Protecting the Kidney from Perioperative Injury

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**Clinical Definitions and Pathogenesis of Acute Kidney Injury (AKI)**

For many years the ability to quantify renal protection was hampered by the lack of a clear clinical definition of acute kidney injury (AKI). In 2000 a group of experts (the Acute Dialysis Quality Initiative) met and defined AKI by five criteria they called RIFLE (Risk, Injury, Failure, Loss, End-stage) 1. The first 3 stages (R,I,F) reflect the increase in serum creatinine (SCr), decrease in estimated glomerular filtration rate (eGFR) or duration of oliguria within a 7-day period; the second two (L,E) reflect renal outcome. Subsequently, the group coalesced into the Acute Kidney Injury Network (AKIN) 2, and simplified the definition into three stages evaluated over 24 hrs, and acknowledged the adverse implications of even small increases in SCr (Table 1):

<table>
<thead>
<tr>
<th>Stage</th>
<th>Serum Creatinine (SCr)</th>
<th>Urine Output (UO)</th>
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<tbody>
<tr>
<td>1</td>
<td>Increase by 1.5-2 x baseline, or by &gt; 0.3 mg/dL</td>
<td>&lt; 0.5 mL/kg/hr x 6 hr</td>
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<tr>
<td>2</td>
<td>Increase by 2-3 x baseline</td>
<td>&lt; 0.5 mL/kg/hr x 12 hr</td>
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<tr>
<td>3</td>
<td>Increase by 3 x baseline, or by 0.5 mg/dL if SCr &gt; 4 mg/dL</td>
<td>&lt; 0.3 mL/kg/hr x 24 hr or anuria &gt; 12 hr</td>
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**Limitations of RIFLE and AKIN Criteria**

Both the RIFLE and AKIN definitions of AKI identify an increasing severity of insult and show good correlation with renal outcome. There is actually poor correlation between oliguria alone and AKI unless there is hemodynamic instability 3, so most studies now use the AKIN SCr criteria only. It may be days before the SCr reaches its peak postoperative value that reflects the nadir GFR 4, which is unhelpful for real-time diagnosis. A more meaningful indicator of actual GFR is obtained by a short (< 2 hr), timed creatinine clearance 5. The RIFLE and AKIN criteria do not address the common postoperative entity of non-oliguric renal failure (NORF) or prerenal oliguria; nor do they offer any insight into the etiology of AKI.

**Renal Biomarkers**

More than 50 biomarkers have been studied as indicators of renal injury 6. Cystatin C, a cysteine proteinase inhibitor released by all nucleated cells and completely filtered by the glomerulus, is advocated as a more stable indicator of GFR than SCr 7. A number of proteins that are released into the urine within hours of ischemia could serve as biomarkers of acute tubular injury: these include neutrophil-gelatinase associated lipocalin (NGAL) 8, 9, interleukin-18 (IL-18) 10, and kidney injury molecule-1 (KIM-1) 11. The most promising biomarker to date is liver-type fatty acid-binding protein (L-FABP), whose urinary concentrations increase earlier and more specifically than NGAL 12. It is conceivable that a reliable renal biomarker – or panel of biomarkers 13 - for AKI may render the RIFLE and AKIN criteria obsolete, but we are not there yet. In the interim they do provide surrogate end-points for randomized controlled trials (RCTs) and allow stratification based upon the severity of injury.

**Renal Autoregulation and Urine Output**

It is important to note that renal autoregulation maintains RBF and GFR through a broad range of perfusion pressure, but does not preserve urine flow, which is very pressure dependent 14. Blood pressure (BP) invariably decreases during anesthesia, and urine flow declines accordingly; when BP returns to normal at emergence, so does urine flow.
An important endogenous mechanism to preserve GFR in the face of decreased RBF or arterial pressure is preferential efferent arteriolar constriction induced by local release of norepinephrine (NE), angiotensin II and arginine vasopressin (AVP). This explains the loss of GFR when a patient under stress is given an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB).

In patients with chronic hypertension autoregulatory responses are reset, so a higher BP may be required to maintain RBF and GFR. In certain states, including AKI, sepsis and possibly cardiopulmonary bypass (CPB), renal autoregulation may be impaired or lost, so RBF becomes much more pressure dependent\(^15\).

