Prevention and Management of Acute Renal Failure in the ICU Patients

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Acute kidney injury

- Acute kidney injury (AKI) has now replaced the term acute renal failure and an universal definition and staging system . (Bellomoet ,2004)
- The prevalence of AKI from US data ranges from 1% (community-acquired) up to 7.1% (hospitalacquired) of all hospital admissions.(Nash,2002)
- An estimated 5–20% of critically ill patients experience an episode of AKI during the course of their illness and AKI receiving RRT has been reported in 49% of all admissions to ICU. (Metnitz,2002)
- Patients who present with uncomplicated AKI, have a mortality rate of 10%.
- Patients presenting with AKI and multiorgan failure have been reported to have mortality rates of over 50%.
- If renal replacement therapy is required the mortality rate rises further to as high as 80% (Liano, 1998)
- Acute renal failure is a frequent complication in critically ill patients and carries a mortality of 50 to 70%. (Schrier,2004)

- Acute kidney injury is defined when one of the following criteria is met.

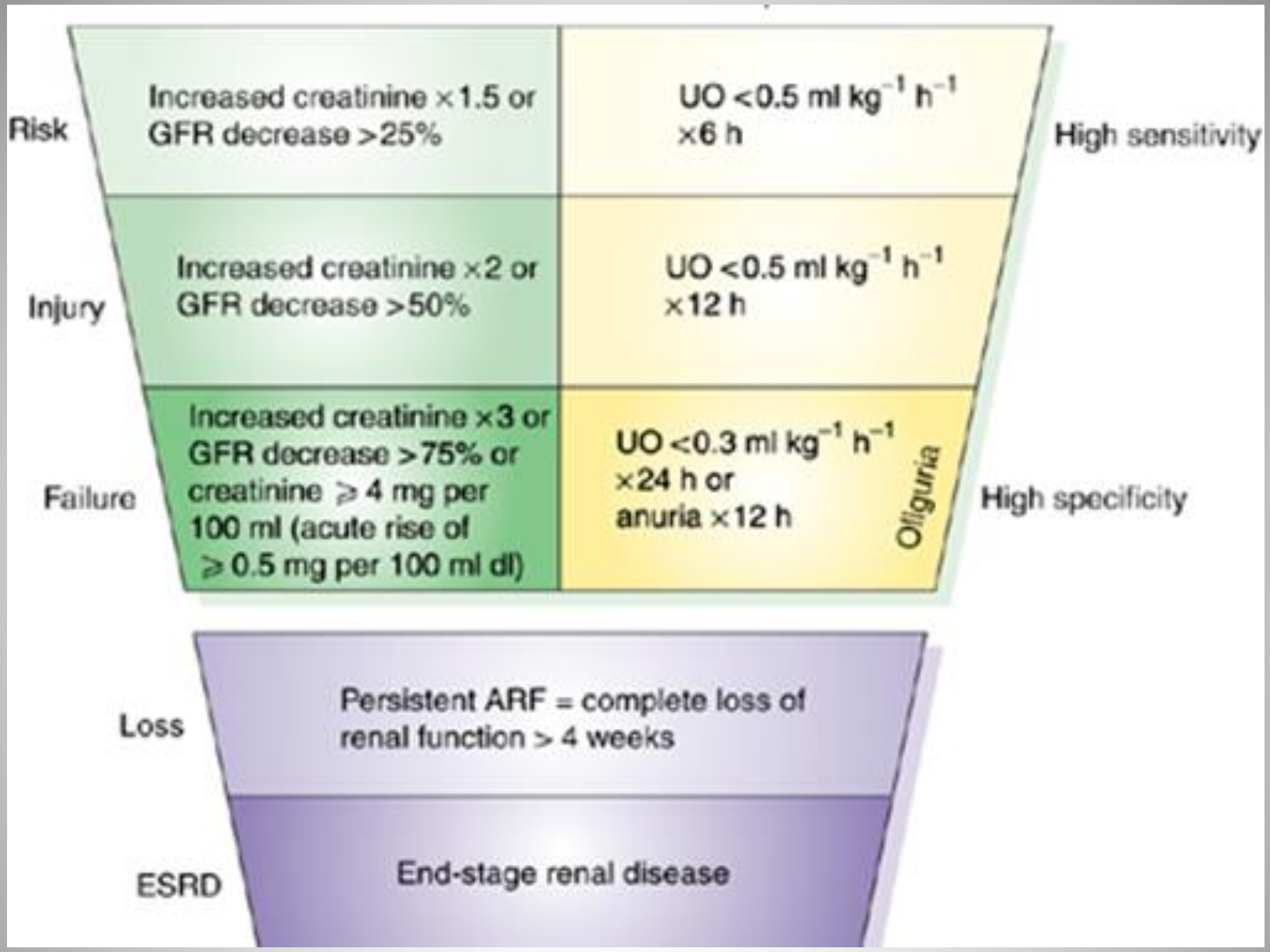
- Serum creatinine rises by 526 mmol/L within 48 hours or

- Serum creatinine rises51.5 fold from the reference value, which is known or presumed to have occurred within one week or

- Urine output is <0.5 ml/kg/hr for >6 consecutive hours

The reference serum creatinine should be the lowest creatinine value recorded within 3 months of the event

- In acute renal injury, the rise in serum creatinine used to define organ failure is delayed approximately 24–48 hours from the insult.



The RIFLE classification separates criteria for serum creatinine and urine output (UO).GFR, glomerular filtration rate; ARF, acute renal failure.

