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Paradigms of acute kidney injury in the intensive care setting

Acute kidney injury (AKI) is not a single disease but a loose collection of syndromes characterized by an abrupt decrease in glomerular filtration rate

- Broad classifications of AKI — according to the dominant aetiology (such as sepsis or nephrotoxicity) as opposed to pseudo-anatomical categories (for example, prerenal or intrarenal) — demonstrate more consistent relationships with pathophysiology and can improve therapeutic approaches
- Broad aetiology-based classification may still be insufficient, as heterogeneity could exist at the molecular level.

Epidemiology. Acute kidney injury (AKI) is estimated to affect 2–3 people per 1,000 individuals in the USA.

However, this approximation is likely to be an underestimate owing to the silent nature of AKI: the incidence could be as high as 15 in 1,000 adults per year in the UK. Moreover, older individuals are disproportionately affected by AKI: the rate of AKI in 2011 among US Medicare patients aged 66–69 years was 14.9 per 1,000 individuals, increasing with age to 18.8 per 1,000 individuals aged 70–74, 26.4 per 1,000 individuals aged 75–79, 35.9 per 1,000 individuals aged 80–84, and 49.6 per 1,000 individuals aged ≥85 .

The consequences of AKI are no less substantial in older individuals. The relative risk of death attributable to AKI is similar across age groups, despite lower overall survival and lower odds of renal function recovery among older individuals.

AKI IN ICU:

- SEPSIS-ASSOCIATED AKI
- SURGERY-ASSOCIATED AKI
- AKI ASSOCIATED WITH RENAL HYPOPERFUSION
- NEPHROTOXIC AKI

Sepsis-associated AKI

Epidemiology. Similar to AKI, sepsis is a disease of elderly individuals and is substantially associated with risk of death in the hospital. Globally, sepsis is found in almost 50% of patients with severe AKI in the ICU.

Pathophysiology.

Sepsis is characterized by a systemic inflammatory response to infection.

Post-mortem studies of patients with septic AKI revealed:

Heterogeneous tubular cellular injury with apical cellular vacuolization but without the characteristic features of extensive tubular apoptosis or necrosis found in severe ischaemic injury.

Sepsis is characterized by systemic vasodilation, profound alterations in the macrocirculation and microcirculation with heterogeneity of regional blood flow distribution.

Renal circulation participates in the systemic vasodilatation of sepsis, but despite an increase in renal blood flow (RBF), oliguria occurs and AKI develops within hours. This dissociation between GFR and RBF can be explained by alterations in the balance of efferent and afferent glomerular arteriolar tone and decreased renal perfusion pressure.

For scenarios in which RBF does decrease during sepsis, this change may be a consequence of AKI rather than a cause. These haemodynamic changes were preceded by substantial increases in plasma pro-inflammatory cytokines (such as IL-6 and tumour necrosis factor (TNF)

Similarly, in clinical sepsis, these early haemodynamic changes with increased cardiac output and vasodilation are likely to be accompanied by endothelial and renal tubular cell inflammatory injuries that consequently induce glomerular hypofiltration, which becomes refractory to global haemodynamic manipulation.

Many mechanisms by which septic AKI causes renal tubular injury have been proposed, including ultrafiltration of circulating microbial toxins and the release of inflammatory mediators that trigger tubular cell stress and injury. Circulating toxins might act on the endothelium, which triggers reduced microcirculatory flow and interstitial infiltration of inflammatory cells.

