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STATE OF THE ART REVIEW

Sepsis associated acute kidney injury

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ABSTRACT

Sepsis is defined as organ dysfunction resulting from the host's deleterious response to infection. One of the most common organs affected is the kidneys, resulting in sepsis associated acute kidney injury (SA-AKI) that contributes to the morbidity and mortality of sepsis. A growing body of knowledge has illuminated the clinical risk factors, pathobiology, response to treatment, and elements of renal recovery that have advanced our ability to prevent, detect, and treat SA-AKI. Despite these advances, SA-AKI remains an important concern and clinical burden, and further study is needed to reduce the acute and chronic consequences. This review summarizes the relevant evidence, with a focus on the risk factors, early recognition and diagnosis, treatment, and long term consequences of SA-AKI. In addition to literature pertaining to SA-AKI specifically, pertinent sepsis and acute kidney injury literature relevant to SA-AKI was included.

Introduction

Sepsis is a life threatening clinical syndrome characterized by organ dysfunction caused by a patient's dysregulated response to infection. Septic shock is a subset of sepsis with increased mortality characterized by hypotension, in which vasoactive drugs are needed to maintain a mean arterial pressure of at least 65 mm Hg and a serum lactate concentration above 2 mmol/L despite resuscitation.[1 2] These Third International Consensus (Sepsis-3) Definitions published in 2016 mark a refinement of the definition of sepsis from the continuum of systemic inflammatory response syndrome, sepsis, severe sepsis, and septic shock that had guided clinical management and research for more than two decades.[3 4] The Sepsis-3 definitions identify the deleterious response to infection more specifically, as they were developed in the context of an enhanced understanding of both the biologic mechanisms of sepsis and the clinical outcomes made evident with the advent of large patient datasets.

Concurrently, the past 15 years have been a period of important progress in the understanding of the incidence, detection, pathobiology, and treatment of kidney dysfunction in the setting of critical illness and in sepsis specifically. From the initial RIFLE definition of acute renal failure in 2004 through the refined KDIGO definition of acute kidney injury (AKI), our ability to recognize and characterize changes in kidney function with traditionally available assessment methods (serum creatinine, urine output) has grown.[5-7] Many serum and urinary biomarkers allow earlier detection of AKI and have the potential to improve supportive care and clinical outcomes.

In this review, written for specialists in critical care medicine and nephrology, we critically review the published literature for sepsis associated acute kidney injury (SA-AKI), with a focus on epidemiology, non-modifiable risk factors, early detection, pathophysiology, modifiable risk factors, treatment, and prognosis.

Sources and selection criteria

We searched several online databases from 2000 to April 2018, including PubMed, the Cochrane database of systematic reviews, and the central register of controlled trials. We used keywords and combinations of keywords such as sepsis, severe sepsis, septic shock, acute kidney injury, acute renal failure, kidney failure, dialysis, and renal replacement therapy. We prioritized large scale, multicenter, randomized trials and large high quality epidemiologic studies when available. However, given the breadth of this review and the dearth of large studies in some aspects of SA-AKI, we thought that it was important to include observational and pre-clinical studies that are driving future investigation in this area. We highlighted the limitations of these studies where relevant.

Definitions

Sepsis

Although sepsis been appreciated as a cause of morbidity and mortality for centuries, consensus definitions have been available only for several decades.[8] The first consensus definitions defined sepsis on a continuum of physiologic and serologic abnormalities that indicated progressive organ failure. The systemic inflammatory response syndrome (SIRS) indicated the potentially injurious inflammatory response, sepsis was defined as SIRS with infection, severe sepsis was sepsis with organ dysfunction, and septic shock was sepsis with persistent hypotension.[3 4] These definitions, with only minor revision, guided bedside clinical practice as well as clinical, translational, and basic research of sepsis for 25 years.

These definitions were critical in advancing our understanding of sepsis, but experience revealed their

Box 1 | Sepsis-3 definitions and quick SOFA (qSOFA) criteria[1]

Sepsis-3 definitions

Sepsis—Life threatening organ dysfunction caused by a dysregulated host response to infection

Septic shock—Sepsis with a requirement for vasoactive therapy to maintain mean arterial pressure ≥65 mm Hg and lactate elevation to >2 mmol/L despite adequate volume resuscitation

qSOFA criteria

- Respiratory rate ≥22 breaths per minute
- Altered mentation
- Systolic blood pressure ≤100 mm Hg

limitations as well. One multicenter observational cohort study found that two criteria for SIRS were met in 87% of patients at admission to the intensive care unit (ICU), in 93% during their stay in ICU, and in 100% of patients with infection.[9] Another multicenter cohort study identified infected patients without SIRS, but mortality was the same in this group and in infected patients with SIRS (hazard ratio 0.94, 95% confidence interval 0.77 to 1.15), suggesting that meeting two criteria for SIRS was not predictive of outcomes.[10] SIRS was recognized as a non-specific marker of both infectious and non-infectious inflammation that did not meaningfully predict clinical outcomes. These observations resonated with an increased understanding of the response to injury, whether infectious or sterile. The critical feature that differentiates infection from sepsis is organ dysfunction that results from the inflammatory response.[11]

The Sepsis-3 definitions were an empirically based response to these limitations. SIRS and severe sepsis were eliminated. Sepsis is defined as "life threatening organ dysfunction caused by the dysregulated host response to infection." Identification of organ dysfunction may be identified as an acute and infection related change of at least 2 points on the sequential organ failure assessment (SOFA) score, which is associated with mortality of approximately 10%.[1 12 13] Screening for sepsis in infected patients may be aided by use of the quick SOFA score, in which the presence of two out of three criteria suggests sepsis. Septic shock is defined as sepsis with hypotension requiring vasopressors to maintain a mean arterial pressure at least 65 mm Hg and a serum lactate concentration above 2 mmol/L despite adequate volume resuscitation, which was associated with mortality of greater than 40% (box 1).[2] The performance of the Sepsis-3 definition in clinical practice remains a point of discussion and contention, however, as there seems to be a loss of sensitivity relative to SIRS and variable performance based on practice setting (emergency department, inpatient ward, ICU). Furthermore, other novel models may provide even more accurate diagnosis and prediction.[14 15]

Table 1 | Acute kidney injury (AKI) diagnostic criteria: RIFLE, AKIN, and KDIGO

	Serum creatinine			Urine output (all)
Staging	RIFLE	AKIN	KDIGO	
Definition of AKI	SCr increase ≥50% within 7 days	SCr increase ≥50% or ≥0.3 mg/dL within 48 h	SCr increase ≥50% in 7 days or ≥0.3 mg/dL within 48 h	-
RIFLE-risk; AKIN stage 1; KDIGO stage 1	SCr increase ≥50% or GFR decrease >25% within 7 days	SCr increase ≥50% or ≥0.3 mg/dL within 48 h	SCr increase ≥50% in 7 days or ≥0.3 mg/dL within 48 h	<0.5 mL/kg/h for 6-12 h
RIFLE-injury; AKIN stage 2; KDIGO stage 2	SCr increase ≥100% or GFR decrease >50% within 7 days	SCr increase ≥100%	SCr increase ≥100%	<0.5 mL/kg/h for ≥12 h
RIFLE-failure; AKIN stage 3; KDIGO stage 3	SCr increase ≥200% or GFR decrease >75% or SCr increase ≥4 mg/dL (with acute rise ≥0.5 mg/dL)	SCr increase ≥200% or ≥4 mg/dL (with acute rise ≥0.5 mg/dL) or need for RRT	SCr increase ≥200% or ≥4 mg/dL or need for RRT	<0.3 mL/kg/h for ≥24 h or anuria for 12 h
RIFLE-loss	Need for RRT >4 weeks	-	-	-
RIFLE-end stage	Need for RRT >3 months	-	-	-

GFR=glomerular filtration rate; RRT=renal replacement therapy; SCr=serum creatinine.

Acute kidney injury

AKI and acute renal failure have long been recognized as a complication of critical illness independently associated with mortality.[16-18] Similar to sepsis, understanding the epidemiology, pathobiology, and treatment of renal dysfunction in the ICU was predicated on establishing a consensus definition.

