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REVIEW

Acute kidney injury in sepsis

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Abstract

Acute kidney injury (AKI) and sepsis carry consensus definitions. The simultaneous presence of both identifies septic AKI. Septic AKI is the most common AKI syndrome in ICU and accounts for approximately half of all such AKI. Its pathophysiology remains poorly understood, but animal models and lack of histological changes suggest that, at least initially, septic AKI may be a functional phenomenon with combined microvascular shunting and tubular cell stress. The diagnosis remains based on clinical assessment and measurement of urinary output and serum creatinine. However, multiple biomarkers and especially cell cycle arrest biomarkers are gaining acceptance. Prevention of septic AKI remains based on the treatment of sepsis and on early resuscitation. Such resuscitation relies on the judicious use of both fluids and vasoactive drugs. In particular, there is strong evidence that starch-containing fluids are nephrotoxic and decrease renal function and suggestive evidence that chloride-rich fluid may also adversely affect renal function. Vasoactive drugs have variable effects on renal function in septic AKI. At this time, norepinephrine is the dominant agent, but vasopressin may also have a role. Despite supportive therapies, renal function may be temporarily or completely lost. In such patients, renal replacement therapy (RRT) becomes necessary. The optimal intensity of this therapy has been established, while the timing of when to commence RRT is now a focus of investigation. If sepsis resolves, the majority of patients recover renal function. Yet, even a single episode of septic AKI is associated with increased subsequent risk of chronic kidney disease.

Keywords: Sepsis, Acute kidney injury, Biomarkers, Creatinine, Renal replacement therapy, Recovery

Introduction

Septic acute kidney injury (AKI) is a syndrome of acute impairment of function and organ damage linked with long-term adverse outcomes depending on the extent of acute injury superimposed on underlying organ reserve. Implicit in this concept is that dysfunction should be reversible and rescue is possible, but that duration of the insult and underlying renal reserve may limit restoration of renal function. Thus, septic AKI is a clinical diagnosis based on specific, context-dependent, and imperfect definitions [1] with azotemia and oliguria still its key diagnostic criteria [2]. In this article, we aim to review recent developments and key aspects of the epidemiology, pathogenesis, prevention, and treatment of septic AKI with the goal of increasing understanding and awareness among clinicians of this increasingly common intensive care syndrome.

Definition and diagnosis of septic AKI

The RIFLE criteria (Risk Injury Failure Loss End-stage renal disease) were proposed by the Acute Dialysis Quality Initiative [1]. More recently, the Kidney Disease Improving Global Outcomes (KDIGO) group produced a unified version of all key criteria (Table 1) [2], which now represent global consensus. Similarly, a new global consensus definition of sepsis has emerged and is likely to be used for epidemiologic and clinical purposes [3]. Logically, septic AKI (or sepsis-associated AKI or AKI in

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Take-home message: Septic acute kidney injury is no longer considered a disease of the macrocirculation, but rather a disorder of the renal microcirculation with associated inflammatory tubular injury. These new ideas have profound diagnostic and therapeutic implications.

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Table 1 Criteria and staging for acute kidney injury

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline OR ≥0.3 mg/dl (>26.5 µmol/l) increase	<0.5 ml/kg/h for 6–12 h
2	2.0–2.9 times baseline	<0.5 ml/kg/h for ≥12 h
3	3.0 times baseline	<0.3 ml/kg/h for ≥24 h
	OR	OR
	Increase in serum creatinine to ≥4.0 mg/dl (353.6 µmol/l)	Anuria for ≥12 h
	OR	
	Initiation of renal replacement therapy	
	OR	
	In patients <18 years, decrease in eGFR to <35 ml/min per 1.73 m^2	

