Acute kidney injury

Claudio Ronco, Rinaldo Bellomo, John A Kellum

Acute kidney injury (AKI) is defined by a rapid increase in serum creatinine, decrease in urine output, or both. AKI occurs in approximately 10–15% of patients admitted to hospital, while its incidence in intensive care has been reported in more than 50% of patients. Kidney dysfunction or damage can occur over a longer period or follow AKI in a continuum with acute and chronic kidney disease. Biomarkers of kidney injury or stress are new tools for risk assessment and could possibly guide therapy. AKI is not a single disease but rather a loose collection of syndromes as diverse as sepsis, cardiorenal syndrome, and urinary tract obstruction. The approach to a patient with AKI depends on the clinical context and can also vary by resource availability. Although the effectiveness of several widely applied treatments is still controversial, evidence for several interventions, especially when used together, has increased over the past decade.

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Department of Medicine, University of Padova, Padova, Italy (C Ronco MD); **International Renal Research Institute of Vicenza, Vicenza, Italy** (C Ronco); **Department of Nephrology, San Bortolo Hospital, Vicenza, Italy** (C Ronco); **Critical Care Department, Austin Hospital, Melbourne, VIC, Australia** (R Bellomo MD); **and Center for Critical Care Nephrology, Department of Critical Care Medicine, University of Pittsburgh, Pittsburgh, PA, USA** (J A Kellum MD)

Correspondence to:
Dr Claudio Ronco, Department of Nephrology, San Bortolo Hospital, Vicenza 36100, Italy
cronco@goldnet.it

Introduction

Acute kidney injury (AKI) is a syndrome. It is an important complication in patients admitted to hospital (10–15% of all hospitalisations)[1] and in patients in the intensive care unit (ICU) where its prevalence can sometimes exceed 50%.[2] Despite its complexity, AKI is traditionally seen as a single disease or classified according to semi-anatomical categories (ie, pre-renal, intrinsic, and post-renal AKI) in reference to the kidney (panel 1).

This simplistic taxonomy is now giving way to more specific syndromic descriptions including among others hepatorenal,[8] cardiorenal,[9] nephrotoxic,[10] and sepsis-associated AKI.[11] This increased specificity is because of increasing evidence that these syndromes have a unique pathophysiology and treatment.

Another major challenge to AKI diagnosis and treatment is that specific syndromes often coexist as illustrated by the overlaps shown in figure 1. Because AKI often arises as part of other syndromes (ie, heart failure, liver failure, and sepsis), which themselves cause substantial morbidity and mortality, it is easy to overlook the significance of AKI as both a marker of disease severity and a determinant of short-term and long-term outcomes.

In patients with septic shock, 60-day mortality is three to five times greater in those who develop AKI.[15] Although this mortality could be a function of greater sepsis severity in patients with severe AKI, the syndrome itself might independently increase mortality by leading to electrolyte and acid-base disorders, fluid accumulation, and metabolic dysfunction, impairing neutrophil function and reducing the patient's ability to clear infection.[16]

Thus, the early and rapid diagnosis and treatment of AKI is an important part of the overall management of patients with the various syndromes that cause or are associated with AKI. By contrast, management of the original disorder, in some cases, might help to resolve the secondary AKI syndrome. Although some aspects might not be modifiable, there is evidence that some causes of AKI can be mitigated in some settings.[17,18]

Consensus definitions and epidemiology

Different terms and different criteria for AKI have been used previously making it impossible to reach accurate conclusions on the epidemiology of this syndrome. International consensus criteria were first introduced by the Acute Dialysis Quality Initiative,[4] and subsequently modified by the AKI Network,[5] and finally by Kidney Disease Improving Global Outcomes (KDIGO)[6] as shown in table 1 and panel 2. Through use of standard criteria, estimates of incidence and prevalence of AKI, and comparisons of outcomes across centres are now possible. Rates of AKI have been described to be as low as 2% in community hospitals, whereas in large academic institutions, rates can reach more than 20% of all hospitalisations.[19,20]

Furthermore, if specific hospital units are studied such as ICU, cardiac surgery, oncology, and transplant centres, rates of AKI can be 50% or more.[2,12] Other aspects have been recently analysed in a global snapshot done in conjunction with the 0by25 initiative.[13,21] AKI rates and causes were highly variable in different countries with specific reference to the local resources and health-care systems. The epidemiology of AKI is schematically described in figure 2.[21–23] Finally, it is important to place

Search strategy and selection criteria

We searched PubMed and MEDLINE for original research papers, reviews and systematic reviews, meta-analyses, editorials, and commentaries published between Jan 1, 2014, and June 30, 2019, using the following search terms: "acute kidney injury", "acute renal failure", "continuous hemofiltration", "continuous renal replacement therapy", and "haemodialysis". We combined the terms "continuous hemofiltration", "continuous renal replacement therapy", and "haemodialysis" with "acute kidney injury" and "acute renal failure". We identified 8679 potentially relevant titles. All titles were scanned. We gave preference to citations from the past 5 years but included selected papers from older literature when more recent studies were not available or when citing the historical basis for clinical practice. 494 relevant articles were selected. For all articles, abstracts were reviewed and the full reference list developed. Additional references were selected from relevant articles and chapters of recent textbooks in the field. Only English language manuscripts were included.

Panel 1: The history of acute kidney injury

In the first part of the 20th century, the diagnosis of acute renal failure, as it was known, was based on abrupt oliguria and rapid development of uraemic symptoms. Patients typically died from the clinical consequences of severe impairment of renal function such as gastrointestinal bleeding, pulmonary oedema, or cardiac dysrhythmias. The main causes of acute renal failure were dehydration, haemorrhagic shock, glomerulonephritis, and acute intoxication. With the introduction of laboratory medicine and the measurement of glomerular filtration rate with exogenous or endogenous markers such as creatinine, diagnosis became easier and more accurate. Autopsy findings late in the course of acute renal failure often showed patchy necrosis of the tubular cells and the term acute tubular necrosis was suggested and gradually became synonymous with acute renal failure. However, even as these results were reported, other studies were done with kidney biopsy and in some conditions, such as sepsis and shock, tubular necrosis was almost absent despite profound kidney dysfunction. Thus, the term, acute tubular necrosis, although still commonly used, can be misleading in many cases.[3]

A similar problem was recognised with the term acute renal failure. Evidence accumulated indicating that even mild alterations in renal function contributed to morbidity and mortality in patients who are critically ill, and thus the term failure seemed inappropriate. Furthermore, variation in the use of haemodialysis or haemofiltration, and the enormous variation in the biochemical criteria used to define the syndrome meant that individual studies could not be compared or combined. In 2002, the Acute Dialysis Quality Initiative assembled an international, interdisciplinary group of experts in Vicenza, Italy, to standardise the definition of what became known as acute kidney injury (AKI).[4] The new definition and classification system known as Risk, Injury, Failure, Loss and End-stage kidney disease (RIFLE)[5] was still based on serum creatinine and urine output, but by standardising the criteria, subsequent epidemiological studies, diagnostic tests, and even interventional trials would likewise be standardised and comparable with each other. In the next decade, rates and outcomes for AKI in more than a million patients were reported in various studies. With time, RIFLE was refined,[6] and ultimately adopted into the Kidney Disease Global Initiative AKI guideline.[6] This guideline is the commonly accepted definition and classification system for clinical trials and clinical practice. However, it will evolve further as more rapid diagnostics are used and as subtypes of AKI are better understood.[7]

AKI in the continuum of kidney disease from acute to chronic. In this continuum, AKI is part of acute kidney disease, which is defined as abnormalities in kidney structure or function that have existed for fewer than 90 days (the point at which chronic kidney disease [CKD] is defined).[6,24]

Clinical presentation

Kidney disease is usually a silent condition. Except for urinary tract obstruction, it does not cause pain or any specific signs or symptoms. Patients can therefore present in two ways. First, a patient might present with an acute illness such as sepsis,[25] or be exposed to a condition known to be associated with AKI such as major surgery.[26] Importantly, such patients might not present to the ICU and it is therefore essential that clinicians working outside the ICU are aware of the clinical presentation of kidney disease and specifically AKI. In ideal circumstances, a premorbid assessment of kidney function within the past 3 months might be available and changes from this baseline state can be detected by measuring serum creatinine or urinary output.