**Perioperative Oliguria and the Prerenal Syndrome**

The etiology of oliguria traditionally has been defined as postrenal, prerenal or intrarenal. Postrenal oliguria implies urinary tract obstruction (renal pelvis, ureters, bladder, urethra or urinary catheter) and typically manifests as anuria if the obstruction is complete. A postrenal etiology should always be evaluated first.

If postrenal obstruction has been excluded, peritral oliguria should be interpreted as a prerenal (physiologic) response to intravascular hypovolemia. The latter may be absolute (acute hemorrhage, severe diarrhea, vomiting, fluid restriction), or relative (congestive heart failure, sepsis, liver failure).

Hypovolemia and hypotension trigger osmoreceptor, volume receptor and baroreceptor reflexes that include the sympathoadrenal and renin-angiotensin systems, aldosterone and AVP (formerly called antidiuretic hormone, ADH). The net effect is avid reabsorption of water and sodium (Na), resulting in oliguria with high urine osmolality (UOsm) and low urine Na (UNa). When normal renal hemodynamics are restored, the stimulus to the tubules abates and normal urinary flow resumes. If hypovolemia is severe and/or combined with nephrotoxic insults, frank AKI may ensue (intrarenal oliguria).

In sepsis and liver failure, circulating endotoxin disrupts the renal circulation and induces a prerenal “vasomotor nephropathy” characterized by oliguria and Na retention (UNa < 10 mEq/L). It is refractory to fluid replacement and responds only to treatment of the underlying condition.

In sum, perioperative oliguria is common, but rarely implies AKI\(^16\). It is a sign of intravascular hypovolemia and should be treated as prerenal until otherwise proven. In contrast, the absence of oliguria does not exclude AKI, because about 75% is non-oliguric (urine flow rate 15-80 mL/hr)\(^17\), a reflection of incremental smaller insults in a protected milieu. Until the role of renal biomarkers becomes established, the most reliable early clinical indicator of AKI and diminished GFR remains a serial decline in measured creatinine clearance.

**The Interface between Prerenal Syndrome and AKI**

In the classic animal model of ischemic acute tubular necrosis (ATN), the nature of the injury depends on the duration of infusion of NE into the renal artery. A brief infusion (< 60 min) results in reversible oliguria; the intact renal tubules avidly conserve Na and water so UNa is low and UOsm high; and oliguria resolves when the NE infusion stops. This is a typical prerenal syndrome.

A longer infusion (60 – 120 min) results in persistent oliguria and subsequent azotemia after NE is stopped: this is ATN. The renal tubules lose their ability to conserve salt and water, so urine sodium is high and osmolality low. When normal renal hemodynamics are restored, GFR remains < 10% of baseline because of tubular obstruction by necrotic cells in the proximal tubule; loss of glomerular-tubular gradient; and back leak of tubular fluid into the interstitial tissue\(^18\). The implication of this model is that the physiologic, reversible prerenal syndrome may deteriorate into frank ATN if the ischemic insult persists long enough. A prerenal (dehydrated) state also sensitizes the kidney to nephrotoxic insults from non-steroidal anti-inflammatory drugs (NSAIDs), aminoglycoside antibiotics, radiocontrast dyes and calcineurin inhibitors. Also in this model, administration of “renal protective agents” (saline, mannitol, vasodilators) prior to NE infusion ameliorates the severity of ATN, akin to the clinical syndrome of non-oliguric acute renal failure (NORF)\(^19\).
Nephrotoxic Pathways to AKI

An isolated insult in a normal milieu almost never induces AKI, but risk increases exponentially when multiple agents are administered in an adverse milieu that may be acute (shock, hypovolemia, CHF) or chronic (advanced age, diabetes, chronic renal insufficiency) \(^20\). The reasons are explained below.

Nephrotoxic agents directly injure target cells but also cause harm by disrupting renal oxygen balance in the medullary thick ascending loop of Henle (mTAL). The hypertonic medulla provides renal concentrating ability, but to do so, RBF must remain very slow (<10% of total RBF) and the tissue PaO\(_2\) is accordingly very low (<10 mmHg). The mTAL is at risk when dehydration further compromises available RBF, and/or there is any disruption to the formation of local nitric oxide or prostacyclin that maintains medullary vasodilation. Nephrotoxic AKI is usually non-oliguric and SCr increases quite slowly.