Bellomo *et al. Crit Care* 2004; **8**: R204–R212.

Staging classification of acute kidney injury (AKI)

Stage	Serum creatinine (SCr) criteria	Urine output criteria
1	Increase 526 mmol/L within 48 hrs or Increase 51.5 to 1.9 X reference SCr	<0.5 mL/kg/hr for >6 consecutive hrs
2	increase 52 to 2.9 X reference SCr	<0.5 mL/kg/hr for >12 hrs
3	increase 53 X reference SCr or increase 5354 mmol/L or commenced on renal replacement therapy (RRT) irrespective of stage	<0.3 mL/kg/hr for >24 hrs or anuria for 12 hrs

New markers of AKI

- Cystatin-C is a 13 kD endogenous cysteine-proteinase inhibitor has been shown to rise earlier than creatinine in ICU patients with AKI
- Urinary neutrophil gelatinase (NGAL)
- kidney injury molecule-1
- interleukin-18 are urinary markers that are being evaluated.

Common causes of AKI in the ICU

- Sepsis
- Major surgery
- Low cardiac output
- Hypovolemia / renal hypoperfusion
- Medications.
- Trauma
- Hepatorenal syndrome
- Cardiopulmonary bypass,
- Abdominal compartment syndrome
- Rhabdomyolysis
- Urinary flow obstruction.

Risk factors for developing AKI

- Age >75 yrs
- Chronic kidney disease (CKD, eGFR <60 mls/min/ 1.73m2)
- Cardiac failure
- Sepsis
- Atherosclerotic peripheral vascular disease
- Liver disease
- Diabetes mellitus
- Nephrotoxic medication
- Hypovolaemia

Renal Oxygenation

- Renal oxygenation is the relationship between renal oxygen delivery (DO_2) and renal oxygen consumption (VO_2) and it can easily be shown that the inverse of this relationship is equivalent to renal extraction of O_2 (O_2Ex).

- Renal O_2Ex in the non-failing kidney is therefore low, 10%, compared with, e.g., the heart, in which O_2E_X is 55% .

- Tubular sodium reabsorption is the major determinant of renal VO_2 ,80% is used to drive active tubular transport of particularly sodium, but also glucose, amino acids and other solutes.

- There is a close linear correlation between glomerular filtration rate (GFR), renal sodium reabsorption and renal VO_2.

Renal and myocardial oxygen/demand supply relationship in postoperative mechanically ventilated patients		
	Kidney	Heart
Oxygen consumption (ml/min)	10	15
Blood flow (ml/min)	750	250
Oxygen extraction (%)	10	55
Ricksten et al. Critical Care 2013		

Renal Oxygenation (Cont.)

- The relatively high renal blood flow is directed preferentially to the cortex to optimize the filtration process and solute reabsorption.