Second, a patient might present with abnormal kidney function of unknown duration and the clinician has to then decide if the condition is AKI, CKD, or both. This scenario can pose a substantial clinical dilemma particularly if the patient's medical history, including baseline renal function, is not well documented.[27] Indeed, baseline renal function often has to be inferred using various sources of information including the medical history, kidney size using imaging, presence or absence of albuminuria, and the history of serum measurements of serum creatinine over time. A decrease in serum creatinine after hospital admission might indicate that AKI had occurred before admission.

Conversely, small decreases in creatinine can reflect the combined effects of changes in volume status, fasting, and bedrest typical of the first few days of hospitalisation. Thus, decreases in serum creatinine, although they do not define AKI, should prompt clinicians to suspect resolving AKI and might be especially useful when baseline function is unknown.[28]

Assessing kidney function

Changes in serum creatinine or urinary output are neither sensitive nor specific for AKI, yet they are the cornerstone of our current diagnostic approach. Although glomerular filtration rate (GFR) can be accurately measured in the research setting, the available technology is cumbersome and time consuming. Thus, changes in kidney function are usually assessed clinically by monitoring solutes that are normally cleared by the kidney (eg, creatinine, cystatin C), and by urine volume over time in the context of the patient's overall volume status (table 1). Changes in serum creatinine lack sensitivity for AKI because in a healthy person, nearly 50% of GFR must be lost before a change in serum creatinine is detectable.[29,30]

Moreover, studies from 2014 confirmed that healthy individuals might have a substantial amount of renal functional reserve. This reserve can be lost progressively even in the presence of a constant baseline GFR.[30,31] Changes in urine output might be more sensitive but appear less specific. In some cases of AKI (eg, acute interstitial nephritis), polyuria can occur as the result of defects in tubular urine concentration ability.

Furthermore, urine output, and to a lesser extent, serum creatinine, are exquisitely sensitive to overall volume status such that hypovolaemia will trigger changes in urine output without the necessity for injury. Indeed, totally different genes are expressed by hypovolaemia versus ischaemia induced changes in kidney function.[32] Thus, changes in function can also lack specificity because they can be initially triggered by hypovolaemia without direct damage to the kidney or by direct damage from ischaemia.

Diagnostic criteria and clinical judgment

AKI is a clinical diagnosis. A clinician has to interpret the changes in kidney function (or lack thereof) in the

context of the clinical picture. Patients who are critically ill and injured who are cared for in modern ICUs are rapidly volume resuscitated making hypovolaemia per se an improbable cause of persistent changes in kidney function. However, some conditions (eg, heart failure) and medications (eg, angiotensin-converting enzyme inhibitors) can mimic hypovolaemia in some ways. Thus, the astute clinician has to consider the various potential causes of altered kidney function and kidney tissue damage (panel 3).[33–48]

The conditions described in panel 3 are not solely for patients who are critically ill. Indeed, outside the ICU, infections like pneumonia are common causes of AKI[25] and medications are also commonly implicated. In the pre-hospital setting and especially in low-income countries where gastrointestinal losses are a major cause of AKI, hypovolaemia is a common problem.

Even in patients who are hospitalised, intravascular hypovolaemia can occur secondary to excess fluid losses from wounds and drains, from the gastrointestinal tract, redistribution of fluid into the extravascular space, decreased fluid intake, and from use of diuretics. Such patients were often labelled as having pre-renal azotaemia rather than AKI. The danger here is that AKI looks the same clinically, and without examining tissue or knowing the long-term clinical consequences (including CKD), it is nearly impossible to be sure that tissue or cell injury has not occurred.[3]

Despite the above challenges and nuances, international consensus criteria have been developed,[4] and later refined,[5,6] for the diagnosis and staging of AKI (table 1). The purpose of these criteria is to standardise the way AKI is reported in clinical trials and in epidemiological studies and to serve as a basis for approaching the diagnosis in individual patients.

There is evidence establishing the value of these criteria. First, in a large before and after study, including more than half a million patients, an electronic clinical decision support system was used to help identity patients who were hospitalised with AKI.[1] The support system analysed previous creatinine data and reported changes when they met KDIGO criteria.[6] The implementation of this clinical decision support system resulted in a small (0·8%), but sustained significant and clinically meaningful reduction in hospital mortality and also a reduction in hospital duration by nearly a third of a day.[1] The clinical decision support system provided no clinical management advice, so the effect can be attributed specifically to informing clinicians that these criteria were met. This reasoning is plausible because subtle changes in renal function are easily missed. In addition, we now have preliminary evidence that a pathophysiological correlate might exist between AKI staging and histology from kidney biopsies.[49] Although typical findings of tubular necrosis appear relatively uncommon, more subtle changes in tubular epithelial cell architecture appear present.

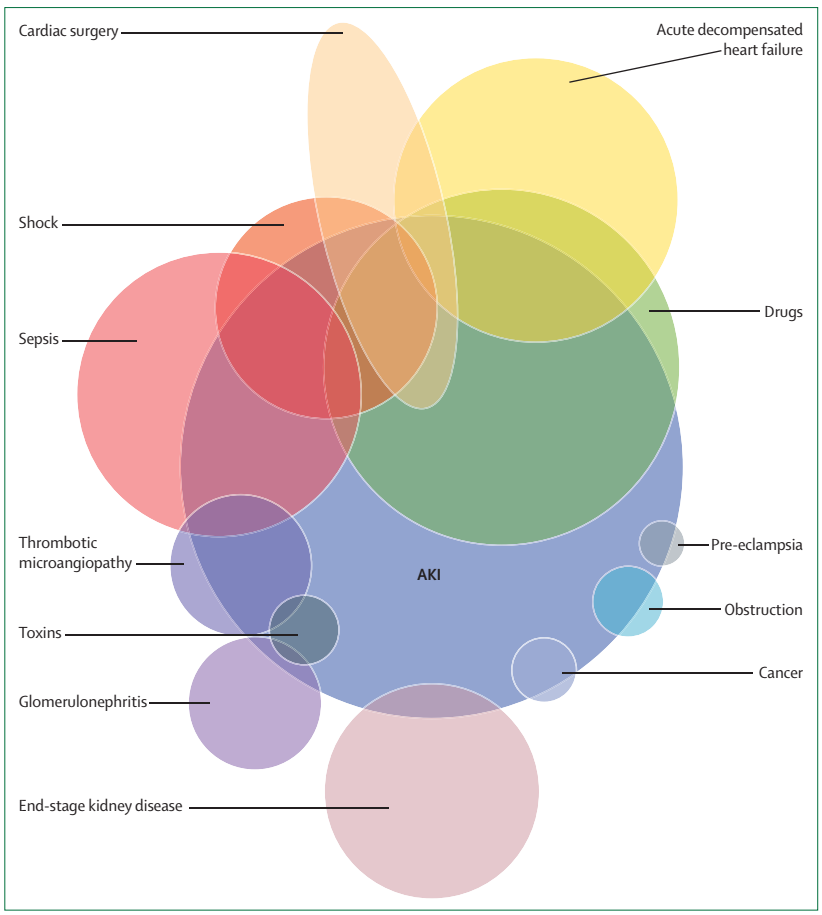

Figure 1: **The clinical spectrum of AKI syndrome**
AKI syndrome can develop as a consequence of different pathological conditions that might or might not lead to AKI depending on the balance between patient susceptibility and intensity of the exposure. Different pathological conditions can also interfere in a combined causality as described by the overlapping of the different circles. The dimension of the circles and the area in common with the AKI circle describe the size of the problem and the frequency of AKI for each pathological condition (in rough approximation based on data compiled from various sources).[2,12–14] AKI=acute kidney injury.