The first widely adopted definition emerged from the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group in 2004.[6] Similar to SIRS based sepsis criteria, the RIFLE classification (risk, injury, failure, loss, end stage kidney disease) used readily available clinical (decreased urine output) and serologic (rise in serum creatinine) markers to better characterize what was termed acute renal failure.[6] Subsequent consensus definitions would use the term acute kidney injury, a more inclusive term that underscores the importance of the injury and consequent change in the renal function. Through this lens, the 2007 definitions of the Acute Kidney Injury Network (AKIN) focused on the initial injury previously deemed risk, injury, and failure of the RIFLE classification, terming them stage 1, 2, and 3 AKI.[5] Loss and end stage kidney disease in the RIFLE system were removed along with the partial reliance on glomerular filtration rate (GFR). Additionally, the AKIN criteria included small changes in serum creatinine (>0.3 mg/dL increase in 48 hours) in the definition of stage 1 AKI.[5] Several large observational trials confirmed the validity of the RIFLE and AKIN revised criteria, as increasing severity of AKI was associated with increasing risk of death.[19 20]

Despite high incidence (22%) and significant effect on outcomes, a concern remained that AKI was underdiagnosed owing to inconsistent screening practices and the tendency for these criteria to miss AKI that occurs before arrival at an acute care setting. The Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines for AKI present the most recent consensus definitions, which again attempt to refine the sensitivity and specificity of the AKI definitions. Table 1 summarizes the RIFLE, AKIN, and KDIGO criteria for AKI. The KDIGO definition emphasizes AKI risk assessment and evaluation while extending criteria to include a rise in serum creatinine of 50% or greater over the presumed baseline within seven days of assessment.[7 21] In an international cross sectional study using these criteria, 57.3% of ICU patients met KDIGO criteria for AKI. The adjusted odds ratio for in-hospital mortality was 1.68 (0.89 to 3.17) for stage 1, 2.95 (1.38 to 6.28) for stage 2, and 6.88 (3.88 to 12.23) for stage 3.[22]

Despite this progress, the sensitivity and accuracy of AKI criteria have been generally acknowledged to remain limited by a reliance on the imperfect assessment methods

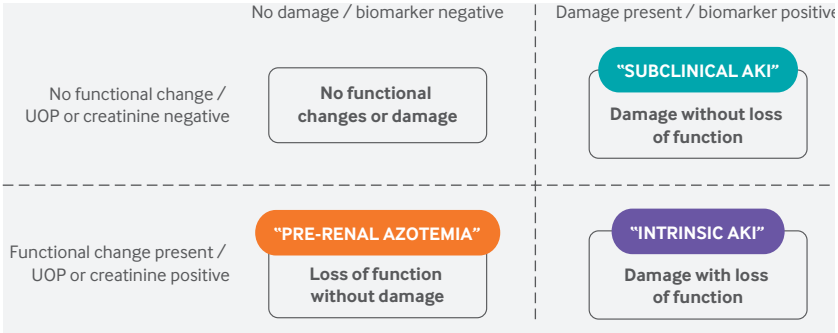

Fig 1 | Acute disease quality initiative criteria: incorporating biomarkers into the definition of acute kidney injury (AKI). Emerging data outside of sepsis associated AKI (SA-AKI) point to the increased risk for adverse outcomes in patients who do not have a change in functional markers of the kidney (eg, serum creatinine or urine output (UOP)). This has led to calls for classification of AKI in terms of changes in function and damage and the resultant 2×2 grid shown. This work has created a new category of patient with "subclinical AKI," those with elevated damage biomarkers in the absence of a change in renal function (UOP or serum creatinine). This group can be thought of as akin to those with a change in function without the presence of damage (traditionally thought of as "pre-renal azotemia") and separate from those with intrinsic AKI (a change in both function and damage). Adapted from Endre et al[23]

on which they are built: urine output and serum creatinine. Some people have called for further refinement of AKI in terms of these traditional functional markers, as well as changes in kidney damage biomarkers (fig 1).[23] Although the emergence of data derived clinical risk scores, renal imaging, functional assays, and biomarkers have shown promise, they have yet to become a part of consensus definitions or guidelines. However, they represent opportunities to refine our diagnosis, evaluation, treatment, and prognosis of AKI.[24]

Sepsis associated acute kidney injury

Many patients meet consensus criteria for both sepsis and AKI and are deemed to have SA-AKI or septic AKI.[25 26] Sepsis is associated with up to 50% of AKI, and up to 60% of patients with sepsis have AKI.[25 27] Independent risk factors or clinical consequences of sepsis and AKI, such as hypovolemia or exposure to nephrotoxic therapies, have confounded the relation between these entities.[28 29] Although the pathophysiologic mechanism remains incompletely understood, it seems evident that the deleterious inflammatory cascade characteristic of sepsis contributes to the AKI as well.[30] Patients with sepsis complicated by AKI have a significantly increased mortality relative to patients without AKI.[26 31 32] Furthermore, patients with AKI associated with sepsis have a significantly increased mortality relative to those with AKI of another etiology.[31]

Table 2 | Risk and prognostic factors for acute kidney injury

Factor	Effect on risk or prognosis	
Present before acute illness		
Age[18-38]	Developing AKI	OR 1.5 (95% CI 1.16 to 1.92) for age ≥65; 1.01 (1.00 to 1.02) for each year
	Death with AKI	OR 1.19 (1.05 to 1.33) for age ≥65; 1.13 (1.01 to 1.26) for each decade
Sex	Developing AKI	Data inconsistent
Race	Developing AKI	Data inconsistent
Chronic kidney disease[39]	Developing AKI	OR 2.9 (2.7 to 3.1) for eGFR 45-59; 6.2 (5.7 to 6.8) for eGFR 30-44; 18.3 (16.5 to 20.3) for eGFR <30 mL/min/1.73 m^2
	Death with AKI	AKI predictive of mortality, but less predictive for patients with more severe CKD
Diabetes mellitus[40]	Developing AKI	OR 10.3 (7.7 to 13.6) for developing stage III AKI
	Death with AKI	OR 1.2 (1.2 to 1.7)
Hypoalbuminemia[24 41]	Developing AKI	OR 2.34 (1.74 to 3.14) with drop 1 g/dL
	Death with AKI	OR 2.47 (1.51 to 4.05) with drop 1 g/dL
Chronic liver disease[18]	Developing AKI	OR 2.18 (1.16 to 4.10)
Heart failure[18-40]	Developing AKI	OR 2.18 (1.12 to 4.44) to 24.0 (18.5 to 31.2)
Caused by acute illness		
Cardiovascular failure[18 40]	Developing AKI	OR 1.84 (1.32 to 2.56)
	Death with AKI	OR 1.8 (1.2 to 2.9)
Mechanical ventilation[42]	Death with AKI	OR 5.1 (2.0 to 12.8)
Liver failure[37]	Death with AKI	OR 1.90 (1.34 to 2.71)
Sepsis[37]	Death with AKI	OR 1.87 (1.33 to 2.62) to 2.1 (1.1 to 1.4)

AKI=acute kidney injury; CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; OR=odds ratio.

Epidemiology

Accurate estimation of the incidence and trend of AKI secondary to sepsis has proved challenging. Even as screening programs and data science help to refine our ability to define AKI associated with sepsis, strictly characterizing AKI as being attributable to sepsis remains difficult given the many confounders common in critically ill patients.

The incidence of sepsis and related morbidity seems to be rising, whereas the mortality rate of patients with sepsis seems to be falling. A comprehensive review of 750 million hospital admissions in the US from 1979 through 2000 found that sepsis increased from 82.7 to 240.4 per 100 000 population, an annualized increase of 8.7%.[33] In-hospital mortality fell from 27.8% to 17.9%. Analyses of data from the subsequent 10-15 years using more robust patient level data from England, New Zealand, Australia, and the US have all shown similar trends, with increasing overall burden of sepsis and decreasing mortality rates.[8 34-36] Rates of AKI and sepsis associated AKI are discussed below.

Risk factors for development of sepsis associated AKI

Much of our understanding of the risk and prognostic factors in AKI comes from studies of patients in general wards, mixed ICU populations, or patients undergoing cardiovascular procedures, in whom the baseline kidney function and the nature and timing of injury can be well defined. Patients with SA-AKI are often included but are not the dedicated or exclusive focus of these studies. However, we believe that identified risk and prognostic factors for AKI in a general population likely confer an equal or even greater risk in patients with sepsis.

Furthermore, the heterogeneity of both the patient population and the focus of any given study can lead to inconclusive and occasionally conflicting data about the risk factors for AKI. The pre-morbid risk factors for AKI most consistently identified include advanced age, chronic kidney disease, and cardiovascular disease. Characteristics associated with the acute illness most commonly linked to AKI included cardiovascular failure, liver failure, and sepsis. Table 2 summarizes these and other risk factors. Potentially modifiable risk factors related to the treatment of patients with sepsis are discussed in the treatment section.

