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Drug-associated acute kidney injury in the intensive care unit

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Epidemiology of acute kidney injury in the intensive care unit

In critically ill patients the development of acute kidney injury (AKI) is frequent and occurs in 15-64% of ICU patients [1-4]. Uchino et al reported from 29,269 critically ill patients in the ICU from 54 study centers that 30% of patients had renal dysfunction upon entering in the ICU and the prevalence of AKI defined by the need for dialysis to be 6% [3]. Mehta reporting on the PICARD experience (Program to Improve Care in Acute Renal Disease) found 64% of patients in the ICU required renal replacement therapy. Most recently a new classification scheme for AKI was established by the Acute Dialysis Quality Initiative Mortality that defines grades of increasing severity of AKI – risk (class R), injury (class I) and failure (class F)-and two outcomes class (loss and end-stage kidney disease) [5]. Using this classification scheme, Hoste et al found that AKI occurred in 67% of ICU admissions with maximum R, I, F class of 12%, 27% and 28%, respectively [6]. Mortality rates in those requiring dialysis renal replacement therapy ranges between 20-70% [2, 3, 7].

Nephrotoxicity due to drugs contributes to between 8-60% of AKI cases in hospitalized patients [8-12]. However in the ICU, patients are more complex and thus the etiology of AKI is less certain and more multifactorial in nature. Thus, in the ICU the incidence of AKI from drug nephrotoxicity is likely less prevalent than that due to sepsis or hemodynamic alterations. In the ICU setting the incidence of AKI from drug nephrotoxicity ranges between 1-23% [2, 4, 7, 13]. Elderly patients are likely more susceptible to AKI from nephrotoxic agents related to the age related decline in glomerular filtration rate or renal blood leading to reduced clearance of the drug, decline in hepatic clearance, altered free drug concentration [14].

In general, drug-induced nephrotoxicity is reversible but given the high morbidity and mortality associated with AKI and the frequent and necessary use of drugs in critically ill patients clinicians should be aware of the potential nephrotoxicities and mechanisms. Thus this review will discuss mechanisms of drug-induced AKI and preventive strategies. We will discuss broadly

different categories by which drugs cause toxic injury to the kidney with selected examples of each. Detailed discussions of various agents can be found in specific chapters elsewhere in the text.

Mechanisms of drug-induced acute kidney injury

There are several mechanisms by which drugs can lead to nephrotoxicity. Table 1 lists these mechanisms along with prototypical drugs that may induce nephrotoxicity. Understanding their mechanism of action will permit the optimal preventative measures.

Hemodynamically mediated nephrotoxicity

Complex factors maintain constancy of renal blood flow and glomerular filtration despite widely varying arterial pressures. Such factors such as the renal nervous system, prostaglandins, angiotensin II, adenosine, tubuloglomerular feedback as well as other factors participate in regulating glomerular filtration rate. Normally drugs that affect renal hemodynamics are unlikely to precipitate AKI alone unless patients have underlying concomitant predisposing factors.

Nonsteroidal anti-inflammatory drugs

Volume contraction from any cause or other forms of prerenal AKI (cirrhosis, congestive heart failure) will increase the incidence of and severity of nephrotoxicity due to nonsteroidal anti-inflammatory drugs (NSAIDs). Conditions such as congestive heart failure, hypotension, volume depletion, 3rd spacing, decrease effective arterial volume are conditions that predispose to NSAID-induced nephrotoxicity. Prostaglandins under these conditions have an important effect to maintain renal blood flow and glomerular filtration rate [15]. Similarly compensatory vasconstriction due to synthesis of angiotensin II, norepinephrine, vasopressin, and endothelin are balanced by vasodilatory prostaglandins. The use of other drugs that increase renin such as diuretics, angiotensin converting enzyme

Table 1. Common drugs associated with nephrotoxicity in the ICU.