Tubular epithelial simplification, tubular epithelial mitosis, and cell sloughing appear to correlate with clinically severe AKI (stage 2–3) and have been reported to achieve a sensitivity of 0·93 (95% CI 0·85–1·00), specificity of 0·95 (0·83–1·00), and area under the receiver-operating characteristic curve of 0·98 (0·98–1·00).[49] An important limitation to such data, however, relates to possible selection bias, small sample size, and the single-centre nature. Large-scale studies of histopathology are not available for AKI. The reason for this is due to the high risk involved with the kidney biopsy procedure in critically ill patients, often anticoagulated or carrying other risks or contraindications. Because AKI mainly occurs in these patients, the evidence provided by histopathological exams made from biopsies is very limited.

Clinical course

Nearly two-thirds of AKI cases resolve within 7 days.[50] When a case does not resolve or relapse occurs with

	Timing	Functional changes		Structural damage*
		Change	Threshold	
Acute kidney injury	≤7 days	Creatinine ≥1·5 times baseline (or increase of ≥0·3 mg/dL within any 48 h period)	Urine volume <0·5 mL/kg for ≥6 h	Undefined
Acute kidney disease	>7 days, <90 days	Creatinine ≥1·5 times baseline (or increase ≥0·3 mg/dL within any 48 h period)	eGFR <90 mL per min (with damage marker) eGFR mL per min per 1·73 m² <60 mL per min	Kidney damage
Chronic kidney disease	≥90 days	Not applicable	eGFR <90 mL per min (with damage marker) eGFR mL per min per 1·73 m² <60 mL per min	Kidney damage

Comparisons are in terms of timing, functional changes, and structural damage. eGFR=estimated glomerular filtration rate. *Kidney damage can be assessed by pathology, urine or blood markers, or imaging. Stuctural criteria are not included in the current definitions for acute kidney injury as none have yet been validated for this purpose.

Table 1: **Comparison of acute kidney injury, acute kidney disease, and chronic kidney disease**

Panel 2: Staging of acute kidney injury according to current Kidney Disease Improving Global Outcomes definition

Stage 1
Creatinine ≥1·5 times baseline or increase of ≥0·3 mg/dL within any 48 h period, or urine volume <0·5 mL/kg for 6–12 h

Stage 2
Creatinine ≥2·0 times baseline or urine volume <0·5 mL/kg for ≥12 h

Stage 3
Creatinine ≥3·0 times baseline or increase to ≥4·0 mg/dL or acute dialysis, or urine volume <0·3 mL/kg for ≥24 h

subsequent lack of resolution, substantially worse clinical outcomes are expected. Patients with stage 2–3 AKI who resolve within 7 days and remain alive and free of renal dysfunction by hospital discharge have a 1-year survival of more than 90%. By contrast, patients who never resolve, have a 47% hospital mortality and, among those who are discharged alive, 1-year survival is only 77%.[50] Thus, it is important to ensure that patients who can recover renal function do so and for those that do, to help insure that they do not have a clinical relapse.[24]

Relapses might reflect additional injuries or recurrent exposures, which are regrettably common.[51] They might also result from renal compensation. Hyperfiltration can result in apparent recovery from AKI, only to then lead to subsequent deterioration. Unfortunately, most patients do not receive nephrology follow-up after AKI.[52] These concepts have led to the conceptual framework depicted in figure 3. From this conceptual framework, it emerges that different situations can occur with possible damage or dysfunction, or coexistence of the two in a frank AKI syndrome. The framework of definitions is detailed in table 1 while the clinical and pathophysiological AKI continuum is schematically depicted in figure 4.

Modern diagnostic methods

Two advances from the past 10 years, the discovery of AKI biomarkers, and the application of computer decision support, have the potential to substantially improve the diagnostic approach to and the treatment of AKI. Several molecules have been identified as potential markers for early detection of kidney damage before serum creatinine rises (table 2).[53–62] However, limitations in specificity (especially in patients with comorbid conditions) and in some cases, sensitivity, have meant that damage markers are used mainly for research purposes.

A second generation of markers was developed mostly in the past 5 years using modern definitions of AKI. Two markers of cell cycle arrest, tissue inhibitor of metalloproteinases 2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP7) have been incorporated into the first diagnostic test for AKI approved by the US Food and Drug Administration—Nephrocheck (Astute Medical, San Diego, CA, USA). This test is also available in many countries around the world. Unlike damage markers, TIMP-2 and IGFBP7 can be released in response to non-injurious, noxious stimuli.[53,63] The molecules are preformed and do not require gene transcription to be expressed.[63,64] These characteristics have led us to refer to them as kidney stress markers (figure 5).[65,66]

Two single-centre studies have shown benefit associated with use of urinary [TIMP-2×IGFBP7] in patients after surgery.[18,67] In one study,[18] biomarker-positive patients who were undergoing cardiac surgery were randomly assigned to receive a care bundle that included fluid management and titrating vasoactive medication. AKI was significantly reduced with the intervention compared with the controls (55·1 *vs* 71·7%; absolute risk reduction 16·6%, 95% CI 5·5–27·9; p=0·004).

In another study,[67] a similar care bundle including early optimisation of fluids and maintenance of perfusion pressure was given to patients undergoing non-cardiac major surgery after testing positive for the biomarker. Overall, AKI rates were not statistically different between groups at 19 (32%) of 60 in the intervention group versus 29 (48%) of 61 in the standard care group (p=0·076). However, rates of moderate and severe AKI, a secondary endpoint, were reduced with the intervention (four [6·7%] of 60 *vs* 12 [19·7%] of 61; p=0·04), as were lengths of ICU stay (median difference 1 day; p=0·035) and hospital stay (median difference 5 days; p=0·04). These results, although statistically significant, have limited robustness given the small

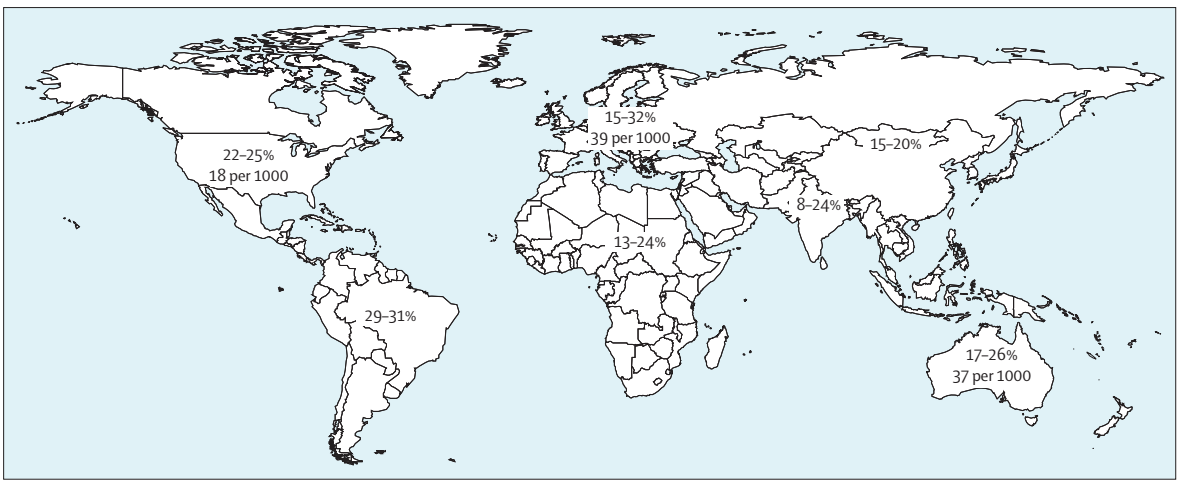

Figure 2: **AKI epidemiology per hospital admission and corresponding incidence by region**
AKI incidence taken from various sources compiled by Susantitaphong and colleagues,[22] Mehta and colleagues,[13] and Hoste and colleagues.[23] Hospitalisation rates for the USA were obtained from the US Centers for Disease Control and Prevention and for other countries from the Organisation for Economic Co-operation and Development. In Europe, hospitalisation rates per population vary from 8·5% in Portugal and 9·6% in the Netherlands, to 25·7% in Germany and 25·3% in Austria. An average rate of 17% was therefore used. For other regions, information on hospitalisation rates is not available. Given that there is a two times variation in population incidence despite similar rates per hospital admission, it seems probable that many AKI occurrences are not captured.[21–23] AKI=acute kidney injury.

sample size. Furthermore, no significant differences were observed in the use of renal replacement therapy (RRT) or in-hospital mortality in either study.