Finally, observational data suggest that AKI may predispose patients to an increased risk of sepsis. In the Program to Improve Care in Acute Renal Disease (PICARD)

Box 2 | Urinalysis scoring systems

Prospective observational cohort studies with discovery and validation cohorts for AKI cast scoring index[51]

Grade 1—no casts or RTE

Grade 2—≥1 cast or RTE but <10% of LPF

Grade 3—many casts or RTEs (10-90% of LPF)

Grade 4—sheet of muddy brown casts and RTEs in >90% of LPF

Prospective observational cohort for development of urinary sediment scoring system[52]

0 points—no casts or RTE seen

1 point each—1-5 casts per LPF or 1-5 RTEs per HPF

2 points each—≥6 casts per LPF or ≥6 RTEs per HPF

Prospective multicenter observational cohort for derivation of urine microscopy score[53]

0 points—no casts or RTE seen

1 point each—1 cast or 1 RTE per HPF

2 points each—2-4 casts or RTEs per HPF

3 points each—≥5 casts or ≥5 RTEs per HPF

HPF=high power field; LPF=low power field; RTE=renal tubule epithelial cells

study, 243 (40%) patients developed sepsis a median of five days after the development of AKI. Although the pathophysiology and correlation between these two events remain unclear, mounting evidence suggests that AKI increases the risk of sepsis and its associated adverse outcomes.[29]

Early detection of SA-AKI

As both sepsis and AKI are independently associated with increased morbidity and mortality, length of stay, and cost of care, early detection is critical to providing opportunities for successful intervention.[43-45] Particularly for AKI, the refined consensus definitions have tended to be more sensitive and allow earlier diagnosis. Regardless of the cause and associated comorbidities, all AKI remains a diagnosis based on increases in serum creatinine or decreases in urine output. Although useful, these measures have limitations that underscore the need for newer methods to detect AKI and SA-AKI.

Limitations of serum creatinine and urine output

The initial limitation of a definition that relies on change in serum creatinine is establishing a baseline serum creatinine. No consensus method exists to establish pre-AKI baseline serum creatinine in the absence of previous values (recent or distant).[46 47] Furthermore, changes in serum creatinine are often delayed owing to renal reserve and the kinetics of AKI. Urine output is insensitive and is often measured accurately only in the ICU setting. Evidence from multiple retrospective cohort studies also suggests that the same stage of AKI diagnosed by serum creatinine and urine output may confer differential risk. Isolated urine output based AKI carries increased morbidity and mortality (compared with no AKI), but these risks are lower than those conferred by serum creatinine based AKI.[48-50]

Emerging SA-AKI detection techniques

Urinalysis and urine microscopy may aid identification of SA-AKI. Three observational studies evaluated a urine microscopy score specifically in a cohort with SA-AKI (box 2).[51-53] SA-AKI shows more renal tubule epithelial cells and cast elements compared with non-septic AKI. In a small prospective, two center study of 83 patients, 43 with SA-AKI, a urinalysis score above 3 was predictive of severe AKI and was highly correlated with biomarkers of tubular injury.[53] Separately, a single center observational study of 423 patients with sepsis showed that new albuminuria was associated with an odds ratio of 1.87 (1.21 to 2.89) for developing SA-AKI, even after adjustment for baseline GFR, severity of critical illness, and exposure to nephrotoxins.[54] These data have yet to be prospectively replicated, but routine dipstick albuminuria has also been shown to be independently associated with lower rates of recovery from AKI.[55]

Most validated AKI risk scores focus on AKI after cardiac surgery or in a general hospital population.[37 56-64] No widely accepted risk score has been validated for risk of SA-AKI, and only one validated score predicts mortality in patients with SA-AKI who need renal replacement therapy (RRT).[65] The performances of non-specific AKI risk scores and other critical illness scores have been disappointing in patients with SA-AKI.[66] A retrospective study investigated the performance of several risk scores (Liano,[63] Simplified Acute Physiology Score II,[66] PICARD,[37] and Demirjan[64]) to detect SA-AKI in 343 patients requiring continuous RRT, but no score provided an area under the curve (AUC) greater than 0.70.[67] A multicenter study of 214 pediatric ICU patients with sepsis assessed the ability of a renal angina index (RAI) and other novel biomarkers to predict SA-AKI.[68] The RAI is a tiered score in which patients are assigned points based on their risk of AKI (due to comorbidities) as well as their degree of injury (change in creatinine clearance). The RAI provided an AUC of 0.80 (0.75 to 0.86) for KDIGO stage 2 or 3 on ICU day 3 and outperformed several biomarkers including neutrophil gelatinase associated lipocalin (NGAL). When RAI was combined with NGAL and other biomarkers, either individually or in pairs, the predictive performance for stage 2 or 3 AKI was significantly improved (AUC 0.84-0.88; P<0.05).[68]

Several serum biomarkers that have been shown to be inversely correlated with GFR may provide an advantage in detecting AKI in patients with sepsis. Proenkephalin and cystatin C are both highly associated with AKI and GFR and increase before serum creatinine in critically ill patients with sepsis (table 3).[70-72] One study evaluated the ability of urinary tissue inhibitor of metalloproteinase-2 and insulin-like growth factor binding protein-7 (TIMP2*IGFBP7), markers of cell cycle arrest, to predict the development of stage 2 or 3 AKI in 232 high risk critically ill patients with sepsis. Forty (17%) patients developed stage 2 or 3 AKI, with TIMP2*IGFBP7 providing an AUC of 0.84. The biomarker performed similarly regardless of severity of illness (SOFA score), and a cutoff of 1.0 provided a sensitivity of 77.5% and a specificity of 75% for the development of severe AKI.[73]

NGAL, which is commercially available in several countries, is up regulated along the renal tubule in the setting of ischemic injury, nephrotoxins, and inflammation. Data have been inconsistent in SA-AKI.[74 75] Multiple studies have shown that plasma NGAL is elevated in

Table 3 | Biomarkers used for detection of acute kidney injury (AKI)

Type of biomarker	Subclass of biomarker	Examples of biomarkers	Comments
Functional biomarker of AKI	Biochemical markers of glomerular filtration/function	Serum creatinine, serum cystatin c, proenkephalin, visible fluorescent injectates[69]	Serum creatinine remains the gold standard, but other novel markers of glomerular function have been shown to rise earlier and with the same accuracy as creatinine. Injectables may represent the future of GFR measurement, with the injection of small dextrans providing rapid determination of GFR at the bedside. May be elevated in the setting of CKD
	Global assessment of nephron function	Urine output	Urine output detects less severe AKI compared with creatinine and can be affected by diuretics and other drugs. Generally needs indwelling catheter for reliable measurement, with measurements being less frequent outside ICU
	Global assessment of nephron capacity	Furosemide stress test, renal reserve testing	These tests interrogate the kidney's capacity for increased function via protein loading (hyperfiltration) or diuretic responsiveness but are not validated in the setting of sepsis
Damage/injury biomarkers	Global assessment of nephron injury	Urinalysis	Urinalysis can detect injury along the entire nephron (from glomerulus to tubules); although scoring systems exist (box 2), none has been widely validated in any setting of AKI.
	Biochemical biomarkers of renal tubular injury	Urinary NGAL, urinary KIM-1, soluble FAS	These remain an area of intense AKI research but have yet to be widely validated in the setting of human AKI
AKI risk biomarkers	Biochemical biomarkers of AKI risk	TIMP2*IGFBP7, plasma NGAL	Increasingly available for clinical use, these markers quantify an individual patient's risk for impending AKI
	Biomarkers of AKI risk	Electronic alerts, electronic risk algorithms	Although not specific to SA-AKI, several alerts have shown their ability to predict the impending development of sepsis and AKI separately. Using these alerts in concert with biochemical biomarkers may help to enrich SA-AKI detection and risk stratification

CKD=chronic kidney disease; GFR=glomerular filtration rate; ICU=intensive care unit; IGFBP7=insulin like growth factor binding protein-7; KIM-1=kidney injury molecule-1; NGAL=neutrophil gelatinase associated lipocalin; SA-AKI=sepsis associated acute kidney injury; TIMP2=tissue inhibitor of metalloproteinase-2.

patients with sepsis even in the absence of AKI.[76] Other studies have shown that elevations of plasma NGAL even in the absence of elevated serum creatinine can identify critically ill patients at risk for severe AKI and inpatient mortality.[77 78] Plasma NGAL has also been shown to be elevated in sepsis regardless of the presence of AKI, but a higher cutoff threshold (454 ng/mL) provided a sensitivity of 72% and specificity of 74% for the detection of AKI.[79] Urinary NGAL and urine kidney injury molecule-1 (KIM-1) have been used to try to quantify renal tubular damage in SA-AKI; although some association has been shown, large scale studies have not validated these findings.[80]

Several other novel biomarkers have been investigated in the setting of SA-AKI, and table 3 summarizes some of these findings and uses the framework from figure 1.[81] Finally, an effort is ongoing to take a step back from biochemical measures such as NGAL or TIMP2*IGFBP7 and use real time data from the electronic health record to identify patients with either sepsis or AKI, and we anticipate that automated alerts for these patients will be combined with biochemical biomarker testing to improve risk stratification and case detection for SA-AKI. We anticipate that electronic risk score and biochemical biomarkers will be incorporated into standard of care over the next decade.[82-84]

Pathobiology of SA-AKI

Recent advances in sepsis related organ dysfunction have enhanced our knowledge of the pathobiology of SA-AKI.[8 85-88] Renal hypotension and associated ischemia had been believed to be the primary lesion in SA-AKI, but more recently several animal models have shown that although tubular cell injury and expression of markers such as KIM-1 are common, inflammation and apoptosis are also playing a role.[89 90] These data fit with the evolving view of multifocal organ injury including macrovascular and microvascular dysfunction and immunologic and autonomic dysregulation. In depth discussions of these pathways are beyond the scope of this review, but we will highlight the animal models that elucidate these pathways. Table 4 summarizes the four most common experimental models, as well as their strengths and limitations.

