Diagnosis of acute kidney injury: Kidney Disease Improving Global Outcomes criteria and beyond

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Purpose of review
Acute kidney injury (AKI) is common. Clear criteria and accurate diagnostic tools are essential to diagnose AKI early and correctly. The aims of this review are to outline some of the pitfalls of the Kidney Disease Improving Global Outcomes (KDIGO) classification and to describe other traditional and novel tools to diagnose AKI.

Recent findings
The KDIGO classification of AKI is based on changes in serum creatinine and urine output. Misdiagnosis of AKI can occur when using only the KDIGO criteria. Potential pitfalls are related to the fact that neither creatinine nor urine output are renal-specific. Other traditional tools to diagnose AKI are blood urea nitrogen, urine chemistry, urine microscopy and renal biopsy. New diagnostic tools, including novel AKI biomarkers and techniques to measure glomerular filtration rate in real time, are being developed and validated.

Summary
Knowledge about the strengths and weaknesses of traditional diagnostic tests is essential to make the correct diagnosis of AKI. New tests and technical innovations offer the prospect of diagnosing AKI earlier and more accurately.

Keywords
acute kidney injury, biomarker, definition, diagnosis, Kidney Disease Improving Global Outcomes classification

INTRODUCTION

Acute kidney injury (AKI) is a syndrome which affects 13–18% of patients admitted to hospital. It is particularly common in patients in the ICU. The impact and prognosis of AKI vary considerably depending on severity, setting (ICU versus non-ICU) and comorbid factors. There is increasing evidence that AKI is associated with significant short and long-term complications, increased mortality and a major impact on healthcare resources [1,2▪▪,3▪]. Prevention and early diagnosis are crucial.

In the last 10 years, the definition of AKI has evolved from the development of the Risk, Injury, Failure, Loss, End-stage criteria in 2004 [4] to the generation of the AKI Network classification in 2007 [5]. In 2012, the Kidney Disease Improving Global Outcomes (KDIGO) committee addressed the important need for a single definition of AKI and merged the Risk – Injury – Failure – Loss – End-stage and AKI Network criteria into a uniform definition [6] (Table 1).

These efforts to standardize the AKI definition are clearly a major achievement and have led to earlier diagnosis and more streamlined management. Although the KDIGO criteria of AKI are very useful to identify patients with AKI, there are patients who have clear evidence of AKI but do not meet the KDIGO criteria, and there are also patients who meet the KDIGO criteria but have not had a significant change in their renal function. The aims of this review are to outline some of the pitfalls of the KDIGO classification, to describe other traditional diagnostic tools to diagnose AKI, and to summarize the current state of novel methods, including biomarkers for AKI and techniques to measure glomerular filtration rate (GFR) in real time.

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KEY POINTS

- Traditional diagnostic tools to diagnose AKI include serum creatinine, blood urea nitrogen, urine output, urine chemistry, urine microscopy and histology. Knowledge of their strengths and limitations is essential to avoid the incorrect diagnosis of AKI.
- The KDIGO definition of AKI is based on changes in serum creatinine and urine output, both of which are not renal-specific. When using only the KDIGO criteria, overdiagnosis and underdiagnosis of AKI can occur.
- The use of new AKI biomarkers offers the prospect of earlier diagnosis of AKI, but evidence that their use changes outcomes is still lacking.
- The validation of novel measurements of GFR in near real-time provides an opportunity for faster and more accurate monitoring of renal function and earlier diagnosis of AKI.

KIDNEY DISEASE IMPROVING GLOBAL OUTCOMES CRITERIA FOR DIAGNOSIS OF ACUTE KIDNEY INJURY

The current KDIGO definition of AKI is entirely based on changes in serum creatinine and urine output (Table 1). Both tests are easily available and cheap but not renal-specific [7,8,9▪,10▪]. The main concerns are that serum creatinine concentrations are affected by muscle mass, can change in response to certain drugs without change in renal function, are not reliable in patients with liver disease and take 24–36 h to rise after a definite renal insult. Urine output can persist until renal function almost ceases and can also be manipulated by diuretics. Importantly, oliguria may be an appropriate response in the setting of hypovolaemia reflecting under-resuscitation rather than injury to the kidney [7].

As per KDIGO classification, AKI is diagnosed if serum creatinine increases by at least 0.3 mg/dl (≥26 μmol/l) in 48 h or rises to at least 1.5-fold from baseline within 7 days (Table 1). This recommendation is based on a landmark study by Chertow *et al.* [11] who analysed the data of 9210 patients admitted to one academic medical centre and showed that a rise in creatinine of at least 0.3 mg/dl was independently associated with an approximately four-fold increase in hospital mortality. Others have reported that even smaller creatinine rises are associated with an increased mortality risk compared with no change in serum creatinine [12].

The obvious question is whether such small changes in serum creatinine always represent changes in renal function. In patients with normal kidney function, a rise in serum creatinine by 0.3 mg/dl may indeed be due to an important reduction in GFR. However, as pointed out by representatives of the National Kidney Foundation – Kidney Disease Outcomes Quality Initiative, in patients with underlying chronic kidney disease (CKD), the same rise in serum creatinine may be within the acceptable daily variation and simply reflect an inconsequential change in GFR [7]. In contrast, in children, an absolute change in serum creatinine by 0.3 mg/dl may indicate relatively large changes in GFR. The KDIGO classification, in its current version, does not take into account baseline renal function and underlying renal reserve. Therefore, some caution is necessary when interpreting small creatinine changes and making the diagnosis of AKI in patients with advanced CKD.

The criteria for AKI stage 3 deserve some special mention. KDIGO recommends that patients with a rise in creatinine to at least 4.0 mg/dl (≥354 μmol/l) should be classified as AKI stage 3 as long as the rise is at least 0.3 mg/dl (≥26 μmol/l) in 48 h or at least 50% in 7 days. As already mentioned, absolute rises in serum creatinine represent different changes in GFR in patients with CKD compared with those who have normal renal function. For instance, a patient with a baseline serum creatinine of 3.9 mg/dl (345 μmol/l) and a creatinine rise of 0.3 mg/dl in 48 h is classified as having KDIGO AKI stage 3, whereas such a rise in a patient with normal baseline renal function is defined as AKI stage 1.

It is clear from epidemiological studies and histological case series that some patients have a slow but persistent (creeping) rise in creatinine level but do not fulfil the criteria for AKI [13▪,14]. Strict application of the current KDIGO criteria will miss these patients and wrongly classify them as 'no AKI'.

The use of weight-based urine output criteria for AKI has attracted some criticism, too, because it may be misleading in obese patients and result in the overdiagnosis of AKI. The European Renal Best Practice Guidelines (2012) recommend using the ideal weight rather than the true weight when calculating urine output in ml/min/kg to avoid a misdiagnosis of AKI [8].

The KDIGO definition of AKI is based on changes of serum creatinine and urine output within a specific time frame. Additional tests are usually necessary to diagnose the underlying cause of AKI. Occasionally, they may also be required to make the diagnosis of AKI, especially in cases in which the creatinine and urine results cannot be interpreted accurately, are misleading, or change only very slowly.

Table 1. RIFLE, AKIN and KDIGO classifications for acute kidney injury

	Serum creatinine criteria			Urine output criteria of all classifications
	RIFLE classification	**AKIN classification**	**KDIGO classification**	
Definition of AKI		Increase in serum creatinine of either ≥0.3 mg/dl (≥26.4 μmol/l) or a percentage increase of ≥50% (1.5-fold from baseline) in 48 h	Rise in serum creatinine by ≥26 μmol/l over ≤48 h, or to ≥1.5-fold from baseline which is known or presumed to have occurred in the preceding 7 days	
Stage I or RIFLE Risk	Increase in serum creatinine to ≥1.5 to two-fold from baseline, or GFR decrease by >25%	Increase in serum creatinine by ≥26 μmol/l (>0.3mg/dl) or increase to more than or equal to 1.5-fold to two-fold from baseline	Rise in serum creatinine by ≥26.5 μmol/l in 48 h, or rise to 1.5–1.9 times from baseline	<0.5 ml/kg/h for >6 h
Stage II or RIFLE Injury	Increase in serum creatinine to >two-fold to three-fold from baseline, or GFR decrease by >50%	Increase in serum creatinine to more than two-fold to three-fold from baseline	Rise in serum creatinine 2.0–2.9 times from baseline	<0.5 ml/kg/h for >12 h
Stage III or RIFLE Failure	Increase in serum creatinine to >three-fold from baseline, or to ≥354 μmol/l with an acute rise of at least 44 μmol/l, or GFR decrease by >75%	Increase in serum creatinine to more than three-fold from baseline, or to ≥354 μmol/l with an acute rise of at least 44 μmol/l, or treatment with RRT irrespective of the stage at the time of RRT	Rise in serum creatinine three times from baseline, or increase in serum creatinine to ≥353.6 μmol/l, or initiation of RRT irrespective of serum creatinine	<0.3 ml/kg/h for 24 h or more, or anuria for 12 h
RIFLE Loss	Complete loss of kidney function for >4 weeks	–	–	
End-stage kidney disease	End-stage kidney disease for >3 months	–	–	

AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; GFR, glomerular filtration rate; KDIGO, Kidney Disease Improving Global Outcomes; RIFLE, Risk, Injury, Failure, Loss, End-stage; RRT, renal replacement therapy.

TRADITIONAL MARKERS OF RENAL FUNCTION

In addition to serum creatinine and urine output, traditional tools to diagnose AKI and to distinguish intrinsic AKI from prerenal AKI include blood urea nitrogen, urine chemistry, urine microscopy and histological examination (Table 2).

Urea

Urea is generated in the liver following metabolism of amino acids and excreted primarily by glomerular filtration. Serum concentrations can be affected by changes in urea production (i.e., gastrointestinal bleed) and changes to tubular absorption during periods of hypovolaemia. This makes urea an unreliable marker of renal function.

Fractional excretion of sodium

Traditionally, the fractional excretion of sodium (FeNa) has been advocated to differentiate between prerenal and established AKI. Its use is based on the fact that intact tubules reabsorb sodium, whereas injured tubules do not. A FeNa less than 1% is traditionally quoted as characteristic of 'prerenal AKI'. In conditions associated with acute tubular injury or established AKI, FeNa is classically more

Table 2. Traditional and novel diagnostic tools

Diagnostic test	Strengths	Weaknesses
Serum creatinine	easily available	not renal-specific
	low cost	late marker after renal injury
		serum levels confounded by muscle mass, drugs, laboratory technique, fluid status
Blood urea nitrogen	easily available	not renal-specific
	low cost	serum levels confounded by liver disease, gastrointestinal bleed and hypovolaemia
FeNa	easily available	difficult to interpret in patients with chronic kidney disease
	low cost	confounded by diuretic treatment
Urine microscopy	noninvasive	operator-dependent
	low cost	requires training and experience
	can provide very valuable information if done properly, (i.e., red cell casts in case of glomerulonephritis)	
Renal histology	can provide very valuable information about cause of AKI and degree of chronic changes	invasive
		requires competency
		bleeding complications
Novel AKI biomarkers	opportunity to diagnose AKI before creatinine rise	costs
	may provide additional diagnostic and prognostic information	significant confounders
Techniques to measure real-time GFR	opportunity to monitor GFR in real time and to diagnose AKI early	costs
		not yet available in clinical practice
		requires training and experience

AKI, acute kidney injury; FeNa, fractional excretion of sodium; GFR, glomerular filtration rate.

than 1%. However, various acute diseases and diuretic administration disturb the typical tubular response and may lead to misleading results [15].