As with any diagnostic test, it is important to use those such as urinary [TIMP-2×IGFBP7] in the intended population in which its test characteristics are favourable—in this case, patients who are critically ill. When used in patients who are low risk, the false positive rate will increase. When used before an injurious exposure has occurred, the test will not forecast AKI. Similarly, the test might not remain positive for a long time after injury, particularly if the insult was not persistent.

Besides biomarkers, other diagnostic tools are undergoing technical and clinical evaluation to refine risk assessment and AKI diagnosis. Among these are real-time GFR measurement, assessment of renal functional reserve (glomerular stress test), and assessment of tubular reserve (furosemide stress test). Despite their potential utility and clear rationale, these tests are still under evaluation and are thus research tools not yet used in clinical medicine.

Finally, information technology is used in large centres to do both pragmatic trials and to establish algorithms for electronic AKI alert procedures.[68–75] Several lines of evidence suggest that electronic data collection and subsequent analysis by expert or machine learning systems could provide support for accurate detection, early diagnosis, and prevention of AKI.

However, evidence is inconclusive as to what specific interventions can be effective when driven by electronic alerts. A randomised trial involving 2300 patients found that clinical adoption of the interventions recommended by the alert system was poor and did not affect outcomes.[74] Subsequently a larger step-wedge trial involving 24000 patients did find partial adoption and an effect on hospital duration.[75] However, the effect size was not much larger than that achieved by provision of the alerts alone without care recommendations.[1]

The pathophysiology of AKI

AKI is a loose collection of syndromes. Thus, its pathophysiology varies according to the myriad of conditions associated with its development.[76] In addition, the pathophysiology of AKI secondary to uncommon immunological diseases of the kidney parenchyma (glomerulonephritis) or direct infection of the renal parenchyma (pyelonephritis) is complex.[77,78] The same applies to acute (but also uncommon) vascular events, which can cause parenchymal injury, and to obstructive disease of the urinary tract.

Drug-induced AKI is also relatively common both in patients who are hospitalised and in the community. However, the pathophysiology and mechanisms of such injury vary from drug to drug and are described in dedicated articles and books.[79,80] Finally, severe hypovolaemia, as can be seen in diarrhoeal diseases or other forms of obvious volume losses, is typically addressed and resolved by rehydration and does not usually raise complex issues of pathophysiology. Thus, here we will focus on AKI conditions such as sepsis, major surgery, cardiac surgery, cardiorenal syndrome, and hepatorenal syndrome, which dominate in patients who are hospitalised[2,14] and remain poorly understood. General risk factors for AKI include advanced age and underlying CKD.

Sepsis-associated AKI

Sepsis is the most common trigger of severe AKI in patients who are critically ill.[2,14] Its pathophysiology,

Panel 3: Causes and pathophysiological mechanisms of AKI

Renal hypoperfusion
Renal hypoperfusion due to several causes (hypovolaemia, systemic vasodilatation, increased vascular resistance, among others) activates adaptive mechanisms (ie, autoregulation mechanisms, sympathetic nervous system, and RAAS) to maintain GFR. When the hypoperfusion is sustained or the adaptive response is inadequate, GFR is initially decreased without parenchymal damage (ie, pre-renal AKI); then, if an adequate renal perfusion is not restored, organ damage can occur (ie, ischaemic acute tubular necrosis). In this case, the sustained inadequate oxygen and nutrient delivery to the nephrons and the ATP-depletion activates epithelial cellular injury and death via necrosis or apoptosis, or both, which ultimately leads to endothelial injury, activation of inflammatory processes, and renal damage and dysfunction.[32–34]

Cardiorenal syndrome type 1
An acute worsening of cardiac function can lead to renal hypoperfusion through a reduction in effective circulation fluid volume or an increase in central venous pressure. Other potential mechanisms involved are sympathetic nervous system and RAAS activation, chronic inflammation, and imbalance in reactive oxygen species, or nitric oxide production.[9,35–37]

Nephrotoxin exposure (toxic acute tubular necrosis)
Nephrotoxic drugs (eg, antibiotics, contrast media, among others) and endogenous toxins (eg, myoglobin, uric acid, among others) are filtered and concentrated (some of them also reabsorbed or secreted) by the nephrons and could reach toxic levels for the tubular cells. Toxins can: (1) have a direct cytotoxic effect on renal tubular epithelial or (2) endothelial cells, (3) determine impaired intrarenal haemodynamics (eg, mesangial cell constriction), and (4) cause precipitation of metabolites or crystals, among others.[33,38]

Sepsis
The exact mechanism for sepsis is still under investigation. Macrovascular and microvascular dysfunction, immunological and autonomic dysregulation, and abnormal cellular response to injury are proposed. An increase in the level of circulating inflammatory cytokines and leucocyte activity can lead to the formation of capillary microthrombi. These, along with redistribution of intrarenal perfusion due to altered vascular tone and shunting, kidney inflammation, and oedema, can decrease capillary blood flow and oxygen delivery and increase venous output pressures. The imbalance in reactive oxygen species or nitric oxide production can contribute to endothelial damage, which leads to increased vascular permeability and worsening interstitial oedema. Septic cardiomyopathy can contribute to renal hypoperfusion.[35,40,41]

Major surgery
The fluid depletion related to several causes (eg, blood losses, increase in insensible losses, extravasation of fluid to the third space, among others) and the systemic effects of anaesthetic drugs (eg, peripheral vasodilation, myocardial depression, among others) are considered the main cause of AKI in patients undergoing surgery. The increased level of circulating cytokines and reactive oxygen species, respectively due to the endotoxin load from impaired visceral perfusion and ischaemic-reperfusion-injury, contributes to renal damage.[42,43]

Intra-abdominal hypertension
The increase of intra-abdominal pressure over certain values leads to a decrease in renal perfusion due to the reduction of both arterial inflow and venous outflow and the increase of Bowman's space hydrostatic pressure. The systemic inflammation, due to the impaired visceral perfusion and the production by the kidney of inflammatory mediators, contributes to kidney damage.[44,45]

Rapidly progressive glomerulonephritis
In patients who are genetically predisposed, different agents activate an autoimmune response that results in glomerular inflammation and injury.[46]

Acute interstitial nephritis
In patients who are genetically predisposed, drugs or infectious agents can activate an immune reaction. The interstitial inflammatory cellular infiltrates stimulate the expression of cytokines that contribute to the amplification of the process and the production of extracellular matrix. If the process is not interrupted at the appropriate times, interstitial fibrosis can occur.[47]

Post-renal AKI
Extrarenal (eg, prostate hypertrophy, retroperitoneal fibrosis, among others) or intrarenal (eg, nephrolithiasis, blood clots, among others) obstruction leads to an increase in intratubular pressure, impaired renal blood flow, and inflammatory processes that can result in severe complications, depending on previous kidney function, the severity of the obstruction, and the time of onset in AKI.[48]

AKI=acute kidney injury. GFR=glomerular filtration rate. RAAS=renin–angiotensin–aldosterone system.

however, remains poorly understood. The overwhelming majority of our pathophysiological theories are derived from animal models and their relevance to human disease remains controversial.[81] However, large animal models of septic AKI show that in Gram-negative bacteraemia renal blood flow increases above normal levels and renal histopathology in the first 48 h is indistinguishable from normal.[82–84]

Two possible mechanisms for increased renal blood but decreased GFR have been proposed and can occur simultaneously: efferent arteriolar vasodilatation[85,86] and intrarenal shunting.[87–89] Such shunting can divert the increased renal blood flow to the cortex and away from the medulla and contribute to decreased medullary oxygenation.[90] These findings support the need for the measurement of renal blood flow in humans. However,

magnetic resonance-based techniques are difficult to use and cannot provide continuous measurements.[91]

Para-amino hippurate clearance is invasive, has only been used in a few patients with established septic shock, and showed a renal blood flow decrease of approximately 20% compared with well patients post-cardiac surgery.[92] There is also limited information on tubular injury early in the course of sepsis.