In a placebo controlled ovine model of SA-AKI following direct infusion of bacteria, renal histology showed patchy and focal changes with limited tubular injury.[89] Animals with SA-AKI actually had higher renal blood flow (RBF) than controls. This differs from the decreased RBF in humans with SA-AKI, measured by phase contrast magnetic resonance imaging, thermodilution, and renal Doppler.[92-94] This disconnect between human and animal data underscores the limitations of our understanding of the relation between RBF and renal function and has led some people to call for an increased role of renal biopsy in the setting of human sepsis. In the US, the National Institutes of Health have recently begun the Kidney Precision Medicine Project, which aims to ethically obtain and evaluate kidney biopsies from patients with AKI to create a kidney tissue atlas, define disease phenotypes, and identify critical cells, pathways, and targets for novel therapies in the setting of sepsis and other forms of AKI; thus we anticipate advancement of our knowledge in SA-AKI in the near future.[95]

Disturbances in microcirculatory oxygen delivery may include both decreased flow and diffusion limitation in the setting of organ edema and inflammation.[96] Although the exact ramifications of altered microcirculation are incompletely understood, sepsis increases expression of inflammatory cytokines and leukocyte activity, which may result in capillary plugging and micro-thrombi. This leads to production of reactive oxygen species and induction of nitric oxide synthase, which may further damage the endothelial barrier and the glycocalyx,[97-99] leading

Table 4 | Animal models used in investigation of sepsis associated acute kidney injury (AKI)

AKI model	Animals	Model description	Strengths/limitations
Non-surgical			
Direct endotoxin administration	Mammalian but predominantly murine	Purified endotoxin (lipopolysaccharide from outer membrane of Gram negative bacteria) is directly injected intraperitoneally or intravenously	Easier and cheaper than surgical models, but animals often need high dose of lipopolysaccharide to produce shock. Lipopolysaccharide concentrations in these models may be 10-200 times the concentrations found in human sepsis. Additionally, cardiovascular response shows earlier cytokine release and hypodynamic cardiovascular response than human sepsis. Value of this model has been questioned despite its convenience and reproducibility[91]
Direct bacterial administration	All mammals but frequently used in larger mammals (porcine and ovine) and also in zebrafish	Live bacteria can be delivered to host (intravenously, intraperitoneally, subcutaneously, or directly into organ (eg, lung)). Can use Gram negative and Gram positive bacteria	Like lipopolysaccharide model, it allows for varied route of infection as well as varied administration (bolus *v* continuous). This allows for reproducibility in follow-up studies, but host response to whole microbe can be variable (as with lipopolysaccharide). Additionally, sudden administration of single strain does not model all forms of human sepsis
Surgical			
Cecal ligation and puncture or intra-abdominal fecal implantation	Mammalian but predominantly murine	Peritoneal cavity is accessed and either cecum is perforated or stool is directly implanted resulting in abdominal sepsis. Similar model uses colon ascendens stent, which allows feces to leak from bowel to peritoneum	Easy, but does not mimic non-abdominal infectious sources. Sepsis is often polymicrobial, which may be case in humans, but large degree of variability exists in severity of sepsis and resultant acute kidney injury. This variability stems from differences in surgical techniques as well. Can be enhanced with biotelemetry
Bacterial implantation models	Mammalian but predominantly murine	Bacterial impregnated substance (most commonly fibrin clot) is implanted in desired locations (intraperitoneal, intravascular).	Replicates hyperdynamic response of human sepsis, but single organism has same limitations as direct bacterial administration. Dose and timing can be altered to maximize effects, but whether it justifies increased costs of surgical procedure (compared with direct bacterial administration) remains unclear

to both structural and functional changes in the setting of SA-AKI (fig 1).

These structural and functional changes may not work in sync. In an ovine model, no association was seen between early SA-AKI and histopathologic lesions on renal biopsy.[90] Septic animals (n=10) had increased mesangial expansion on electron microscopy compared with non-septic animals, but no significant structural disturbances were found compared with controls (n=5).[90] Although surprising, these findings may be valid given that larger animals better mimic the human cardiovascular response in sepsis.[90 100-102] More specifically, ovine autoregulatory responses in untreated shock and shock treated with vasoactive drugs are similar to those in human kidneys with AKI.[100 101 103] Increased investigation of the interplay of the inflammatory cytokines and infiltrating cells and apoptosis will further our knowledge on the effect of these factors on the renal histology and the macrocirculation and microcirculation.

Prevention and medical treatment

In this section, we will explore prophylactic and therapeutic interventions in the setting of developing and established SA-AKI. This will include considerations in the general care of the patient with sepsis that have been shown to affect the incidence or severity of AKI, as well as therapies specifically targeted to the injured kidney.

Resuscitation

Inflammation in sepsis leads to endothelial failure and consequent loss of veno-motor tone and barrier function. The resultant reduction in the mean systemic pressure and relative hypovolemic state, paired with decreased systemic vascular resistance, results in hypotension.[8] Prompt resuscitation of the circulation with administration of intravenous fluids is a key component of sepsis management.[104-106] However, excessive administration and accumulation of fluids in an attempt to treat hypotension or oliguria after AKI is common and harmful.

In a randomized trial of a conservative versus a liberal fluid strategy in 1000 patients with acute respiratory distress syndrome (ARDS), the patients in the conservative fluid arm not only had more ventilator-free and ICU-free days but had a non-significant trend toward less AKI needing RRT than those in the liberal fluid arm (10% *v* 14%; P=0.06).[107] Additional analysis of this trial and other studies of fluid management have also shown the harms of excess fluid during and after the development of AKI.[108-110] Postulated mechanisms driving this phenomenon include cardiac overload with falling cardiac output, resultant renal venous hypertension, increasing resistance, and decreased renal perfusion pressures.

Separately, edema driven rises in intra-abdominal pressure may inhibit renal venous drainage, further exacerbating the elevation of renal vascular pressure.[43 111 112] High quality resuscitation care of the patient with sepsis includes an initial modest bolus of resuscitation fluid (30 mL/kg within the first three hours) followed by a frequent assessment with dynamic measures of fluid responsiveness to determine whether additional fluids or vasoactive drugs are indicated.[113] Over-resuscitation and under-resuscitation have both been associated with adverse outcomes in the setting of shock. Recent studies have shown that protocolized resuscitation strategies did not improved outcomes, but a minimal degree of resuscitation is needed to mitigate the risk of adverse outcomes. Finally, clear evidence shows that in addition to the risks of under-resuscitation, in the setting of AKI, volume overload from aggressive over-resuscitation is also harmful, creating a J or U shaped curve for resuscitation and mortality.[104-106 114]

Selection of resuscitation fluids

An equally important emerging literature suggests that the type of resuscitation fluid may affect sepsis and SA-AKI outcomes. Perhaps the most definitive and consistent finding pertains to the use of hyperoncotic starch solutions. These solutions should be avoided in sepsis and in all other patients at risk for AKI, as multiple studies have shown that hydroxyethyl starches are associated with increased risk of AKI and need for RRT compared with a variety of crystalloid solutions.[115-119]

Other researchers have studied the effect of crystalloid solutions versus other, non-hyperoncotic starch colloids such as albumin in the setting of sepsis with risk for SA-AKI. In the SAFE trial, 1218 patients with severe sepsis were prospectively randomized to receive either albumin (n=603) or saline (n=615). Patients receiving albumin had higher central venous pressures over the first three days and a non-significant trend to decreased mortality but no difference in RRT rates across the two groups (18.7% *v* 18.2%; P=0.98).[120] Subsequent studies of albumin have also found modest improvements in outcomes such as hemodynamic variables but have not shown improvements in AKI or mortality.[121-124] This high quality literature has not shown significant benefit to albumin containing regimens, so their use cannot be recommended over less costly crystalloid solutions.

More recently, multiple studies have compared outcomes between balanced and hyperchloremic crystalloid solutions, with some but not all suggesting that hyperchloremic solutions may be associated with increased AKI and mortality.[125-128] One retrospective cohort of 60 734 adults with septic shock found that patients receiving exclusively isotonic saline had higher inpatient mortality than those who were co-administered balanced solutions (20.2% *v* 17.7%; P<0.001).[124] Two large prospective trials have recently added to this literature.[129 130] A pragmatic, cluster randomized, multiple crossover trial at a single center with 15 802 patients showed no difference in the primary endpoint of hospital-free days but did show that balanced solutions were associated with a lower rate of a composite endpoint of major adverse kidney events (all cause mortality, need for RRT, and doubling of serum creatinine from baseline) within 30 days (14.3% *v* 15.4%; P=0.01).[129] Subset analysis of patients with sepsis also showed that balanced crystalloids were associated with an even greater reduction in major adverse kidney events, as well as the 30 day mortality component of the composite endpoint.[130] Additionally, among the patients who derived the most benefit in these trials were those who had developed some degree of hyperchloremia and kidney injury before enrollment in the study.[129 130]Although the relatively low volumes of resuscitation fluid (approximately 2 L over the first three days) in these trials likely differ from practice, they add to a mounting body of data suggesting that balanced crystalloid solutions may improve renal outcomes and survivorship in non-selected and septic critically ill patients.

