Learning Objectives:
1. Describe the epidemiology of perioperative renal dysfunction
2. Describe the predictors of perioperative renal dysfunction
3. Examine the evidence for interventions to prevent and treat perioperative renal dysfunction

Clinical Definitions of Acute Kidney Injury (AKI)
A primary impediment to establishing the role of interventions that provide renal protection are the myriad definitions of what is now called acute kidney injury (AKI). In 2000 a group of experts calling themselves the Acute Dialysis Quality Initiative (ADQI) met and defined AKI by the five RIFLE criteria (Risk, Injury, Failure, Loss, End-stage). The first 3 stages (RIF) were based upon the degree of increase in serum creatinine (SCr), decrease in estimated glomerular filtration rate (eGFR) or duration of oliguria; the second two (LE) on renal outcome. Subsequently, the group coalesced into the Acute Kidney Injury Network (AKIN) and simplified the definition into three functional stages, as well as acknowledging the potential adverse implications of even small increases in SCr (Table 1):

Table 1: AKIN Criteria for AKI

<table>
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<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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<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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Although both the RIFLE and AKIN definitions of AKI identify an increasing severity of insult and show good correlation with renal outcome, they do not offer any insight into the nature of the kidney injury itself. The latter is essential in developing appropriate interventions for renal protection. For this reason we need to consider potential mechanisms of perioperative AKI.

Renal Biomarkers
More than 50 biomarkers have been studied as indicators of renal injury. Cystatin C, a cysteine proteinase inhibitor, is released by all cells and completely filtered by the glomerulus. It has been suggested as a more stable indicator of GFR than SCr. The best studied biomarkers are proteins that are released by ischemic injury to the proximal tubule, and include neutrophil-gelatinase associated lipocalin (NGAL), interleukin-18 (IL-18), and kidney injury molecule-1 (KIM-1).

It is possible that a panel of biomarkers might be more predictive of AKI than any used alone. It is quite likely that in the near future the classification of AKI will be based on early detection of urinary biomarkers rather than delayed changes in SCr or urine flow. It is also conceivable that biomarkers may 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. Blood pressure (BP) invariably decreases during anesthesia, and urine flow declines accordingly; when BP returns to normal at emergence, so does urine flow.

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.

Mechanisms of Perioperative AKI:
Although the mechanisms below are presented separately, they all overlap and the pathogenesis of clinical AKI is invariably multifactorial.
Ischemia and Ischemia Reperfusion Injury

The normal renal response to hypovolemia or decreased renal blood flow (RBF) is enhanced tubular sodium (Na) and water reabsorption, the so-called prerenal syndrome. Urine Na is typically < 10 mEq/L and urine osmolality (Osm) is increased to 2-3 times serum Osm. These changes are readily reversible by restoring intravascular volume and RBF.

A more severe but transient decrease in RBF (e.g. cardiogenic or hemorrhagic shock; suprarenal cross-clamping; renal transplantation) provokes intense renal cortical constriction that results in injury to the proximal tubular (PT) epithelial cells, which slough and form obstructing casts. Even though RBF is usually quickly restored, tubular obstruction, backleak and glomerular feedback sustain low GFR. Tubular concentrating ability is lost so urine Na increases to > 80 mEq/L, and urine Osm equals serum Osm (isosthenuria).

This entity is called acute tubular necrosis (ATN), and is characterized by persistent low GFR in the face of normal RBF on renal ultrasound. Perioperative ATN is often ameliorated by renal protective interventions (fluids, vasodilators etc) and in about two-thirds of cases, urine output continues between 15-80 mL/hr (non-oliguric renal failure, NORF). Because the tubular infrastructure is preserved in ATN, if there are no ongoing insults the kidney can recover in 7-10 days.

A similar reversible injury can be caused by nephrotoxins, but the tubules of the renal medulla form the target zone. To facilitate the hypertonic milieu that provides urinary concentration, the medulla normally has very slow RBF and low tissue oxygen tension\(^\text{13}\). Nephrotoxins may cause direct tubular injury or further decrease RBF by inhibiting endogenous vasodilators such as nitric oxide or prostacyclin.