Mechanisms	Drugs	Clinical Findings
Hemodynamic	Radiocontrast agents, calcineurin inhibitors, angiotensin inhibitors, angiotensin receptor blockers, NSAIDs, interleukin 2	Benign urine sediment, FENa <1%, UOsm >500
Acute tubular necrosis (exogenous toxins)	Aminoglycosides, amphotericin, cisplatin, radiocontrast agents, methoxyflurane, outdated tetracyclines, cephalosporins, mithramycin, calcineurin inhibitors, pentamidine, IVIG, ifosfamide, zoledronate, cidofovir, adefovir, tenofovir	FENa>2%, UOsm <350, urinary sediment contains granular casts, renal epithelial cells
Acute tubular necrosis (endogenous toxins-rhabodmyolysis)	Lovastatin (statins), ethanol, barbiturates, diazepam	Elevated CPK, granular casts
Acute tubular necrosis (hemoglobin)	Quinine, quinidine, sulfonamides, hydralazine, triamterene, nitrofurantoin	Elevated LDH, decrease haptoglobin
Allergic interstitial nephritis	Penicillins, rifampin, sulfonamides, thiazides, cimetidine,phenytoin, allopurinol, furosemide, NSAIDS, ciprofloxacin, pantoprazole, omeprazole, atazanavir, bevacizumab	Rash, fever, eosinophilia, eosinophiluria, pyuria
Osmotic nephrosis	Mannitol, immune globulin, dextrans, hetastarch	Urine sediment shows vacuole containing cells
Papillary necrosis	NSAIDs	Hematuria, renal tissue
Obstruction (intratubular precipitation)	Acyclovir, methotrexate, sulfonamides, triamterene, indinavir, foscarnet, gancyclovir	Sediment might be benign despite obstruction
Obstruction (post renal)	Methylsergide, ergotamine, methyl dopa, hydalazine	Benign sediment, hydronephrosis
Thrombotic microangiopathy	Mitomycin, cyclosporin, bevacizumab, gemcitabine	Decreased hemoglobin, haptoglobin, elevated LDH, schistocytes

inhibitors (ACEI) or angiotensin receptor blockers (ARBs) when used concomitantly with NSAIDs leads to a reduced prostaglandin synthesis, renal vasoconstriction and AKI [16]. Because the kidney medulla is relatively hypoxic [17], a decrease in medullary blood flow may exacerbate the already hypoxic medulla leading to AKI. Radiocontrast agents in addition to being a direct tubule toxin induces vasoconstriction [18] and when administered in patients using NSAIDS may lead to AKI[19]. Vasopressors, often used in the ICU's, as well as amphotericin can precipitate AKI when NSAIDs are concomitantly used. Similarly, acute nephrotoxicity due to calcineurin inhibitors, and vasopressors contributes to toxicity especially when used with NSAIDs. The renal effects of NSAIDS are dose, drug and duration related. Aspirin is the least likely to cause AKI but nonselective and selective NSAIDS were associated with AKI [20]. In a nested case-controlled study, new NSAID users were followed for hospitalization with a diagnosis of AKI. Within 30 days of therapy the relative risk for AKI was similar for rofecoxib (RR = 2.31, 95% CI: 1.73, 3.08), naproxen (RR = 2.42, 95% CI: 1.52, 3.85), and nonselective, non-naproxen NSAIDs (RR = 2.30, 95% CI: 1.60, 3.32) and celecoxib (RR =1.54, 95% CI: 1.14, 2.09 were similar [20]. Thus despite the selectivity of Cox-2 inhibitors they do not seem to have renal sparing effects and the nephrotoxic potential is similar to COX-1 inhibitors [20, 21, 22].

ACEI/ARBs

ACEI and ARBs are commonly prescribed drugs used for hypertension, congestive heart failure and in chronic kidney disease. These drugs affect renal hemodynamics through an decrease in efferent arteriolar tone and intraglomerular capillary pressure [23]. The use of these drugs under normal circumstances when renal perfusion is adequate poses very little problem. However when these drugs are used in states of prerenal azotemia, renal artery stenosis or concomitantly with other drugs such as NSAIDs, renal failure may ensue. In general AKI under these circumstances is reversible following their discontinuation.