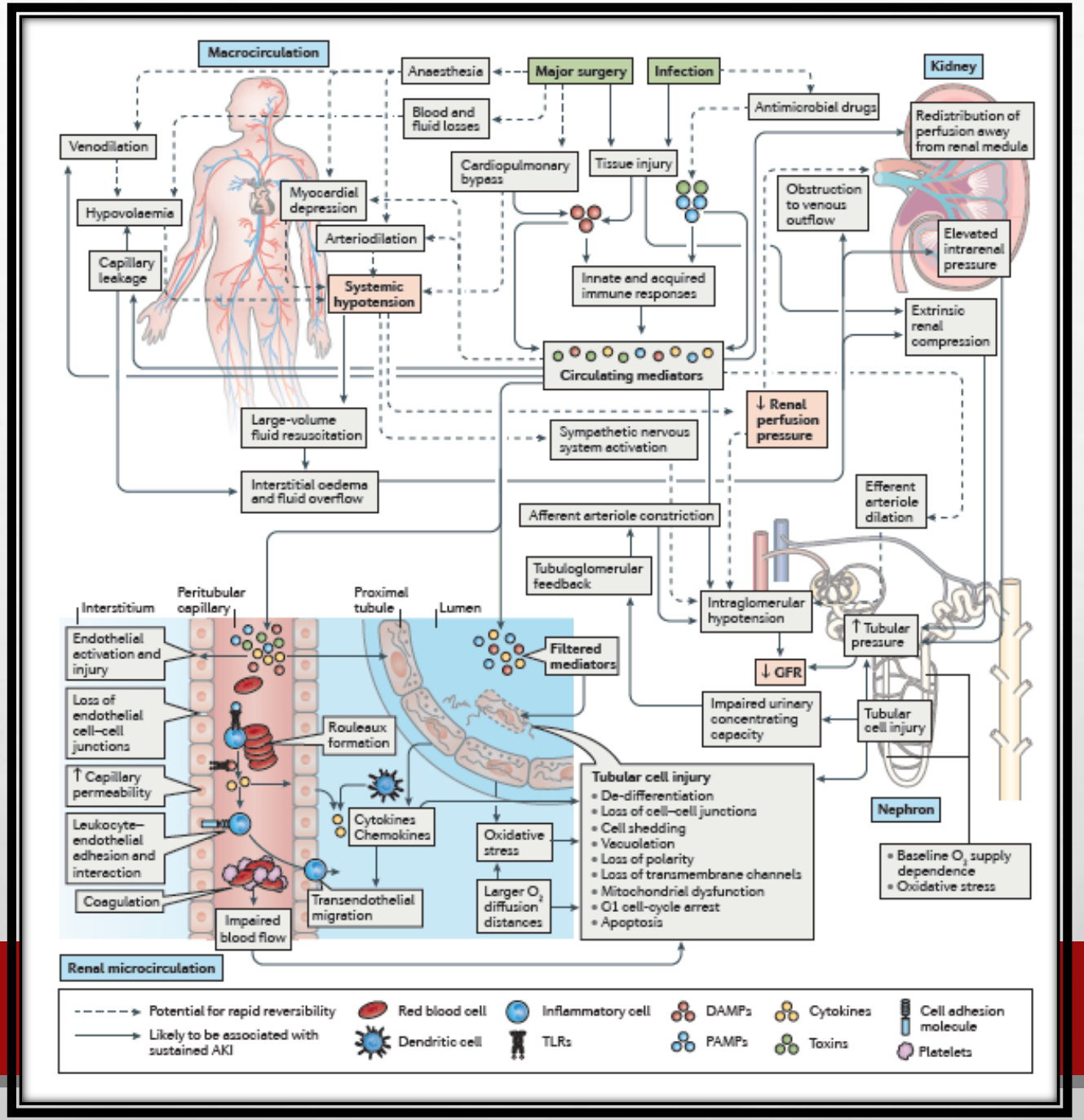
The inflammatory processes involved in septic AKI might be mediated by Toll-like receptors (TLRs) expressed on tubular and endothelial cells that recognize damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs).
Receptor activation then triggers local release of additional pro-inflammatory mediators and the recruitment of peritubular inflammatory infiltrating cells.

Sepsis also induces

1. angiopoietin 2 expression and release
2. reduces angiopoietin 1 receptor activation

leads to vascular leakage.

Renal tubular responses to this inflammatory milieu including: autophagy, mitochondrial dysfunction, loss of cell polarity and, to a limited degree, necroptosis and apoptosis — lead to sustained AKI and potentially to fibrosis and development of chronic kidney disease (CKD).