Urine microscopy

Microscopy of a fresh noncatheterized urine sample can yield important diagnostic information, especially if a glomerular disorder or vasculitis is suspected in which case it may show dysmorphic red cells or red cell casts. It may also help to differentiate prerenal AKI from acute tubular injury. Classically, in prerenal AKI, the sediment is bland or may contain hyaline casts, whereas free epithelial tubular cells or cellular casts may be seen in AKI due an ischaemic or nephrotoxic insult. Unfortunately, in clinical practice, urine microscopy is often less clear-cut, especially as both conditions may coexist.

Urine microscopy appears to have utility not only in diagnosing specific renal disorders but also in predicting severity of AKI and outcome. In 2008, Chawla *et al.* [16] reported that an 'AKI cast scoring index' based on tubular and granular casts was predictive of severity and nonrecovery from AKI. In 2010, Perazella *et al.* [17] showed that urine microscopy and a modified urine sediment score were predictive of progressive AKI, need for renal replacement therapy and death.

However, despite these positive results and its low cost, urine microscopy is not utilized very often any more, predominantly because it is operator-dependent and requires training and experience and ideally a fresh noncatheterized urine sample.

Renal biopsy

Occasionally, a renal biopsy may be necessary to diagnose the exact cause of AKI after prerenal and obstructive causes have been eliminated and concern about an underlying parenchymal or glomerular renal disease exists. It can provide information which is often not available through other means. However, in critically ill patients, it is only rarely performed mainly because of concerns about bleeding and the perceived low yield.

Interestingly, Chu *et al.* [13▪] showed that diffuse histologic changes of AKI can be present without sufficient changes in serum creatinine. Among 303 patients with biopsy-proven acute parenchymal renal lesions including acute interstitial nephritis, crescentic glomerulonephritis and acute thrombotic microangiopathy, only 198 patients (65%) had creatinine or urine output changes which met the KDIGO criteria for AKI. The main reason for not fulfilling the criteria for AKI was a slower creatinine rise than that required by the KDIGO classification.

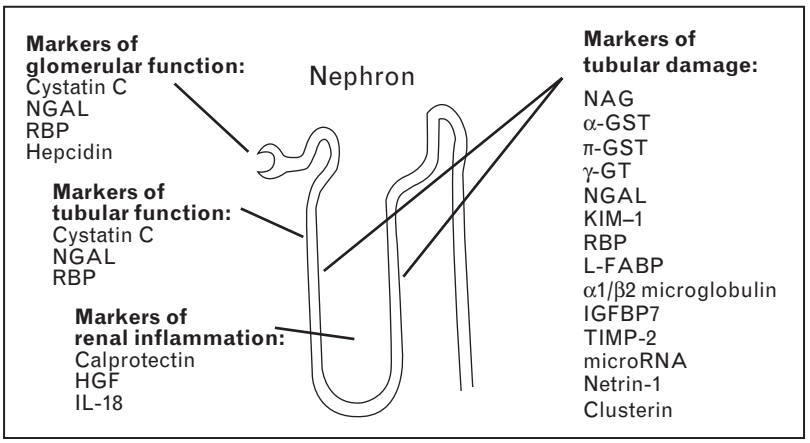

FIGURE 1. Origin and function of novel acute kidney injury biomarkers. GST, glutathione S-transferase; γ-GT, γ-glutamyl transpeptidase; HGF, hepatocyte growth factor; IGFBP-7, insulin-like growth factor-binding protein-7; IL-18, interleukin 18; KIM-1, kidney injury molecule-1; L-FABP, liver-type fatty acid-binding protein; NAG, *N*-acetyl-β-D-glucosaminidase; NGAL, neutrophil gelatinase-associated lipocalin; RBP, retinol-binding protein; TIMP-2, tissue metalloproteinase-2.

NOVEL DIAGNOSTIC TOOLS

There is an ongoing search for more accurate and sensitive tests to diagnose early AKI.

Biomarkers

The availability of new renal biomarkers provides additional tools to identify patients with AKI, especially in settings in which the creatinine rise is delayed or difficult to interpret [18▪▪,19▪▪]. Biomarkers of AKI vary in their origin, function, distribution and time of release following renal injury (Fig. 1). They can be broadly divided into the following:

(1) Markers of glomerular function: small molecular weight proteins that are present in the systemic circulation and undergo glomerular filtration (i.e., serum creatinine, cystatin C).
(2) Markers of tubular function: molecules that are filtered and undergo tubular reabsorption (i.e., retinol-binding protein).
(3) Markers of tubular injury, damage or repair: molecules that are released as a result of direct renal cell damage, inflammatory activation or following gene upregulation [i.e., kidney injury molecule-1 (KIM-1), interleukin-18 (IL-18), tissue metalloproteinase-2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP7)].

The most-studied biomarkers are neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, KIM-1 and IL-18. Although the use of most biomarkers is still predominantly limited to research studies, cystatin C and NGAL have been commercialized and are now available in some hospital laboratory platforms.

The performance of most biomarkers is variable and depends on the patient case-mix, cause of AKI, clinical setting, associated comorbidities and timing of biomarker measurements. In homogeneous populations, such as after cardiopulmonary bypass surgery, biomarkers such as NGAL, KIM-1, cystatin C and IL-18 have been found to detect AKI before serum creatinine changes significantly [20–24]. However, in heterogeneous populations with diverse acute and chronic medical problems, such as patients in the ICU or in the emergency department, individual biomarker performance is reduced [20,25].

Recent studies identified a unique cohort of patients with a transient elevation in urinary and plasma NGAL levels without detectable changes in serum creatinine [26,27]. Affected patients had a greater risk of complications, a longer stay in ICU and a higher risk of dying compared with patients without elevated NGAL levels. A review of 10 large observational NGAL studies including 2322 critically ill patients with predominantly cardiorenal syndrome showed that both the cohort of biomarker-positive, creatinine-negative patients and the creatinine-positive, biomarker negative group had an increased risk of renal replacement therapy and mortality [26]. Similarly, two studies in critically ill patients with a clinical diagnosis of 'prerenal AKI' showed that levels of cystatin C, IL-18 and KIM-1 were detected at concentrations intermediate between patients without AKI and those with AKI for more than 48 h [28,29]. These latter observations

suggest that what is often described as 'prerenal AKI' may simply be the mild end of a continuum of renal injury, rather than a reversible functional form of AKI without cellular damage.

Some studies have evaluated biomarker panels rather than individual markers in isolation. For instance, in a diverse population of 744 critically ill patients without evidence of AKI at enrolment, the product of urinary (TIMP-2) × (IGFBP7) performed well at predicting development of moderate-to-severe AKI (area under the receiver operating characteristic 0.80) [30]. Performance was significantly superior to all previously described markers of AKI. In a follow-up study, Bihorac *et al.* [31▪] validated this biomarker combination in a separate cohort of 420 critically ill patients and confirmed that a urinary (TIMP-2) × (IGFBP7) greater than 0.3 $(ng/ml)^2/1000$ identified patients at risk for imminent AKI (sensitivity 92%). Critically ill patients with (TIMP-2) × (IGFBP7) more than 0.3 $(ng/ml)^2/1000$ had seven times the risk of AKI compared with critically ill patients with a test result below 0.3.

The decision how to utilize novel biomarkers in critically ill patients remains a challenge, in particular, in light of the dynamic nature of AKI and the presence of confounding factors. The problem is complicated further by the fact that the results of biomarker tests may depend on the laboratory method used. Glassford *et al.* [32▪] measured total plasma and urine NGAL and different subtypes of NGAL simultaneously in a cohort of ICU patients using different commercially available immunoassays and research assays and found significantly different results depending on the method used.

There is an expectation that some of the new biomarkers will be incorporated into future definitions of AKI. In 2011, the international Acute Dialysis Quality Initiative group recommended the addition of biomarkers to the definition, staging and differential diagnosis of AKI to complement the KDIGO classification [19▪▪]. Although this is a logical proposal, to date, there are insufficient quantitative biomarker data for AKI staging. Also, biomarker-guided interventions have not yet been shown to improve outcome [20,33].

MEASUREMENT OF GLOMERULAR FILTRATION RATE

In clinical practice, GFR cannot be measured directly. However, several investigators, often in collaboration with commercial companies, are working on the development of techniques to measure GFR in real time. Rabito *et al.* [34] demonstrated that such monitoring is possible. They measured external whole tissue radioactivity after intravenous injection of Tc-labeled diethylenetriaminepentaacetic acid and showed that this method represented an accurate, fast and convenient way to measure total and individual kidney GFR. Commercial attempts have been initiated to develop rapid, sensitive, reproducible and affordable techniques to measure real GFR and to diagnose AKI early [35,36]. Knowing the actual GFR would not only define and stage AKI earlier and more accurately but also improve clinical management, for instance drug dosing.

NOVEL IMAGING TECHNIQUES

Magnetic resistance imaging is being investigated for the measurement of GFR [37▪▪]. However, given its complexity, costs and need for patient transport, its use is likely to remain limited to the research setting.

CONCLUSION

To date, the diagnosis of AKI is based on traditional markers of renal function. Knowledge about their strengths and weaknesses is crucial to avoid underdiagnosis and overdiagnosis of AKI (Table 2). The KDIGO classification is based on changes in serum creatinine and urine output and provides consensus criteria for defining AKI. The development of new diagnostic tools, including biomarkers and techniques to measure GFR in real time, offers new opportunities and the prospect of diagnosing AKI earlier and more accurately.

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Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
- ▪▪ of outstanding interest

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This excellent review describes traditional and future tools to measure GFR.

Systemic consequences of acute kidney injury

Wilfred Druml

Purpose of review
Acute kidney injury (AKI) is a frequent and serious event associated with a high rate of complications, with an increased risk of progression to multiple organ dysfunction and excessive 'attributable' mortality. AKI affects all physiologic functions and organ systems with interrelated mechanisms, including the 'classical' consequences of the uremic state, the inflammatory nature of AKI *per se* and resulting systemic effects, the modulating effect of AKI in the presence of an (inflammatory) underlying disease process and the multiple untoward effects induced by renal replacement therapy (RRT) and anticoagulation.

Recent findings
A rapidly increasing body of evidence is clarifying these systemic effects that are the reflection of a broad common pathology that ultimately results in an 'augmented' inflammation and impairment of immunocompetence. This includes the release of cytokines and inflammatory mediators, increase in oxidative stress, activation of various immune cells, neutrophil extravasation, generalized endothelial injury, increased vascular permeability and tissue oedema formation.

Summary
These systemic phenomena associated with AKI induce distant organ injury affecting all organ systems with clinically the most relevant effects being exerted on the lungs, the intestines and liver and the heart and predispose the progression to multiple organ dysfunction syndrome and death. Currently available renal replacement therapy modalities are incapable of compensating for these systemic consequences of AKI.

Keywords
acute kidney injury, distant organ injury, immunocompetence, inflammation, systemic effects

INTRODUCTION

Until quite recently, many nephrologists and also intensivists were convinced that acute kidney injury (AKI) is a rather harmless complication because renal function can easily and practically indefinitely be supported by modern renal replacement therapies (RRTs). For many decades, the opinion prevailed that a patient is dying not from but rather just with AKI, that survival is determined by the severity of the underlying disease but not by renal dysfunction *per se*.

A rapidly increasing body of evidence is contradicting this conventional view and underlines the fact that AKI presents an extremely serious complication in a critically ill patient that exerts a fundamental impact on the course of disease, the evolution of associated complications and on prognosis independent of the type and severity of the underlying disease process, so that patients are (also) dying of sequelae of AKI and also of side effects of currently available renal replacement modalities, respectively [1,2].