Other drugs that cause altered glomerular hemodynamics

Drugs such as cyclosporine and tacrolimus, belong to a class of commonly used immunsuppressants for organ transplantation referred to as calcineurin inhibitors. Calcineurin inhibitors are associated with early prerenal azotemia and oliguria (<50 mL/h urine output) due to vasoconstriction [24]. Calcineurin inhibitor-induced vasoconstriction is thought to be due to: 1) effects on the endothelium, 2) an increase in sympathetic activity, 3) an increase in adenosine 4) a relative decrease of nitric oxide and transforming growth factor-beta 1, and 4) an increase in endothelin-1, reactive oxygen and nitrogen species [25-27]. Other factors that may lead to renal vasoconstriction are drugs such as NSAIDs and ACEI/ARBs. In addition, drugs that may increase blood levels of calcineurin inhibitors such as ketoconazole are likely to lead to an increase in nephrotoxicity. Cyclosporine metabolism occurs in the liver via hepatic cytochrome P-450 microsomal enzymes [28]. Ketoconazole, an imidazole derivative, inhibits the cytochrome P-450 enzyme system leading to an increase in cyclosporine levels and potential toxicity. The early AKI from calcineurin inhibitors associated with prerenal indices is rapidly reversible upon discontinuation of the drug.

Intrinsic acute kidney injury

Acute kidney injury may be due to tissue parenchymal injury as manifested by direct tubule toxicity, acute interstitial nephritis, osmotic nephrosis and thrombotic microangiopathy.

Acute tubular necrosis

Direct tubule injury occurs with different classes of drugs and is commonly associated with antibiotics, chemotherapeutic agents, bisophosphonates, immunosuppressive agents and contrast agents (Table 1).

Cidofovir or tenovir, antiviral nucleotide analogues with activity against DNA viruses are associated with dose dependent AKI in 12-24% of patients [29] with urinary abnormalities that resemble Fanconi's syndrome (proteinuria, glucosuria, and bicarbonate wasting [30, 31]. The predilection for proximal tubule injury is due to its uptake in this segment across the basolateral membrane by the human organic anion transporter (hOAT) [32]. Probenecid blocks this transporter and reduces the cytotoxicity by reducing intracellular accumulation of these drugs [32]. Renal function usually improves upon discontinuing antiviral nucleotide analogues however they can lead to end stage renal disease [33].

Aminoglycosides including gentamicin, tobramy-

cin, amikacin, streptomycin, neomycin, kanamycin, paromomycin, netilmicin, and spectinomycin are approved by the Food and Drug Administration (FDA) for clinical use in the United States. Gentamicin, tobramycin, and amikacin are the most frequently prescribed for use intravenously although tobramycin has been prescribed for inhaled use especially in patients with cystic fibrosis. All forms have been associated with AKI (7-9%) [34-36] including inhaled tobramycin [37, 38]. The renal toxicity was reported to be 3.9%, 30%, 30% in the first week, during the second week and after 2 weeks of therapy, respectively [39]. Aminoglycosides are organic bases that are freely filtered and taken up by megalin located on the apical membrane of the S_1/S_2 segments of the proximal tubule and collecting duct. Aminoglycosides rapidly traffick retrogradely through the Golgi complex and to the ER and are finally released into the cytosol [40]. Renal toxicity is frequently reversible. Risk factors for aminoglycoside-induced nephrotoxicity include sepsis, preexisting renal disease, age, diabetes, liver disease, hypovolemia, concurrent use of other drugs or exposure to contrast and the use of diuretics [29].

Allergic interstitial nephritis (AIN)