The experimental data available show that the degree of tubular injury is generally mild and that acute tubular necrosis is uncommon.[84] However, even mild tubular injury can contribute to loss of GFR via activation of the tubuloglomerular feedback reflex.[93]

Sympathetic system activation[94] and neurohormonal responses unique to the kidney appear to be activated in the setting of AKI.[95] They include activation of the renin–angiotensin–aldosterone system, activation of the renal sympathetic system, and activation of the tubuloglomerular feedback system.[96] Such findings might reflect association rather than causation. However, their activation has been reported in experimental models of general anaesthesia, which also show markedly decreased renal blood flow by the administration of anaesthetic agents, even in the absence of surgery.[97]

Cardiorenal syndrome

In the case of acute decompensated heart failure, the condition of cardiorenal syndrome type 1 (AKI due to cardiac disease) can develop because of a low cardiac output state, renal vein congestion, or both.[98,99] Both conditions can affect kidney perfusion pressure while compensatory mechanisms can become insufficient to maintain blood flow autoregulation. Inflammation, neurohormonal activation, and concomitant drug toxicity with the presence of pre-existing kidney CKD can contribute to the development of the syndrome.[37,38,98,100–102]

Hepatorenal syndrome

The hepatorenal syndrome is perhaps the most extensively studied of the AKI syndromes in terms of neurohormonal changes.[103,104] This syndrome is associated with high amounts of activation of the renin–angiotensin–aldosterone system, suggesting that neurohormonally driven vasoconstriction leads to its development. In this regard, decreased systemic blood pressure secondary to systemic vasodilatation is considered a key event in triggering this response.[105]

Cardiac surgery-associated AKI

Mortality associated with cardiac surgery is low compared with that in the past, other major surgeries, and other causes in hospital, but the occurrence of AKI is common.[106] The pathophysiology of cardiac surgery-associated AKI remains poorly understood and multifactorial.[106] Key factors are likely to include postoperative low cardiac output (including right-heart failure), organ congestion, preoperative risk factors, predisposing conditions such as CKD, and diabetes (common in this population). Decreased perfusion and oxygen delivery during cardiopulmonary bypass are probably important and can be visually shown with microvascular imaging.[107,108] The effects of free haemoglobin together with systemic inflammation are likely to also be important.

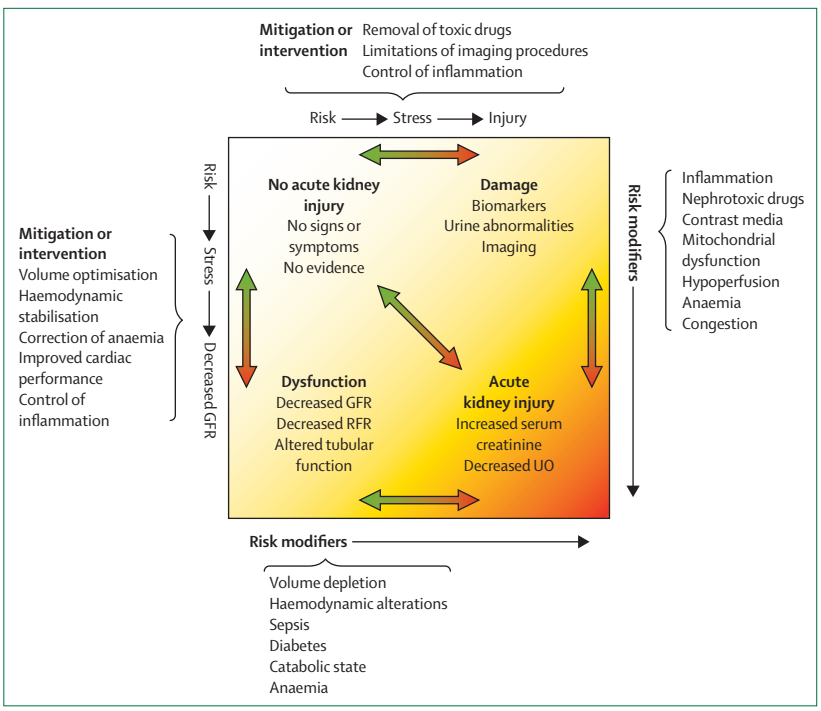

Figure 3: **Conceptual framework of AKI syndrome based on functional and damage criteria**
In the top left panel, no evidence of damage or dysfunction might identify a normal clinical condition; in the bottom left panel, a progressive decrease in GFR with increase in serum creatinine shows kidney dysfunction alone. This dysfunction might occur with the use of an angiotensin-converting-enzyme inhibitor, which can reduce GFR without damaging the kidney. In the top right panel, kidney damage is identified by specific biomarkers, but no dysfunction is present (normal serum creatinine). This condition has also been described as subclinical AKI. In the bottom right panel, both damage and dysfunction are present. Red arrows show progression, whereas green arrows show regression or recovery. Progression or regression can be affected by risk modifiers or by specific interventions. AKI=acute kidney injury. GFR=glomerular filtration rate. RFR=renal functional reserve. UO=urine output.

Distant organ effects of AKI

In many conditions, the presence of AKI can induce dysfunction or damage of distant organs. This effect on distant organs can be the case in cardiorenal syndrome type 3 (cardiac disease precipitated by or contributed to by AKI), in which the heart is affected with myocardial contractility defects and inflammatory infiltrates in the cardiac tissue. Another example is represented by the multiple interactions with the lungs.[109,110] The effect of acute or chronic uraemia on brain physiology and cognitive function has also been studied,[111] as have the effects of AKI on the liver.[111–113] There is a clear need to explore crosstalk and interactions between different organ systems in patients who are critically ill.[102,114–117]

The literature on complex syndromes with multiorgan involvement emphasises the need for multidisciplinary management. In these conditions, the level of multiple organ dysfunction makes combined forms of extracorporeal organ support highly recommended or even mandatory.[118,119]