Minimum criteria for acute kidney injury include an increase in SCr by ≥ 0.3 mg/dl (>26.5 µmol/l) observed within 48 h; or an increase in SCr to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or urine volume <0.5 ml/kg/h for 6 h

sepsis) should describe a syndrome characterized by the simultaneous presence of both Sepsis-3 and KDIGO criteria. Nonetheless, clinical judgment is still required [4], and a more modern framework for rapid clinical diagnosis is evolving which is based on novel biomarkers of renal injury (Table 2). Thus, future definitions of AKI may soon include such biomarkers. Irrespective of definition, knowledge of baseline renal function remains important and is needed to apply the KDIGO diagnostic criteria. Unfortunately, a baseline creatinine may not be available, and a patient with suspected septic AKI and unknown baseline function might have sepsis with chronic kidney disease (CKD), septic AKI, or both. Ancillary tests and checklists might be helpful to make the correct diagnosis [4]. In the absence of baseline information, however, an estimated GFR using the Modification of Diet in Renal Disease (MDRD) equation has been used in patients without a history of CKD (Table 2) [1]. Finally, although urinalysis and urinary biochemistry have limited clinical utility [5], urine output remains important not only for diagnosis but also for risk prediction [6]. However, urinary output and creatinine are increasingly being complemented by novel biomarkers of AKI.

Novel biomarkers

Over the last decade several biomarkers have been evaluated for their capacity to detect kidney "stress" and/or "damage" and to predict the development of AKI. They apply to septic AKI as well. The strong interest in biomarkers relates to the desire to achieve early diagnosis in order to deliver prevention and early therapy when it may be most effective. Biomarkers can provide additional insights into AKI pathophysiology and are complementary to functional tests [7]. These biomarkers might also detect renal stress or damage before functional change is evident (preclinical AKI) or even in the absence of functional change (subclinical AKI). In other cases, low biomarker levels may help diagnose physiologic in contrast with pathologic oliguria. Their role in different renal syndromes including septic AKI is a rapidly evolving area of research. Neutrophil gelatinase-associated lipocalin (NGAL) has been the most extensively investigated renal biomarker [8]. NGAL is upregulated in kidney tissue exposed to nephrotoxic or inflammatory stress, but also released by activated neutrophils with specific forms of the molecule released from the kidney (monomeric) and neutrophils (dimeric) [9]. Unfortunately, commercial assays only measure a mixture of the different forms making their specificity, reproducibility, and diagnostic accuracy unclear and creating uncertainty regarding the role of NGAL as a biomarker of AKI. In a pooled analysis of >2000 critically ill patients, one-fifth were NGAL-positive without an increase in serum creatinine (subclinical AKI or false positive results). Yet, these patients were at greater risk of subsequent renal replacement therapy (RRT), longer ICU and hospital stay, and death [10]. Similar findings were observed in emergency department patients [11] and support the existence of a state of subclinical damage, which is associated with worse renal outcomes, and can only be detected by novel biomarkers. Other molecules have been studied as biomarkers of AKI. Among these, kidney injury molecule (KIM-1) appears to perform similarly to NGAL [7] but has not been studied in a large cohort of septic ICU patients. Cell cycle arrest may be protective during cellular stress. Two major regulatory proteins involved in initiating cell cycle arrest were recently discovered to play a role in AKI: tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor binding protein-7 (IGFBP-7). In 2013, a prospective, observational, international investigation

Table 2 Criteria for diagnosing AKI

Criterion/test	Utility	Limitations	Comments
Serum creatinine	Cheap, easily measured, readily available, well-known relationship to disease	Slow to change in response to injury, insensitive—no changes until >50% loss of function	Increases of ≥50% over ≤1 week or ≥0.3 mg/dl over ≤48 h used as consensus criteria for AKI
Urine output	Faster to change than creatinine, cheap and easy to measure	Non-specific, insensitive to certain forms of AKI, not reliably measured outside the ICU	<0.5 ml/kg/h ≥ 6 h used as consensus criteria for AKI
Serum cystatin C	Experience from CKD	Similar to creatinine	
Urine sediment	Can help identify specific causes of AKI (e.g., glomerulonephritis)	Not standardized and usually non-specific	
Kidney damage markers	Measure cellular injury rather than organ function	Not standardized nor completely validated in humans	uKIM-1, uNGAL, others
AKI risk markers	Measures of kidney stress or systemic inflammatory states rather than injury per se	Measures of kidney stress or systemic states rather than injury per se	u[TIMP-2]·[IGFBP-7], pNGAL
Functional stress tests	Examine capacity for increases in function by stressing the system	Test are not well standardized	Protein load, furosemide