Already in 1996, Levy *et al*. [3] have shown in a cohort analysis in patients with contrast-induced nephropathy that patients who have acquired AKI have a 6.5 times elevated risk of dying as compared with patients with the same severity of illness but without AKI. Individuals who died after developing AKI had a complicated clinical course characterized by sepsis, bleeding, delirium and respiratory failure; most of these complications occurred after the onset of AKI, but deaths from conventional 'renal causes' were rare.

In still the largest study to date and the first study in critically ill patients, the impact of AKI requiring RRT on prognosis was evaluated in an Austrian multicentre trial [4]. The risk of dying was four times higher in patients with AKI than in individuals without the need for RRT (62.8 vs.

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KEY POINTS

- Acute kidney injury (AKI) is a systemic disease process affecting all physiologic functions and organ systems of the body and exerting a fundamental 'attributable' impact on the course of disease, associated complications and prognosis.
- The interrelated mechanisms by which these systemic side effects are mediated include the acute uremic state, the injured kidney as an inflammatory focus, modulation of the underlying disease process and the multiple untoward side effects of renal replacement therapy.
- These multiple consequences of AKI are the reflection of a common underlying pathology that can be labelled as 'augmented inflammation' and is also associated with a profound impairment of immunocompetence.
- The side effects induce a broad pattern of distant organ injury with the clinically most relevant organs affected being the lungs, the intestines and liver and the heart and predispose the progression to MODS and death.
- Currently available renal replacement modalities cannot compensate for these multiple untoward side effects and more effective techniques of renal support will have to be developed to improve the dismal prognosis of patients with AKI.

15.8%). In a case–control comparison of patients with AKI and controls matched for age, sex, severity of disease and treatment centre, there was still a 67% increase in mortality in patients with AKI after adjustment ($P < 0.01$).

These findings were confirmed in many subsequent studies on various patient populations with AKI [5,6]. Just recently, in a large Finnish multicentre trial, the 'attributable' risk of 90-day mortality associated with AKI was 19.6% [7▪▪].

The prognosis of AKI has not fundamentally changed during the last decades with mortality still exceeding 60% for ICU patients with AKI stage 3 requiring RRT [4]. Currently available 'renal replacement' modalities that admittedly are rather simple cannot really replace the multiple metabolic, endocrine and also immunologic renal functions. Thus, these modalities are incapable of compensating for the broad spectrum of negative consequences of AKI.

MECHANISMS BY WHICH ACUTE KIDNEY INJURY EXERTS SYSTEMIC SIDE EFFECTS

The mechanisms by which an AKI exerts such a fundamental impact on the course of disease and outcome have been a major focus of research during resent years and are increasingly understood. AKI certainly is not a disease process restricted to the kidneys, and is not only associated with the 'classical' complications of acute uremia such as derangements in electrolyte and volume homeostasis but exerts profound effects on practically all biologic functions and organ systems of the body [8]. We have to recognize that AKI presents as a pan-metabolic, pan-endocrine and pan-organ problem. As R. Kelly [8] states, it 'is more than a kidney disease' or to cite an older saying 'acute renal failure is not a ''cute'' renal failure' [2].

Conceptually, these mechanisms are multifaceted and can be grouped into four distinct underlying mechanisms (Table 1).

These include the 'classical' pattern of the acute uremic state, the inflammatory nature of AKI and resulting distant effects, the modulating effect of AKI in the presence of an (inflammatory) underlying disease process and last but not least the multiple untoward effects induced by RRT and anticoagulation, respectively.

These mechanisms are interrelated and cannot be strictly separated from each other, and in many patients, AKI will exert a broad pattern of untoward effects on the course of disease.

THE ACUTE UREMIC STATE

The effects of acute uremia *per se* even in the absence of the inflammatory focus of the injured kidney, and which are also present after bilateral nephrectomy, are complex and affect all metabolic and endocrine pathways of the body. Many consequences are described in analogy to findings in chronic kidney disease only, but there is an increasing number of investigations that focus on the specific alterations in acute uremia [9▪▪].

Findings include 'classical' renal consequences, such as electrolyte derangements and the disruption of volume homeostasis with the latter having attracted much attention during recent years. It was convincingly demonstrated that fluid accumulation, a positive fluid balance in an ICU patient, is associated with many negative consequences and a worse prognosis [10▪,11,12]. This adverse effect on prognosis is not only evident at the beginning or during RRT but also in earlier stages of AKI [11].

However, in AKI, there are also fundamental alterations in cellular ion transport and increased concentrations of intracellular calcium [13]. There is an accumulation of uremic toxins, an induction of metabolic acidosis, impairment of mineral metabolism, a depletion of the antioxidative system, a broad spectrum of metabolic alterations affecting all metabolism of amino acid/ protein, of carbohydrates

Table 1. Systemic consequences of acute kidney injury: mechanisms involved

Mediated by the acute uremic state ('uremic intoxication')	Metabolic derangements (carbohydrate, lipid, amino acid/protein metabolism)
	Endocrine alterations (insulin resistance, hyperparathyroidism)
	Metabolic acidosis
Mediated by the injured kidney (the kidney as the 'offender')	
	Increased release and impaired catabolism of cytokines
	Activation of immunocompetent cells
	Release of humoral factors promoting distant organ injury
AKI as a modulator of the course of disease	
	Augmentation of an underlying inflammatory process
	Progression to MODS
Mediated by renal replacement therapies	
	Haemodynamic stress
	Loss of nutrients (amino acids, antioxidants)
	Activation of protein catabolism
	Induction of an inflammatory reaction

AKI, acute kidney injury; MODS, multiple organ dysfunction syndrome.

and lipids, altered secretion and action of hormones [9▪▪].

Taken together, acute uremia *per se* is a generalized disease affecting all physiologic processes and the functions of distant organs such as the heart [14].

Acute kidney injury and immunocompetence

Potentially, from a clinical point of view, the most important consequence of AKI is the profound impact on immunocompetence. This certainly also results from a broad pattern of factors such as metabolic and nutritional derangements, the accumulation of soluble molecules and of uremic toxins, increase in oxidative stress, the impaired clearance function of reticuloendothelial system, the prolonged inflammatory process and the multiple side effects of RRT [15▪].

There is an evolving concept that the kidneys have to be perceived (also) as an important immunologic organ. This not only pertains to the role of the kidneys in cytokine homeostasis (many cytokines are degraded within the tubular system). The kidneys themselves are an important source of inflammatory mediators and activated cell systems, and have an important role in antigen presentation and dendritic cell stimulation [16].

In renal failure, the immune system on the one side is chronically (over-) stimulated but inadequately can respond only to further stimuli, potentially as a result of exhaustion [17].

The result of this impairment of immunocompetence is an extremely high rate of infections in patients with AKI [18]. In individuals on RRT, the need for vascular access and intravascular catheters further increases this risk. Infections present the most important causes of death in patients with AKI and this has not changed during the last decades [19,20].

ACUTE KIDNEY INJURY AS AN INFLAMMATORY FOCUS

AKI presents an inflammatory process. Toxic, septic, ischemic and, ischemia-reperfusion mediated injury all will elicit a local inflammatory response. Activated tubular and immunocompetent cells, such as polymorph nuclear cells, macrophages and T-cells, and the release of various soluble inflammatory mediators induce an inflammatory cycling between the tubular system and the interstitium [16,21▪].

Originally, this inflammatory process is confined to the kidneys but eventually transforms into a systemic inflammatory reaction by the release of activated immunocompetent cell populations and soluble factors into the circulation. In animal experiments, gene expression and apoptosis is increased already within several hours after induction of AKI also in nonrenal tissues and organs [22–24]. This actually presents a leading mechanism by which remote organ injury is mediated.

ACUTE KIDNEY INJURY AS A MODULATOR OF AN UNDERLYING DISEASE PROCESS

A fundamental effect of AKI is its profound role in modulating an underlying disease process. The

kidneys have a central role in cytokine homeostasis [25,26▪▪]. Cytokines, as for several other peptide hormones, are degraded within the tubular system. With decreasing renal function, the renal clearance of cytokines is impaired and thus plasma concentrations will rise.

As was shown in several experiments, the induction of sepsis or the infusion of endotoxin causes an augmented increase in plasma cytokine levels, such as tumour necrosis factor-alpha (TNF-α) or interleukin (IL)-6, in the presence of tubular dysfunctions as compared with control animals without renal injury [27].

This modulation function exerts a profound impact on the course of the underlying disease process. Pneumonia in the presence of an AKI has a more pronounced impairment of gas exchange [28]. Mortality from sepsis is much higher in the presence of tubular injury than in animals with no renal dysfunction [29]. Also, in humans, there is a tight correlation between plasma cytokine concentrations and outcome [30,31▪▪].

So certainly, it is of utmost importance in which clinical context AKI evolves. AKI will have no major impact on the course of disease and of prognosis if it presents as an isolated organ dysfunction in an otherwise healthy individual but will exert a pronounced effect in a patient with an underlying inflammatory disease process and will promote the progression to MODS.

THE MULTIPLE UNTOWARD EFFECTS, THE 'DARK SIDE' OF RENAL REPLACEMENT THERAPY

All types of RRT exert a broad pattern of potential side effects, which – in analogy to the biotrauma induced by mechanical ventilation – can be termed as 'dialytrauma' or 'filtration-trauma' (Table 2). RRT actually may present an independent risk factor for mortality in patients with AKI [32].

These negative effects are mediated by haemodynamic consequences (impairment of tissue/ organ perfusion), by the loss of nutrients (such as a depletion of antioxidants) and by mechanisms of bioincompatibility, such as generation of reactive oxygen species and the induction of an inflammatory reaction.

Certainly, these negative side effects are more pronounced during conventional intermittent haemodialysis. The better 'renal' prognosis in patients treated by continuous RRT (CRRT) than haemodialysis during their ICU stay may be explained by these less pronounced side effects [33▪].

Nevertheless, CRRTs are also associated with several untoward effects such as nutrient and electrolyte (phosphate) losses and induction of a 'low-grade' inflammation [34].

Table 2. Side effects of renal replacement therapies ('dialytrauma' – 'filtrationtrauma')

Haemodynamic consequences	Microvascular stress (systemic/ regional)
Osmolality shifts	'Dysequilibrium'
Activation of cells	Thrombocytes, granulocytes, monocytes
Activation of plasmatic cascade systems	
Stimulation of protein catabolism	
Formation of ROS, AGEs	
Loss of nutrients	Amino acids, vitamins, trace elements, antioxidants
Loss of peptides/protein	Albumin, hormones, cytokines
Loss of electrolytes	Phosphate, magnesium
Side effects of anticoagulation (heparin)	
Augmentation of inflammation	
Increased risk of infections	

AGE, advanced glycation endproduct; ROS, reactive oxygen species.

We had to learn during recent years that also the type of anticoagulation can induce many negative side effects. Especially, unfractionated heparin that remains the standard type of anticoagulation in many parts of the world activates various cell populations such as thrombocytes and granulocytes and interacts with many proinflammatory pathways [35]. In contrast, citrate not only suppresses coagulation but also inhibits the activation of cells, such as thrombocytes, granulocytes and also of other cascade systems, such as the complement system and thus may mitigate the inflammatory reaction induced by RRT [36].

DISTANT ORGAN INJURY IN ACUTE KIDNEY INJURY

On the basis of these profound and multifaceted systemic effects, AKI will exert negative consequences on many if not all organ systems of the body, inducing nonrenal, 'distant' organ injury (Table 3) [8,26▪▪,37,38,39▪▪]. Even unilateral ischemic injury causes an inflammatory reaction in the contralateral 'healthy' kidney [40]. The mechanisms by which the organs are affected present combinations of the factors discussed above. Most findings have been described in animal experiments. However, depending on the organ system involved, this may have clinically extremely relevant consequences.