Vasoactive drugs

The selection of the ideal vasopressor in the setting of shock (regardless of AKI status) has been the source of several large scale multicenter trials.[103 131-135] In the setting of SA-AKI, traditional agents such as norepinephrine (noradrenaline), epinephrine, vasopressin, and dopamine, as well as more novel agents such as angiotensin II and levosimendan, have been investigated.

Norepinephrine has been a mainstay of treatment of septic shock, showing the ability to increase mean arterial pressure (MAP) and improve renal perfusion. Norepinephrine has been generally regarded as the first line agent for septic shock on the basis of many clinical trials suggesting either better outcomes or fewer adverse events than with other vasoactives.[131 136-139] However, ovine data suggesting that norepinephrine may exacerbate renal medullary hypoxia as the kidney attempts to preferentially shunt blood flow to the cortex in SA-AKI have led some researchers to revisit other agents in the setting of septic shock and SA-AKI.[100 140] Vasopressin is of particular interest, as the Vasopressin and Septic Shock Trial (VASST) comparing norepinephrine with vasopressin showed similar outcomes and no increased adverse events across all study patients and a survival benefit in subgroup analysis of patients with less severe shock.[141]

The VANISH trial was a prospective, double blind, randomized clinical trial with a two by two (vasopressin or norepinephrine, hydrocortisone or placebo) factorial design in the setting of septic shock.[131] Patients were randomly allocated to vasopressin (titrated up to 0.06 U/min) and hydrocortisone (n=101), vasopressin and placebo (n=104), norepinephrine and hydrocortisone (n=101), or norepinephrine and placebo (n=103). No difference by vasopressor was seen in the development of AKI in patients who survived (vasopressin group 57.0%, norepinephrine group 59.2%), in AKI-free days among patients who died in the hospital (vasopressin group 33.3%, norepinephrine group 29.4%), or in serious adverse events. These data may suggest that vasopressin is a viable first line alternative to norepinephrine.

However, not all vasoactive agents have performed so favorably. During norepinephrine shortages from 2008 to 2013 (≥20% decrease from baseline usage), a retrospective cohort study of 26 US hospitals showed an increase in inpatient mortality to 39.6% during the shortage compared with 35.9% with typical norepinephrine use, representing an odds ratio of 1.15 (1.01 to 1.30; P=0.03).[133] Phenylephrine and dopamine were the most common agents used in place of norepinephrine during the shortage. Paired with other trial data, many people have suggested that phenylephrine and, to an even greater extent, dopamine should be avoided as first line treatment of septic shock.[132 136 138 139]

Angiotensin II, a hormone in the renin-angiotensin-aldosterone system, is a novel agent recently investigated in the setting of shock.[103 135] In the Angiotensin II for the Treatment of High Output Shock (ATHOS-3) trial, 344 patients with vasodilatory shock (259 of whom had sepsis) who were receiving 0.2 µg/kg/min (or equivalent) of a vasopressor were randomized to receive either angiotensin II or placebo.[135] Angiotensin II led to a significant increase in the MAP from baseline within the first three hours of infusion. MAPs were increased in 69.9% of patients in the angiotensin II arm compared with

23.4% of the placebo arm (odds ratio 7.95, 4.76 to 13.3; P<0.001). An improvement was also seen in the cardiovascular SOFA score, with scores decreasing a mean of −1.75 points for patients in the angiotensin II arm compared with −1.28 in the placebo arm (P=0.01). No difference was seen in inpatient mortality.[135] A small subgroup analysis of patients treated with RRT showed that those receiving angiotensin II needed less RRT, were more likely to survive through day 28 (53% *v* 30%; P=0.012), and were more likely to be alive and RRT free by day 7 (38% *v* 15%; P=0.037) compared with placebo. If these results are validated in larger cohorts, angiotensin II may represent a novel treatment for SA-AKI.[103]

Levosimendan is a calcium sensitizing drug with inotropic properties that has been used to treat decompensated heart failure, with small studies showing its ability to increase creatinine clearance and urine output compared with dobutamine.[134 142] Unfortunately, in a large scale, double blind, randomized trial investigating the addition of levosimendan (compared with placebo) in adults with sepsis (MAKE-28), no difference was seen in renal outcomes.[134] Thus, no data support its use in the treatment of SA-AKI.

Norepinephrine and vasopressin remain consensus first line agents for the treatment of septic shock, although treatment should be tailored to the individual patient. Although previous studies have shown that MAP targets higher than the 65 mm Hg recommended in sepsis guidelines decreased the rate of RRT in patients with hypertension, this did not translate to improved survival.[143] A higher MAP should be targeted only with active surveillance to evaluate for adverse effects from these potentially harmful agents.

Mechanical ventilation

Critically ill patients with sepsis and septic shock often need mechanical ventilation with positive pressure (PPV) to provide support with oxygenation, ventilation, and airway protection in the setting of organ failure. PPV has long been known to have potentially deleterious effects on kidney perfusion and function.[144] More recently, a high quality systematic review and meta-analysis of studies reporting a relation between the use of invasive mechanical ventilation and the subsequent onset of AKI or comparing high and low tidal or positive end-expiratory pressure with the development of AKI found that the pooled odds ratio for development of AKI in the setting of mechanical ventilation was 3.16 (2.32 to 4.28), with similar findings in a subset that allowed multivariate analysis (3.48, 1.85 to 6.92).[145]

Work from animal models and clinical trials suggest that the mechanism is likely multifactorial. PPV increases intrathoracic pressure, reducing venous return, cardiac output, and renal perfusion.[146-149] This proposed mechanical mechanism is supported by several landmark clinical trials of ARDS. In a randomized controlled trial (RCT) of low tidal volume ventilation in ARDS, renal failure was seen less often in patients in the lower tidal volume intervention arm.[150] A more recent RCT of lung recruitment and titrated positive end-expiratory pressure (PEEP) did not report renal outcomes but noted a higher incidence of need to increase vasoactive drugs (34.8% *v* 28.3%; P=0.03) in the recruitment and titrated PEEP group who had significantly higher plateau pressures.[151] However, these findings have not been consistent across all trials. An RCT of high versus low PEEP in 767 patients with ARDS did not show a difference in the rate of kidney injury, although the rates were low in both groups.[152] Furthermore, neither tidal volume nor PEEP had a modifying effect in a patient population with a low percentage of ARDS in the meta-analysis showing the threefold increased risk in AKI with mechanical ventilation.[145]

Mechanical ventilation probably also induces both neurohormonal and inflammatory changes that potentially increase the risk for AKI. Both mechanical ventilation and the ventilator strategy of permissive hypercapnia are known to induce sympathetic tone and the renin-angiotensin system, decreasing renal blood flow, redistributing renal flow to the medulla, and decreasing GFR.[146-148] Additionally, mechanical ventilation at any volume or pressure has consistently been shown to create a cascade of inflammation including multiple interleukins, tumor necrosis factor α, and Fas ligand that may contribute to AKI.[148]

In aggregate, these mechanical, neurohormonal, and inflammatory effects of mechanical ventilation predispose to AKI. However, mechanical ventilation is unavoidable in many patients, and the ventilation strategy is largely dictated by the effect on oxygenation and overall survival. Whether a given strategy would potentially protect the kidney independent of and without sacrificing the support of the respiratory system is not clear. High tidal volumes and high intrathoracic pressures seen with recruitment maneuvers are likely best avoided. Permissive hypercapnia offers a potential benefit as a ventilator strategy, but it is not without its pitfalls, and clinicians must use this technique with caution in patients with right heart failure and increased intracranial pressures among others.[147] Finally, alternatives to invasive mechanical ventilation such as high flow oxygen systems, helmet non-invasive ventilation, and face mask non-invasive ventilation may confer a different risk, but insufficient data are available to recommend that one or the other modality should be used on the basis of consideration of the risk for AKI.[145 153 154]

Drug treatment strategies for SA-AKI

The prophylactic use of diuretics, specifically furosemide, to prevent AKI has been shown to be unsuccessful and potentially harmful in critically ill patients.[155 156] Similarly, diuretics have not been shown to ameliorate or attenuate AKI once it is established.[157] Thus, the routine use of diuretics for the prevention or treatment of SA-AKI cannot be recommended. However, their utility in regulating and maintaining fluid balance fosters their continued use in the setting of critical illness despite their inability to improve renal outcomes.