Drugs may produce an idiosyncratic or allergic reaction leading to inflammation and infiltration of immune cells such as lymphocytes, monocytes, plasma cells and eosinophils leading to injury to the renal tubules and interstitium. Renal dysfunction in drug-induced AIN is believed to be the cause of AKI in 3-15% of all cases [41, 42] and 27% of undiagnosed cases with normal size kidneys by ultrasound [43]. Most cases of AIN in the ICU stem from antibiotics due to the frequency of sepsis encountered requiring multiple antibiotics. A number of drugs have been associated with AIN including beta-lactams, quinolones, rifampin, macrolides, sulfonamides, NSAIDS, diuretics, cimetidine, randitine and proton-pump inhibitors (Table 1). Recently bevacizumab, a recombinant humanized monoclonal immunoglobulin G antibody to vascular endothelial growth factor (VEGF) used in clinical trials to treat cancer, has been reported to cause interstitial nephritis [44]. In addition there are other causes of interstitial nephritis including infections, immune mediated diseases, glomerular diseases and other idiopathic causes [41, 42, 45]. The onset may range from 3 days to 20 days [22] and maybe accelerated following rechallenge [46]. In general the clinical presentation includes, fever, rash and eosinophilia. However this triad only occurs in one third of the patient who actually have the disease. In addition AIN is often accompanied by low grade proteinuria and biopsy findings consistent with interstitial infiltration of immune cells.

Nephrotic syndrome

Bisphoshonates are used for treatment of hypercalcemia, fracture prevention and in patients with metastatic cancer. This class of drugs reduce morbidity from hypercalcemia is increasingly recognized to cause nephrotoxicity [14]. Both pamidronate and zoledronate have been associated with nephrotoxicity that features nephrotic syndrome with a collapsing glomerular sclerosis [47]. The mechanism is unkown and the return of renal function is slow.

Crystal deposition

Drug crystallization and deposition in kidneys cause AKI [48]. The main cause of injury is due to the relative insolubility of drugs in urine leading to precipitation within the tubule lumen that in most instances are pH dependent [49]. Drugs such as acyclovir, sulfonamides, methotrexate, indinavir, and triamterene may lead to crystal deposition [21, 48]. Tumor lysis syndrome leading to uric acid and calcium phosphate crystals may occur in the setting of malignancies. Acyclovir commonly used to treat VZV and HSV infections is associated with AKI particularly in those receiving high doses (500 mg/m^2) over a relatively short period of time. The incidence is thought to be 12-48% [50] [51-54] and in approximately 50% of the cases, the renal insufficiency is reversible. Indinivar, a protease inhibitor used in the treatment of HIV induces crystal formation [55] and deposition in the kidney [56] due to its relative insolubility in urine.

Drug-induced thrombotic microangiopathy (TMA)

A number of drugs have been reported to be associated with TMA. Although a direct casual relation has not been established, cumulative evidence exist for some drugs. Generally they fall into several categories including antineoplastics, immunotherapeutics and anti-platelet agents [57] Chemotherapeutic agents often encountered in the ICU are associated with drug-induced TMA. Such drugs include: mitomycin, cyclosporine, tacrolimus, quinine, ticlodipine,

clopidogrel and others (Table 1) [56, 58, 59]. Recently bevacizumab has been added to the list of drugs causing TMA [60].

Osmotic nephrosis

Osmotically active agents such as intravenous immunoglobulin (IVIG), mannitol and dextran induce tubule damage through swelling and vacuolization [29, 61]. Drugs that may induce high osmotic pressures include mannitol and IVIG. The latter case, hyperosmotic damage or the stabilizing agent, sucrose, may lead to AKI. Hetastarch, used in the ICU as a volume expander is known to be a risk factor for AKI, especially in septic patients [62].

Risks associated with acute kidney injury

Despite the significant progress made in understanding the biology and mechanisms of acute kidney injury (AKI) in animal models, translation of this knowledge into improved management and outcomes for patients has been limited. In fact, with few exceptions pharmacological therapies to prevent AKI have not been successful. Thus, prevention of AKI must be a priority to avoid the morbidity and mortality associated with this event.