Endogenous nephrotoxicity usually involves heme compounds (bilirubin, myoglobin, RBC stroma) resulting in so-called pigment nephropathy. Exogenous nephrotoxins include aminoglycosides, calcineurin inhibitors (cyclosporine A, tacrolimus), amphotericin, radiocontrast dyes, non-steroidal anti-inflammatory drugs (ketorolac) etc. The risk of nephrotoxic injury increases exponentially with the number of nephrotoxic insults and risk cofactors (e.g. hypovolemia, CHF, diabetes, age), and it is quite common for ischemic and nephrotoxic insults to co-exist and exacerbate each other\(^\text{13}\).

A sustained ischemic insult may ultimately result in full thickness cortical necrosis, which, if bilateral, results in irreversible loss of renal function (end stage renal disease, ESRD). It is characterized by uniform absence of RBF on renal ultrasound.

Vasomotor Nephropathy

This refers to an entity encountered in sepsis and liver failure, where RBF is markedly decreased despite increased total cardiac output. It is caused in part by circulating endotoxin which results in disordered renal circulation as well as direct endothelial injury, and a prerenal picture (low urine sodium). However, fluid administration alone is usually not helpful and the condition resolves only when the underlying cause is resolved (e.g. removal of an abscess, liver transplantation).

Vascular Injury and Elevated Renal Vein Pressure

Renal arterial vascular injury is usually caused by atherosclerotic embolism or thrombosis, and may result in patchy or complete cortical necrosis, identified by partially or completely absent RBF on renal ultrasound. Renal vein thrombosis is equally devastating.

Elevated renal venous pressure occurs in abdominal compartment syndrome, when intra-abdominal pressure (IAP) is increased to >20 mmHg due to hemorrhage or severe edema. Oliguria in the face of high IAP may be reversible only by surgically decompressing the abdomen.

Acute on Chronic Renal Failure

Patients with chronic kidney disease (CKD) may develop superimposed AKI with relatively minor hemodynamic instability. The risk of postoperative AKI (and mortality) increases exponentially with the severity of CKD from grade 3 to 4 to 5 (eGFR 30-59, 15-29 and < 15 mL/min/1.73m\(^2\) respectively\(^\text{14, 15}\).

Systemic diseases (e.g. scleroderma, SLE) that involve occult or quiescent CKD may flare as a consequence of surgical stress or trauma.
Principles of Perioperative Renal Protection
1. Preserve intravascular volume and cardiac output. About 25% of total cardiac output goes to the kidneys; thus, RBF is very dependent on cardiac output. The best way to preserve cardiac output is to preserve intravascular volume.
2. Maintain renal perfusion pressure, especially in states where autoregulation is lost.
3. Maintain high tubular flow, especially in pigment nephropathy.
4. Enhance tubular oxygen balance by inhibiting the ATP-dependent sodium-chloride transport system using diuretic agents.

Pharmacologic Renal Protection
Numerous agents have demonstrated renoprotection in animal studies that has not translated into the clinical arena. Most agents provide incremental rather than definitive protection, and there have been few if any multimodal studies. The timing of the intervention is also crucial – the later the intervention is delivered, the more established, and more difficult to reverse, is the AKI. Finally, any benefit from pharmacologic prophylaxis depends on maintenance of intravascular volume and renal blood flow. No pharmacologic agent should replace simple rehydration!

Agents that have demonstrated renal protective properties include:
1. Diuretic agents, which increase tubular flow: mannitol (osmotic diuresis), furosemide (loop diuresis)
2. Dopaminergic agonists, which increase RBF and inhibit sodium reabsorption: dopamine, fenoldopam
3. Calcium channel blockers, which cause renal vasodilation and decrease nephrotoxic injury: diltiazem, nitrendipine
4. Natriuretic peptides, which cause renal vasodilation and oppose the renin-angiotensin-aldosterone axis: ANP (anaritide), BNP (nesiritide), urodilatin
5. Free radical scavengers, such as N-acetylcysteine (NAC).
6. Urinary alkalizing agents, such as sodium bicarbonate

Of all of the above agents, only fenoldopam and nesiritide have undergone favorable meta-analysis. Low dose dopamine predictably increases urine flow but does not affect renal outcome. NAC appears to have favorable effects in radiocontrast nephropathy (RCN) only. A small pilot study of urinary alkalization with sodium bicarbonate is promising, but judgment awaits the findings from a large RCT in progress.

References