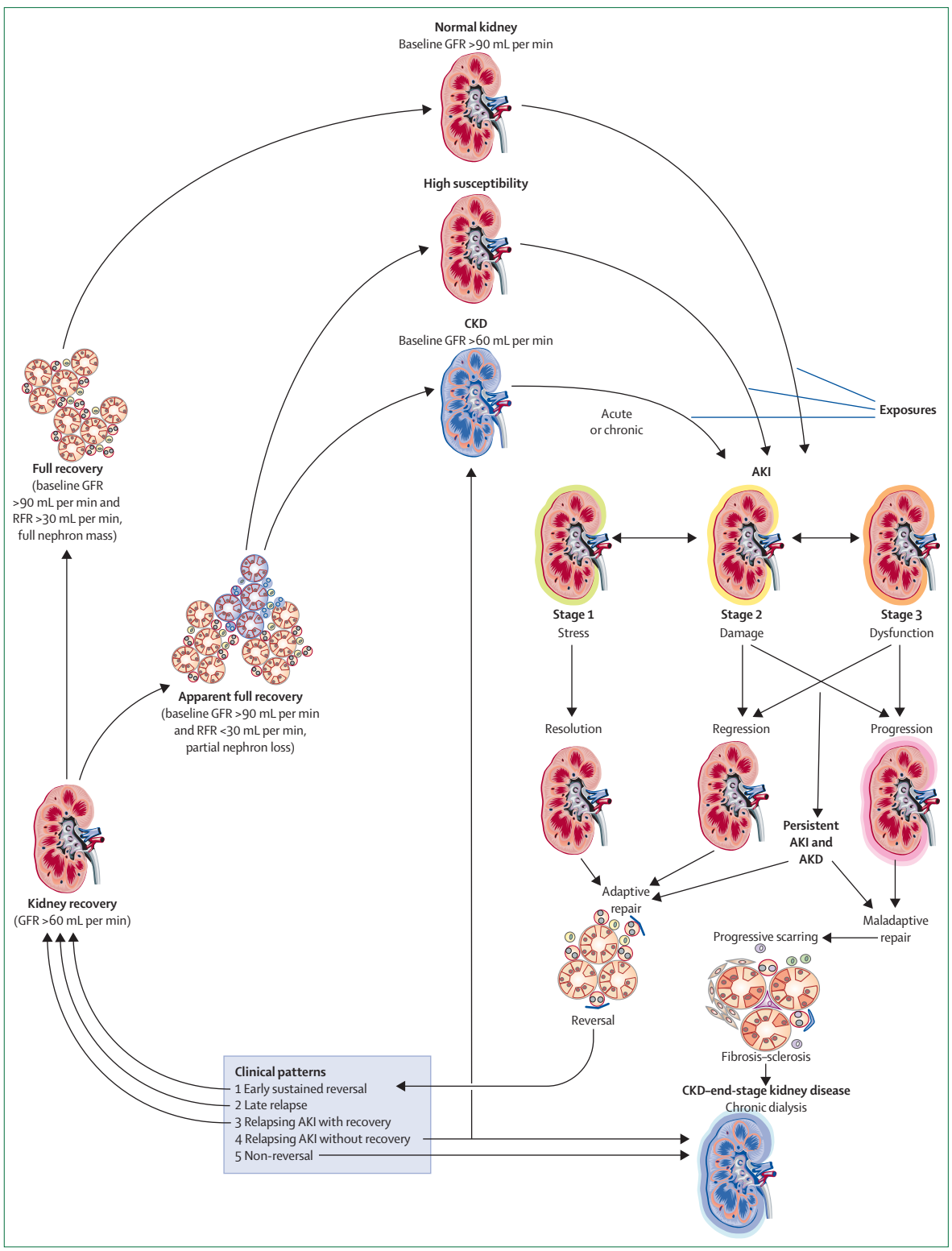

Figure 4: **The continuum of AKI**
Different original conditions are possible (normal, increased susceptibility, or CKD). When exposure causes injury or dysfunction or both, different outcomes are possible depending on risk modifiers and patient's response. Normal kidney: normal baseline GFR (>90 mL per min) and intact RFR (>30 mL per min); highly susceptible kidney: baseline GFR >90 mL per min and RFR <30 mL per min or previous history of AKI. AKI=acute kidney injury; syndrome defined by the current Kidney Disease Global Initiative diagnostic criteria and classified into three stages depending on values of serum creatinine and UO. Reversal is within 7 days. AKD=acute kidney disease; acute condition of the kidney that can precede, coexist, or follow an episode of AKI but not necessarily leads to or results from AKI. The temporal window is 90 days. AKD can reverse or progress to CKD. CKD=chronic kidney disease; a chronic condition of the kidney that might precede, coexist, or follow an episode of AKI. CKD is a steady state condition defined by Kidney Disease Global Initiative criteria into five stages. ESKD=end-stage kidney disease requiring dialysis (corresponds to stage 5 CKD). GFR=glomerular filtration rate. RFR=renal functional reserve. UO=urine output.

	Sample type	Class	Appearance or peak after injury*	Functional role in the kidney
Tissue inhibitor of metalloproteinase-2; insulin-like growth factor-binding protein 7	Urine	Stress	Immediately after cardiopulmonary bypass;[53] peaks at 6–24 h	Cell-cycle arrest: can induce cell-cycle arrest—thought to be a protective mechanism[8]
Neutrophil gelatinase associated lipocalin	Urine or plasma	Damage	<4 h after cardiopulmonary bypass;[54] peaks at 4–6 h	Iron trafficking: binds to iron-siderophore complexes in renal tubular epithelial cells; tubular epithelial genesis: forms an iron-siderophore complex (holo-neutrophil gelatinase associated lipocalin), which is secreted by the ureteric bud, and can induce the genesis of tubular epithelium;[55] anti-inflammatory and anti-apoptotic[56]
Kidney injury marker-1	Urine	Damage	12–24 h; peaks at 2–3 days[57]	Renal recovery and tubular regeneration: clearance of apoptotic bodies[58]; anti-inflammatory effect[59]
Liver-type fatty acid binding protein	Urine	Damage	Unknown	Fatty acid uptake and intracellular transport: mobilises lipid peroxides from cytoplasm of tubular epithelial cells to tubular lumen; *L-FABP* gene expression is increased by peroxisome proliferator activated receptor-α[60] and hypoxaemia[61]
Cystatin C	Serum or urine	Function	NA	None, filtration marker; cystatin C is normally taken up by renal tubular epithelial cells; as such its appearance in the urine indicates tubular dysfunction
Pro-enkephalin	Serum	Function	NA	None, filtration marker

NA=not applicable. *Available evidence for the time from injury to detection of the marker. Filtration markers have a variable relationship to injury so specific times are not possible to establish.

Table 2: **Characteristics of acute kidney injury biomarkers**

Prevention of AKI

The first principle of AKI prevention is to treat its cause or trigger. The second principle is to ensure that further insults are avoided. Systemic haemodynamics should be optimised so that, irrespective of the trigger, further damage does not occur and adequate renal perfusion and perfusion pressure are maintained. If intravascular volume is compromised, it must be rapidly restored by administration of intravenous fluids.

The extent of fluid administration and whether a degree of fluid overload is permissible remains unknown and is likely to be modulated by the clinical context. Such administration, however, must be both rapid and sufficient but also judicious (figure 6). In this setting, although of unproven benefit, haemodynamic monitoring is a standard of care. Such monitoring can be achieved by means of physical examination (ie, assessment of capillary return, peripheral skin perfusion, neck vein inspection, and measurement of blood pressure and heart rate).

However, in patients who are more severely ill, invasive haemodynamic monitoring (eg, central venous catheter, arterial cannula, and even cardiac output monitoring in some cases) is a standard of care. Adequate oxygenation and haemoglobin concentration (at least >70 g/L) must be maintained or rapidly restored. In 2019, a large randomised trial showed that such a restrictive approach does not increase the risk of AKI.[120]

If patients remain hypotensive (eg, mean arterial pressure [MAP] <65 mm Hg) after adequate intravascular volume expansion, restoration of MAP will require the addition of vasopressor drugs. If an adequate volume has been provided and MAP is also adequate, yet the patient develops AKI, cardiac output might be inadequate and needs to be measured. In this setting, correction of a low cardiac output state can require inotropic drugs or even mechanical devices. The importance of adequate fluid therapy in patients undergoing major abdominal surgery has been highlighted by the recent RELIEF trial.[121]

In a study of 3000 such patients, a restrictive intravenous fluid regimen, designed to provide a net zero fluid balance, was associated with an 8·6% rate of AKI compared with a 5·0% rate with standard fluid therapy (p<0·001). By contrast, in patients with septic shock, protocolised resuscitation resulted in more fluids administered but no decrease in the rates of AKI observed or its duration or severity.[12,122]

Fluid composition has also been the subject of substantial investigation. The use of hydroxyethyl starch has been shown to result in increased rates of AKI especially in patients with sepsis,[123,124] while saline has been shown to increase the risk for the composite of death, dialysis, and persistent renal dysfunction compared with fluids that are more similar to physiological ones such as Ringer's lactate solution.[125,127]

Avoidance of other nephrotoxic drugs is another important step in preventing AKI or shortening its course.[127] However, no specific drug-based intervention has been consistently and reproducibly shown to be kidney protective. Thus, there is no established pharmacotherapy for AKI. Among patients undergoing cardiac surgery, off-pump coronary artery bypass grafting has been shown to attenuate renal injury. However, the magnitude of effect is small and the inferior quality of grafting is a major concern.[128] AKI prevention and protection measures from further insults have been implemented in the past 3 years using urinary biomarkers for risk assessment. Biomarker-driven application of specific bundles derived from KDIGO recommendations, or structured organisation of nephrology rapid response teams has permitted reductions in the occurrence of severe AKI cases and the requirement of RRT in a substantial number of cases.[18,67]

Contrast-associated AKI is becoming less frequent because of reduced toxicity and lesser amounts of contrast media used for imaging techniques. However, prevention measures should still be considered for