In preclinical and small clinical studies, systemic administration of alkaline phosphatase has shown protection in SA-AKI.[158-160] Alkaline phosphatase has been thought to be effective through the direct dephosphorylation of endotoxin leading to attenuated inflammation and organ dysfunction and improved survival rates.

Table 5 | Therapies in sepsis associated acute kidney injury (SA-AKI): previous efforts and novel ongoing investigations

Agent	Mechanism of action	Comments
Traditional agents that have not shown benefit in SA-AKI		
Statins (hydroxymethyl glutaryl coenzyme A reductase inhibitors)	Anti-inflammatory properties, cardiovascular risk reduction, pleotrophic effects	Did not reduce AKI risk in patient with pneumonia associated sepsis[166]; meta-analysis of seven RCTs showed no effect on mortality across statin agents and several dosing ranges[167]
N-acetyl-cysteine	Potent scavenger of reactive oxygen species, improves glutathione stores	Wealth of animal data support its ability to prevent AKI in sepsis models,[168 169] but no human data support its use in SA-AKI or other AKI settings[170 171]
Tight glucose control	Theoretically decreases oxidative stress and endothelial dysfunction	Large scale prospective RCT of surgical ICU patients showed 41% reduction in AKI requiring RRT with blood sugar between 80 and 110 mg/dL,[172] but this effect was not validated in several follow-up studies including investigation specifically in patients with sepsis (although this was a 2×2 design that included pentastarch).[115] Follow-up studies in ICU patients showed no renal effects and perhaps signal for increased mortality with blood sugar 81-108 mg/dL[173]
Erythropoietin	Hematologic growth factor with anti-inflammatory and anti-apoptotic effects	Most investigation of erythropoietin and AKI has occurred in cardiac surgery patients, but two large trials investigating its use in mixed ICU populations failed to show improvement in AKI outcomes.[174 175] However, <20% of patients in both these studies had sepsis/septic shock.
Steroids (glucocorticoids and mineralocorticoids)	Classes of hormones that work to control carbohydrate and protein metabolism (glucocorticoids) and control electrolyte and fluid balance (mineralocorticoid) with anti-inflammatory properties	Role of steroids remains controversial in setting of sepsis, but two recent studies showed limited effects on SA-AKI. APROCCHSS trial, which looked at hydrocortisone and fludrocortisone, showed no difference in need for RRT between patients who did and did not receive steroids (27% *v* 28.1%).[176] ADRENAL trial showed no difference in use of RRT (30.6% in hydrocortisone group; 32.7% in placebo group; P=0.18), and no difference in number of days spent alive and RRT free (P=0.29)[177]
Promising novel agents that need further investigation		
Alkaline phosphatase	Will dephosphorylate endotoxins, perhaps leading to weakened inflammatory response	In a prospective, randomized, double blind, placebo controlled trial (n=36), intravenous infusion of alkaline phosphatase improved endogenous creatinine clearance and was associated with lower biomarkers of renal tubular injury, with no reduction in RRT rates.[178] A recent multicenter international trial was not successful in replicating these improved AKI rates but did show improved 28 day mortality in setting of SA-AKI[161]
Thiamine	Thiamine deficiency is associated with anaerobic metabolism and increased lactates. Ensuring thiamine repletion may improve mitochondrial function in setting of sepsis	In secondary analysis of a single center randomized, double blind, placebo controlled trial of 70 patients with septic shock, those randomized to receive intravenous thiamine (200 mg twice a day for 7 days) had less severe AKI and fewer patients receiving RRT[179]

AKI=acute kidney injury; ICU=intensive care unit; RCT=randomized controlled trial; RRT=renal replacement therapy.

A recent international, randomized, double blind, placebo controlled, dose finding adaptive phase IIa/IIb study included 301 adults with SA-AKI.[161] In the dose finding portion of the trial, 120 patients were randomized to receive recombinant alkaline phosphatase in a dose of 0.4, 0.8, or 1.6 mg/kg of the drug or placebo, with 1.6 mg/kg being determined to be the optimal dose. Then 82 patients received 1.6 mg/kg of alkaline phosphatase compared with 86 receiving placebo. Although the study did not show a decrease in the primary endpoint of time corrected AUC of creatinine clearance for days 1 to 7, it did show decreased mortality in patients receiving alkaline phosphatase. More stage 3 AKI occurred in patients receiving alkaline phosphatase (11/111; 9.9%) than in those receiving placebo (5/116; 4.3%).[161] However, given the decreased 28 day mortality (17.4% in patients receiving 1.6 mg/kg compared with 29.5% of those in the placebo group), some possibility exists that although it is not a treatment for SA-AKI, recombinant alkaline phosphatase may play a role in the treatment of sepsis itself.

A large body of preclinical work has investigated several pathways to potentially intervene and prevent or treat SA-AKI, and although this work has focused on molecules such as the caspase and interleukin inhibitors, to date it has not translated into human investigations of SA-AKI.[162-165]Table 5 summarizes several clinical trials that have investigated novel and traditional agents in the setting of SA-AKI. Additionally, table 6 provides information about clinical trials found on www.clinicaltrials.gov that are actively recruiting patients with SA-AKI.

Renal replacement therapy

Much of the data around the use of RRT in the setting of SA-AKI are informed by larger trials that have investigated dose, timing, and modality of RRT in the broader population of ICU patients needing RRT.[185-189] However, several investigations have focused on patients specifically with SA-AKI, and these are discussed below and summarized in table 7.

The sepsis and SA-AKI specific data around the timing of RRT point to potential harm with earlier initiation. In a recent multicenter, randomized controlled trial, patients with early stage septic shock who had RIFLE-failure AKI (table 1) were randomized to receive RRT within 12 hours of meeting entry criteria (early) or after a 48 hour delay (if possible and if needed—delayed arm).[190] In this French trial, which was stopped early for futility, 58% (138/239) of the early group and 54% (128/238) of the delayed group had died (P=0.38). Additionally, 93 (38%) patients in the delayed arm never needed RRT. In addition to this SA-AKI specific large scale study, evidence suggests that starting RRT early in patients with sepsis may not be beneficial.

In a prospective, randomized, multicenter French trial, 80 patients received either 96 hours of hemofiltration (25 mL/kg/h) or conservative management within 24 hours of any sepsis induced organ failure (including non-renal organs, with a baseline serum creatinine of 188 µmol/L). This early start, sometimes in the absence of SA-AKI, led to increased adverse outcomes including worsening organ failure.[191] Then, in a recent post hoc analysis of the AKIKI (Artificial Kidney Initiation in Kidney Injury) trial in 174 patients in each arm with septic shock, no difference in 60 day mortality was seen between the early and delayed arms. A significant increase was seen in renal recovery, as measured by urine output, in patients in the delayed arm.[197] These findings, suggesting benefits of delayed RRT, were not replicated by a recent trial

Table 6 | Trials that are actively recruiting patients with sepsis associated acute kidney injury (SA-AKI) as of autumn 2018

Agent/intervention	Mechanism of action	Study population	Study design
Reltecimod[180]	Peptide that binds CD28 co-stimulatory receptor and modulates immune response	Adult ICU patients (n=120) with underlying abdominal infection and stage 2/3 AKI	Phase II randomized, placebo controlled, multicenter study assessing ability of reltecimod to achieve recovery from abdominal SA-AKI
Adsorptive filter[181]	Use of PrismafleX eXeed (Hospal) using ST150SET copolymer of acrylonitrile and sodium methylsulfonate (AN 69) with polyethylenimine treated surface	Adult ICU patients (n=110) with SA-AKI requiring dialysis	Prospective, multicenter, randomized trial assessing cytokine concentrations and patient outcomes using absorptive filter
Balanced crystalloids versus 0.9% normal saline[182]	Balanced solutions (Ringer's acetate) have been shown to improve AKI and MAKE outcomes in ICU patients	Adult ICU patients (n=236) with sepsis	Prospective, double blind, single center, parallel assignment trial of normal saline or Ringer's acetate to determine incidence and severity of AKI in patients with sepsis
L-carnitine[183]	Has been shown to enhance glucose and lactate oxidation and improve smooth muscle and cardiac function in setting of critical illness	Adult ICU patients (n=272) with sepsis/septic shock	Prospective, double blind, placebo controlled, multicenter trial investigating effect of L-carnitine on short and long term outcomes in patients with septic shock
Peripheral arterial tonometry/ renal plasma flow/blood pressure measurement and renal function assessment[184]	Measurement of residual kidney function in pediatric patients and young adults with SA-AKI to determine effect on host and long term development of kidney disease	Pediatric and young adult (<24 years old) (n=45) with severe sepsis	Prospective, cross sectional, control-cohort study. Patients with SA-AKI will be monitored after discharge for formal measurement of glomerular filtration rate, renal plasma flow, and peripheral arterial tonometry to determine long term effect of SA-AKI on renal function

AKI=acute kidney injury; ICU=intensive care unit; MAKE=major adverse kidney event.