- Blood flow in the outer medulla is less than 50% of the cortical blood flow to preserve osmotic gradients and to enhance urinary concentration .
- The combination of low medullary perfusion, high oxygen consumption of the medullary thick ascending limbs (mTAL) and the countercurrent exchange of oxygen within the vasa recta, results in a poorly oxygenated outer medulla.
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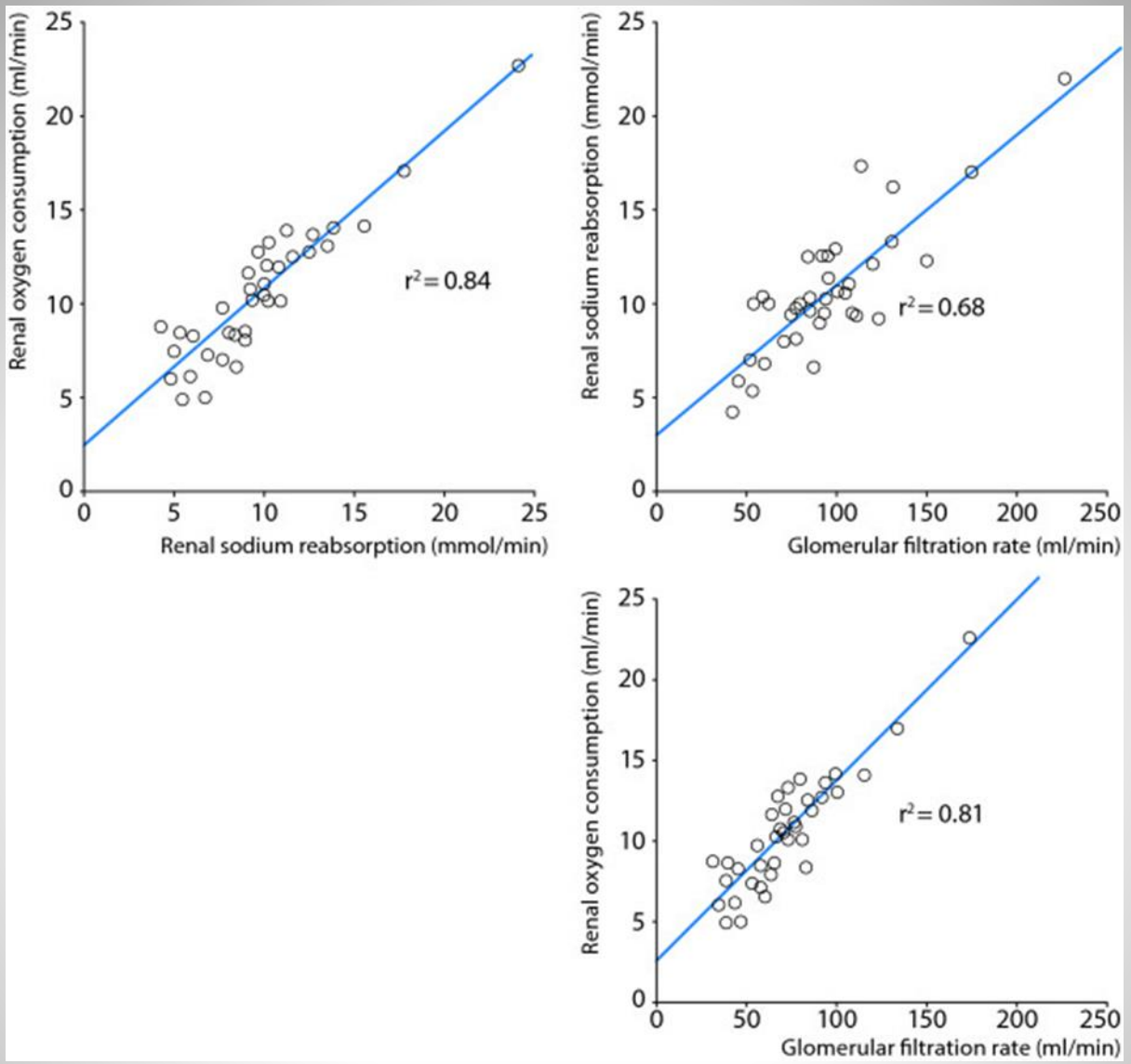
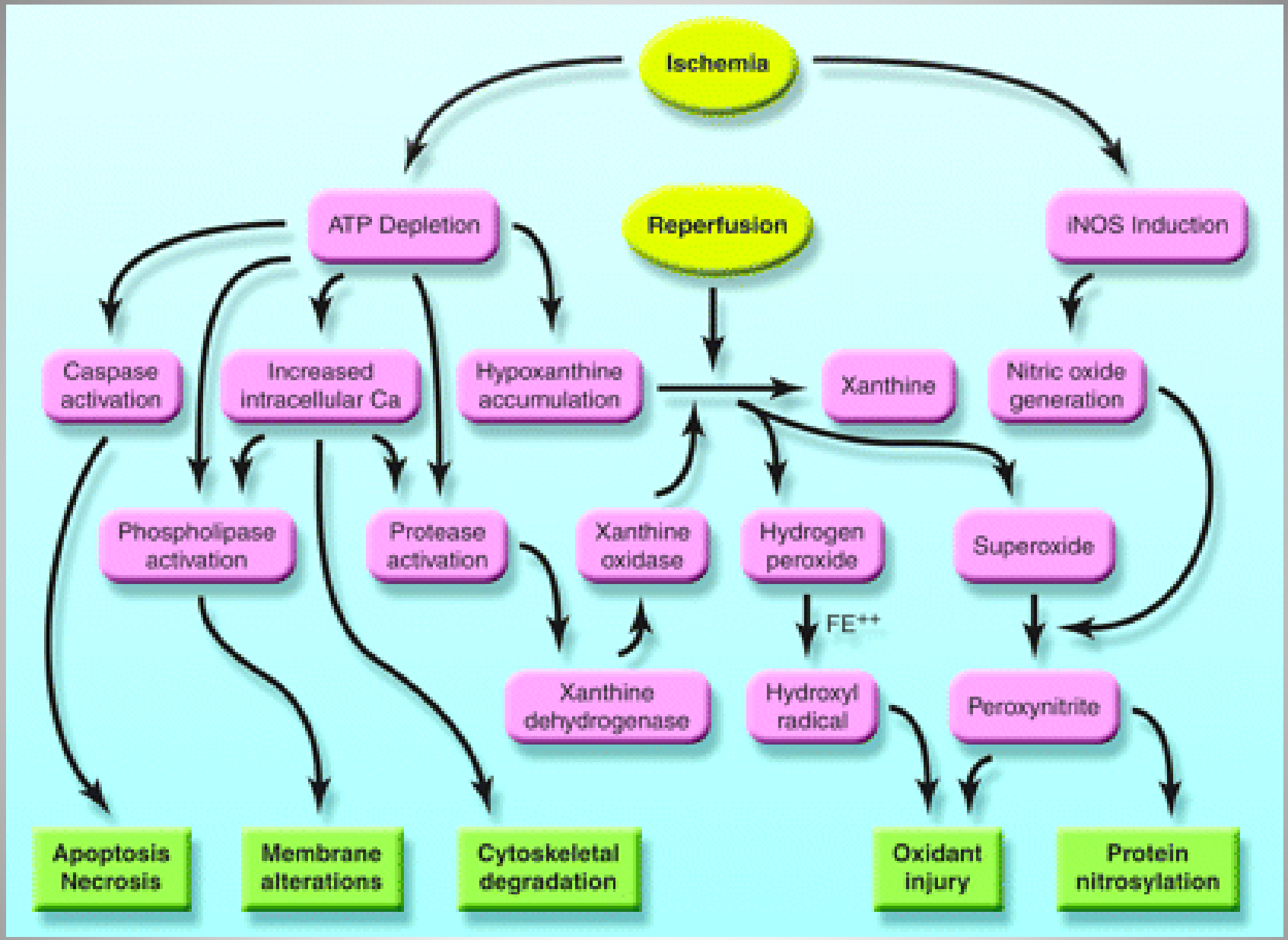
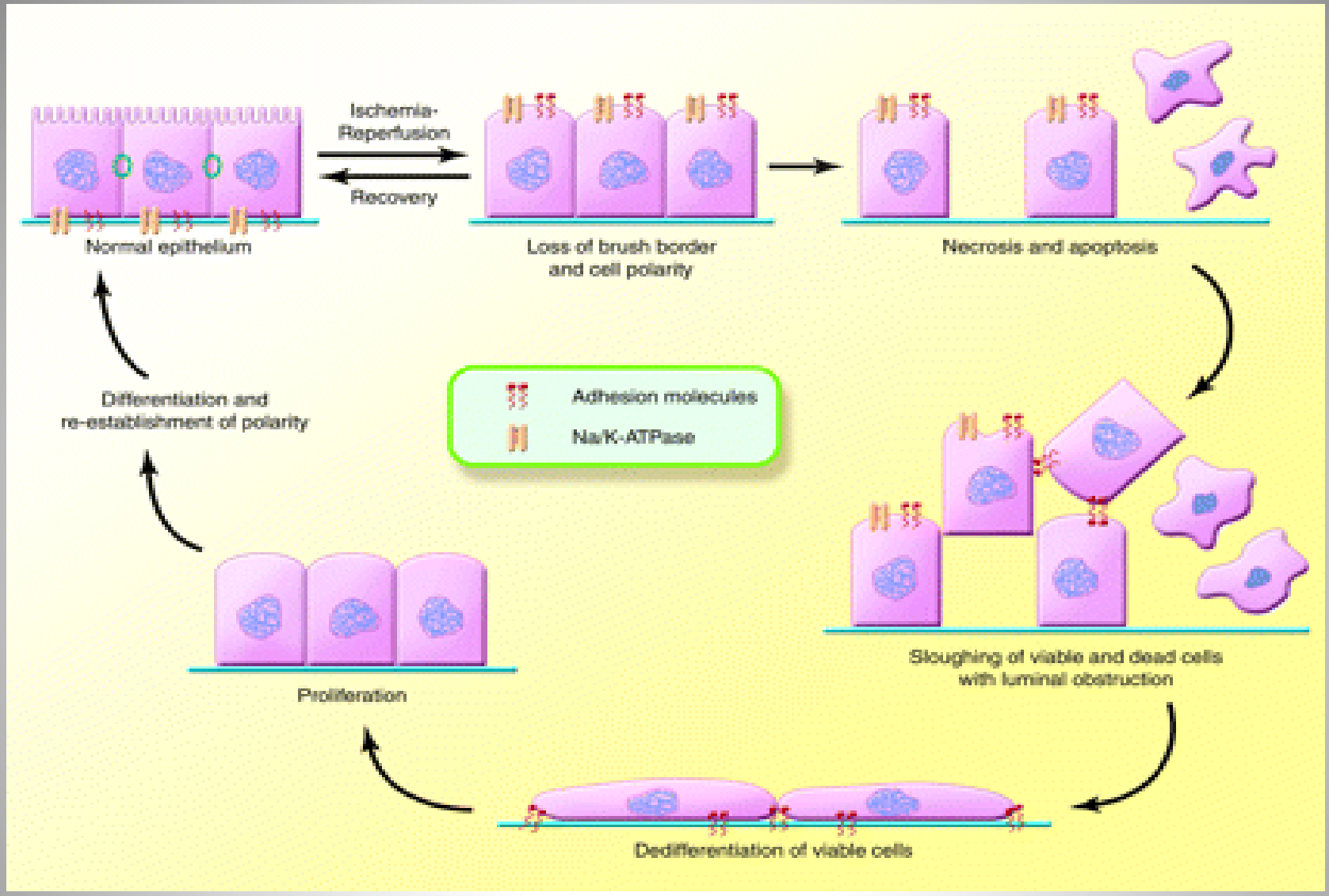
- Oxygen availability is, therefore, low in the outer medulla, which has an oxygen tissue partial pressure (PO_2) of 10-20 mm Hg compared to 50 mm Hg in the cortex.