Table 3. Some pathophysiologic consequences of acute kidney injury

Pulmonary	Lung oedema, alveolitis, pneumonia, pulmonary microhaemorrhage
Cardiovascular	Hypercirculation, vasodilation, cardiomyopathy, pericarditis
Gastrointestinal	Impairment of motility, erosions, ulcerations, haemorrhage, intestinal oedema, bacterial translocation, pancreatitis, colitis
Neuromuscular	Neuropathy, myopathy, encephalopathy
Immunologic	Impairment of humoral and cellular immunity and immunocompetence
Haematologic	Anaemia, thrombocytopenia, haemorrhagic diathesis
Metabolic	Insulin resistance, hyperlipidemia, activation of protein catabolism and so on

These multiple organ injuries are the reflection of a broad underlying pathology that can be generally labelled as 'augmented inflammation'. They include the release of cytokines and inflammatory mediators, activation of various immune cells, neutrophil extravasation, increase in oxidative stress with resulting generalized endothelial injury, increased vascular permeability and tissue oedema formation. These generalized phenomena predispose the progression to multiple organ dysfunction syndrome (MODS).

As a reflection of organ cross-talk and the closely interconnected communication between kidney and other organs, any injury to nonrenal distant organs mediated by AKI causes repercussions on the kidney itself by various bidirectional pathways.

In the experimental situation, some of these systemic consequences can be blocked or mitigated using neutralizing antibodies against various cytokines, such as IL-6 or TNF-α or by inhibition/depletion of immune cells [24,41–43,44▪].

Lung injury in acute kidney injury

Potentially, the clinically most relevant remote organ injury in AKI pertains to the pulmonary system [45,46]. On the one side, the lungs are the first organ system receiving blood draining from the kidneys and containing proinflammatory humoral factors and activated cell systems [47]. On the other side, any injury within the pulmonary system becomes clinically apparent immediately by alterations in gas exchange and lung mechanics.

Pulmonary alterations are characterized by increased vascular permeability, alveolar oedema formation, neutrophil extravasation and tissue migration, and evolution of multiple microhaemorrhages [24,48].

The impact of AKI on the lungs is a rather tricky problem: There is not only an increase in endothelial permeability and oedema formation but at the same time an inhibition of the compensatory mechanisms by downregulation of sodium-potassium pump and aquaporin channels, so resolution of pulmonary oedema is blocked [49–51].

AKI and lungs are 'sisters in crime' wherein AKI prolongs the need for mechanical ventilation, aggravates lung injury and impedes weaning. On the other side, both (injurious) mechanical ventilation and pulmonary inflammation can impair renal function [52].

Intestines and liver

A rather new finding but clinically of utmost importance is the intestinal consequences of AKI [53]. During AKI and/or hypervolemia, the intestinal integrity and barrier function is disrupted, mucosal permeability is increased predisposing to the translocation of endotoxin and/or of live microorganisms. This mechanism can contribute to endotoxinemia in AKI and aggravate the inflammatory status.

As a result of these intestinal disturbances in AKI, the liver also becomes an important affected organ system in the context of remote organ injury [54▪,55]. Blood from the intestines containing endotoxin and inflammatory mediators is drained via the portal system into the liver resulting in Kupffer cell activation and the augmented release of cytokines into the circulation.

Heart

Myocardial function is compromised by various bidirectional and interconnected pathways in AKI, a finding that is termed cardiorenal syndrome type 3 [56▪]. Mechanisms include several aspects of the (acute) uremic state *per se* (uremic cardiomyopathy, pericarditis, volume overload, electrolyte disturbances, acidosis) and the multiple effects of inflammation both on the heart and the vascular system/haemodynamics [14,57].

Inflammatory mediators such as TNF-α and IL-6 exert profound effects on left ventricular

remodelling, myocyte hypertrophy and apoptosis, ultimately resulting in a progressive reduction of myocardial contractility [58].

Other organ systems

As remote organ injury is the result of a generalized disease process affecting all tissues and organs, it is not surprising that in AKI, also other organs are affected. An example is the brain wherein an increased extravascular fluid accumulation and upregulated cellular apoptosis have been demonstrated [59].

AKI still is a leading risk factor for the development of upper gastrointestinal haemorrhage again pointing to generalized microvascular injury [60].

CONCLUSION

The kidneys in AKI, certainly initially, mostly are 'victims' of a systemic disease process such as a shock state or sepsis. However, because the acute uremic state and renal tissue injury induce a broad pattern of negative repercussions on the organism, the kidneys in AKI become 'offenders' exerting a multifaceted spectrum of untoward effects on all biologic functions and organ systems.

Thus, we have to recognize that AKI is not a negligible but rather an ominous complication that – in spite of the availability of modern renal replacement modalities – exerts a profound effect on morbidity and mortality. AKI is a dangerous condition; the patients do not – as usually is assumed – die with but also (at least in part) from AKI.

As a clinical consequence, preventive measures to avoid the evolution of AKI are of utmost importance. If AKI has become manifest, we have to try to optimize RRT in a way that the multiple negative effects of the acute uremic state are mitigated. In this respect, the timing and dosage of RRT have been shown to play a crucial role.

However, for future advances and more consistent improvements of prognosis of patients with AKI, more effective techniques of renal support will have to be developed that can compensate various renal functions and more appropriately deserve the labelling 'renal replacement'.

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Conflicts of interest

There are no conflicts of interest.

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Renal disease presenting as acute kidney injury: the diagnostic conundrum on the intensive care unit

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Purpose of review
Acute kidney injury (AKI) is commonplace in most ICUs. In many cases the cause is believed to be multifactorial with sepsis being a major component. However, occasionally intrinsic renal disease will present to the ICU and as such critical care practitioners should be aware of this possibility and the ways in which such conditions may present.

Recent findings
Although a relatively rare occurrence the treatment for patients with intrinsic renal disease, particularly those who present as part of a vasculitic process, differs considerably from usual organ support employed on intensive care. Recent studies indicate that the outlook for these patients is poor particularly when the diagnosis is delayed. The use of serological investigations as well as other diagnostic techniques are discussed.

Summary
Not all AKI as described by changes in creatinine and urine output which presents or develops on the ICU is the same. AKI is a syndrome which encompasses many conditions and as such is nondiagnostic. Clinicians, when faced with AKI should satisfy themselves as to the likely cause of the AKI.

Keywords
acute kidney injury, antineutrophil cytoplasmic antibodies, pulmonary renal syndrome, small-vessel vasculitis, tubulointerstitial nephritis

INTRODUCTION

Acute kidney injury (AKI) is a commonly encountered medical problem, manifest by a loss of glomerular filtration, which results in a decreased ability to appropriately excrete soluble nitrogenous wastes together with impaired fluid and electrolyte homeostasis [1]. Traditionally, such changes were thought to be associated with severe reductions in function associated with oligo-anuria. However, a considerable body of evidence now exists which demonstrates that what was hitherto considered a relatively modest change in kidney function is of great significance, particularly in the critically ill [2–4]. AKI is defined by an abrupt decrease in kidney function and as such is a broad clinical syndrome which may encompass an array of causes. These may be nonspecific, such as ischaemia or toxic injury, may include extrarenal disease, both prerenal and postrenal, and also will include specific renal diseases. Moreover, more than one of these conditions may coexist in the same patient at the same time. Also, because the manifestations and clinical sequelae of AKI can be similar regardless of cause, AKI encompasses both direct injury to the kidney as well as acute impairment of function [5▪▪]. It follows that the treatment of the injury should be tailored towards the underlying cause given that currently there are no specific therapies for AKI available and to-date attempts to improve outcomes have focussed solely on improving the basic elements of clinical management [6]. Such an approach is supported by studies examining the cause of death

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KEY POINTS

- AKI is a syndrome and does not confer a diagnosis. Therefore, effort must be made in defining the cause of the AKI where possible.
- Intrinsic renal disease may present to the ICU as part of a multisystem process, including DAH.
- Measures such as simple urine testing for proteinuria, haematuria and casts may provide much information regarding the presence of intrinsic renal disease.
- Serological testing, such as the use of ANCA, may provide much information regarding the type of intrinsic renal disease present.
- Under certain conditions renal biopsy may be necessary and transjugular renal biopsy provides a feasible and relatively well tolerated alternative to percutaneous biopsy.

in patients with AKI. For example, a single-centre study in the United Kingdom demonstrated 21.9% mortality in all patients with AKI but death was attributable to AKI in only 3% [7]. The most common cause of death was sepsis (41.1%) followed by cardiovascular disease (19.2%) and malignancy (12.9%); therefore, when considering intrinsic renal disease as a cause of AKI, it may well occur in tandem with other conditions. This review will focus on the features which may point the critical care clinician towards making such diagnoses which, if confirmed, may require a change in treatment strategy.

THE CAUSE OF ACUTE KIDNEY INJURY IN THE ICU

AKI complicates the intensive care stay of approximately 50% of patients although this varies widely depending on case mix, with surgical ICUs, for example, generally having a lower reported incidence [8]. Despite this there are few robust data on the actual cause of AKI and this is no more obvious than in the perception of acute tubular necrosis as being one of the major causes of AKI. Acute tubular necrosis remains a histopathological diagnosis but as renal biopsies are rarely undertaken in the critically ill the diagnosis is therefore often presumed [9]. Although some urinary indices, such as the fractional excretion of sodium, may point to the diagnosis, such investigations although of some utility in single organ AKI are fraught with inaccuracies in the critically ill [10▪▪]. In order to try and elucidate the cause of AKI in any patient a careful clinical evaluation should occur. This should include, where possible, accurate history taking, including a comprehensive drug and social history. Physical examination must include evaluation of fluid status as well as searching for signs of infection and sepsis. These findings may then point the clinician towards rarer causes of AKI, including intrinsic disease. Of paramount importance is the investigation of the urine in particular the presence of proteinuria, haematuria and cellular casts. In the absence of an active urinary sediment the likelihood of there being significant intrinsic disease is less likely.

THE OBSTRUCTED KIDNEY

Ultrasonography should be performed if urinary obstruction cannot be confidently excluded; however, it should be borne in mind that the cardinal sign of obstruction, hydronephrosis, may be absent where another cause of oliguria exists or indeed in the early phase of obstruction where the pelvicalyceal system is relatively noncompliant. If there is a high index of suspicion then the ultrasound may be repeated at a later stage. Very rarely patients may present with anuric nondilated obstructive nephropathy and the obstruction may be confirmed by retrograde ureteropyelography and subsequent ureteric stenting [11]. The mechanisms involved in the development of the nondilated obstructive nephropathy remain unclear although various hypotheses have been proposed including a decrease in the elasticity of the excretory tract or encasement of the collecting systems. However, in the limited case series published the cause of the nondilated obstructive nephropathy is often related to the existence of an underlying disease process which is often commonly complicated by urinary tract dilatation [12].

TUBULOINTERSTITIAL NEPHRITIS

Tubulointerstitial nephritis (TIN) or acute interstitial nephritis is a cause of AKI characterized by an inflammatory infiltrate in the kidney interstitium [13]. TIN is associated with several systemic diseases as well as autoimmune disorders but 75% of cases are induced by drug therapy with antibiotics being the most likely culprits [14] (Table 1). Presentation is often nonspecific with patients often asymptomatic and oliguria occurring in approximately 50% of cases [14]. However, presentation may be related to the cause of the TIN, for example, in drug-induced TIN, findings of an allergic type response may be prevalent [15]. AKI complicating drug therapy is often severe with approaching 50% of patients requiring renal replacement therapy [16].

