on standards that health care facilities should meet before services are provided to their 34 million employees [206]. One of the four patient safety practices recommended by Leapfrog group is the use of computer prescriber-order entry (CPOE) system which they indicate could save up to 58,300 lives per year and prevent 522,000 medication errors if implemented by all non-rural hospitals in the United States. Also, the Coalition for Critical Care Excellence of the Society of Critical Care Medicine developed a manual on CPOE system requirements for Intensive Care Unit Use in which they state that the most seriously ill patients are cared for in the ICU, and it is reasonable to conclude that a CPOE system should result in reduced errors and improved outcomes [207].

Two approaches that can minimize iatrogenic complications in ICU patients are the inclusion of a critical care clinical pharmacist as a member of the multidisciplinary ICU team, and implementing integrated clinical decision support and CPOE systems. Information provided should be based upon the latest pharmacy and nursing standards with respect to mixing and administering medications, and data on drug incompatibility, rates of drug administration, and drug-drug/drug nutrient interactions. The role of the clinical pharmacist has evolved to a state where many hospitals have critical care pharmacists that provide services ranging from assuring safe and accurate dispensing of medications to optimizing pharmacotherapeutic outcomes at the bedside [208]. Since many critically ill patients have impaired kidney function, pharmacists often focus on appropriate drug dosing in these patients to minimize ADEs. Proper monitoring of serum aminoglycoside concentrations, for example can reduce the incidence of nephrotoxicity [11,209]. Adjusting the dosage of a renally cleared beta-lactam antibiotic in a patient with renal insufficiency may minimize the risk of seizures and renal failure associated with rhabdomyolysis.

Fourteen articles that evaluated the clinical and economic impact of the critical care pharmacist were recently summarized [210]. Most of the studies used a before-after methodology (level IV evidence), comparing the impact of the pharmacist to a period of time in which there was not a pharmacist attending rounds in the ICU. Examples of interventions by the pharmacist include clarifying drug orders, therapeutic

drug monitoring and adjusting the dosage of drugs to the degree of renal dysfunction, discontinuing therapy after an appropriate course of therapy, and recommending appropriate use of drugs such as sedatives, analgesics, and antibiotics. Documented clinical outcomes include reduced rates of ventilator-associated pneumonia, medication errors, and inappropriate drug concentrations. A landmark study revealed that a pharmacist providing information to the prescriber while on rounds in the ICU reduced the incidence of preventable ADEs by 66% [211]. Economic outcomes related to clinical pharmacist interventions include an annualized reduction in drug costs, mainly from cost avoidance, ranging from \$9,000 to nearly \$100,000, and potential annual savings of \$270,000 from the reduction in preventable ADEs. A recent study of clinical pharmacists attending rounds on an internal medicine service for three months revealed a 78% reduction in the rate of preventable ADEs compared to the medical service without the clinical pharmacist on rounds [212]. The most common intervention of these pharmacists was adjustment of drug dosage. While cost-effectiveness studies have not been formally conducted, the costs of implementing clinical pharmacy services are primarily the salary and fringe benefits of the pharmacist.

The Leapfrog Group in 2003 surveyed institutions serving their clients and found only 4.9% of hospitals had CPOE fully implemented [206]. A larger survey of over 960 hospitals in 2002 revealed 16% had CPOE available in some locations but only 9.6% had it available in all locations of the hospital [213]. Twenty-six articles evaluating the impact of CPOE and clinical decision support systems on appropriate drug use, medication safety, and costs were recently summarized [214,215]. Most of the studies were randomized clinical trials (Level II), however there are only a few institutions represented and most have developed their own computer system. Results of CPOE improving prescribing include more appropriate use of prophylactic heparin and H2 blockers, fewer drugs prescribed in excess dosages, more drugs used according to guidelines, fewer toxic serum concentrations of theophylline and aminoglycosides, and fewer laboratory tests ordered. Additional findings include 55-88% reduction in medication errors and 17-70% fewer ADEs. In a recent before-after study in a 20-bed pediatric ICU, CPOE reduced medication errors by 99.4% and potential ADEs by 41% [216]. One institution evaluated a computer-guided algorithm for dosing in patients with renal insufficiency [217]. In alternating eight-week intervals of nearly 100,000 orders of nephrotoxic or renally-cleared drugs, there was a significantly higher percent of appropriately dosed drugs which was associated with a shorter adjusted length of stay with computer-assisted dosing.) A 700-bed academic medical center assessed the potential impact of CPOE by having pharmacists evaluate 17,808 drug orders written in one week [218]. There were 1111 prescribing errors (6.2% of all orders) and the investigators concluded 31% were clinically significant and most commonly involved incorrect dosage of anti-infectives, cardiovascular, and opioid analgesic agents. Of all errors, 64% were rated as likely to be prevented with CPOE and 43% of these were potentially harmful errors that were preventable.