- **The close relationships between renal sodium reabsorption, renal oxygen consumption and glomerular filtration rate in postoperative patients (n = 37) undergoing uncomplicated cardiac surgery**.
- Ricksten *et al. Critical Care* 2013

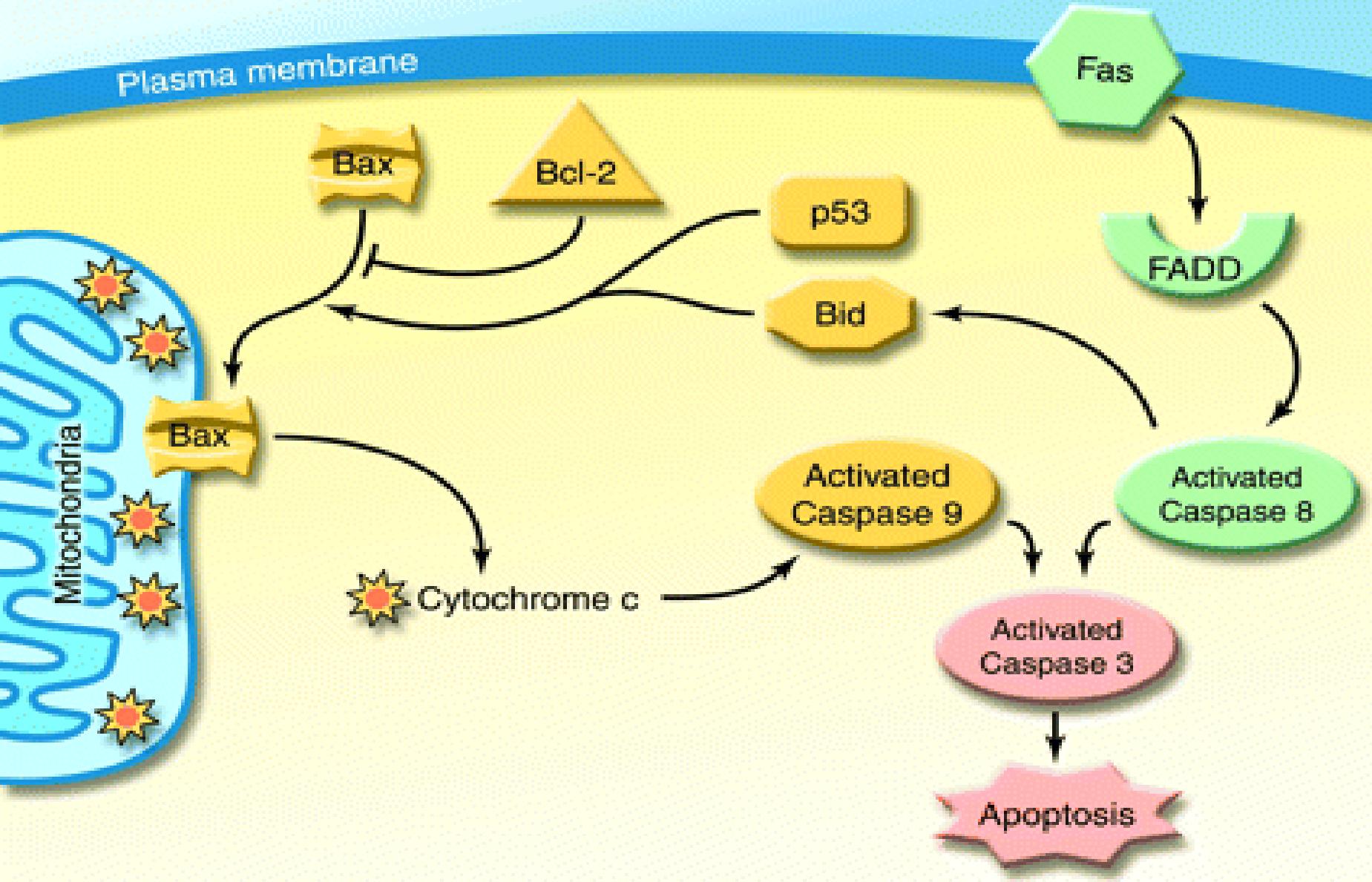


Alterations in tubule cell metabolism after ischemic acute kidney injury (AKI). Illustration by Josh Gramling—Gramling Medical Illustration



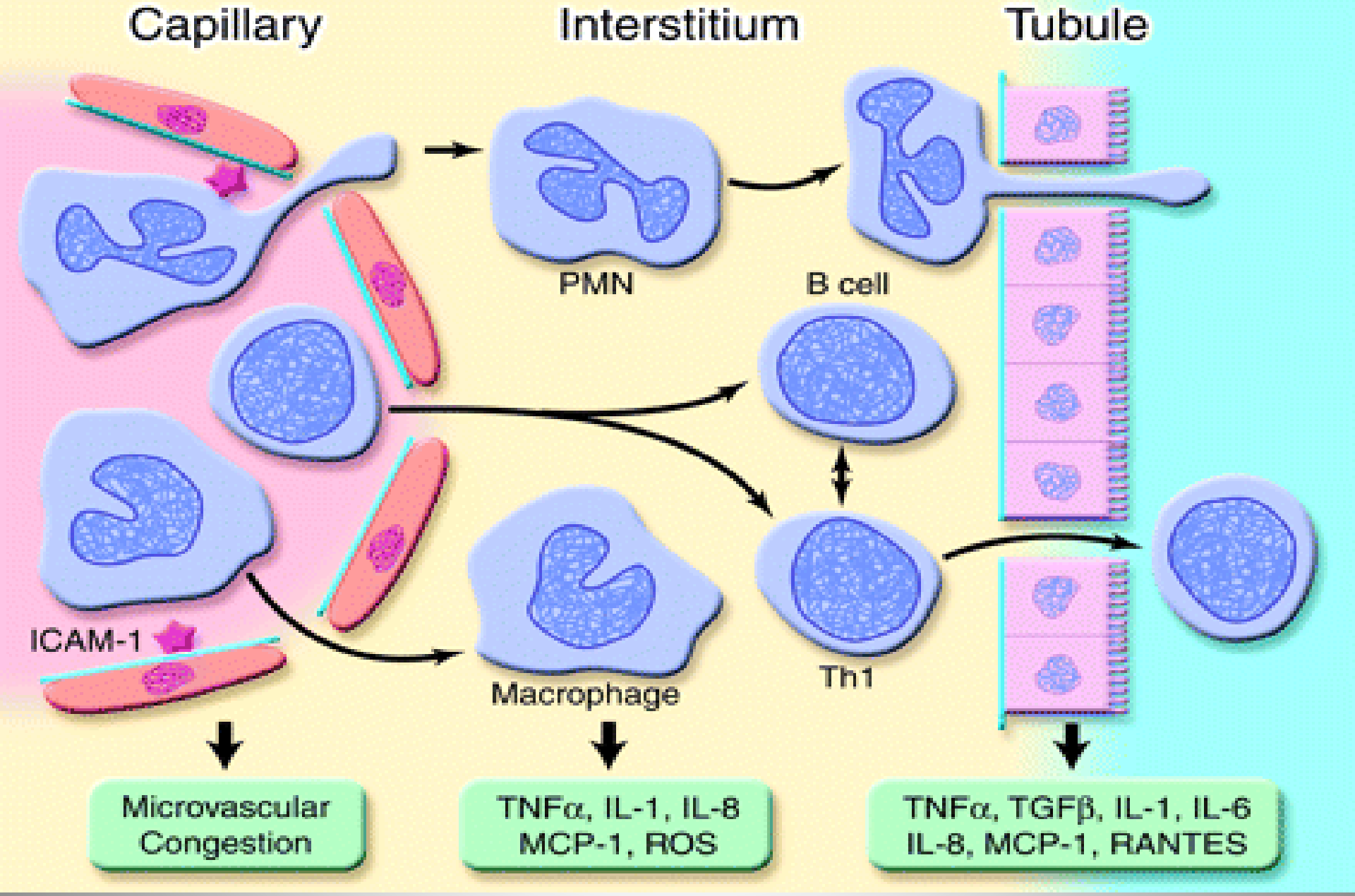
Alterations in tubule cell structure after ischemic AKI.