Aminoglycosides

Aminoglycosides are absorbed into intracellular lysosomes where they inhibit oxidative phosphorylation and ATP synthesis \(^21\). Their nephrotoxicity is related to sustained high trough serum levels \(^22\), and can be ameliorated by hydration, monitoring of serum levels and creatinine clearance, and once-daily administration \(^23\).

Non-steroidal Anti-inflammatory Drugs (NSAIDs)

Cyclooxygenase-1 (COX-1) inhibition by NSAIDs (e.g. indomethacin, meclofenamate or ketorolac) impairs medullary vasodilator prostaglandin synthesis. During stress, this results in decreased RBF and GFR, diuretic unresponsiveness and hyperkalemia \(^24\).

Calcineurin Antagonists

Cyclosporine A and tacrolimus induce sympathetic hyperreactivity and renal vasoconstriction. This is counteracted by calcium channel blockers, which provide renoprotection after cadaveric renal transplantation \(^25\).

Radiocontrast Agents

Hyperosmolar radiocontrast agents induce osmotic diuresis (hypovolemia), RBC crenation (obstructed microcirculation), and free oxygen radical release (tubular toxicity). The risk of radiocontrast nephropathy (RCN) is increased by hypovolemia, diabetes, and CHF \(^26\), and may be ameliorated by hydration, low-osmolar radiocontrast agents, bicarbonate or N-acetylcysteine (see below) \(^27\).

A Clinical Approach to Oliguria

Oliguria Algorithm:
1. Assume that oliguria is prerenal \(^28\)
2. Evaluate, monitor and treat intravascular volume deficits
3. Maximize renal blood flow by optimizing hemodynamic function
4. Maintain renal perfusion pressure with vasoconstrictor therapy (NE ± AVP)
5. Consider diuretic therapy (see below)
6. Counteract diuretic resistance (see below)

Diuretic Therapy

Therapeutic

Diuretic therapy should be reserved for oliguria that persists despite optimization of intravascular volume, hemodynamic status and renal perfusion pressure \(^29\). Administration of diuretic agents to “make urine” or relieve edema in the face of intravascular hypovolemia or hypotension results exacerbates volume depletion and increases the risk of AKI.
**Prophylactic**
Diuretic agents induce renal cortical vasodilation (dopaminergic agents, loop diuretics), prevent tubular obstruction (osmotic, loop diuretics), suppress reflex vasoconstriction (dopaminergic agents, natriuretic peptides), and decrease tubular VO\(_2\) (dopaminergic agents, loop diuretics)\(^{30}\). Prophylactic mannitol is commonly used in aortic cross clamping, CPB, and pigment nephropathy (rhabdomyolysis, intravascular hemolysis, jaundice)\(^{31}\). However, there is little evidence that diuretic therapy is more effective in maintaining GFR than fluid volume loading alone\(^{32-34}\).

**Diuretic Resistance**
*Acute tolerance* or the “braking phenomenon” refers to diuretic tachyphylaxis that occurs with hypovolemia, or when repeated doses contract the ECF and activate Na retention; it is counteracted by fluid repletion\(^{35}\). Caveat: a diuretic agent or low dose dopamine is no substitute for rehydration!

*Chronic tolerance* refers to the situation that arises when long term administration of loop diuretics triggers compensatory hypertrophy of the distal tubule\(^{36}\).

Generalized edema refractory to diuretic therapy is encountered in acute and chronic kidney disease (CKD), renal insufficiency, CHF, cirrhosis and the nephrotic syndrome. The pharmacokinetic handling and pharmacodynamic effects of diuretics are markedly altered. In uremia, endogenous organic acids compete with loop diuretics for active transport sites at the proximal tubule\(^{37}\). Renal clearance of furosemide is inversely proportional to the BUN and GFR\(^{38}\). Depleted intravascular volume markedly increases proximal Na reabsorption, restricting Na available for diuretic action at the mTAL\(^{39}\).