A more wide-reaching use of technology involves ICU telemedicine whereby patients at ICUs in several hospitals receive supplemental monitoring and management by physicians located at remote sites using telemedicine and information technology. In a before-after study of 2140 patients from two ICUs of a large tertiary care hospital, remote ICU care significantly reduced hospital mortality from 12.9% to 9.4% and

ICU length of stay from 4.3 days to 3.6 days [219]. This was accompanied by a 25% reduction in variable costs per case. These same authors recently implemented a system that identifies patients with renal insufficiency and provides dosing recommendations for renally cleared drugs at the time the drug is prescribed [220]. Preliminary results reveal 78% of prescriber's accepted the recommendations and there was a perception of increased patient safety.

These computer-based systems require considerable funds to develop and maintain. For a 500 bed institution, CPOE is estimated to cost at least \$8 million with \$1.3 million in recurring costs per year [215]. At Brigham and Womens hospital, the cost of their system in 1993 was \$1.9 million, but they project an annualized cost savings of \$5-10 million [202]. Furthermore, some authors provide critical appraisal of CPOE by emphasizing that these systems only marginally decrease the incidence of actual ADEs and since cost-effectiveness studies have not been done, the jury is still out on its true benefits [221].

Consensus Statement: Implementing computer based prescriber-order entry and clinical decision-support systems along with an appropriately trained ICU pharmacist as part of the intensivist-led multidisciplinary critical care team provides the optimal approach to minimize medication errors and adverse drug events (including drug induced nephrotoxicity) in critically ill patients.

Recommendations for Clinical Practice: While the established mechanism to report ADEs is via the Medwatch form, less than 10% of all ADEs are reported using this system, which suggests there is considerable degree of under reporting [222]. For any country, we recommend the development of a seamless system to catalogue suspected drug-associated kidney injury using, for example, the RIFLE criteria [223], that may decrease the threshold of reporting potential ADEs associated with the kidney. This streamlined system may accelerate the dissemination of information to optimize patient safety (grade E).

With the documented benefit of pharmacy services, we recommend ICUs have drugs readily available (ie a satellite pharmacy) that are checked by a pharmacist before being administered to the patient. Furthermore, a clinical pharmacist should be a member of the ICU team. If there is not a formalized ICU team, a clinical pharmacist should review all drug orders before being dispensed for appropriateness and safety based upon patient-specific conditions, and communicate any issues to the prescriber in a timely fashion. Clinical pharmacy services should be accessible 24/7 by the ICU pharmacists or appropriately trained pharmacist on-call (grade E).

CPOE and clinical decision-support systems should be implemented for critically ill patients (grade C). These systems should provide for seamless communication between clinical, laboratory and pharmacy information systems. Since isolated serum creatinine concentrations should not be used to assess kidney function to guide drug dosing, automated calculations of creatinine clearance or estimated GFR, based on local protocol (MDRD, CG, Schwartz) should be available to guide drug dosing for patients with kidney dysfunction for relevant clinical situations. Automated systems should also identify relevant patient and drug-related risk factors associated with kidney dysfunction, and alert prescribers when drugs are ordered that have drug concentration monitoring available. These include: aminoglycoside, vancomycin (older

Vancomycin assays are affected by interference with crystalline degradation products, which occur in patients with kidney dysfunction), phenytoin, digoxin, cyclosporine/tacrolimus/sirolimus, mycophenolate, procainamide/NAPA, lidocaine, theophylline, phenobarbital /pentobarbital, carbamezapine, valproic Acid, LMWH (Anti Factor Xa), nitroprusside (thiocyanate), methotrexate, lithium.

Recommendations for Future Research: We propose studies that evaluate the cost-effectiveness of the ICU pharmacist as part of the intensivist-led multidisciplinary ICU team that uses computer-based prescribing and clinical decision support systems to optimize pharmacotherapy and minimize errors and adverse drug events.

**Authors:**

In alphabetic order.

Joseph Dasta. School of Pharmacy, Ohio State University, Columbus Ohio. Email: [dasta@dendrite.pharmacy.ohio-state.edu](mailto:dasta@dendrite.pharmacy.ohio-state.edu).

Stuart Goldstein. Department of Pediatrics, Texas Childrens Hospital, Baylor College of Medicine, Houston Texas. Email: [slgoldst@TexasChildrensHospital.org](mailto:slgoldst@TexasChildrensHospital.org).

Thomas Golper. Department of Medicine, Vanderbilt University. Email: [thomas.golper@Vanderbilt.edu](mailto:thomas.golper@Vanderbilt.edu).

Miet Schetz. Department of Intensive Care, University of Leuven. Email: [marie.schetz@uz.kuleuven.ac.be](mailto:marie.schetz@uz.kuleuven.ac.be).

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