Illustration by Josh Gramling—Gramling Medical Illustration



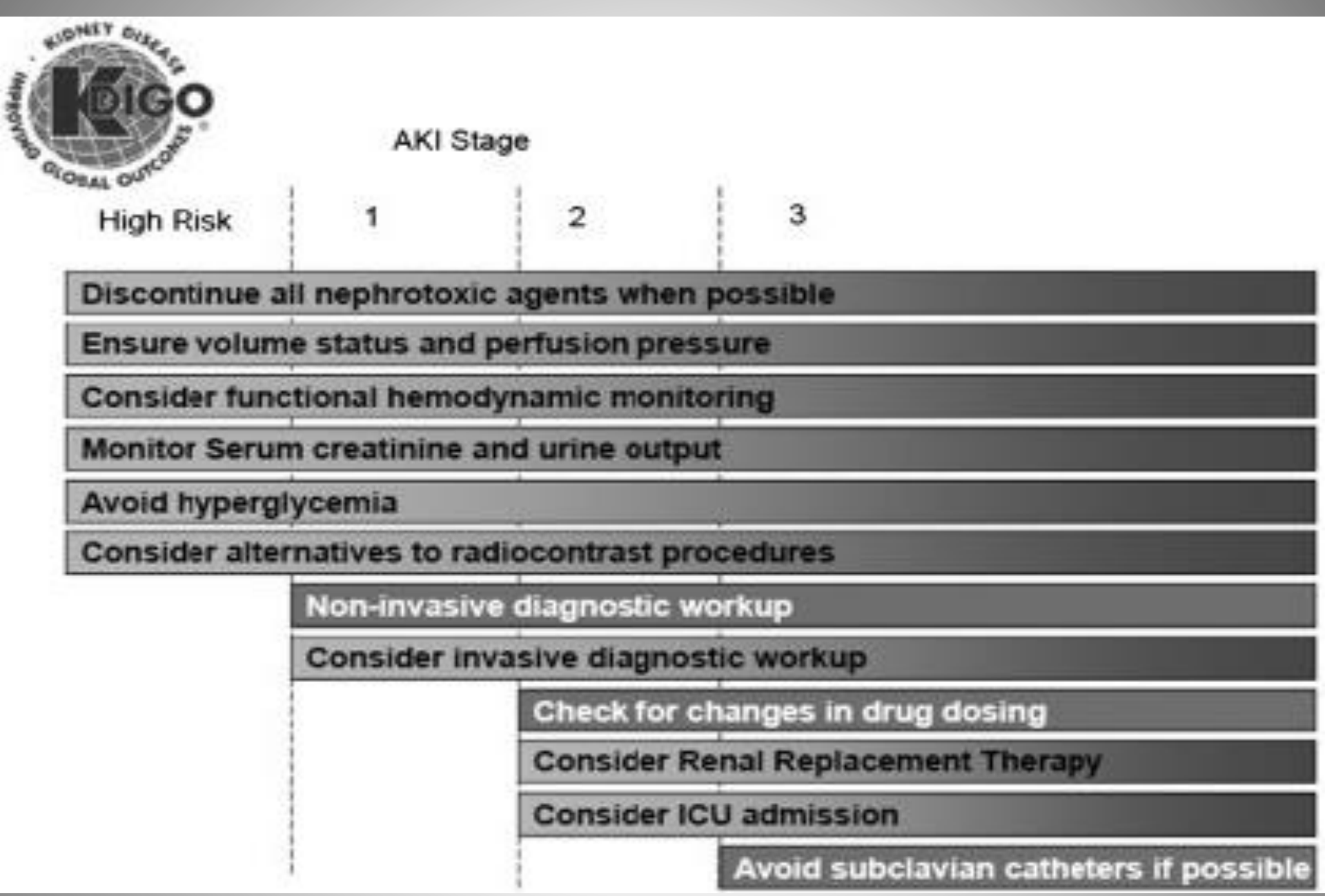
Major apoptotic pathways in human ischemic AKI.

Illustration by Josh Gramling—Gramling Medical Illustration



Alterations in the microvasculature and inflammation in ischemic AKI.