Table 1. Causes of tubulointerstitial nephritis

Drugs	Nonsteroidal anti-inflammatory agents, penicillins, rifampicin, sulphonamides, quinolone antibiotics, allopurinol, proton pump inhibitors, aminosalicylates, indinavir
Systemic diseases	Sjogren's syndrome, sarcoidosis, systemic lupus erythematosus (SLE)
Infections	Viruses (EBV, CMV), legionella, leptospirosis, TB, streptococcus, corynebacterium
TINU syndrome	Tubulointerstitial nephritis and uveitis

TB, tuberculosis; TINU syndrome, tubulointerstitial nephritis and uveitis syndrome.

Definitive diagnosis of TIN is made by renal biopsy although this is often unnecessary given that a common culprit drug is often identified. Herein lies the problem on ICU and why the diagnosis is often overlooked as many of the critically ill are on drug(s) that can cause TIN. Although renal biopsy is the gold standard other factors may point to the diagnosis. A characteristic urinary sediment may be found which typically reveals white cells, red cells, and white cell casts together with a variable degree of proteinuria which is rarely nephrotic. Eosinophilia may also be present where an allergic response predominates and although eosinophiluria (defined as >1% of urinary white cells) has been described it is not useful in distinguishing TIN from other causes of AKI and hence is of limited utility in the ICU. Unfortunately, there are limited data as to the prevalence of TIN in the critically ill which probably reflects the fact that renal biopsies are rarely undertaken [17].

PULMONARY RENAL SYNDROME(S)

Pulmonary renal syndrome is the association of diffuse alveolar haemorrhage (DAH) with a rapidly progressive glomerulonephritis [18,19]. Patients with pulmonary renal syndrome may present with features consistent with DAH following disruption of the alveolar-capillary basement membrane. By definition, patients may also present as an AKI due to the rapidly progressive glomerulonephritis. As a consequence, these patients may present to the ICU in a variety of ways and represent a major challenge as clinical outcome is based on early accurate diagnosis and aggressive treatment [20,21]. There are numerous potential causes of the pulmonary renal syndrome as highlighted in the below list:

(1) ANCA-positive vasculitis;
   (a) granulomatosis with polyangiitis (Wegener's),
   (b) microscopic polyangiitis,
   (c) Churg–Strauss [eosinophilic granulomatosis with polyangiitis (EGPA)],
(2) anti-glomerular basement membrane (GBM) disease (Goodpasture's disease);
   (a) ANCA-negative vasculitis,
      (i) Behcet's,
      (ii) Henoch–Schonlein purpura,
      (iii) immunoglobulin A (IgA) nephropathy,
      (iv) mixed cryoglobulinaemia,
(3) autoimmune connective tissue disease;
   (a) systemic lupus erythematosus,
   (b) scleroderma,
   (c) polymyositis,
(4) drug-induced vasculitis;
   (a) hydralazine,
   (b) propylthiouracil,
   (c) D-penicillamine,
(5) thrombotic microangiopathy;
   (a) thrombotic thrombocytopenic purpura,
   (b) antiphospholipid syndrome,
(6) idiopathic pulmonary-renal syndrome.

Antineutrophil cytoplasmic antibodies

The small vessel pauci-immune vasculitides account for most causes of the pulmonary renal syndrome(s) and include granulomatosis with polyangiitis (GPA: formerly known as Wegener's granulomatosis), microscopic polyangiitis and Churg–Strauss syndrome. These are complex, immune-mediated disorders in which tissue injury results in a presumed initiating inflammatory event (e.g., infection, toxic exposure) followed by a highly specific immune response. This is partly directed against previously shielded epitopes of neutrophil granule proteins, leading to autoantibodies known as antineutrophil cytoplasmic antibodies (ANCA). These antibodies were first described in 1982 in patients with pauci-immune glomerulonephritis and testing for these ANCA plays a critical role in the diagnosis and classification of the small vessel vasculitides (SVV) [22,23]. Debate continues to rage, however, regarding their ultimate importance in the pathogenesis and pathophysiology of these conditions. In vasculitis, the two relevant target antigens for ANCA are proteinase 3 (PR3) and myeloperoxidase (MPO). Both PR3 and MPO are located in the azurophilic granules of neutrophils and the peroxidase-positive lysosomes of monocytes. However, it should be noted that these antibodies although

associated with SVV are not pathognomonic and reliance upon immunofluorescence testing alone should be avoided with confirmation using antigen-specific enzyme-linked immunosorbent assays for PR3-ANCA and MPO-ANCA [24]. The question then arises as to whether further treatment can be undertaken without confirmation through histology. Although some may undertake treatment without tissue biopsy in which the clinical presentation is highly consistent with SVV the potential complications from treatment are significant. Treatment involves high dose steroid induction followed by cytotoxic treatment using cyclophosphamide and although tumor necrosis factor-alpha inhibitors and anti-CD20 therapies are gaining favour the potential complications must be borne in mind [19]. Therefore, all reasonable attempts should be undertaken to obtain histopathological proof before commencing treatment but if this is not possible then tissue biopsy should be performed where possible when the patient is more stable. Interestingly, the importance of biopsy has been demonstrated in one study where ANCA positivity in the presence of a mildly active urinary sediment and a serum creatinine of less than 1.5 mg/dl was consistent with SVV in only 47% [25]. Reassuringly, in those with a clinical picture of a rapidly progressive glomerulonephritis and ANCA positivity the specificity rose to at least 98%. Therefore, biopsy is still required to document the presence or absence of a SVV in ANCA-positive patients in whom the tissue diagnosis cannot be confirmed less invasively (e.g., biopsy of a nasal lesion) as the potential toxicity of present therapies for ANCA-positive diseases is too great to rely upon serology alone.

Pulmonary renal syndrome associated with antineutrophil cytoplasmic antibodies-positive vasculitis

SVV may present with vague symptoms of fever, lethargy and weight loss. Other organs (neurological, gastrointestinal, cardiac, cutaneous) may be involved, causing possible clinical manifestations of purpura, peripheral neuropathy and heart block (Table 2). GPA is characterized by granulomatous inflammation of the respiratory tract, a systemic necrotizing vasculitis and usually (in 80% of cases) a necrotizing glomerulonephritis and subglottal stenosis may be present which may lead to difficulties in intubation [25]. PR3 or cytoplasmic ANCA is most prevalent. The incidence is highest in Northern Europe and the majority (90%) of patients affected are Caucasian.

Churg–Strauss syndrome involves vasculitis in combination with granulomas, asthma and eosinophilia. MPO or perinuclear ANCA is most prevalent.

Table 2. Summary of common presenting features of small-vessel vasculitides

Presenting feature	GPA	MPA	CSS
Constitutional upset	++	++	++
Sinusitis	+++	+	+++
Asthma	–	–	+++
Cough/dyspnoea	+++	+	++
Rash	+	+	++
Abdominal pain	+	+	+
Hypertension	+	+	+
Proteinuria/haematuria	+++	+++	++
Cardiac failure	+	+	++
Mononeuritis multiplex	+	+	++

CSS, Churge–Strauss syndrome; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis.

Microscopic polyangiitis involves a systemic necrotizing vasculitis but with no granulomas or asthma. MPO ANCA is most prevalent.

Pulmonary renal syndrome associated with anti-glomerular basement membrane disease

This involves anti-GBM antibodies directed against type IV collagen in the GBMs of glomeruli and alveoli. It is very rare, with an incidence of 1 per 1 000 000 per year. There is a bimodal age distribution, with peaks in the 3rd and 7th decades. Around 50–70% of patients will present with DAH, which is usually precipitated by smoking, pneumonia or fluid overload [26,27]. Anti-GBM antibodies may sometimes be detected in patients with ANCA vasculitis (dual-positive). The clinical course of these patients is more typical of vasculitis than Goodpasture's disease.

Pulmonary renal syndrome associated with antineutrophil cytoplasmic antibodies-negative vasculitis

This occurs rarely in IgA nephropathy, Henoch–Schonlein purpura, Behcet's disease and mixed cryoglobulinaemia. IgA nephropathy and HSP involve deposition of IgA immune complexes within alveoli causing alveolar haemorrhage. Chronic viral infection causing mixed cryoglobulinaemia stimulates monoclonal antibody production and hence an immune complex-mediated vasculitis.

Pulmonary renal syndrome associated with connective tissue disorders

This is most commonly associated with systemic lupus erythematosus and systemic sclerosis; less

often with rheumatoid arthritis, polymyositis and mixed connective tissue disease. The mechanism of cellular injury involves immune complex-mediated small vessel vasculitis. DAH occurs in 2% of patients with systemic lupus erythematosus. Systemic lupus erythematosus may also cause DAH due to antiphospholipid syndrome.

Pulmonary renal syndrome associated with drug-induced vasculitis

Drug-induced vasculitides are usually ANCA-positive. Hydralazine, propylthiouracil and D-penicillamine may induce formation of immune complexes in pulmonary and renal capillaries.

Pulmonary renal syndrome associated with thrombotic microangiopathies and cryoglobulinaemias

Pulmonary renal syndrome may occur in thrombotic microangiopathies, such as antiphospholipid syndrome, thrombotic thrombocytopenic purpura, malignancies and infection. Cryoglobulinaemic vasculitis results from the deposition of cryoglobulins on the vessel walls, activating the complement cascade resulting in immune complex-mediated small vessel vasculitis [28]. The classical clinical triad of purpura, weakness, and arthralgia is present in up to 80% of patients and may be associated with other manifestations, including AKI. Indeed, renal involvement is the most common cryoglobulinaemic vasculitis related visceral manifestation with AKI seen in more than 30% of cases. Presenting as a multisystem disorder is not uncommon and although ICU experience is scant results from one centre suggest early ICU referral may translate into an excellent initial outcome [29].

THE ROLE OF THE RENAL BIOPSY IN THE ICU

As pointed out, the heterogeneity of AKI dictates that treatment is often directed at the potential cause(s) of AKI and histological diagnosis is often not considered. This is in stark contrast to the management of AKI outside the ICU environment in which the renal biopsy is an essential tool in the management of most nephrological conditions [30]. However, the findings on renal biopsy must be interpreted in the context of both clinical and laboratory features. Careful patient selection as well as the use of real-time ultrasound has minimized risks associated with this procedure but percutaneous biopsy does carry both a morbidity and mortality risk [31]. Significant complications include haemorrhage, infection and arteriovenous fistula formation with complication rates reported ranging from 3 to 13% with a mortality risk of up to 0.2% [32,33]. Although intrinsic AKI is suspected, depending on diagnosis, a delay in initiating appropriate treatment may prevent salvage of renal function. Under such conditions, histological diagnosis may be necessary but percutaneous biopsy is often contraindicated in our intensive care patients (see Table 3) [34]. Alternative approaches include open renal biopsy, although in modern practice this is rarely performed, or laparoscopic renal biopsy. The laparoscopic approach is a safe and effective alternative to the open procedure and delivers good results in terms of biopsy yield as well as a low complication rate [35,36]. Transjugular renal biopsy has been used successfully to obtain renal tissue in high-risk patients with results and complication rates comparable to conventional renal biopsy, but this technique has rarely been used in the ICU setting [37–39]. Although transjugular renal biopsy cannot be considered a routine procedure or replace the conventional approach, it does lend itself to situations where a tissue biopsy is required but circumstances preclude this such as patients with multiple pathologies on the ICU.

Although histology may aid diagnosis in the ICU, few data are available on percutaneous renal biopsy in ICU patients. A 10-year retrospective multicentre study conducted in 10 French ICUs found 77 patients, 57% of whom were mechanically ventilated, underwent percutaneous renal biopsy of which 68 were on a native kidney rather than a transplant. Biopsy related complications occurred in 22% patients of which two had to undergo renal embolization. Interestingly, in over half of the patients a specific diagnosis was made with 48% having a vasculitis, 23% had thrombotic microangiopathy and 6% TIN [40].