Macrocirculation
Anaesthesia
Major surgery
Infection
Kidney
Antimicrobial drugs
Blood and fluid losses
Redistribution of perfusion away from renal medulla
Venodilation
Cardiopulmonary bypass
Tissue injury
Obstruction to venous outflow
Myocardial depression
Hypovolaemia
Arteriodilation
Elevated intrarenal pressure
Capillary leakage
Systemic hypotension
Innate and acquired immune responses
Extrinsic renal compression
Circulating mediators
↓ Renal perfusion pressure
Large-volume fluid resuscitation
Sympathetic nervous system activation
Interstitial oedema and fluid overflow
Efferent arteriole dilation
Afferent arteriole constriction
Tubuloglomerular feedback
Interstitium
Peritubular capillary
Proximal tubule
Lumen
Intraglomerular hypotension
↑ Tubular pressure
Endothelial activation and injury
Filtered mediators
↓ GFR
Loss of endothelial cell–cell junctions
Rouleaux formation
Impaired urinary concentrating capacity
Tubular cell injury
↑ Capillary permeability
Tubular cell injury
• De-differentiation
• Loss of cell–cell junctions
• Cell shedding
• Vacuolation
• Loss of polarity
• Loss of transmembrane channels
• Mitochondrial dysfunction
• G1 cell-cycle arrest
• Apoptosis
Nephron
Cytokines Chemokines
Oxidative stress
Leukocyte–endothelial adhesion and interaction
Coagulation
Transendothelial migration
Larger O2 diffusion distances
• Baseline O2 supply dependence
• Oxidative stress
Impaired blood flow
Renal microcirculation
Potential for rapid reversibility
Likely to be associated with sustained AKI
Red blood cell
Dendritic cell
Inflammatory cell
TLRs
DAMPs
PAMPs
Cytokines
Toxins
Cell adhesion molecule
Platelets

Outcomes. The inflammation associated with septic AKI is coupled to long-term outcomes, as elevated plasma concentrations of inflammatory and apoptosis biomarkers (such as IL-8) have been associated with nonrecovery of renal function and death in critically ill patients receiving renal replacement therapy (RRT)

In patients with sepsis-associated AKI, renal recovery — even partial recovery — seems to confer significant benefits such that 1-year survival is indistinguishable from that of patients with sepsis but without AKI. This seemingly good prognosis for patients with renal recovery may disguise substantial underlying kidney damage that could take years to manifest.

It will be important to determine whether septic AKI increases the risk of CKD years later, even in patients who recover renal function prior to hospital discharge. If so, angiotensin-converting enzyme (ACE) or angiotensin receptor inhibition might be effective at preventing progression of CKD

Surgery-associated AKI

Epidemiology :the incidence of AKI among patients undergoing surgery varies by surgical setting: ~18% of patients undergoing cardiac surgery develop AKI compared with ~13% of patients undergoing major abdominal surgery; the incidence is ≥50% in procedures such as liver transplantation or emergency aortic surgery.

Pathophysiology:

Multiple etiological factors predispose to perioperative AKI; depending on the surgical context, these include:

1.haemodynamic alterations

2. exposure to exogenous and endogenous nephrotoxins

3. ischaemia–reperfusion injury

4. renal artery embolization

5. activation of neurohormonal responses to hypotension and tissue injury (the sympathetic nervous system and the renin–angiotensin–aldosterone system)

6. inflammation and oxidative stress.

Furthermore, patients requiring surgery often have multiple comorbidities (for example, CKD, diabetes, hypertension and heart disease) that may impair renal autoregulation, chronically activate neurohormonal responses and predispose to tubular injury. Importantly, pre-existing CKD is an important risk factor for postoperative mortality and has been consistently identified as the strongest risk factor for perioperative AKI.

Increased postoperative concentrations of both pro-inflammatory and anti-inflammatory cytokines (IL-6 and IL-10, respectively) were associated with an increased risk of AKI after cardiac surgery. Sustained systemic inflammatory responses are also common after major abdominal surgery, and increased IL-6 production and upregulation of TLR4 and TLR5 expression. This relationship may also be bidirectional, given the importance of the kidney in clearing inflammatory mediators from the circulation.