Illustration by Josh Gramling—Gramling Medical Illustration



Stage-based management of acute kidney injury. Shading of boxes indicates priority of action: solid shading, actions that are equally appropriate at all stages; graded shading, increasing priority as intensity increases. AKI, acute kidney injury.

Kellum *et al. Critical Care* 2013

I.V. Fluids

- Both relative and overt hypovolemia are significant risk factors for the development of AKI.
- Fluid resuscitation is widely believed to be protective.
- Large multi-center studies have also shown that a positive fluid balance is associated with :

  Increased 60-day mortality .

  Prolonged Mechanical Ventilation.

  Development of intra-abdominal hypertension.

Bouchard **et al.***Kidney Int* 2009

- Results of the ***Fluids and Catheters Treatment Trial (FACTT)*** suggest that, in selected patients with acute lung injury, conservative fluid management may not be detrimental to kidney function. Mean fluid balance over 7 days was 2136 ml in the conservative group versus 16,992 ml in the liberal fluid strategy group. In addition, compared with the liberal strategy, the conservative strategy increased the number of ventilator-free days, reduced the number of ICU days, and had similar 60-day mortality.
- These benefits were not associated with an increase in the frequency of RRT, which occurred in 10% of the conservative-strategy group and 14% of the liberal-strategy group, despite slightly.
- Wiedemann et al.2006N Engl J Med 2006;354:2564–2575.

- Specific groups of patients may benefit from fluid administration to prevent AKI—even if renal hypoperfusion is not its prevailing mechanism.
- These specific conditions include :

Myoglobinuria

Surgery

The use of nephrotoxic drugs such as

Amphotericin B

Platinum

Contrast media

The use of drugs associated with tubular precipitation of crystals such as:

Acyclovir

Sulphonamides

Methotrexate

Should We Use Crystalloids or Colloids for Fluid Resuscitation?

- Crystalloids distribute to the whole extracellular space, and only a portion remains in the blood- stream.
- This increases the risk for tissue edema.
- Hyperchloremic acidosis has been reported causing renal vasoconstriction as well as altered perfusion of other organs such as the gut. Wilkes et al.2001, Aesth.Analg.
- A recent Cochrane review concluded that there is no evidence that resuscitation with colloids, instead of crystalloids, reduces the risk of death in patients with trauma, burns, or following surgery .Perel et al. 2007, *Syst Rev*

- (**SAFE**) Study, nearly 7,000 patients who were critically ill were fluid resuscitated with either 4% albumin or 0.9% saline. No differences between the groups in the percentage of patients who required RRT ,number of days of RRT and in the number of days of mechanical ventilation.

  Finfer et al. *N Engl J Med* 2004

- Schortgen et al 2008, in multicenter international investigation found thatfluid resuscitation with crystalloids or gelatin was associated with a lower incidence of AKI than resuscitation with artificial hyperoncotic colloids (dextran in 3% of patients and starches in 98% of patients) (adjusted odds ratio, 2.48) or hyperoncotic albumin (adjusted odds ratio, 5.99); the incidence of renal adverse events was similar in patients resuscitated using modern starches (i.e., 130 kD/0.4) or older starches.

- ***VISEP*** study of more than 500 patients with severe sepsis, fluid resuscitation with hyperosmotic colloids (hydroxyethylstarch 200 kD/0.5) was associated with higher incidence of renal dysfunction and need for RRT than in patients resuscitated with crystalloids.

  Brunkhorst et al.. N Engl J Med 2008;358:125–139.

I.V. Fluids(cont.)

- A recent meta-analysis described 11 randomized trials with a total of 1,220 patients: seven trials evaluating hyperoncotic albumin and four trials evaluating hyperoncotic starch .
- Hyperoncotic albumin decreased the odds of AKI by 76% while hyperoncotic starch increased those odds by 92%. Parallel effects on mortality were observed.
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- The renal effects of hyperoncotic colloid solutions appeared to be colloid specific, with albumin displaying renoprotection and hyperoncotic starch showing nephrotoxicity.

- CRYSTAL trial
- Patients with severe sepsis assigned to fluid resuscitation with HES 130/0.42 had an increased risk of death at day 90 and were more likely to require renal replacement therapy compared with those receiving Ringer's acetate. At 90 days after randomization, 201 of 398 patients (51%) assigned to HES 130/0.42 had died, as compared with 172 of 400 patients (43%) assigned to Ringer's acetate;. In the 90-day period, 87 patients (22%) assigned to HES 130/0.42 were treated with renal replacement therapy versus 65 patients (16%) assigned to Ringer's acetate and 38 patients (10%) and 25 patients (6%), respectively, had severe bleeding .

Estrada et al, *Critical Care* 2013, **17**:310

Vasopressors and Inotropes

- In case of vasoplegic hypotension as a result of sepsis or SIRS vasopressors along with fluid resuscitation need to be considered.
- Du¨nser et al,2009 indicated that any MAP of 60 mmHg may be onsidered adequate for patients with septic shock.
- Bourgoin et al, 2005 showed that additional benefits with regards to renal function were not observed when a target MAP of more than 85 mmHg was compared to a target of 65 mmHg.
- Restoration of MAP from 60 to 75 mm Hg improves renal DO2, GFR and renal oxygenation in patients with vasodilatory shock and AKI. The pressure-dependent renal perfusion, filtration and oxygenation at levels of MAP below 75 mm Hg reflect a more or less exhausted renal autoregulatory reserve.

Redfors B et al, *Intensive Care Med* 2011, 37:60–67.