CKD chronic kidney disease, *AKI* acute kidney injury, *uKIM-1* urinary kidney injury molecule-1, *uNGAL* urinary neutrophil gelatinase-associated lipocalin, *uTIMP-2* urinary tissue inhibitor of metalloproteinase-2, *IGFBP-7* insulin-like growth factor binding protein-7, *pNGAL* plasma neutrophil gelatinase-associated lipocalin

of critically ill patients, including many with septic AKI [12], found an area under the receiver operating characteristic curve (AUC) of 0.80 for [TIMP-2]·[IGFBP-7] for the prediction of KDIGO stage 2 and 3 AKI. These markers were significantly superior to all previously described biomarkers. Moreover, tubular cells may undergo cell cycle arrest (as demonstrated by cell cycle arrest biomarkers in the urine) [12] to decrease energy consumption and protect themselves. This phenomenon may then result in activation of the tubulo-glomerular feedback mechanism [13], which would contribute to a decrease in GFR aimed at attenuating ultrafiltration. However, this theoretical framework, like others, remains speculative. These biomarkers may also help change the definition of AKI in the future and contribute to a better understanding, diagnosis, prevention, and treatment of septic AKI (Fig. 1). Other approaches to assess renal function have been considered. They include the furosemide stress test, and assessment of the response to protein loading [14] and the application of real-time GFR measurements [15]. None of these approaches have yet been tested for their accuracy and robustness in large multicenter studies and remain investigational in nature. However, there is no evidence at this time that knowledge of biomarker values in septic AKI allows better and more successful early treatment. Thus, current epidemiologic information remains linked to traditional diagnostic criteria.

Epidemiology of septic AKI

Several cohort studies have described the frequency of sepsis among patients with AKI. The multinational Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) [16] found sepsis in nearly half the cohort. Septic AKI was associated with higher risk of in-hospital mortality. More recently, an international consortium confirmed these findings [17]. Angus et al. examined 192,980 patients with severe sepsis from seven US states using diagnostic codes [18]. AKI occurred in 22% and was associated with a mortality of 38.2%. The Sepsis Occurring in Acutely ill Patients (SOAP) cohort study recruited patients admitted to 198 ICUs across Europe [19]. Of 3147 patients, 37% had sepsis. AKI occurred in 51% of cases and was associated with an ICU mortality of 41%. The FINNAKI study enrolled 2901 critically ill consecutive patients from 17 Finnish ICUs [20]. Among the 918 patients with severe sepsis, 53% met the KDIGO criteria for AKI. In the recent Vasopressin vs. Norepinephrine as Initial Therapy in Septic Shock (VANISH) trial, AKI occurred in about 45% of patients, and AKI requiring RRT developed in 30% of patients [21].

There may also be genetic susceptibility to AKI in general and to septic AKI specifically. Polymorphism of cytokine-controlling genes has been associated with