Multiple factors and procedures can result in haemodynamic instability during surgery, including:

1. The dilatory properties of anaesthetic agents
2. Blood and fluid losses
3. Poor cardiovascular reserve
4. Artificial circulation during cardiopulmonary bypass (CPB)

appropriate management of intraoperative haemodynamic changes, and preoperative and postoperative optimization of intravascular volume, cardiac output and oxygen delivery is associated with a substantial reduction in the incidence and severity of perioperative AKI among high-risk patients.

Outcomes. Despite great heterogeneity in its pathophysiology, perioperative AKI of any severity — unlike what has been observed in sepsis-associated AKI — even in cases of complete resolution, is associated with increased risks of CKD and death in the years after surgery.

AKI associated with renal hypoperfusion

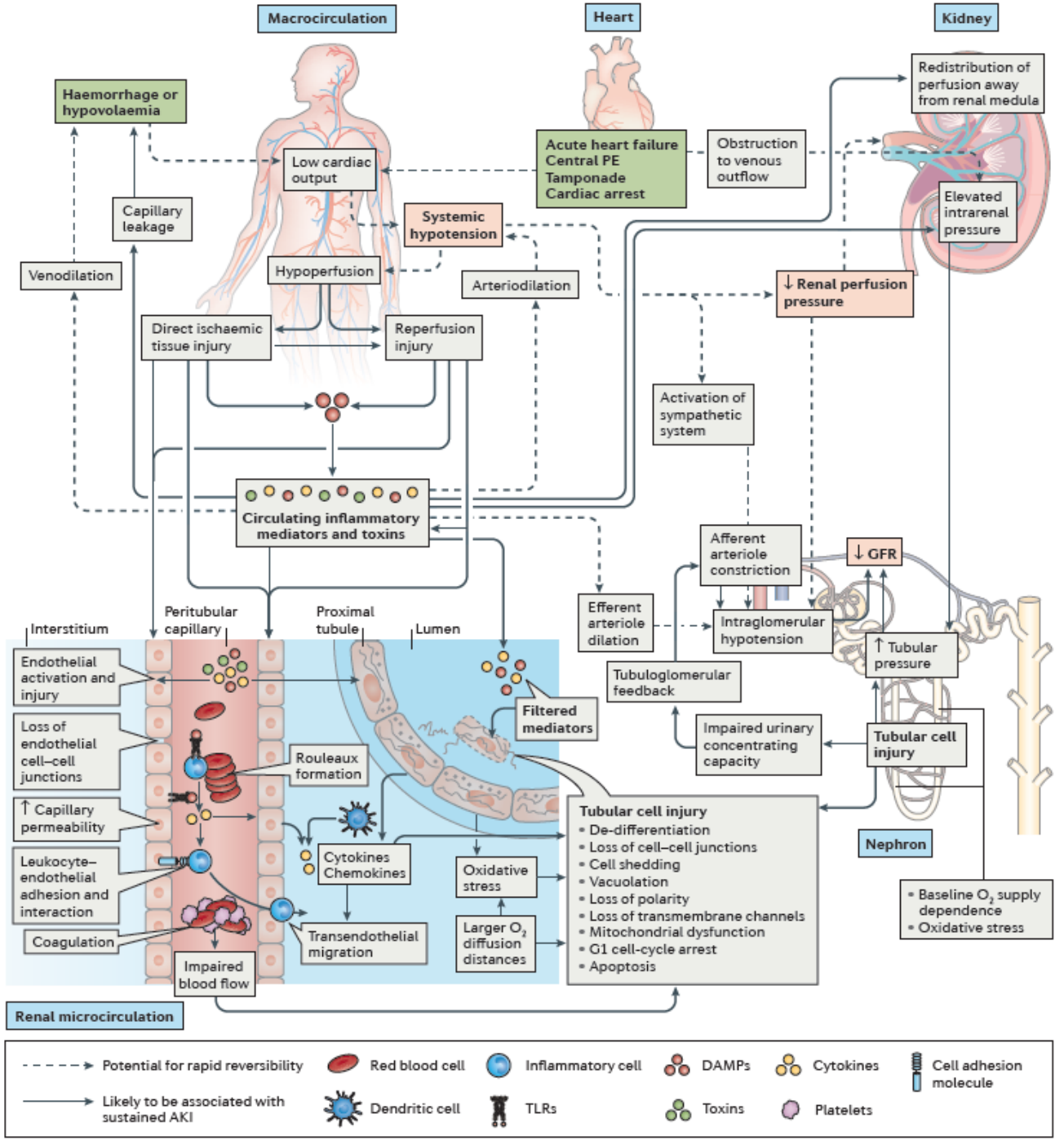
Epidemiology.AKI that is directly attributable to a gross reduction in RBF is less common in the developed world. Nevertheless, severe reductions in RBF can still occur, most commonly in specific contexts, such as following abdominal aortic dissection, sustained cardiac arrest or exsanguinating trauma. Its epidemiology is difficult to define.