ICU OUTCOMES

Few studies have specifically addressed the outcomes of patients with intrinsic renal disease

Table 3. Contraindications to percutaneous renal biopsy

Absolute contraindications	Relative contraindications
Active urinary sepsis	Use of antiplatelet agents
Hydronephrosis	Solitary kidney
Uncooperative patient	Small kidneys
Bleeding diathesis	
Renal malignancy	
Widespread cystic disease	

Adapted from [34].

presenting to the ICU as an AKI. Some limited data do exist, however, for patients with vasculitis presenting to ICU [41,42,43▪]. Reported mortality rates vary from 11 to 33% depending on presentation as well as severity of illness. For example, patients presenting with DAH have mortality rates of less than 50%. Unsuprisingly, severity scores such as APACHE II and/or SAPS II are good predictors of ICU mortality rather than severity scores based on vasculitic activity [41,42]. A more recent retrospective study identified 31 adult patients admitted with systemic vasculitis in which 52% died in ICU [43▪]. By univariate analysis, mortality was associated with higher SOFA and SAPS II scores. The need for a catecholamines, renal replacement therapy, or the occurrence of ARDS significantly worsened the prognosis.

CONCLUSION

Although rare, intrinsic renal disease may present to the ICU. This may be part of a pulmonary renal syndrome with DAH being a prominent feature or may present as an AKI alone. Characteristic features on examination and from the history when available may raise the index of suspicion that intrinsic renal disease may be present. Urinalysis including simple dipstick testing is mandatory and this may also prove a potential pointer in aiding diagnosis. Serological testing is of help but in certain cases only histopathological testing will confirm the diagnosis.

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Conflicts of interest

C.E.A. declares no conflicts of interest.

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Retrospective study on 31 patients with systemic vasculitis which highlights some of the presenting features as well as the poor prognosis of these patients.

Contrast-associated AKI in the critically ill: relevant or irrelevant?

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Purpose of review
Iodinated contrast media are frequently administered in ICU patients. Recent studies challenge the relevance of contrast media toxicity in ICU patients and relate occurrence of acute kidney injury to baseline characteristics and severity of illness.

Recent findings
Various findings in studies with kidney biomarkers indicate the causal relationship between contrast media exposure and kidney damage. Contrast media exposure not only causes direct tubular damage and renal hypoperfusion but also initiates the formation of reactive oxygen species in its turn causing tissue damage. The route of administration determines the incidence of contrast-induced acute kidney injury with a higher incidence when contrast media are administered by intra-arterial route versus intravenous route. The impact of contrast-associated acute kidney injury on hospital length of stay, the need for renal replacement therapy and survival remains a matter of debate because of discrepancies between observational versus case-matched studies and limitations of the individual studies.

Summary
There are diverse pathophysiologic mechanisms explaining the causal relationship between the administration of contrast media and the development of acute kidney injury. Some studies challenge the relevance of contrast media toxicity in ICU patients. However, limitations of the available studies in ICU patients preclude firm conclusions. A precautionary approach in the administration of contrast media is justified.

Keywords
angiography, contrast-induced acute kidney injury, contrast-enhanced computed tomography, critically ill, intensive care unit

INTRODUCTION

Iodinated contrast media are frequently administered in ICU patients; most in the setting of a contrast-enhanced computed tomography (CE-CT) scan used for diagnosis of, for example, a focus of intra-abdominal infection. Data from patients who underwent coronary angiography or percutaneous coronary intervention indicate that 5 to 16% of these patients develop contrast-associated acute kidney injury (CA-AKI) [1]. CE-CT scans in outpatients are typically associated with a very low risk for CA-AKI [1–4,5▪▪]. This may be explained by difference in risk factors and baseline characteristics between these cohorts, but also by the route of administration.

An evaluation of the epidemiology of CA-AKI has been hampered by the use of different definitions of CA-AKI, but also by the observation that serum creatinine (Scr) and creatinine clearance may fluctuate during hospital and ICU admission [6,7]. This corroborates with findings in studies in which cases exposed to contrast media were compared to matched controls [6,8,9,10▪]. Other case-control studies showed increased risk for CA-AKI in patients with decreased kidney function [11▪], and also increased mortality [12].

ICU patients with multiple organ dysfunction have a risk profile for CA-AKI that is not comparable

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KEY POINTS

- Contrast media are nephrotoxic via diverse pathophysiologic mechanisms.
- Case-control studies in ICU patients challenge the clinical relevance of contrast media nephrotoxicity.
- Observational studies show that one out of six ICU patients will develop CA-AKI after contrast media exposure.
- CA-AKI in ICU patients is associated with need for RRT and mortality.
- Limitations of the existing studies preclude firm conclusions for ICU patients.

to that of patients who undergo coronary procedures or CE-CT scan as an outpatient. It is therefore improbable that data from non-ICU patients are also valid in this specific cohort. A specific problem for evaluation of CA-AKI in ICU patients is that it is difficult to differentiate whether AKI occurs as a consequence of contrast media administration or is the resultant of risk factors for AKI, such as sepsis, decreased cardiac output or administration of nephrotoxic drugs. Hence, we prefer in ICU patients the terminology CA-AKI, instead of the classic terminology contrast-induced AKI. Cohort studies [7,13–20,21▪▪] in ICU patients show increased need for renal replacement therapy (RRT) and mortality in ICU patients who have CA-AKI. However, similar to non-ICU patients, case-control studies [7,16,20] in ICU patients could not show increased risk for AKI in patients who were exposed to contrast media.

Given these considerations, some actually challenge the clinical relevance of CA-AKI in ICU patients. In this manuscript, we will discuss the available evidence on CA-AKI in ICU patients.

NEPHROTOXICITY OF CONTRAST MEDIA

The crucial question in the discussion on the relevance of CA-AKI is whether contrast media is indeed causing damage to the kidney. Scr concentration reflects glomerular filtration rate (GFR), which is only an indirect measure of damage to the kidney. GFR may be decreased because of damage to the kidney, but also other nonkidney-related causes, such as hypovolemia or cardiogenic shock, may lead to decreased GFR. As such, increase of Scr is not a proof of damage to the kidney. More recently discovered kidney biomarkers, such as neutrophil gelatinase-associated lipocalin (NGAL), and kidney injury molecule-1 are set free from the kidney after damage to the kidney. Therefore, the finding that NGAL and kidney injury molecule-1 are increased after contrast exposure indicates a causal relationship between contrast media exposure and damage to the kidney after contrast exposure [22–27]. Most of these data were recorded in coronary angiography patients. A recent study [28] in ICU patients showed that plasma NGAL concentration was associated with need for RRT but was not able to differentiate CA-AKI and non-CA-AKI patients. A possible explanation for this may be sepsis-related release of NGAL from white blood cells. This contrasting finding in a cohort of ICU patients nicely illustrates that data from studies on CA-AKI in non-ICU patients cannot be automatically extrapolated to ICU patients.

PATHOPHYSIOLOGY OF TOXICITY OF CONTRAST MEDIA

The mechanisms of nephrotoxicity of contrast media are complex and not completely understood. Contrast media cause direct tubular damage and also renal hypoperfusion. Renal hypoperfusion leads to hypoxia and sets off a cascade of events with formation of reactive oxygen species (ROS) that in turn causes also tissue damage (Fig. 1) [29–31,32▪]. This myriad of pathophysiologic mechanisms may be the explanation why drugs targeted at one mechanism, for example antioxidative therapy, are not able to prevent CA-AKI.

RENAL HYPOPERFUSION

Intravenous (i.v.) injection of contrast media causes an initial increase in renal blood flow but is then followed by a more prolonged decrease in blood flow and GFR. The result will be renal ischemia, particularly in the medulla. This vasoconstriction is unique to the kidney as systemic vascular responses to contrast media in all other vascular beds are marked by vasodilatation.

INCREASED OSMOTIC PRESSURE

In order to produce primary urine, the glomerulus needs a pressure gradient; the pressure in the glomerulus needs to be higher than in the proximal tubule. Increased osmotic pressure by contrast media in the proximal tubules and Bowman's capsule leads to increased pressure, and so in a lowered hydrostatic filtration pressure gradient across the filtering membrane of the glomerulus [33]. In addition, increased osmolality by contrast media leads to osmotic diuresis. Increased urinary flow in turn will activate tubular-glomerular feedback resulting in renal vasoconstriction and decreased GFR.

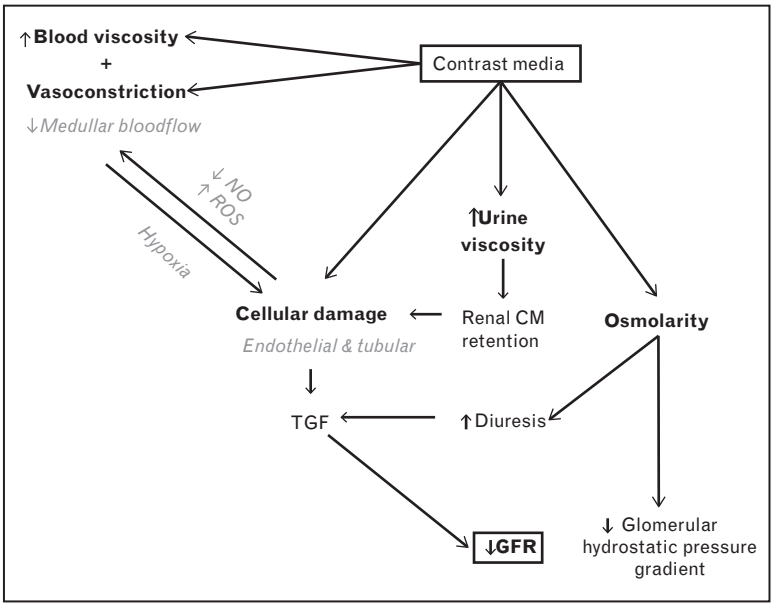

FIGURE 1. Pathophysiology of nephrotoxicity of contrast media. CM, contrast media; GFR, glomerular filtration rate; NO, nitric oxide; ROS, reactive oxygen species; TGF, tubulo glomerular feedback.

OSMOTOXICITY

Another cause for hypoperfusion is dehydration due to contrast media-induced osmotic diuresis.

Historically, we have moved from high-osmolar to low-osmolar and iso-osmolar contrast media (HOCM, LOCM, IOCM). HOCM are the oldest and have an osmolality of 1400–1600 mOsm/kg H_2O. These agents are currently very limitedly used for parenteral contrast administration. LOCM have been developed subsequently and have an osmolality of approximately 600 mOsm/kg H_2O. IOCM, such as iodixanol, have an osmolality of 290 mOsm/kg H_2O. Comparison between HOCM versus LOCM showed that LOCM exposure was associated with a lower risk for CA-AKI in patients with preexisting decreased kidney function [34,35]. The benefit of IOCM over LOCM for prevention of CA-AKI seems limited. Only in patients with CKD, IOCM offered a benefit for prevention of CA-AKI [36]. These studies support the notion that osmolality is not the decisive factor for CA-AKI at osmolality levels of LOCM or IOCM [37]. Differences in nephrotoxicity between agents of similar osmolality hint toward other contributing factors.