Preventive strategies rely on knowledge of the risk factors that are commonly associated with diverse causes of AKI, here specifically focusing on acute tubular necrosis (ATN). Three major categories of insults can lead to ATN: renal ischemia, nephrotoxins and pigmenturia (hemoglobinuria or myoglobinuria). It is clear from multiple human and animal studies that several insults are usually present to result in AKI [12, 13, 63-65]. For example, patients may experience bacteremia, sepsis, hypotension, exposure to aminoglycoside antibiotics that individually may not lead to AKI, but collectively lead to severe ATN. This is especially true in critically ill patients. Rasmussen and Ibels examined the risk factors for the development of ATN in 143 carefully selected patients [66]. The following were considered possible acute and causative insults: hypotension (74%), sepsis (31%), contrast media (25%), aminoglycoside exposure (25%), pigmenturia (22%) and volume depletion (35%). Nearly two-thirds of the patients had suffered more than one insult before the clinical appearance of AKI. Other studies [67-69] have showed similar results with sepsis, volume depletion, impaired cardiac output and exposure to nephrotoxins being the most common exposures in those patients developing ATN.

Specific clinical settings are particularly prone to the appearance of AKI. One of the most common and lethal is AKI in the context of multi-organ failure. Liano and colleagues studied more than 200 cases of intensive-care unit (ICU)-associated AKI and demonstrated that 11% had none, 24% had one, 40% had two and 26% had concomitant failure of three or more organ systems [7]. Groeneveld et al found that 90% of ICU patients with AKI had multi-organ failure [70]. Most often, other organ systems failed before AKI was apparent. What these studies make evident is that AKI (especially in the ICU) usually occurs in the context of additional organ system dysfunction and multiple insults (hemodynamic instability leading to renal ischemia, impaired cardiac output, intravascular volume depletion, sepsis and exposure to nephrotoxins). Attention to these risks is paramount to any effort to protect the kidney.

Advanced age is one of the most important risk factors for AKI. Feest and colleagues performed a prospective 2-year study of 450,000 patients and found that more than 70% of AKI cases occurred in patients age > 70 years [70]. In those patients aged 80-89 years, the risk of AKI was 56-fold higher than the reference population of those aged < 50 years. Certainly, much of this risk is attributable to co-morbidities seen in the elderly (impaired renal reserve due to chronic kidney disease, impaired left ventricular dysfunction, diabetes mellitus, concomitant medicine use such as non-steroidal anti-inflammatory agents (NSAIDS), etc).

Other clinical settings that are at particularly high-risk for the development of AKI include: sepsis/infection [4], HIV infection [71], post-operative states [72], trauma and burns [73], non-renal solid organ transplantation [74], heart failure [75], cardiac surgery [76], liver disease [77], bone marrow transplantation [78], and rhabdomyolysis [79]. Within each of these clinical settings, studies have demonstrated several associated factors that significantly increase the risk for AKI (Table 2). Not surprisingly, these factors are remarkably consistent across these clinical settings. For example, in a study of patients with sepsis, AKI was associated with older age, higher baseline serum creatinine values, and hepatic failure [80]. In patients undergoing cardiac surgery, risk factors associated with the development of AKI in multiple studies have

Table 2. Common risk factors associated with the development of AKI.

Clinical settings
ICU/multiple-organ failure
Sepsis/infection
Post-operative (especially cardiac and vascular surgery)
Trauma
Burns
HIV
Non-renal solid organ transplantation
Bone marrow transplantation
Liver disease
Patient-specific factors
Advanced age
Diabetes mellitus
Impaired renal function
Impaired cardiac function
Volume depletion
Multiple nephrotoxic medications
Radiocontrast agent exposure
Medication use
NSAIDS/Cox-2 inhibitors
Aminoglycoside antibiotics
Amphotericin B
ACE-inhibitors/angiotensin-receptor antagonists
Calcineurin inhibitors
Chemotherapeutic agents (cisplatin, ifosfamide)
Illicit drug use (cocaine)
Deliberate or accidental ingestion of toxins (ethylene glycol)
Occupational toxins (heavy metals, organic solvents)
Herbal remedies (aristolochic acid)

Table 3. An example of a risk-scoring scheme and its application in predicting the risk for contrast-induced nephropathy.