Pathophysiology. contributing factors include:

1. Intravascular volume depletion and hypotension through internal or external fluid losses from the circulation
2. Conditions associated with chronic neurohormonal activation, systemic hypotension and fluid retention
3. Medications that cause renal vasoconstriction
4. Endothelial and vascular injury after ischaemia
5. innate and adaptive immune responses in microcirculatory dysfunction after reperfusion

High venous pressures have been shown to predict deterioration of renal function in hospitalized patients with advanced chronic cardiac failure; however, cardiac output and left ventricular function did not. This deterioration presumably occurs because the venous outflow pressure from the kidney is normally low but increases with right-sided heart failure. because the kidney is in a poorly compliant capsule, it is more sensitive to venous congestion.

Outcomes. Patient outcomes are likely to be strongly determined by the underlying conditions, with advanced chronic heart or liver failure conferring a poor prognosis. However, in the specific context of myocardial infarction-related cardiogenic shock, RRT-requiring AKI has been shown to predict substantially elevated short-term mortality as well as long-term risks of chronic dialysis and death.


Macrocirculation
Heart
Kidney
Haemorrhage or hypovolaemia
Low cardiac output
Acute heart failure
Central PE
Tamponade
Cardiac arrest
Obstruction to venous outflow
Redistribution of perfusion away from renal medula
Capillary leakage
Systemic hypotension
Elevated intrarenal pressure
Venodilation
Hypoperfusion
Arteriodilation
↓ Renal perfusion pressure
Direct ischaemic tissue injury
Reperfusion injury
Activation of sympathetic system
Circulating inflammatory mediators and toxins
Afferent arteriole constriction
↓ GFR
Efferent arteriole dilation
Intraglomerular hypotension
↑ Tubular pressure
Tubuloglomerular feedback
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Lumen
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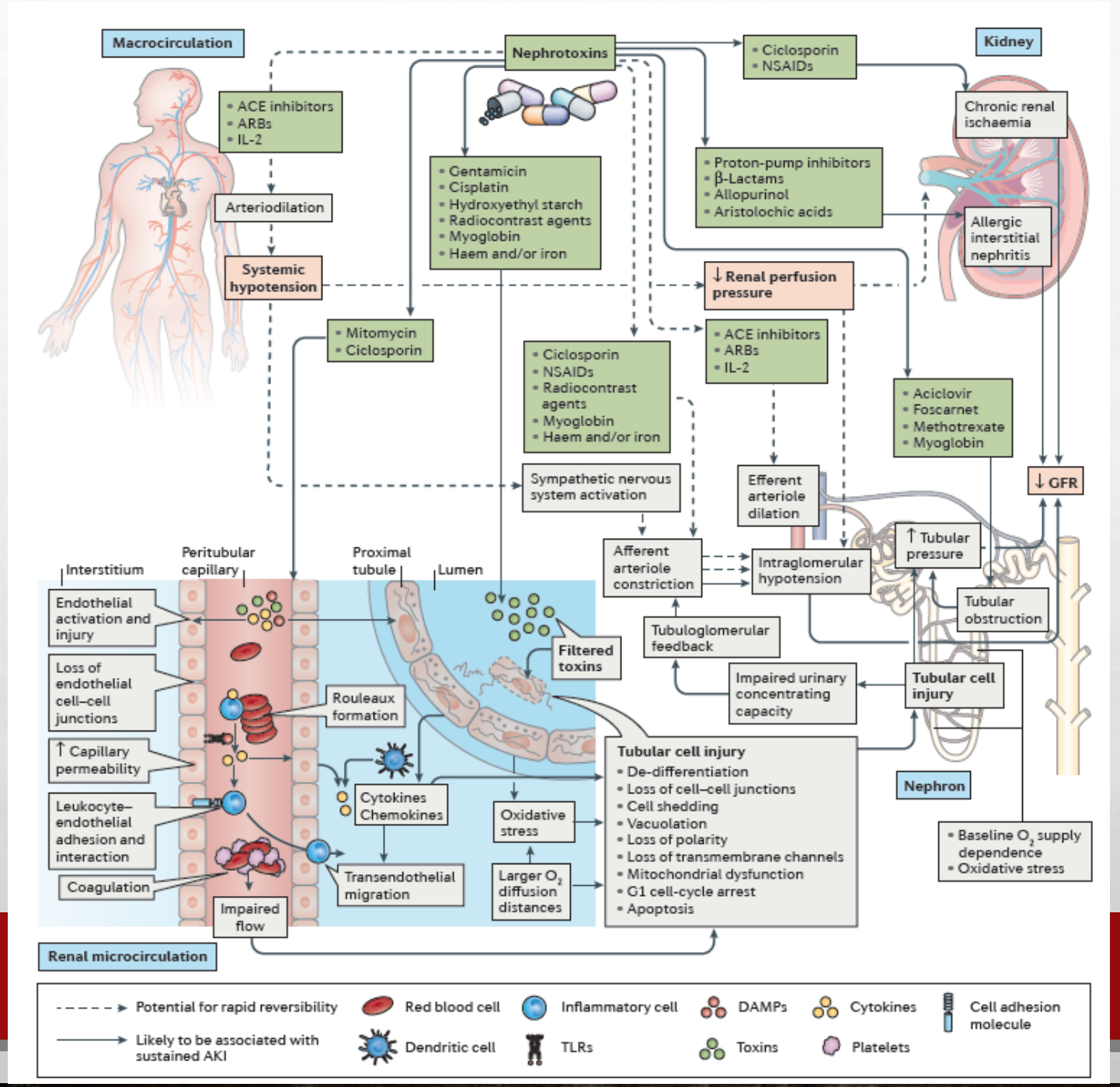
Nephrotoxic AKI