Vasopressors

- A study comparing Dopamine with Norepinephrine as the initial vasopressor in patients with shock showed no significant differences between groups with regard to renal function or mortality. However, there were more arrhythmic events among the patients treated with dopamine.

  De Backer D et al, *N Engl J Med* 2010, **362:**779-789.

- Compared with Norepinephrine, Vasopressin increases blood pressure and enhances diuresis, but has not been proven to enhance survival or to reduce the need for RRT .Although there is some suggestion that vasopressin may reduce progression to renal failure and mortality in patients with septic shock.

  Gordon AC et al,*Intensive Care Med* 2010, **36:**83-91

Vasodilators

- It has also been speculated that a Dopamine-induced inhibition of proximal tubular Na+ reabsorption may increase delivery of Na+ to potentially ischemic distal tubular cells in the medulla, which would increase their oxygen demand.

  Bellomo R. *J Intensive Care Med* 2005, 20:199–211.

- Redfors et al. 2010, showed that low-dose dopamine induced a 45–55 % increase in renal blood flow. GFR was not significantly affected by dopamine , renal VO2 was not affected and, consequently, renal oxygenation was improved.

- Dopamine can trigger tachyarrhythmias and myocardial ischemia, decrease intestinal blood flow, cause hypopituitarism, and suppress T-cell function.

- **Fenoldopam** reduces the need for RRT and in-hospital death in cardiovascular surgery patients as concluded by Landoni et al. 2008.

Vasodilators (cont.)

- ANP : a pooled analysis of studies that examined oliguric AKI did not show any significant benefit from ANP for RRT requirement or mortality.

  Nigwekar et al.. *Clin J Am Soc Nephrol* 2009, 4:261-272.

- Nesiritide (b-type natriuretic peptide) is the latest natriuretic peptide introduced for clinical use. Sackner-Bernstein and colleagues ,2005,analyzed mortality data from 12 randomized trials; three trials provided 30-day mortality data, and found a trend towards an increased risk of death in nesiritide-treated subjects.
- Rolofylline ,adenosine antagonism ,as compared with placebo,did not provide a benefit with respect to the three primary end-points. Massie *N Engl J Med* 2010, **363:**1419-1428 .

Diuretics

- **Furosemide** :No significant reduction was found for in-hospital mortality or for RRT requirement. It may be useful in achieving fluid balance to facilitate mechanical ventilation according to the lung-protective ventilation strategy in hemodynamically stable patients with acute lung injury.

- In ischemic-induced AKI there is a diversion of oxygen consumption from Na^+ reabsorption to other oxygen-consuming pathways due to

  1) higher production of reactive oxygen species by infiltrative immune cells.

  2) high level of NO, which regulates the renal oxygen consumption.

- This may partially explain why strategies designed to inhibit renal oxygen consumption (e.g., loops diuretics) have failed to improve the prognosis of patients suffering from AKI.

- Mannitol administered just before clamp release, during renal transplantation reduces the incidence of post-transplant AKI, as indicated by a lower requirement of post-transplant dialysis.

- Mannitol may be beneficial in rhabdomyolysis by stimulating osmotic diuresis and by lowering the intracompartmental pressure in the affected crushed limbs.

Avoiding nephrotoxins

- Aminoglycosides exhibit a major dose-limiting toxicity leading to drug-induced AKI
- The risk of AKI attributable to aminoglycosides is sufficiently high (up to 25% in some series).
- Once-daily dosing strategies generally result in less AKI when compared with multiple-dose dosing strategies,
- Aminoglycoside aerosol delivery systems are now in use to provide high intrapulmonary antibiotic levels with minimal systemic and kidney concentrations of the antibiotic.
- Significant nephrotoxicity with the use of inhaled tobramycin has been described

- Lipid formulations of amphotericin B have versus conventional amphotericin B as the lipid formulations are less nephrotoxic than amphotericin B deoxycholate

- Alternatively it may be best to avoid polyene antifungal agents entirely and use alternative agents, such as the azoles and echinocandins .

Insulin and blood sugar

- Pooled analyses of early multicenter studies have failed to confirm the early observations of beneficial effects of intensive insulin therapy on renal function.
- the risk of hypoglycemia with this approach is significant, and the survival benefits of intensive insulin therapy are in doubt
- The international Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation study found a 90-day mortality of 27.5% in the intensive insulin therapy group (target blood glucose range 81 to 108 mg/dl (4.5 to 6.0 mmol/l)) and a 90-day mortality of 24.9% in the conventional glucose control (target ≤180 mg/dl (≤10.0 mmol/l)) (OR for intensive control = 1.14; 95% CI = 1.02 to 1.28; *P* = 0.02)
- There was no significant difference between the two treatment groups in incidence of new RRT (15.4% vs. 14.5%).

Hormonal Manipulation

- **Thyroxine** has no effect on any measure of AKI severity compared with placebo was found .

- **Corticosteroids** for renal protection failed to demonstrate any effect of dexamethasone on the transient renal impairment observed in the post-operative period .

- **Erythropoietin :**A retrospective cohort study in 187 critically ill patients requiring RRT used a propensity-adjusted analysis and found an improvement in renal recovery in patients administered EPO .
- Erythropoietin may reduce kidney dysfunction by
  - Decreases apoptosis
  - Reduce the expression of proinflammatory mediators
  - Activates endothelial nitric oxide synthase
  - Stimulates of endothelial progenitor cell
  - Stimulates vascular repair and by mobilizing endothelial progenitor cells and increasing tubular cell proliferation

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