Risk factor		Score
Hypotension		5
Intra-aortic balloon pump		5
Congestive heart failure		5
Age > 75 years		4
Anemia		3
Diabetes		3
Contrast media volume		1 for each 100 ml
Serum creatinine > 1.5 mg/dL		4
	or eGFR 40-60 ml/min	2
	eGFR 20-40 ml/min	4
	eGFR < 20 ml/min	6

Risk score	Risk of contrast-induced nephropathy	Risk of dialysis
≤ 5	7.5%	0.04%
6-10	14.0%	0.12%
11-16	26.1%	1.09%
≥ 16	57.3%	12.6%

Adapted from: Mehran R, et al. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. J Am Coll Cardiol 2004; 44: 1393-1399.

been: severe left ventricular dysfunction (especially that requiring use of an intra-aortic balloon pump), prolonged cardiopulmonary bypass, older age, diabetes mellitus, and pre-existing renal impairment [81-83]. This last factor is perhaps the most important with the risk of AKI requiring dialysis approaching 10-20% in those patients undergoing cardiac surgery with a baseline serum creatinine between 2.0 and 4.0 mg/dL [84]. In patients exposed to radiocontrast agents, the key risk determinants for AKI include: chronic kidney disease stage III or greater (estimated GFR < 60 ml/min), diabetes mellitus, volume depletion, nephrotoxic drug use, preprocedural hemodynamic instability, anemia, congestive heart failure and hypoalbuminemia [85]. The importance of baseline renal function in this setting is exemplified by one registry study that demonstrated an incidence of AKI of 2.5% in patients with mild renal impairment (serum creatinine 1.2 to 1.9 mg/dL), which rose to 30.6% in those patients with more severe renal impairment (serum creatinine ≥ 3.0 mg/dL) [86].

Identification of risk factors has been used to produce clinical AKI predictive scoring systems that attempt to better quantify cumulative risk. These scoring systems are most useful *in situ*ations where a possible nephrotoxic exposure is to occur at a defined time (such as cardiac surgery or radiographic contrast exposure). They provide a very useful framework to identify patients who are at risk and thus may benefit from renal protective strategies. For example, a scoring system developed at the Cleveland Clinic utilizes 13 pre-operative variables to predict a risk for post-cardiac surgery AKI [87]. Similar scoring systems have been developed by others for cardiac surgery and for other settings such as radiocontrast media exposure [88-90]. An example of one such risk-scoring scheme for contrast-induced nephropathy is shown in Table 3 [90]. These scoring systems attempt to identify a small number of high-risk patients and thus will have good negative predictive power but will often lack positive predictive power. Many of these predictive scoring systems have not been validated across different population groups and thus are limited in their utility.

One important factor that limits the determination of risk for AKI is the poor sensitivity of serum

Table 4. General approaches for the prevention of AKI.

1.	Avoidance of nephrotoxins Recognition of potential nephrotoxic agents Recognition of high risk patients and clinical settings Avoidance of concomitant use of multiple nephrotoxins Use of lowest dose and for shortest time possible If applicable, monitoring of drug dose Frequent monitoring of renal function Maintain euvolemia
2.	Minimization of nosocomial infection
3.	Extracellular fluid expansion (maintain good urine output, stable hemodynamics)
4.	Avoid agents that impair renal blood flow autoregulation (NSAIDS, ACE inhibitors, ARBs)
5.	Pharmacological Interventions – if applicable (Table 5)
6.	Use of computer surveillance systems

Table 5. Examples of specific renal protective strategies.

Exposure	Strategy
Radiocontrast agents	IV hydration (normal saline) [95] IV sodium bicarbonate [96] N-acetylcysteine [108, 109] Vitamin C [123] Iso-osmolar contrast [124]
Aminoglycoside antibiotics	Once-daily dosing [125] Monitoring of drug levels
Tumor lysis (uric acid)	Allopurinol/rasburicase [126] IV hydration/urine alkalinization
Ethylene glycol ingestion	Ethanol/fomepizole [127] Hemodialysis
Rhabdomyolysis	IV hydration/urine alkalinization [128] ± mannitol [129]
Methotrexate	IV hydration/urine alkalinization [48]
Acyclovir	IV hydration [54]
Calcineurin inhibitors	Monitor drug levels [130] ± calcium-channel blockers [131]
Amphotericin B	Use of lipid formulation [132]