VISCOSITY

The renal medulla sustains a more pronounced worsening in perfusion than other areas of the kidney. The medulla is in normal circumstances already at the rim of oxygen debt. Increased viscosity will lead to decreased blood flow, and this in turn will lead to insufficient supply of the metabolic demand of the medullary thick ascending limb resulting in production of ROS and superoxides, which induces medullary thick ascending limb damage due to oxidative stress [32▪,38]. In addition to this, decreased blood flow will also contribute to prolonged exposure of the tubule cells to contrast media. The proximal and distal convoluted tubules, which are not so compromised by hypoxia and hypoperfusion as the renal medulla, also show cell damage after the use of contrast media [30,39,40]. This suggests that oxidative stress caused by hypoperfusion and hypoxia is not the only factor playing a role in CA-AKI *in vivo*. Increased viscosity by contrast media resulting in decreased tubular flow may worsen adverse effects of contrast media because a prolonged contrast media retention in the kidneys leads to longer exposure of contrast media direct toxic effects.

TUBULAR CELL DAMAGE

The administration of contrast media may induce direct cell damage causing both oxidative stress and medullary hypoperfusion. In addition, vasoconstriction leads to ischemia and further cell damage. In-vitro studies [41,42] demonstrate that all types of contrast media, independent of their properties, lead to a marked constriction of outer descending medullary vasa recta by reducing nitric oxide. There is also a significantly increased vasoconstrictor response to angiotensin II causing local ischemia and the formation of ROS [32▪,38]. ROS may exert tubular and vascular damage and might therefore

further intensify renal parenchymal hypoxia due to endothelial dysfunction and deregulation of tubular transport.

ROUTE OF ADMINISTRATION: INTRA-ARTERIAL VERSUS INTRAVENOUS

In recent years, a controversy emerged as to whether CIA-AKI is dependent on the route of administration. From *et al.* [12] found that i.v. contrast media administration was associated with an increase in 30 day and overall mortality compared to intra-arterial administration, after adjustment for risk factors. One explanation for this difference might be that i.v. injections during CT results in a much greater injected dose rate compared with multiple small doses of intra-arterial injections during coronary procedures. Others found that after adjustments for patient-related risk factors CA-AKI incidence is similar after intra-arterial and i.v. contrast media administration [43,44]. Many others reported opposite findings, with low or no risk for CA-AKI after CE-CT scan [1–4,5▪▪,9].

Unfortunately, comparisons are heavily biased by differences in patient characteristics and risk factors for AKI between patients who received i.v. and intra-arterial contrast media. It is virtually impossible to account for all these differences (known and unknown), when comparing the different patient cohorts. Selection bias may also play a role. High-risk patients for AKI are often excluded for CE-CT examination, whereas high-risk patients are seldom excluded for intra-arterial coronary procedures.

In its 2011 update, the Contrast Media Safety Committee of the European Society of Urogenital Radiology [45] stated that CA-AKI incidence is higher after intra-arterial administration compared with i.v. administration. As i.v. administered contrast has a longer transit time before reaching the kidneys, i.v. administered contrast may have a lower concentration when it enters the kidneys, compared to intra-arterial-administered contrast. The intra-arterial route may have higher risk for AKI, especially coronary angiography via the femoral access site, possibly secondary to a greater risk for haemorrhage, (compared to radial approach). Also, passage of the catheter through the aorta and passing by the ostia of the renal arteries may lead to release of plaque material into the renal arteries, contributing to AKI [46▪].

EPIDEMIOLOGY OF CONTRAST-ASSOCIATED ACUTE KIDNEY INJURY

In contrast to the abundant literature on the epidemiology of CA-AKI after coronary procedures, there are only few studies published on the epidemiology of CA-AKI in ICU patients. Important limitations of these existing studies are low patient numbers included and single-centre design. In addition, different definitions of CA-AKI hamper comparisons. A final limitation is the use of Scr for the definition of CA-AKI. Scr reflects GFR and so kidney function. However, Scr concentration may also be influenced by other variables, such as volume status, muscle mass, sex and race [47]. Most of these variables will impact on Scr only on a longer term; however, changes in volume status of the patient can on a short-term influence Scr, whereas GFR remains similar [48]. This is relevant in patients who are prehydrated before undergoing a CE-CT scan. In these patients, Scr may be diluted, and hence not adequately reflecting GFR. In other words, Scr-based definitions of CA-AKI may underestimate the true incidence and severity of CA-AKI.

OCCURRENCE OF CONTRAST-ASSOCIATED ACUTE KIDNEY INJURY

For this review, we included only studies that reported on CA-AKI in ICU patients. We identified nine cohort studies [13–20,21▪▪] on the epidemiology of CA-AKI in ICU patients and evaluated CA-AKI when defined by the classic definition of CA-AKI (increase of Scr of 25% or greater or >0.5 mg/dl within a 48–96 h period) or the more recent KDIGO definition for AKI (Scr increase of 50% or greater within a week, or 0.3 mg/dl or greater within 48 h). When defined by the classic definition, CA-AKI had a median incidence of 16.3% (interquartile range: 11.5–16.8%), similar to the incidence of 15.7% (interquartile range: 15.1–16.8%) when defined by the KDIGO definition for AKI (Fig. 2).

OUTCOME OF CONTRAST-ASSOCIATED ACUTE KIDNEY INJURY PATIENTS

Some advocate that the definition for CA-AKI is so sensitive that we are observing only a minor and temporal increase of Scr without clinically relevant events. For this review, we summarized the available data on length of stay (LOS), need for RRT, and mortality.

LENGTH OF STAY

There are only two studies that reported on LOS, and unfortunately they report conflicting results. Rashid *et al.* [15] found no difference in LOS in the ICU and hospital between CA-AKI patients and no CA-AKI patients in their single-centre study including 139 ICU patients. Hoste *et al.* [17] found in their

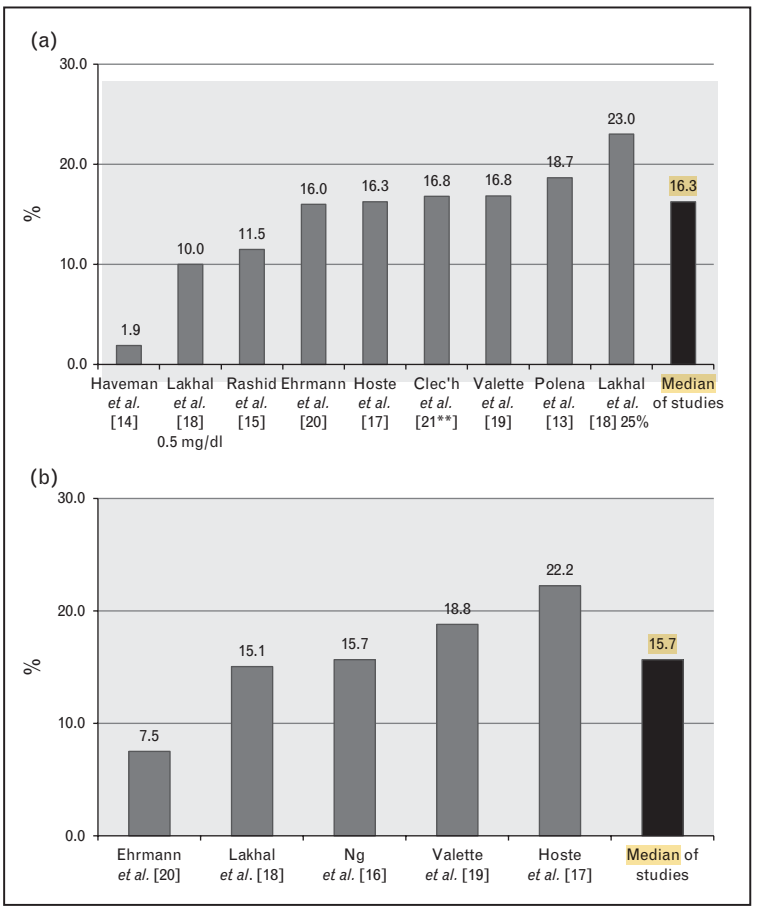

FIGURE 2. Incidence of contrast associated-acute kidney injury in ICU patients. (a) Incidence of contrast-associated acute kidney injury in ICU patients, defined as an increase of serum creatinine of 25% or 0.5 mg/dl or greater within a 48–96 h time period. (b) Incidence of contrast-associated acute kidney injury in ICU patients defined by the KDIGO classification for acute kidney injury.

single-centre cohort study ($n = 787$ patients) that LOS in the ICU was increased, whereas LOS in the hospital was shorter in CA-AKI patients. As LOS in the ICU may be determined by many factors that do not include severity of illness, LOS in the ICU is a less relevant measure. In summary, the available evidence on the impact of CA-AKI on hospital LOS is conflicting and weak as it is generated by only two single-centre studies ($n = 926$).

RENAL REPLACEMENT THERAPY

CA-AKI patients had increased risk for RRT in observational studies (Fig. 3a). However, in two case-control studies, we found no effect on risk for RRT, and in fact found a trend for increased risk for patients who had no contrast media exposure (Fig. 3b).

MORTALITY

Similar to RRT, CA-AKI patients are at greater risk for hospital mortality in observational studies (Fig. 4a). One study [17] reported also long-term follow-up and found that CA-AKI patients had higher 60-day, 90-day and 1-year mortality.

The development of CA-AKI is the consequence of contrast media exposure, but also risk factors for AKI and severity of underlying disease may impact on outcome. In the three studies [17,18,21▪▪] in ICU patients in which the impact of CA-AKI was corrected for other variables in a multivariable analysis, CA-AKI remained associated with mortality with an odds ratio ranging between 2.73 and 3.48.

Another technique for assessment of the relative impact of exposure to contrast media on outcomes is a matched case-control design, in which contrast media-exposed patients are matched to patients with similar baseline characteristics and severity of disease. In the two studies [16,20] that used this methodology, contrast media-exposed patients had similar mortality compared with patients who had no contrast media administered (Fig. 4b).

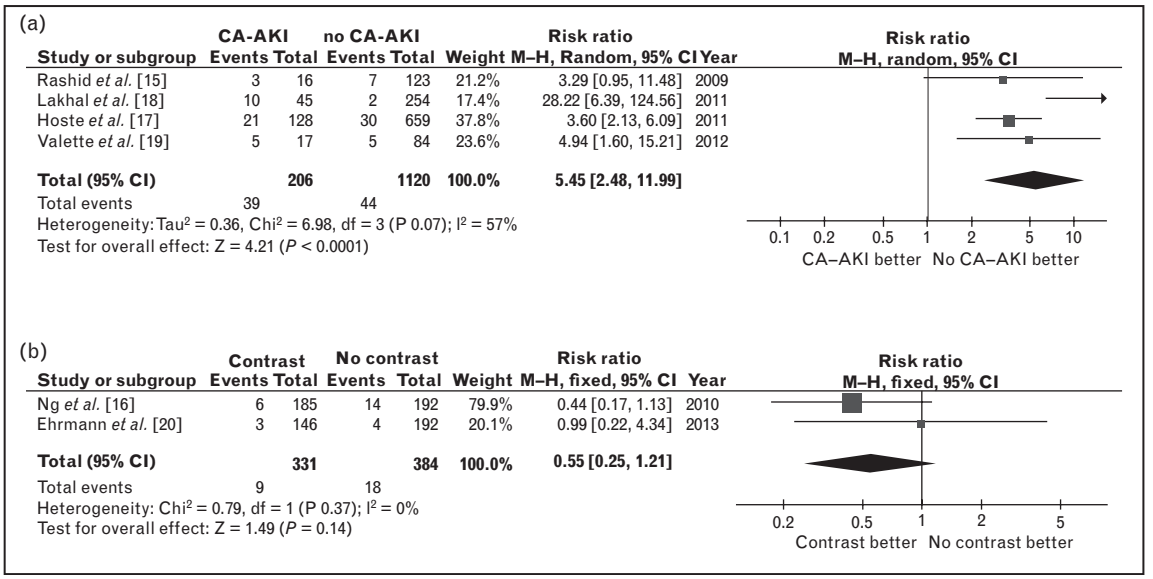

FIGURE 3. Risk for renal replacement therapy. (a) Risk for renal replacement therapy: comparison of patients with and without contrast-associated acute kidney injury. (b) Risk for renal replacement therapy: comparison of patients with and without contrast media exposure.