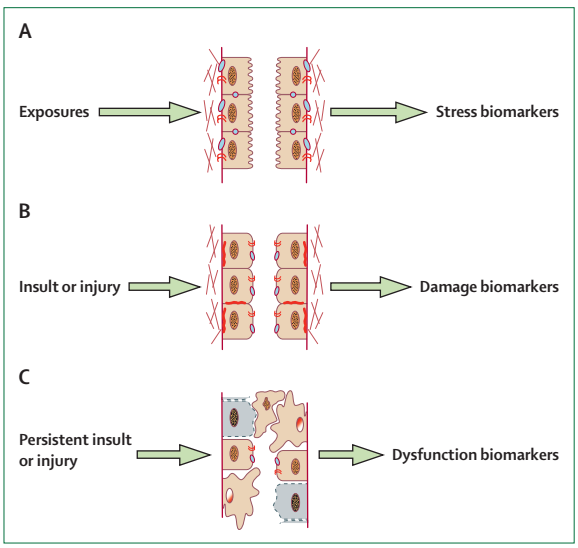

Figure 5: **Events in the development of acute kidney injury and relevant biomarkers**

(A) Cellular stress detected by cell-cycle arrest biomarkers (eg, tissue inhibitor of metalloproteinase-2 and insulin-like growth factor-binding protein 7). The condition is potentially reversible and cell damage might or might not occur. (B) Cellular damage characterised by alteration of cell metabolism and expression of adhesion molecules. The process is detected by damage biomarkers (molecules not appropriately handled at the tubular level like albumin and cystatin C, or constitutive or induced molecules at tubular level like N-acetyl-β-D-glucosaminidase and kidney injury molecule-1, or molecules produced by infiltrating immune cells like neutrophil gelatinase associated lipocalin and interleukin-18. (C) Exfoliation of viable cells into the tubular lumen with obstruction, necrosis, and apoptosis of tubular cells. Kidney dysfunction and decreased glomerular filtration rate detected by endogenous or exogenous filtration markers like cystatin C, creatinine, and dye.

individual patients, especially in particular settings such as oncology or interventional cardiology.[129–131] A pivotal multicentre randomised controlled trial has shown that N-acetylcysteine and bicarbonate do not provide additional protection beyond hydration therapy.[132]

Acute management of established AKI

Clinical and pharmacological management

Once AKI is both advanced and established, the focus of management should remain on delivering the same interventions used to prevent its development.[133] However, an additional focus of medical management should be directed to the prevention or rapid treatment of complications. Such management might vary in complexity from fluid restriction to the initiation of extracorporeal RRT. Nutritional support is an accepted standard of care. However, no level 1 studies exist to define what optimal nutritional therapy should be in patients with AKI. Calorie and protein intake, as for other patients in the hospital or ICU, seems acceptable. The use of specific renal nutritional solutions is not supported by evidence. There are no specific vitamins or trace element requirements. Potassium levels should be monitored. Hyperkalaemia (>6 mmol/L) should be promptly treated. If serum potassium is more than 7 mmol/L or electrocardiographic signs of hyperkalaemia appear, RRT should be rapidly implemented.

Metabolic acidosis is common but rarely requires treatment if mild or moderate. A randomised controlled trial of 389 patients in the ICU, however, has shown a potential beneficial effect of bicarbonate therapy in severe metabolic acidosis in association with AKI.[134]

Anaemia might require correction, and a target of more than 70 g/L is considered appropriate. To avoid drug toxicity or drug-induced complications, drug therapy must be adjusted to account for the loss of renal function. Stress ulcer prophylaxis has not been specifically studied in patients with AKI, but is considered advisable in patients who are ventilated in the ICU.[135] Great attention should be paid to the prevention of infection. Loop diuretics can help manage fluid balance in patients who are polyuric. However, in patients who are oliguric or have fluid overload, early RRT is advisable. Severe azotaemia (urea >30–35 mmol/L or creatinine >300–400 µmol/L) is best treated with RRT unless recovery is imminent or already under way.

Cardiorenal syndrome type 1 can be reversed resolving the condition of low cardiac output state or improving renal function. However, the pharmacological and supportive treatment should be paralleled with removal of toxic drugs, restricting imaging procedures with contrast agents, and control of the inflammatory response.[137]

Hepatorenal syndrome is a form of AKI. Several studies and meta-analyses suggest that a long-acting vasopressin derivative (terlipressin) improves GFR and probably patient outcomes in this condition.[137] However, this effect could simply be related to an increase in MAP, which can also be achieved with other vasoactive drugs and highlights the importance of perfusion pressure in this setting.[138] In addition, randomised controlled trials suggest that the addition of albumin to terlipressin could achieve further levels of renal protection.[139]

RRT and extracorporeal support

In some patients, AKI is severe enough to require RRT.[133,140,141] No single set of criteria exists to justify such intervention. However, clinicians must consider factors like potassium levels, fluid status, acid-base status, creatinine and urea levels, urine output, the overall course of the patient's illness, and the presence of other complications.[142]

The best time to start RRT remains controversial. Three randomised trials from 2016–17 have attempted to address this issue. The first[143] assigned 620 patients in the ICU with KDIGO AKI stage 3 to immediate RRT or delayed RRT (in which RRT was started in response to severe hyperkalaemia, severe metabolic acidosis, pulmonary oedema, 72 h of oliguria, or a blood urea concentration of >37 mmol/L). Such a delayed interventional strategy did not affect mortality, but decreased the use of RRT, the incidence of catheter-related bloodstream infection, and shortened the time to diuresis.

This trial was criticised for comparing late with very late RRT and for using intermittent haemodialysis (instead of continuous RRT) in a large proportion of patients, even though the majority of patients were on vasopressor therapy. The second trial[144] assigned 231 patients with KDIGO stage 2 AKI to early or delayed (within 12 h of stage 3 or not at all) RRT. It found that early RRT (all by continuous RRT) reduced mortality from 54·7% to 39·3% and increased the chance of renal recovery. This study was criticised for not being multicentric, including a cohort of only surgical patients, and being dominated by post-cardiac surgery AKI.[145] The third trial[146] focused on patients with sepsis and AKI in French ICUs and assigned 488 patients with septic shock with the equivalent of stage 3 KDIGO AKI to either RRT within 12 h or a delay of 48 h if renal recovery had not occurred.

The study found no significant differences in mortality or other patient-centred outcomes. It was, however, criticised for using intermittent haemodialysis in a third of patients despite the presence of shock, an uncommon approach in most ICUs in Australia, New Zealand, North America, and the UK. Furthermore, 9% of patients died during the delay of 48 h and another 17% required emergent RRT. In light of this continuing controversy, a much larger trial involving 3000 patients was started and is now close to completion.[147]

Once a decision is made to begin acute RRT, three forms of RRT are available: continuous RRT, intermittent RRT either in the form of intermittent haemodialysis or slow extended dialysis, and peritoneal dialysis.[148–150] Because of its clearance limitations, difficulty with fluid removal, and complications, peritoneal dialysis is rarely used in adults in high-resource countries[150] but is frequently used in many resource-limited countries. In such countries, there has been increased interest in its use as a logistically efficient method of dialysis. In this context, several studies have reported satisfactory performance and outcomes.[150,151]

There is much controversy as to whether intermittent or continuous RRT should be used. No suitably powered randomised controlled trials have been done to address this issue. The small to medium sized studies done, however, do not suggest a difference in patient survival. Accordingly, on the basis of patient survival, intermittent haemodialysis, slow extended dialysis, or continuous RRT all appear acceptable options for RRT.[152] However, a body of observational evidence and meta-analyses suggest that, compared with continuous RRT, the use of intermittent haemodialysis might be associated with delayed renal recovery.[153]

After a seminal study of RRT intensity,[154] two large multicentre randomised controlled studies (the ATN study[155] and the RENAL study[156]) have defined the standard for