**Strategies for Overcoming Diuretic Resistance**\(^{36,37}\)
1. Restore normal hemodynamics.
2. Administer higher doses of diuretic agent
3. Concomitant administration of human albumin\(^{40}\)
4. Continuous diuretic infusion (furosemide 1-10 mg/hr)\(^{41}\)
5. Dual segment nephron blockade (loop + thiazide)\(^{39}\)
Combination Diuretic Therapy (Loop + Thiazide)

<table>
<thead>
<tr>
<th>Loop Diuretic</th>
<th>Thiazide Diuretic</th>
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<tbody>
<tr>
<td>furosemide 20-40 mg IV</td>
<td>chlorothiazide 125-250 mg IV</td>
</tr>
<tr>
<td>bumetanide 1-5 mg IV</td>
<td>metolazone 2.5 mg PO bid</td>
</tr>
<tr>
<td>torsemide 10 mg IV</td>
<td></td>
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<tr>
<td>ethacrynic acid 25-50 mg IV</td>
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**Pharmacologic Interventions to Prevent and Reverse AKI**

**Mannitol**

Mannitol is an “inert” sugar that may provide renal prophylaxis by expanding the intravascular volume, which increases preload, cardiac output and atrial natriuretic peptide (ANP) release. It also induces an osmotic diuresis that may prevent tubular obstruction; releases intrarenal prostaglandins; and attenuates reperfusion injury by scavenging of free radicals. For the greatest effect mannitol should be present at the time of the renal insult. Mannitol’s benefit is well established in animal models of AKI but there are few human RCTs that confirm this.

**Loop diuretics**

Loop diuretics (furosemide, bumetanide, torsemide, ethacrynic acid) inhibit Na reabsorption at the mTAL, and can attenuate AKI if administered prior to a renal ischemic or nephrotoxic insult. However inappropriate diuresis to “make urine” or relieve anasarca may induce a severe prerenal syndrome and exacerbate nephrotoxic insults. High-dose (2-10 mg/kg) IV furosemide used to “convert” oliguric to non-oliguric AKI does not alter its outcome.

**Dopaminergic agonists**

Stimulation of DA_1 receptors causes renal vasodilation as well as inhibition of active Na transport in the proximal tubule, leading to natriuresis and diuresis. Stimulation of presynaptic DA_2 receptors inhibits NE release and promotes peripheral vasodilation but appears to attenuate the beneficial effects of DA_1 effectors on RBF.

**Dopamine**

Despite the lack of definitive evidence, “low dose” dopamine (0.5–3.0 µg/kg/min) has been widely used as a renal protective agent. However, plasma dopamine levels vary markedly (up to ten-fold) in different individuals, and it is likely that in many cases dopamine benefits the kidney by its beta-adrenergic actions (increased cardiac output, renal blood flow and perfusion pressure). There is little if any evidence that prophylactic administration of low dose dopamine has a positive impact on renal outcome. The use of low-dose dopamine is often limited by unpredictable tachycardia, supraventricular and ventricular arrhythmias, which likely reflects the inter-individual variability of plasma dopamine levels.

**Fenoldopam**

Fenoldopam is a phenol-dopamine analog that is a selective DA_1-receptor agonist, with relatively rapid onset and offset and an elimination half-life of 10 min. At infusion rates of 0.03-0.3 µg/kg/min it induces dose-dependent increases in RBF. In 1998 fenoldopam was approved in the US for the short-term parenteral treatment of hypertension, but there has been considerable interest in the use of low dose (< 0.05 mcg/kg/min) fenoldopam for renal protection. A meta-analysis of 16 studies representing 1290 ICU or perioperative patients concluded that fenoldopam consistently and significantly reduced the risk for AKI, need for dialysis, ICU length of stay and inhospital mortality. A meta-analysis that focused on cardiac surgery (6 studies, 440 patients) found a significant benefit on the risk of AKI only, and an increase in the need for vasopressor therapy. With regard to nephrotoxic AKI, a large study of prophylaxis in RCN showed no benefit, although a small retrospective one suggested amelioration of RCN when fenoldopam was directly infused into the renal arteries.
N-Acetylcysteine

N-Acetylcysteine (NAC) is an antioxidant long used as an antidote to acetaminophen toxicity. Initial studies indicated efficacy in the amelioration of RCN in high-risk patients undergoing contrast radiography, with decreased AKI and mortality in patients undergoing percutaneous coronary intervention. However, a recent large (2308 patients) prospective RCT could not confirm this benefit. NAC has not been shown to be effective in preventing AKI during cardiac surgery with CPB.

Sodium Bicarbonate

Through free radical scavenging, alkalinization of the urine (pH > 6.5) with sodium bicarbonate (NaHCO₃) or acetazolamide may theoretically ameliorate renal tubular injury. There are conflicting data on the protective effects of NaHCO₃ versus normal saline for protection against RCN. A large meta-analysis (12 trials, 1854 subjects) concluded that although hydration with NaHCO₃ decreases RCN by SCr criteria, it has no impact on the need for dialysis or in-hospital mortality. In an RCT on 100 patients, a 24-hr infusion of NaHCO₃ during high-risk cardiac surgery decreased the incidence of a >25% rise in postoperative SCr, without any other benefit. Clearly, large RCTs are needed to clarify the risk-benefit ratio of urinary alkalinization on the incidence and outcome of AKI.