Epidemiology. In the ICU, some forms of nephrotoxic exposure are unavoidable, as >20% of the 100 drugs most frequently administered to adult patients are classified as nephrotoxic. Nephrotoxicity contributes to ~8–60% of AKI among patients in the ICU, drug nephrotoxicity has been reported to contribute to 19% of RRT-requiring AKI cases. Nephrotoxic exposure is likely to be increasing owing to the more aggressive medical management of complex conditions with nephrotoxic drugs, in particular in oncology and with bone marrow transplantation.

Pathophysiology. The biological effects of nephrotoxins are highly varied.

1. Injury to the kidney may occur secondary to renal haemodynamic alterations
2. Tubular cell damage by direct toxicity or osmotic injury
3. Obstruction of the tubular lumen
4. Direct or indirect (immunological) interstitial inflammation
5. Vascular injury triggering thrombotic microangiopathy.

Outcomes. The long-term outcomes of nephrotoxic AKI are not well established. Most cases of nephrotoxicity are acute, non-oliguric and resolve with discontinuation of the causal drug. For some drugs, or when other AKI risk factors coexist, mixed patterns of injury result in heterogeneity of recovery .


Macrocirculation
Nephrotoxins
Kidney
• ACE inhibitors
• ARBs
• IL-2
• Ciclosporin
• NSAIDs
Chronic renal ischaemia
Arteriodilation
• Gentamicin
• Cisplatin
• Hydroxyethyl starch
• Radiocontrast agents
• Myoglobin
• Haem and/or iron
• Proton-pump inhibitors
• β-Lactams
• Allopurinol
• Aristolochic acids
Allergic interstitial nephritis
Systemic hypotension
↓ Renal perfusion pressure
• Mitomycin
• Ciclosporin
• Ciclosporin
• NSAIDs
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Understanding paradigms of AKI

The scientific foundation for acute kidney injury.