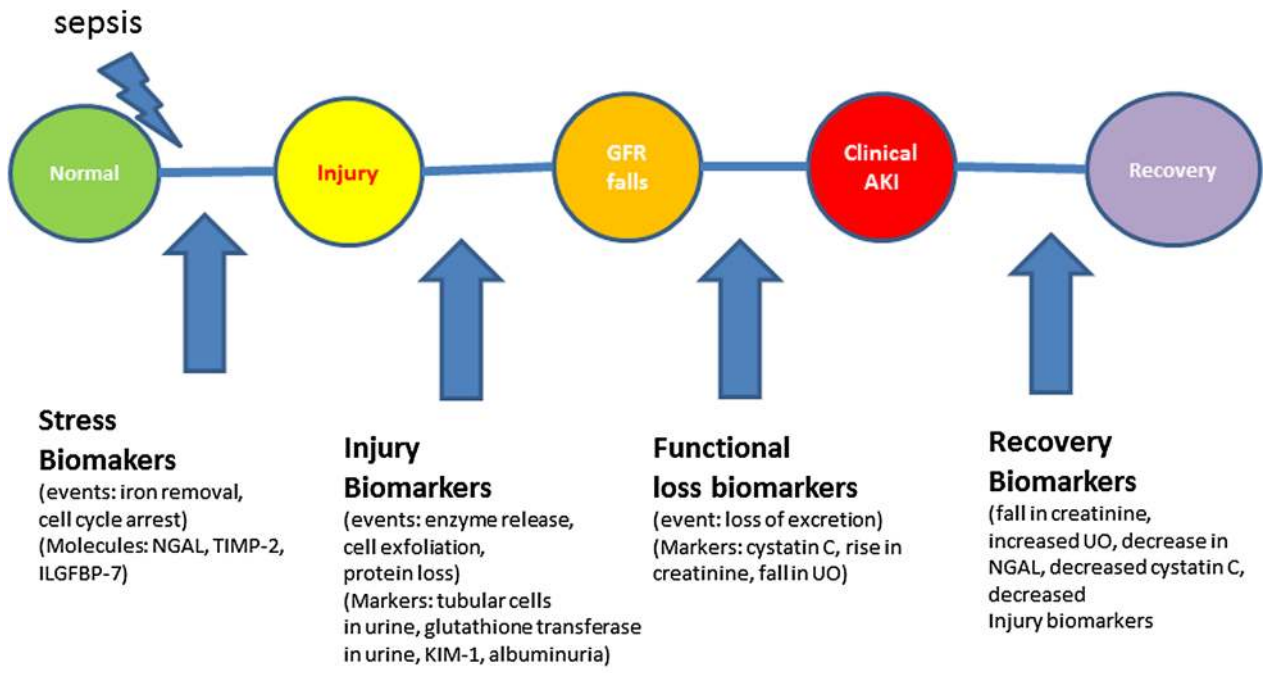

Fig. 1 Potential contribution of novel renal injury biomarkers to the detection, prevention, and treatment of septic AKI

sepsis and polymorphism of catechol-O-methyl transferase activity has been associated with AKI risk [22]. More recently a genome-wide association study of patients with AKI (including septic AKI) found that polymorphism of the likely controller of a transcription factor (on chromosome 4) involved in innate immunity pathways was associated with greater risk of AKI. Similarly, another gene involved in the likely control of transforming growth factor beta (on chromosome 22) was also associated with greater risk [23].

The outcomes of critically ill patients with sepsis [24] and AKI requiring RRT [25], however, have improved in recent years. It remains unclear if these improvement reflect a true decline in mortality or greater diagnostic sensitivity or more liberal indications to initiate RRT. Moreover, little is known about AKI in septic general ward patients. The advent of the Sepsis-3 definitions will force a reassessment of the characteristics and outcomes of sepsis-associated AKI. However, such assessment must logically be based on an understanding of its pathophysiology.

Pathophysiologic theories

Our understanding of the pathogenesis of septic AKI is limited, but it is now clear that septic AKI is profoundly different from ischemic AKI both in the experimental setting and in the clinic. It is markedly affected by our inability to monitor renal blood flow (RBF), microvascular flow, cortical and medullary perfusion and oxygenation, and tubular well-being. Thus, animal models of septic AKI have been developed to enable sophisticated and invasive measurements that cannot be performed in humans. In early experimental studies of septic AKI, global RBF was reported to decline after the administration of endotoxin [26]. These endotoxin-based experiments, which were associated with a hypodynamic systemic circulation, led to the view that human septic AKI must be due to renal vasoconstriction and ischemia [26]. More recent studies of hyperdynamic sepsis have demonstrated that the renal circulation participates in the systemic vasodilatation of sepsis. Thus, in such models, septic AKI develops in the presence of increased RBF [27, 28].