Natriuretic Peptides

The natriuretic peptides (22-32 amino acids) oppose the sympathoadrenal, renin-angiotensin, aldosterone, and AVP systems, counteract the vasoconstrictor and anti-natriuretic responses induced by hypovolemia, and induce vasodilation and natriuresis that protect against hypervolemia and hypertension. Their vasodilator and renal effects are mediated by cyclic guanosine monophosphate (cGMP), which increases glomerular filtration fraction by afferent arteriolar vasodilation.

Atrial (A-type) natriuretic peptide (ANP) is synthesized by modified atrial myocytes and released by atrial stretch and increased CVP. Brain (B-type) natriuretic peptide (BNP) is synthesized in the cardiac right and left ventricles, and is released by ventricular dilation. Assay of BNP (and its precursor, N-terminal-pro-BNP) is used as an ER diagnostic tool for acute CHF, and BNP levels correlate with outcome in acute myocardial ischemia as well as heart failure. C-type natriuretic peptide (CNP) is synthesized in the endothelium of the great vessels. Urodilatin is a renal 22-amino acid peptide that has less vasodilator activity than ANP.

Anaritide

Anaritide is the human recombinant formulation of ANP. Parenteral administration decreases systemic BP by arterial and venodilation, increases GFR, induces natriuresis, and reverses renovascular hypertension. In animal models of ischemic or nephrotoxic ATN anaritide demonstrated great promise as a rescue agent. However a 504 patient RCT showed improved dialysis-free survival in oliguric (urine output < 400 mL/day) patients only, and outcome was actually worse in patients with non-oliguric ARF. A follow up study on 222 patients with oliguric ARF found no difference in renal outcome between anaritide and placebo. The lack of benefit of anaritide appears to be related to hypotension induced by its vasodilator effect, and attests to the importance of maintenance of renal perfusion pressure when renal autoregulation is impaired.

Nesiritide

Nesiritide is the human recombinant formulation of BNP, approved by the FDA for the parenteral treatment of patients with advanced decompensated CHF. In these patients it provides preload and afterload reduction, enhances cardiac function, and also can promote a sustained diuresis with improvement in pulmonary congestion, edema and anasarca. The major adverse effect is dose-related hypotension, which can impair renal function. However, in an RCT of 279 patients with impaired ventricular function (EF <40%) undergoing CPB for coronary revascularization or mitral valve surgery, patients who received low dose nesiritide had increased urine output, an attenuated postoperative increase in SCr, and improved survival six months after surgery.

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Vasopressor Therapy

Renal autoregulation maintains RBF and GFR over a wide range of renal arterial pressure. In certain situations, notably ATN itself, severe sepsis, and possibly during cardiopulmonary bypass, autoregulation appears to be lost or attenuated. Moreover, in these situations systolic BP may fall below the normal autoregulatory limit. Hypotension results in strikingly decreased RBF, which is restored by normalization of renal perfusion pressure - even if this is achieved by vasoconstrictor therapy.

Established Acute Renal Failure

In established acute renal failure (stage 3 AKI) there is an almost complete loss of renal autoregulation, so that hypotension during intermittent hemodialysis (HD) provides a repetitive ischemic insult to the kidney that delays or prevents renal recovery from ATN. In animal models of ischemic ATN, the renal vasculature develops a smooth muscle injury that renders it relatively unresponsive to the vasoconstrictor effect of NE. This suggests that during intermittent HD, BP should be supported with fluids or even pressor therapy, and that continuous venovenous hemodialysis (CVVHD), which provides greater hemodynamic stability, should be used in the ICU.

Vasodilatory Shock

In severe sepsis with vasodilatory shock, impaired autoregulation is implicated by the dramatic improvement in renal function that is observed when BP is normalized by the use of vasopressor therapy. This response has been observed with infusions of NE and low dose AVP. As well as restoring overall renal perfusion pressure, AVP preferentially constricts the efferent arteriole, thereby improving glomerular filtration pressure, filtration fraction and GFR.

REFERENCES


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