creatinine values for detection of mild degrees of renal injury. In fact, there is no practical, "real-time" method to provide accurate determination for mild degrees of kidney injury. Oliguria certainly heralds the presence of significant kidney dysfunction, but most causes of AKI are non-oliguric [91]. Thus, a relatively large decrease in glomerular filtration rate (GFR) may be associated with only small changes in the serum creatinine (especially true in those patients with normal baseline renal function). Furthermore, the serum creatinine is influenced by variables such as production rate, muscle mass and the volume of distribution. Thus, a cirrhotic patient who may be malnourished and volume expanded may appear to have a "normal" serum creatinine value when, in fact, there is significant kidney impairment [92]. All of this makes heightened awareness of the clinical setting and risks associated with AKI more important in the early detection of AKI. Careful attention to even small increases in serum creatinine as well as attention to urine abnormalities (presence of granular casts) is critical for the early detection of AKI. It is hoped that sensitive biomarkers of kidney injury may ultimately allow identification of patients at the earliest signs of AKI.

Renal protective strategies

Strategies used to prevent AKI can be broadly separated into generalized approaches and those approaches which are more specifically targeted to a particular risk factor (Tables 4 and 5). Certainly improvements in overall ICU care that focus on the risk factors identified above should reduce the incidence of AKI. In fact, early and aggressive therapy of hemodynamically unstable patients in the emergency department using a combination of IV hydration and pressor agents led to an impressive 88.5% reduction in the incidence of AKI [93]. Thus careful attention to volume status and maximization of cardiac output along with minimization of exposure to nephrotoxic agents should be employed in all at risk patients. Agents that impair the critical autoregulation of renal blood flow such as NSAIDs, ACE inhibitors, angiotensin-receptor antagonists (ARBs) should be avoided. Plasma concentrations of selected nephrotoxic drugs (aminoglycosides, calcineurin inhibitors) should be monitored closely and cumulative dose should be limited. Despite these clear recommendations, Weisbord and co-workers found that 16% of patients who were at clear risk for the development of contrast-induced nephropathy never received pre-procedural IV fluids and 8% of these patients were prescribed NSAIDS or COX-2 inhibitors [19].

One strategy to reduce the incidence of AKI has adopted a computer surveillance system that notifies physicians via e-mail messages whenever a small rise in serum creatinine occurs in their patients who are receiving potential nephrotoxic medications [94]. This notification system led to earlier cessation of offending

drugs and a decrease in the incidence of severe AKI from 7.5 to 3.4%.

Specific strategies to reduce the incidence of acute kidney injury

Intravenous fluids clearly reduce the risk of AKI across a spectrum of etiologies. For example, in the prevention of contrast-induced nephropathy, one study compared IV hydration with 0.9% saline at 1 ml/kg/hour beginning 12 hours prior to the study with unrestricted oral fluids. The incidence of AKI (as defined by a 0.5 mg/dL or greater rise in serum creatinine) was 3.7% in the IV hydration group and 34.6% in the oral fluid group [95]. Saline-based therapies may not be as effective as a bicarbonate-based solution in this setting [96], however confirmation will be necessary from other centers.

In the setting of sepsis, while IV fluid resuscitation is clearly critical, the optimal form of volume support is not known. Three meta-analyses have compared crystalloid versus colloid solutions with at least no difference or perhaps a slight increase in mortality associated with colloid solutions [97-99]. In a multicenter randomized controlled trial of resuscitation fluids (saline versus albumin), there was no difference between the fluids in 28-day mortality, organ failure, days on renal replacement therapy, days on mechanical ventilation, or hospital days [100]. The Cochrane group concluded that albumin administration in severely ill patients was associated with increased mortality as compared with other IV fluids [101]. Other colloid solutions such as hydroxyethylstarch and gelatin have also been studied and do not seem to have an advantage over crystalloids [102]. In fact, hydroxyethylstarch was associated with a higher risk of AKI than gelatin [62]. In the preoperative setting, the use of IV fluids to "optimize" cardiac performance (as guided by pulmonary artery catheter measurements) has been shown to be beneficial with a reduction in the incidence of AKI from 4.8% to 1.5% in patients undergoing vascular surgery [103]. However, volume expansion to supranormal cardiac indices along with normal mixed venous oxygen saturation had no effect on the incidence of AKI and can not be routinely recommended [104].