investigating timing of RRT in ICU patients (32% with severe sepsis).[186] One large scale, non-SA-AKI specific trial is recruiting participants to further investigate the optimal timing of RRT.[198]

Dose of RRT has been extensively studied in the setting of SA-AKI, with several studies showing no benefit to the increased dosing of RRT (table 7).[193-196] Much of the dosing guidelines stem from two large scale multicenter randomized controlled trials; however, these two trials were not exclusively done in the setting of SA-AKI. The Veterans Administration-NIH Acute Renal Failure Trial Network enrolled 1055 patients, 579 (54.9%) of whom had sepsis; the Randomized Evaluation of Normal versus Augmented Level (RENAL) Replacement Therapy Trial studied 1465 patients, 723 (49.3%) of whom had severe sepsis. Their combined results have shown that if continuous RRT is needed, the recommended delivered dose should be 20-25 mL/kg/h, with close attention being paid to all drug dosing.[187 188] Clinicians should remember that the delivered dose is often lower than the prescribed dose, so in the setting of SA-AKI the dosing of continuous RRT should be at least at the 30-35 mL/kg/h range to ensure adequate delivery.[187] Finally, as these two large scale studies and smaller ones specific to SA-AKI have shown, higher doses (for example, 70 mL/kg/h) of continuous RRT do not improve patients' survival.[187 188 194]

Limited data suggest a benefit with any specific RRT modality. An RCT randomized 77 patients with AKI needing continuous RRT to receive either 35 mL/kg/h of continuous veno-venous hemofiltration or continuous veno-venous hemodialysis (63 (82%) of whom had sepsis).[189] The results showed no difference in renal recovery or 60 day mortality (56% *v* 55%).[189] Finally, no data support the use of intermittent hemodialysis over continuous RRT (or vice versa) in the setting of SA-AKI. Although several studies have investigated this question, meta-analyses and large RCTs have shown no difference.[199-201] Thus, physicians should start an RRT modality that they are comfortable with and that can achieve the guideline recommended dose of a Kt/V of 3.9 per week in the setting of intermittent dialysis and a delivered dose of 20-25 mL/kg/h in continuous RRT, as well as one that will achieve the desired clearance and ultrafiltration for each specific patient.[7]

The use of extracorporeal therapies to remove circulating endotoxin has been studied in the setting of septic shock. In several, predominantly Japanese, trials using polymixin B hemoperfusion, these techniques have shown a mortality benefit.[202] Similarly, the EUPHAS (Early Use of Polymxyin B Hemoperfusion in Abdominal Septic Shock) trial showed that patients randomized to receive two sessions of polymyxin B hemoperfusion (n=34) (compared with conventional therapy, n=30) had improved MAPs, lower critical illness scores, and lower 28 day mortality (32% *v* 53%; P=0.01). Importantly, not all of these patients had AKI or the need for RRT (n=19), as enrollment was based solely on the presence of septic shock.[203] In a follow-up study (Evaluating the Use of Polymyxin B Hemoperfusion in a Randomized controlled trial of Adults Treated for Endotoxemia and Septic shock; EUPHRATES), 450 eligible patient with documented endotoxemia and shock were enrolled and randomized to potentially receive two hemoperfusion treatments 24 hours apart (or placebo).[204] However, polymyxin B hemoperfusion was not associated with a significant difference in mortality at 28 days, with 37.7% mortality in the treatment group and 35.5% mortality in the sham cohort (P=0.49). In fact, 10.8% of the treatment group had a worsening of their sepsis compared with 9.1% of the sham group.[204] Not enough evidence exists to recommend the use of hemoperfusion in the setting of septic shock or SA-AKI.[24]

Renal recovery and other long term outcomes

Recently, several reviews on renal recovery following AKI have been written, but no formally accepted definition of renal recovery exists.[205 206] For the past decade, several paradigms of AKI recovery have been hypothesized.[24 207 208] Proposed definitions range from total recovery (return of serum creatinine to baseline) to persistent AKI requiring RRT which becomes end stage renal disease (ESRD). Importantly, serum creatinine is not ideally suited to accurate measurement of renal reserve and may not be the best biomarker to quantify recovery, especially given the effect of muscle wasting on serum creatinine in critical illness. Most recently, ADQI proposed the concept of acute kidney disease, which separated out the first seven days of AKI (as per the KDIGO guidelines), calling this first week AKI but differentiating days 8-90 as

Table 7 | Summary of trials of timing and dose of renal replacement therapy (RRT) in sepsis associated acute kidney injury (SA-AKI)

Study	Indication for study	Comparison	No of patients with sepsis	Outcome and comments
Barbar et al[190]	Timing of RRT	Early stage septic shock patients with RIFLE-failure randomized to starting RRT immediately versus delayed start after 48 h if needed	All 488 patients had septic shock	This study, which was stopped early owing to futility, found no difference in 90 day mortality between patients in early arm (58%) and delayed strategy arm (54%). Additionally, 38% in delayed arm did not go on to receive RRT
Payen et al[191]	Timing of RRT	CVVH at 25 mL/kg/h versus usual care started within 24 h of first organ failure (including non-renal organs)	All 76 patients had sepsis; 37 randomized to CVVH and 39 to usual care arm	No improvement in outcomes with early continuous RRT. No difference in 28 day mortality (54% in CVVH group; 44% in usual care group; P=0.10)
Guadry et al[192]	Timing of RRT	Patients with acute tubular necrosis and stage 3 AKI randomized to immediate start of RRT versus delayed strategy requiring metabolic or respiratory derangement to start RRT	250/311 randomized to early start and 244/308 to delayed arm	No difference in 60 day survival (P=0.79). Patients randomized to delayed strategy were more likely to have increased urine output (1 L/day off diuretics or 2 L/day with diuretics). More patients in early initiation arm had infections (10% *v* 5%; P=0.03) and hypophosphatemia (22% *v* 15%; P=0.03)
Zhang et al[193]	Dose of RRT	Patients were randomly assigned to receive 50 or 85 mL/kg/h of hemofiltration	All 280 patients had sepsis, with 139 receiving 50 mL/kg/h and 141 receiving 85 mL/kg/h	No difference in 28 (57.4% *v* 58.3%) or 90 (59.6% *v*. 63.3%) day survival in this cohort of patients with sepsis and a traditional indication for RRT (P>0.05 for both)
Joannes-Boyau et al (IVOIRE)[194]	Dose of RRT	Patients with septic shock and at least a doubling of creatinine or 12 hours of oliguria randomized to receive 35 or 70 mL/kg/h	All 138 patients had septic shock, with 71 receiving 35 mL//kg/h and 66 receiving 70 mL//kg/h	No difference in 90 day mortality (56.1% *v* 50.7%; P=0.53), nor in ventilator, ICU, or hospital-free days at 90 days. Despite supplementation, more hypophosphatemia occurred in high dose group (P<0.01)
Park et al[195]	Dose of RRT	Patients with sepsis and at least a doubling of creatinine or 12 hours of oliguria randomized to receive 40 or 80 mL/kg/h	All 212 patient had sepsis, with 107 in 40 mL/kg/h arm and 105 in 80 mL/kg/h arm	No difference in 28 day mortality (64.5% *v* 65.7%; P=0.50) or 90 day mortality (74.8% *v* 78.1%; P=0.60). No difference in renal survival or cytokine concentrations between groups. No difference in electrolyte disturbances (potassium, phosphate, or magnesium) between groups
Chung et al (RESCUE)[196]	Dose of RRT	Burn patients with septic shock and AKI (<20 mL/h of urine for 24 h or increase in serum creatinine of 2.0 mg/dL in men or 1.5 mg/dL in women) randomized to receive 70 mL/kg/h of CVVH for 48 h or usual care	All 37 patients had sepsis, with 14 in control arm and 23 in 70 mL/kg/h arm	No difference in 28 day mortality (36% *v* 22%; P=0.45) or renal recovery among survivors. No difference in adverse events or electrolyte disturbances between groups

AKI=acute kidney injury; CVVH=continuous veno-venous hemofiltration; ICU=intensive care unit; RIFLE=risk, injury, failure, loss, end stage kidney disease.

acute kidney disease. This period serves as a framework for defining recovery and the potential progression to chronic kidney disease (CKD)/ESRD (fig 2).[24]

Given the lack of consensus for definitions of recovery from all cause AKI, data specific for SA-AKI recovery are lacking. In a prospective observational cohort of 1753 critically ill patients with AKI, SA-AKI (n=833) was associated with increased risk of inpatient mortality but was also associated with a trend toward lower serum creatinine (median 106 (interquartile range 73-158) *v* 121 (88-184) µmol/L; P=0.01) and dependence on RRT (9% *v* 14%; P=0.052) at hospital discharge (n=920).[31] These differences were at least in part due to patients with non-septic AKI having more CKD before admission. This potential association between SA-AKI and improved renal function at the time of discharge is in contrast to a recent study defining patterns of recovery in 16 968 critically ill patients with stage 2 or 3 AKI.[208] Early reversal, defined as no longer meeting KDIGO stage 1 criteria within seven days, was subcategorized into sustained reversal, relapse with subsequent recovery, and relapse without recovery. Sepsis was associated with an increased risk of relapse compared with patients with early sustained reversal (odds ratio 1.34 (1.18 to 1.52); P<0.001).[208] A retrospective study also showed that diabetes makes recovery from SA-AKI less likely (41.1% in non-diabetic SA-AKI versus 60% in diabetic SA-AKI; P<0.001).[209] Given the size and observational nature of these datasets, further investigation of SA-AKI associated renal recovery is needed.