In a study of 160 original articles of animal models [29], if the model reported a high cardiac output (CO), RBF was either preserved or increased. However, despite such global renal hyperemia, oliguria and AKI develop rapidly (hours) and are marked. This phenomenon, where RBF is dissociated from glomerular filtration rate (GFR), requires explanation. Changes in intrarenal

hemodynamic (microvasculature) may logically provide such an explanation. For example, GFR may be decreased by changes in the relationship between the afferent and efferent glomerular arterioles, with greater efferent than afferent dilatation leading to loss of intraglomerular filtration pressure. This theory offers an explanation for the dissociation between perfusion and function in septic AKI (a phenomenon also seen in man [30]) but remains empirically untested. In this regard, the renal microcirculation may be a key area in determining function, injury, and recovery as it lies at the interface of endothelial and immune cells. In the most vascular organ in the body, it appears logical that it should be fundamental to both function and dysfunction [31].

Despite increased RBF, ischemia may still occur. More recent experimental evidence supports the view that in septic AKI, there is redistribution of flow away from the renal medulla to the renal cortex with a degree of medullary deoxygenation [32–34]. This change in regional distribution of blood flow implies the activation of intrarenal shunting pathways [35].

There is also limited systematic information on the renal tubules in sepsis, while GFR may be lost as described above. A pathophysiological theory of tubular injury has suggested that ultrafiltration of toxic blood is the inciting mechanism for tubular stress and then damage [13]. According to this theory, during sepsis, blood is full of small and medium-sized molecules (cytokines, chemokines, complement fragments, and the like), which have a toxic effect on tubular cells when concentrated in the ultrafiltrate acting on the luminal surface of the tubules [13]. This "inflammatory theory of AKI" is supported by experimental observations [36]. For example, pathogen-associated molecular patterns such as lipopolysaccharide can interact with Toll-like receptors (TLR) on tubular cells, and experimental studies have shown that the administration of TLR antagonists can attenuate septic AKI [36]. Moreover renal endothelial and tubular cells both express cytokine receptors and release pro-inflammatory molecules which can recruit T cells to the kidney and blood from septic patients can induce tubular cell apoptosis in vitro [36]. Thus, one of the renal responses to inflammation may be directed to decreased energy consumption with autodigestion of organelles (autophagy), digestion and dysfunction of mitochondria (mitophagy), and loss of cell polarity [37]. How these complex inflammatory events, which now include the release of histones, microparticles, and micro RNA, affect renal function remains unknown [36].

However, many of the above theories are based on animal models of sepsis and do not fully address the microscopic anatomical changes that might occur in renal tissue.

Animal models and histopathology

Most early in vivo models of septic AKI do not replicate the typical hyperdynamic state seen in man [38]. Moreover, models of renal ischemia are not relevant to the pathophysiology of septic AKI. Sheep, however, develop a cardiovascular response to sepsis similar to humans, and they have been used extensively to study septic AKI using live Gram negative bacteria infusions which overcome the flaws of endotoxin-based models [28, 33]. However, the choice of bacteria, strain, amount, and infusion rate can alter the septic response and standardization is difficult. Polymicrobial abdominal sepsis can be induced by cecal ligation and puncture (CLP), bowel ischemia, or intra-abdominal implantation of feces. These methods of inducing sepsis are relatively easy, but the amount and type of bacteria released are variable with a variable severity of sepsis that does not consistently lead to AKI. Clinicians need to understand these factors when interpreting data acquired from models including renal histopathology.