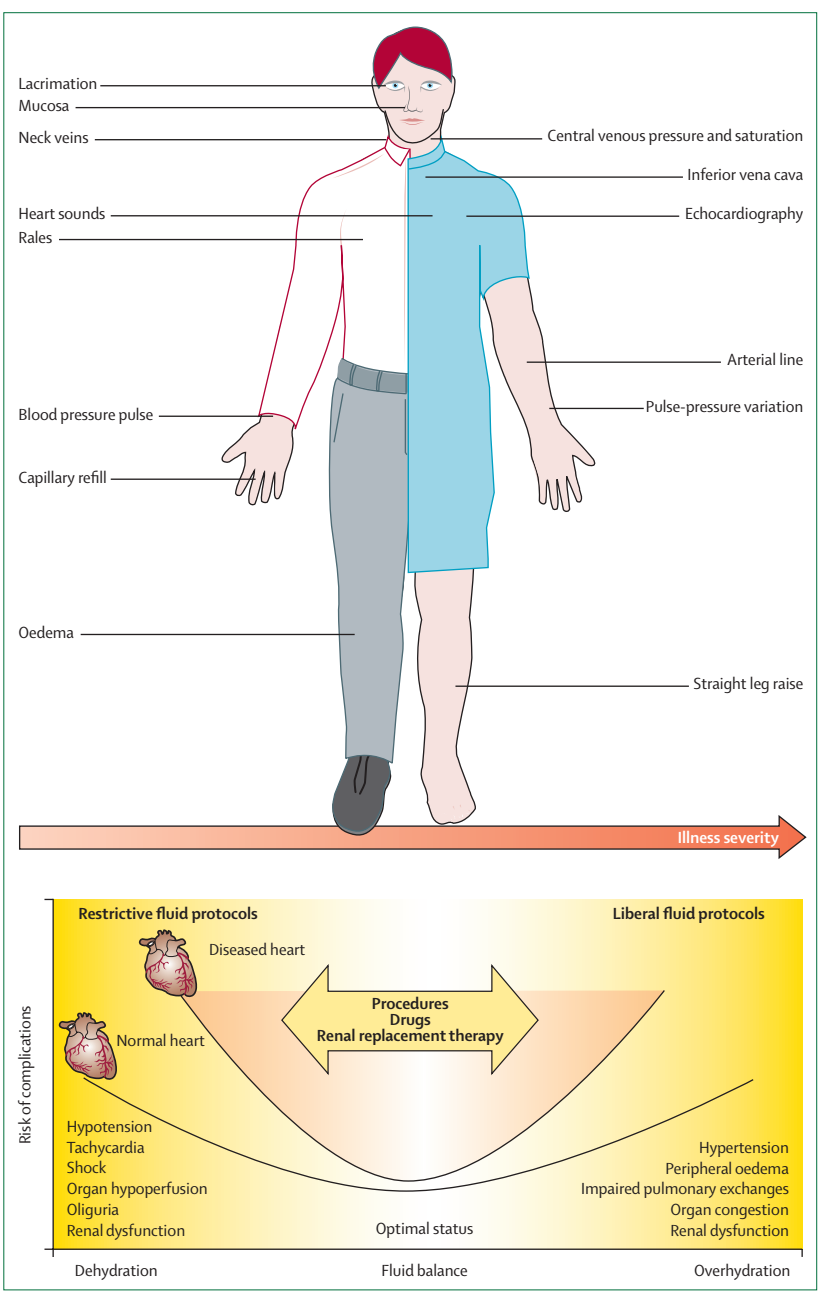

Figure 6: **Risk for complications related to fluid balance in patients with normal and compromised heart function**

In a non-critically ill patient (left) fluid status is assessed by history and physical examination. In the proper context (eg, diarrhoeal illness) with consistent signs and symptoms (eg, dry mucous membranes, increased thirst), physical examination findings will often suffice. In more complex patients (eg, underlying congestive heart failure) or in those with critical illness (eg, septic shock), more invasive methods will often be required (illustrated by the right side of the figure). Little evidence exists that one form of functional haemodynamic monitoring is superior to another but dynamic measures (eg, pulse-pressure variation) are superior to static measures (central venous pressure). Bottom panel: relationship between hydration status and complications in acute kidney injury is a u-shaped curve. In the case of fluid restrictive protocols, the patient might experience hypotension and organ hypoperfusion perpetuating the damage to the kidney. The same problem can occur in case of too liberal policies where the congestive state might impair kidney function and cause severe clinical complications.

solute removal intensity at a delivered dose of continuous RRT equivalent to 20–25 mL/kg per h of effluent generation. Importantly, in both studies, all patients with AKI on vasopressor support received continuous RRT, implying that continuous RRT is considered the standard of care in patients who are haemodynamically unstable.[157]

Although these two pivotal trials defined the standard of solute clearance, no large multicentre randomised controlled trials have yet addressed the issue of volume control. Thus, even though there is concern about the impact of a positive fluid balance on renal and patient outcomes,[158] volume management remains guided by individual clinical judgment.[159] Once RRT is started, there is uncertainty about when it should be stopped. No randomised controlled trials have addressed this issue. Observational studies have suggested that a spontaneous urine output of more than 500 mL per day seems to have sufficient discrimination to be used for the purpose of considering a trial of continuous RRT cessation.[160]

In the appendix, we schematically summarise the subsequent steps that should be considered and implemented from the first patient observation to the development of AKI and the prescription of RRT. Once the targets for RRT have been identified, the right prescription in terms of modality and operational parameters should be made, ensuring continuous monitoring and a data-driven feedback on therapy modification. In this process, technology can help to prescribe, deliver, and monitor the treatment and to modify the various steps based on personalised dynamic criteria.[161–166]

AKI as a risk factor for CKD

Over the past decade, multiple studies have shown a strong epidemiological link between AKI and the subsequent development of CKD.[167–172] The additional risk of end-stage kidney disease after AKI has been estimated at an additional 0·4 extra cases per 100 person-years, and the additional risk of CKD after AKI has been estimated at ten extra cases per 100 person-years.[171] If the link between AKI and CKD is causal, the public health consequences of AKI in terms of CKD and end-stage kidney disease epidemiology are substantial.

Several mechanisms have been proposed, which once triggered by AKI, could contribute to the development of CKD. These mechanisms can be activated by AKI independently of the cause or trigger[173] and involve a process that has been termed maladaptive repair[174] (figure 4). In experimental models, this process appears to involve transformation of tubular cells into fibroblasts, inflammatory cells are recruited, which also contribute to the secretion of pro-fibrotic cytokines, the transition of endothelial cells to mesenchymal cells, pericyte transformation into myofibroblasts, and activation of multiple processes that resemble those seen with renal senescence.[175–178]

These observations suggest that optimisation of post-AKI care might be an important novel aspect of AKI management.[179] Importantly, however, not all episodes of AKI lead to death or to CKD, so studies evaluating the effects of short-term interventions to prevent AKI on long-term outcomes will need much larger sample sizes. Two recent studies from 2017 and 2018 evaluating balanced crystalloids compared with saline have shown small effects.[125,126] Both trials found small effects on rates of death, dialysis, and persistent kidney dysfunction favouring balanced fluids, and each study required enrolment of more than 10 000 patients.

Post-AKI care

Patients with AKI tend to have worse medium-term to long-term outcomes than other patients who did not develop AKI.[180,181] This observation suggests the opportunity to improve care by close follow-up of patients who have one or more episodes of AKI during hospital or ICU admissions.[182] These patients seem particularly fragile and might require specific medical interventions.[183] Of course, this extension of care will require additional resources and might be challenging to do in many communities. Risk prediction models that can identify patients at high risk for subsequent CKD following AKI could be very helpful in targeting patients most likely to benefit from this care.[184]

Conclusion

AKI is undergoing substantial evolution in terms of definition and classification, understanding of pathophysiological mechanisms, and interaction with other disciplines and organ systems. Epidemiology describes an increasing incidence partly due to a more thorough clinical evaluation and detection. New biomarkers and advanced diagnostic techniques represent an important advancement in the field, leading to implementation of timely and effective preventive and protective measures.

The management of patients with AKI has improved together with the improvements in hospital and intensive care quality, supported in part by sophisticated technology of extracorporeal organ support, a more personalised pharmacological therapy, and a standardised and protocolised management of physiological endpoints. This Seminar reports on the new concepts that have emerged in the past 5 years corroborated by the most recent contributions to the literature. In many areas, controversies still exist but consensus has been reached in several protocols and treatments so that true benchmarking and quality control are possible.

Several regions are still left behind and preventable causes of AKI should be reduced or eliminated. Access to new technologies might also be limited in several geographical areas and this limitation will represent a challenge for the near future: a sustainable and effective approach to this deadly syndrome, which is affordable and effective in large populations and communities where death and complications still occur at unacceptable frequency.

Contributors
All authors contributed equally to the manuscript, writing sections of initial draft and then each revising other sections.

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