The apparent return of GFR to normal levels may not guarantee resolution of AKI, as the remaining nephrons may increase their function to maintain GFR while masking nephron loss and tubular atrophy. Thus, clinical assessment of pathological versus physiological reductions in GFR may be impossible.

Progress in AKI research has also been substantially limited by a lack of available patient biopsy tissue, as emphasized by multiple investigators. Furthermore, as AKI contributes to the development of CKD, patient biopsy samples could represent a considerable asset to the scientific communities trying to understand this relationship.

Endophenotyping of acute kidney injury. Apart from describing the paradigms of AKI by aetiology, several investigators have also sought to define AKI subtypes by examining patterns of gene expression in response to kidney injury. These subtypes are sometimes referred to as ‘endophenotypes’ or simply ‘endotypes’

Model systems	Technique	Findings	Potential clinical benefit
Comparison of ischaemia–reperfusion-induced and mercuric chloride-induced rat models of AKI	Microarray analysis	Spatiotemporal differences in RNA expression levels, such as haem oxygenase 1.	• Improved diagnosis • Identification of drug targets
Comparison of ischaemia–reperfusion-induced and LPS-induced mouse models of AKI	Chromatin immunoprecipitation	Upregulated expression of some genes (such as those encoding TNF and NGAL) in both models with some insult-specific expression patterns.	Identification of potential drug targets
Porcine model of septic AKI	Whole-kidney gene expression analysed by quantitative real-time PCR	Differences in gene expression between sepsis AKI and sepsis without AKI. Inflammation, metabolism and apoptotic molecular responses in early septic AKI.	• Identification of potential drug targets • Guiding mechanistic research
• Dehydration versus ischaemia–reperfusion injury in mice • Humans with brief (<72 h) or long-term (>7 day) AKI	• RNA sequencing of specific kidney regions isolated by laser microdissection • RNA sequencing of human urine	Activated genes included different, functionally unrelated signal transduction pathways and were expressed in different regions of the kidney. Brief and long-term AKI in humans also showed different RNA expression.	• Identification of potential drug targets • Guiding mechanistic research
NGAL luciferase reporter assays in mice exposed to dehydration versus LPS	NGAL expression via luciferase reporter	LPS resulted in kidney NGAL expression, whereas a 50% increase in creatinine with dehydration did not.	Clarify specificity of NGAL for intrinsic AKI
Multicentre study of 744 patients with a mixed aetiology of AKI	340 candidate molecules examined in urine and plasma	Urinary TIMP2 and IGFBP7 were topic candidates in discovery and validation for stage 2–3 AKI within 12 h. TIMP2 was somewhat better for septic AKI according to the AUC.	Discovery and validation of biomarkers

Disparities between physiological reductions in GFR and established tubular injury could be revealed by novel AKI biomarkers.

Ischaemia–reperfusion, cisplatin and endotoxin insults induced renal NGAL expression, whereas volume depletion that was sufficient to induce a 50% increase in serum creatinine level did not.

patients with increased AKI biomarkers (NGAL or kidney injury molecule 1 (KIM1; also known as HAVCR1)) but without significantly elevated serum creatinine levels remained at increased risk of a composite of dialysis or death compared with those without increased NGAL, KIM1 or creatinine levels.

NGAL has proved less discriminating in the development of septic-associated or adult cardiac-surgery-associated AKI than in other types of AKI, possibly because subclinical AKI is common in these settings or because neutrophils themselves may be a source of NGAL in the setting of systemic inflammation.

tissue inhibitor of metalloproteinases 2 (TIMP2) and insulin-like growth factor-binding protein 7 (IGFBP7), which are involved in G1 cell-cycle arrest, were shown to predict the development of severe AKI in both adults and children after ICU admission in the context of sepsis, surgery, trauma and nephrotoxic exposure.

Conclusions. Overall, despite some advances in biomarker development, the scientific foundation for distinct phenotypes of clinical AKI is weak, and early tissue analysis of human AKI has not been carried out on a large scale.

Finally, a crucial need exists for longitudinal epidemiological studies and samples (blood, urine and tissue) that would enable the testing of multiple hypotheses as to the nature of AKI and its pathophysiology and outcomes.

THANKYOU