In some patients, vasopressor agents are required to maintain hemodynamic stability. Few direct comparisons exist to support one vasopressor over another [105]. However, accumulating evidence supports the use of norepinephrine in patients with septic shock with a retrospective study demonstrating reduced mortality with norepinephrine over other vasopressors [106]. Furthermore, animal data demonstrates that reversal of septic hypotension with norepinephrine leads to increases in renal blood flow [107]. There are no studies that compare the renal outcomes between catecholamine therapy and vasopressin.

One renal protective strategy that is often overlooked is the intensive control of blood glucose levels in critically ill patients [107]. Insulin therapy reduced the risk of AKI that required dialysis by 41% in one trial [107]. While the mechanism of this effect is not known, this easily implemented strategy should be considered in all at risk patients.

N-acetylcysteine has been widely advocated as a renoprotective agent especially in the setting of radiocontrast media exposure. Several meta-analyses have shown that N-acetylcysteine can reduce the incidence of contrast-induced nephropathy by nearly 50% [108, 109]. However, in other settings such as post-cardiac surgery, N-acetylcysteine has not proved to be of benefit [110]. Furthermore, N-acetylcysteine may be of less benefit in those patients with moderate or severe chronic kidney disease [111].

Many other renal protective strategies have been attempted with poor results. Dopamine at doses between 0.5 to 5.0 ug/kg/minute has been promoted as a therapy to increase renal blood flow, induce natriuresis and diuresis and perhaps increase GFR. However, in multiple settings ranging from sepsis, contrast exposure, and cardiac surgery dopamine has not been shown to be beneficial in preventing AKI (reviewed in 56)[112]. Fenoldopam is a more selective dopamine A-1 agonist that increases renal blood flow to the cortex and outer medulla. A recent meta-analysis of 16 small trials has suggested that there may be a small benefit in reducing the risk of AKI [113]. However, most of the studies in this meta-analysis were underpowered and a larger, randomized clinical trial is required before this therapy can be recommended. Other agents that have been used and have shown no or at best marginal benefits include: atrial natriuretic peptide [114], clonidine [115], calcium channel blockers [116], furosemide [117], inotropic agents [118], growth factors [119, 120], and theophylline [121], as well as numerous others. These failures highlight the critical importance

of nonpharmacological therapies.

One controversial strategy is the use of prophylactic dialysis to prevent AKI. This has been evaluated in the setting of high-risk patients undergoing coronary angioplasty [122]. In this study, patients with baseline serum creatinine values > 2 mg/dL were randomized to either IV fluids or IV fluids with hemofiltration that was commenced 4-6 hours prior to the procedure and continued for 18-24 hours after contrast administration. The group receiving extracorporeal therapy had a lower incidence of AKI requiring dialysis, a lower hospital mortality rate. However, the invasiveness and cost of this therapy as well as inherent flaws in the study (difference in total IV hydration, lack of N-acetyl cysteine use, difference in loop diuretic use between groups) prevents this strategy from being used more widely.

There are several preventative strategies that are specific to either clinical states (rhabdomyolysis) or nephrotoxic exposures. These are listed in Table 4 and discussed elsewhere in more detail. In these specific instances, these steps, in addition to the general strategies discussed above, may be employed to reduce the risk of AKI. However, it is critical to realize that these strategies are useful only when applied prophylactically to at-risk patients or are applied very soon after a renal insult.

Currently, the best evidence supports the use of non-pharmacological strategies in reducing the risk of AKI. Maintenance of blood pressure, avoidance of nephrotoxins, attention to risk factors and small changes in serum creatinine afford the greatest benefit. In certain specific instances, use of pharmacological agents such as N-acetylcysteine may be of use but more generalized pharmacological approaches to the prevention of AKI have not yet come to fruition. Thus, vigilance and rapid response with conservative measures are warranted in all patients.

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