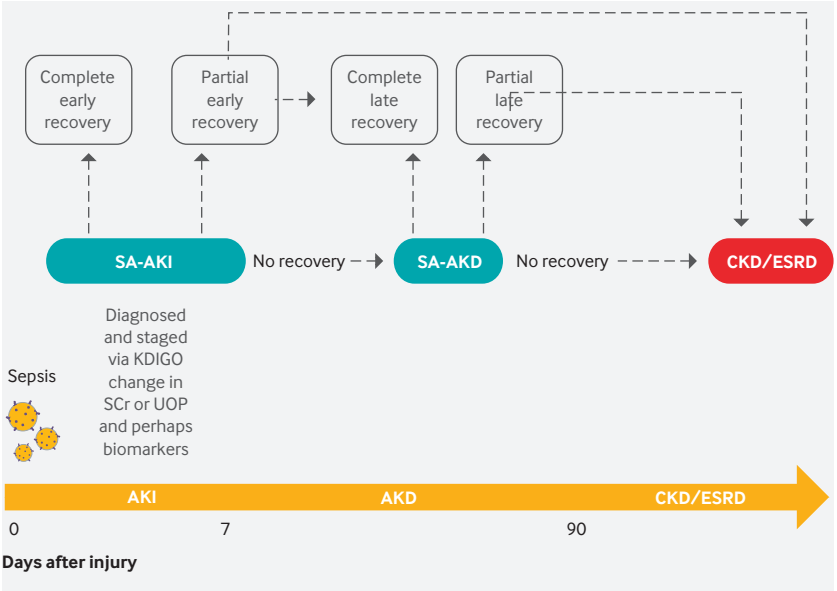

Fig 2 | Potential outcomes in the setting of acute kidney injury (AKI) and acute kidney disease (AKD). The figure shows the potential progression through the various stages of sepsis associated AKI (SA-AKI). AKI may occur over the first 7 days, when it can lead to persistent injury and become SA-AKD. During AKI, patients may have complete or partial recoveries, but some may have persistent injury without recovery. Longitudinally, this lack of recovery may become chronic kidney disease (CKD) or its most severe form end stage renal disease (ESRD). UOP=urine output; SCr=serum creatinine. Adapted and modified from Chawla et al 2017[24] and Forni et al 2017[205]

Evidence in settings other than sepsis shows that inpatients with AKI are more likely to be readmitted within 30-90 days.[210-212] Specific data on SA-AKI are lacking. However, Americans aged 50 years or older with a history of severe sepsis have been shown to be 2.5 times more likely to be readmitted to hospital for AKI within 90 days than comorbidity matched patients without sepsis.[213] In addition to readmission, some evidence

Box 3 | Summary of management strategies for sepsis associated acute kidney injury (SA-AKI)

Screening and diagnosis

- Closely monitor both urine output and serum creatinine in patients with sepsis
- Given limitations of urine output and serum creatinine, consider adoption of emerging risk scoring systems or serum biomarkers

Supportive care

- Use best practice strategies for patients with sepsis
  - Early administration of appropriate antibiotics
  - Achieve control or removal of source of infection
  - Adequate resuscitation with intravenous fluids while avoiding over-resuscitation
  - Use norepinephrine, vasopressin, or both as initial vasoactive drug(s)

Avoid further kidney injury

- Avoid potentially nephrotoxic drugs when possible
- Avoid potentially nephrotoxic contrast loads when possible
- Do not use hydroxyethyl starches

Treatment of SA-AKI

- Early initiation of renal replacement therapy (RRT) has not been shown to be superior to conventional timing of initiation of RRT
- The delivered dose of continuous RRT (CRRT) should be 20-25 mL/kg/h, which often requires dosing CRRT at 30-35 mL/kg/h
- Higher dose RRT (70-85 mL/kg/h) has not been shown to be superior to lower dose RRT (35-50 mL/kg/h)

points to increased risk for the development of post-AKI CKD, although limited supporting prospective data are available.[214-218] The Assessment, Serial Evaluation, and Subsequent Sequelae of AKI (ASSESS-AKI) study is following several hundred critically ill patients with and without SA-AKI to determine its impact on long term renal function in those who survive their index hospital admission.[219] In the future, biochemical (such as those discussed in table 3) or functional biomarkers such as renal functional reserve (for example, monitoring the kidney's ability to hyper-filter in the setting of a protein load)[220] may play a role in determining which patients with SA-AKI recover function and which progress to persistent AKI and eventual CKD and ESRD disease.

QUESTIONS FOR FUTURE RESEARCH

- Is there an ideal intravenous fluid and vasoactive drug to prevent or ameliorate early sepsis associated acute kidney injury (SA-AKI)?
- What is the best way to identify acute kidney injury at its earliest?
- Does removing endotoxin or endogenous cytokines via continuous renal replacement therapy or adsorption in the setting of SA-AKI have clinical utility?
- Can pairing biomarkers of renal injury with early interventions (therapeutic or pharmacologic) prevent SA-AKI?
- How do outcomes of SA-AKI differ from those of other forms of acute kidney injury?
- Does the paradigm of acute kidney disease accurately reflect the clinical course of SA-AKI?

GLOSSARY OF ABBREVIATIONS

ADQI—Acute Dialysis Quality Initiative
AKI—acute kidney injury
AKIN—Acute Kidney Injury Network
ARDS—acute respiratory distress syndrome
AUC—area under the curve
CKD—chronic kidney disease
ESRD—end stage renal disease
GFR—glomerular filtration rate
ICU—intensive care unit
IGFBP7—insulin-like growth factor binding protein-7
KDIGO—Kidney Disease: Improving Global Outcomes
KIM-1—kidney injury molecule-1
MAP—mean arterial pressure
NGAL—neutrophil gelatinase associated lipocalin
PEEP—positive end-expiratory pressure
PICARD—Program to Improve Care in Acute Renal Disease
PPV—positive pressure ventilation
RAI—renal angina index
RBF—renal blood flow
RCT—randomized controlled trial
RIFLE—risk, injury, failure, loss, end stage kidney disease
RRT—renal replacement therapy
SA-AKI—sepsis associated acute kidney injury
SIRS—systemic inflammatory response syndrome
TIMP2—tissue inhibitor of metalloproteinase-2

Guidelines

Both the KDIGO and National Institute for Health and Care Excellence (NICE) guidelines for AKI are high quality reviews, but neither focuses specifically on AKI in critically ill or septic patients.[7 221] One high quality multi-society guideline covers AKI in critically ill patients generally and offers guidance for several subsets of ICU patients, but does not cover SA-AKI specifically.[222]

Conclusion

Despite progress in our understanding of the factors that drive the pathobiology of SA-AKI, it remains a common and highly morbid complication of a common critical illness. Epidemiologic data suggest that population change and the continued march of intensive medical interventions are likely to increase its burden. Vigilance for risk factors for SA-AKI

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

A 62 year old man with a previous history of postoperative sepsis associated acute kidney injury (SA-AKI) who had a hospital limited course of renal replacement therapy four years ago with the subsequent development of post-AKI chronic kidney disease accepted an invitation to review the manuscript as a patient reviewer for *The BMJ*. He reviewed the paper in its entirety, providing suggestions on which sections were most and least relevant to his personal history. As a result of this input, we emphasized the effect of SA-AKI on the potential development of chronic kidney disease as well as the limited treatment options in the setting of AKI. The patient asked us to emphasize the importance of continuing to work to discover and validate treatment options in the setting of acute kidney injury (and chronic kidney disease) and to remind people of the importance of nephrology care in the setting of kidney disease.

risks is essential so that preventive strategies may be implemented. We must consider how the choices we make with the fundamental elements of our critical care practice (fluid, vasoactive, and ventilator management) affect the kidneys. Patients at risk for SA-AKI should be screened aggressively to allow early identification and implementation of a care plan (box 3), and further study is needed to allow us to understand the factors involved in and the likelihood of renal recovery and future risk after an episode of SA-AKI.

However, even perfect implementation of current best practice is unlikely to significantly ameliorate the burden of SA-AKI. Novel translational animal models, the wealth of data available in modern electronic health records, and a myriad novel clinical biomarkers present a tremendous opportunity to refine our understanding of SA-AKI, and may allow us to set a new course for prevention, treatment, and renal recovery.

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