WHY DO OBSERVATIONAL STUDIES SHOW DIFFERENT DATA COMPARED TO MATCHED-CONTROL STUDIES?

In the previous paragraphs, we have provided the evidence that contrast media indeed is nephrotoxic. It is therefore not surprising that observational studies show that CA-AKI occurs in approximately one out of six ICU patients who have contrast media exposure and is associated with increased risk for RRT and mortality. This association between contrast media and mortality remained when corrected for covariates in three individual studies. On the other hand, these data could not be confirmed in the two matched case-control studies. How can we explain these conflicting data? In the following discussion, we will discuss some elements that may explain the discrepancies between the observational and case-control studies.

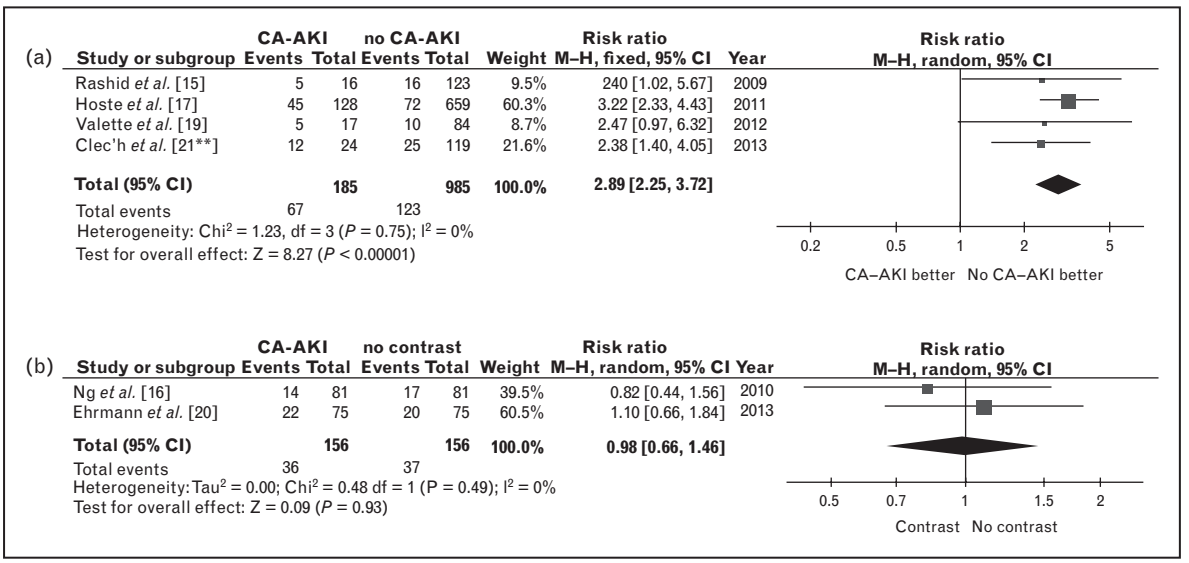

FIGURE 4. Comparison of risk for hospital mortality. (a) Risk for hospital mortality: comparison of patients who had contrast-associated acute kidney injury, and those who did not. (b) Risk for hospital mortality: comparison of patients who had contrast media exposure to those who had no exposure to contrast media.

SELECTION BIAS

Selection or inclusion bias may play an important role. As physicians, we are trained to prevent harm by diagnostic or therapeutic procedures – 'primum non nocere'. Before ordering a contrast media procedure, good clinical practice requires that we weigh the pros and cons of contrast media administration. Physicians are therefore less inclined to order an examination that requires contrast media administration for patients with higher risk of developing AKI. Therefore, the contrast media-exposed group will include less patients with increased risk for CA-AKI, and similarly the control group, without contrast media administration, will include more patients with increased risk for CA-AKI.

A randomized study comparing contrast media and placebo infusion could overcome this selection bias. Unfortunately, we fear that ethical considerations and lack of equipoise among physicians will make it at present impossible to perform such a study.

LACK OF POWER, SINGLE-CENTRE DESIGN AND INCOMPLETE MATCHING

Confounders, that is other potential sources for AKI, such as hypotension, fluid restriction, haemorrhage, nephrotoxic medication . . . are not always identified or investigated. Matching is a technique to account for this and reduce the impact of confounders. However, the matched-controlled studies include relatively small number of patients (only 312 patients were included in the two matched control studies), leading to potentially underpowered studies. In addition, matching should in theory result in two groups with similar baseline characteristics, severity of illness and risk for AKI. This is typically done on a few variables, such as age, sex, severity of illness score, or reason for admission, or on a propensity score obtained by multivariate analysis. The more variables that are taken into account, and the closer the variables match (for example, APACHE II score may differ maximum 1 point), the closer the control patient will match the case patient. It is clear that an ideal match in which patient and control are identical and with similar risk profile is difficult to obtain.

Finally, the single-centre design of the case-control studies also precludes firm conclusions and external validity of the findings.

DILUTION OF SERUM CREATININE

Patients who received contrast media will more likely have received i.v. prehydration for prevention of CA-AKI. As discussed above, this may dilute Scr and lead to lower Scr concentration. In other words, the relationship between GFR and Scr is not the same before and after prehydration. Some patients may actually have experienced damage to the kidney with decreased GFR, but this remained undetected because of the effect of prehydration on Scr.

PREVENTION OF CONTRAST-ASSOCIATED ACUTE KIDNEY INJURY

The first step in prevention of CA-AKI is the identification of patients at risk. Risk factors for CA-AKI are administration of nephrotoxic agents (NSAIDs, angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers, metformin), pre-existing chronic kidney disease (eGFR <60 ml/min/1.73 m^2 for intra-arterial contrast, and <45 ml/min/1.73 m^2 for i.v. contrast), diabetes mellitus, cirrhosis, heart failure or other causes of impaired renal perfusion [17,19,21▪▪,49▪–51▪]. In these patients, alternative imaging methods need to be considered, and if possible nephrotoxic medication should be discontinued before the procedure. If contrast media-enhanced radiological imaging is necessary, the lowest possible dose of iso-osmolar or low-osmolar iodinated contrast media should be administered in patients at risk for CA-AKI. In addition, i.v. volume expansion with crystalloid solutions is recommended. Classically, 1 l hypertonic saline 0.9% (NaCl 0.9%) is administered 6–12 h before contrast media administration, and 1 l for 12 h during and following administration. An alternative regimen is with a 154-mmol sodium bicarbonate solution ($NaHCO_3$) or NaCl 0.9% at 3 ml/kg/h for 1 h preceding contrast media administration, and at 1 ml/kg/h for 6 h during and following contrast media administration [52]. Meta-analyses of underpowered studies comparing both strategies favour the use of the bicarbonate regimen. However, as the bicarbonate solution is not available in many countries, it needs to be prepared by the pharmacy or the nurses at the bedside, and is therefore prone to possible medication errors. Also, the evidence is considered weak, as it comes from smaller and heterogeneous studies and meta-analyses [49▪,50▪]. N-acetylcysteine (NAC) may also prevent development of CA-AKI, supposedly by the scavenging properties of this molecule. The evidence on NAC for prevention of CA-AKI is also based on smaller, heterogeneous studies, and therefore weak. This is especially so for i.v. administration of NAC, the route of administration often used in ICU patients [53▪]. The cost and risk profile for this molecule is favourable, so that the current guidelines still recommend the use of oral NAC [49▪,50▪]. Since the data collection of the latest guidelines, the first

adequately powered ACT study in coronary and peripheral angiography patients could not demonstrate any benefit for NAC, making this recommendation less strong [54].

The evidence for the two strategies that are most often used, crystalloid prehydration and NAC, is weak. This will be addressed in the PRESERVE study, which is an adequately powered study that will prospectively evaluate the effect of NaCl versus $NAHCO_3$ prehydration, and oral NAC versus placebo in coronary and non-coronary angiography [55]. The PRESERVE study is currently recruiting patients.

Several pharmacologic agents, such as theophylline, vitamin C and statins, have shown benefit for prevention of CA-AKI [56▪,57,58▪–60▪]. The evidence for these agents was collected in smaller studies, most in non-ICU patients, and is therefore at present weak [61].

A small study demonstrated benefit of the prophylactic use of continuous hemofiltration in high-risk patients with advanced chronic kidney disease [62]. As these patients were compared with standard treatment in a non-ICU setting, it is uncertain whether the intervention with CVVH, or stricter follow-up in an ICU, contributed to the benefit.

Prevention of CA-AKI in ICU patients is listed below:

(1) Identify patients at risk and consider alternative imaging in patients at risk,
   (a) Risk factors:
      (i) older age,
      (ii) CKD:
         intra-arterial contrast: eGFR less than 60 ml/min/1.73m^2,
         i.v. contrast: eGFR less than 45 ml/min/1.73m^2,
      (iii) Diabetes mellitus,
      (iv) Heart failure,
      (v) Cirrhosis,
      (vi) Decreased renal perfusion,
      (vii) Nephrotoxic medication:
         Aminoglycosides,
         ACEI/ARBs,
         NSAIDs,
         Metformin,
(2) Discontinuation of nephrotoxic medications (NSAIDs, metformin, diuretics),
(3) Prehydration with near-isotonic crystalloid solution,
   (a) 154 mmol/l $NaHCO_3$ solution: 846 ml glucose 5% + 154 ml of 1000 mEq/l $NaHCO_3$,
      (i) 3 ml/kg for 1 h before contrast media exposure followed by 1 ml/kg for 6 h during and following contrast media exposure,
   (b) NaCl 0.9%, different schemes have been studied:
      (i) 3 ml/kg for 1 h before contrast media exposure followed by 1 ml/kg for 6 h during and following contrast media exposure,
      (ii) 1 ml/kg for 6–12 h before contrast media exposure, followed by 1 ml/kg/h for 12 h during and after contrast media exposure (this scheme is less feasible in an ICU setting),
(4) Use lowest dose of contrast media,
(5) Use low-osmolar or iso-osmolar contrast media,
(6) Interventions with low evidence in ICU patients,
   (a) Pharmacologic prevention,
      (i) Oral NAC,
      (ii) Theophyllin,
      (iii) Vitamin C,
      (iv) Statins,
   (b) Prophylactic hemofiltration.

CONCLUSION

Contrast media are causing damage to the kidney via diverse pathophysiologic pathways. Increased concentration of biomarkers after contrast media administration may indicate that this damage indeed leads to damage of the kidney. The occurrence rate of CA-AKI in ICU patients is approximately 16%, and multivariate analysis shows that contrast media administration is associated with increased mortality. Case-control studies in ICU patients challenge the impact of contrast media on occurrence of AKI and suggest that baseline characteristics and severity of illness of ICU patients are the determinants of AKI. However, limitations of these studies preclude firm conclusions. Therefore, future research has to further clarify the impact of contrast media administration on relevant CA-AKI on outcome in this specific population. Similarly, prevention strategies for CA-AKI are studied in smaller studies and seldom in ICU patients and have therefore a weak evidence base in this cohort.

Acknowledgements

None.

Conflicts of interest

E.H. has received lecturing fees from Astuste Medical and an academic grant for research on kidney biomarkers in ICU patients. W.V. and W.D.C. have no conflicts of interests to declare.

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