Structural lesions of the kidney have been thought to contribute to the renal dysfunction of septic AKI. In particular, acute tubular necrosis (ATN) is assumed to account for such dysfunction. However, in human septic AKI postmortem studies, ATN is uncommon [39, 40]. Similarly, ATN is uncommon in experimental septic AKI [41]. Moreover, ATN may not be a useful term because it lacks a clear definition, is not quantifiable, and does not account for the functional changes seen during sepsis. In this regard, studies have compared the histology of postmortem renal tissue of those who died with and without sepsis. They found more minor tubular lesions, leucocyte infiltration, and apoptosis in septic kidneys [39, 40]. These changes were only focal, most nephrons appeared normal, and indices of renal dysfunction poorly predicted renal histological changes. Thus, like RBF, histology appears dissociated from function. The picture is further clouded by the sampling of tissue from patients dying following variable severity of renal dysfunction, premorbid renal disease, therapeutic interventions, nephrotoxin exposure, and severity of illness.

Recently, a controlled experimental study of septic AKI in sheep concurrently monitored renal function, renal blood flow, obtained sequential renal biopsies over 48 h, and undertook systematic histological assessment [42]. As severe septic AKI developed, RBF and renal oxygen consumption were unchanged and the only histological abnormality was minor focal mesangial expansion on electron microscopy. Thus, there is a disconnect between function and structure in septic AKI, and the early changes in renal function with sepsis appear to primarily represent a functional rather than structural disease. If it is true that early (first 24–48 h) septic AKI represents

functional changes in the microvasculature and tubules, then early intervention and prevention of progression acquire great importance.

Prevention

There is a strong rationale to prevent the occurrence of AKI. The first priority for prevention is the identification of patients at increased risk. Such information is crucial to the development of a prevention and treatment plan (Fig. 2). Recent evidence has focused on clinical risk prediction [43], novel kidney damage biomarkers [44], automated electronic alerts embedded within electronic health records [45], and the concept of the renal angina index (RAI) [46]. Moreover, adaptive risk identification tools can be developed for adult critically ill patients, integrating known susceptibilities (i.e., age, diabetes mellitus, heart failure, chronic kidney disease, liver disease, malignancy) and other potentially modifiable factors (i.e., urine output, fluid balance). Such tools could be integrated into an ICU bedside clinical decision support system [47]. Risk identification tools can now be used in combination with novel kidney damage urine biomarkers [7]. Recent data have suggested that urine TIMP2·IGFBP-7 significantly improved risk prediction when added to a nine-parameter clinical model [48].

To date, implementation of automated alerts for AKI has not been shown to consistently improve processes of care or outcomes. However, in an ICU setting, among patients who had an automated alert issued for AKI, more interventions were given (i.e., diuretics, fluid, vasopressors); time to intervention was shortened and a greater proportion recovered kidney function to baseline [45]. Patients at increased risk should have appropriate adjustment, discontinuation, or avoidance of nephrotoxins, including unnecessary exposure to contrast media. Beyond such seemingly obvious interventions, only a limited number of preventive treatments are potentially available.

Antibiotics and source control

Earlier and appropriate antimicrobial therapy, along with septic source control, has been associated with lower risk of AKI [49]. For each hour that appropriate antimicrobial therapy was delayed, the risk of AKI increased by approximately 40%. Moreover, earlier antimicrobial therapy was associated with greater likelihood of kidney recovery within 24 h [49]. Finally, experimental studies focused on immune modulation and microcirculatory performance have characterized a number of possible new interventions. None, however, have yet been tested in robust clinical trials.

Hemodynamic optimization

Early goal-directed therapy (EGDT) failed to show benefit for reducing AKI, utilization of RRT, or kidney recovery [50]. The ProMISe [51], ProCESS [52], and ARISE trials [53] demonstrated no difference in mortality or improved renal outcomes with EGDT. However, post hoc analysis from a multicenter trial suggested, among patients with mild AKI, that addition of low-dose vasopressin

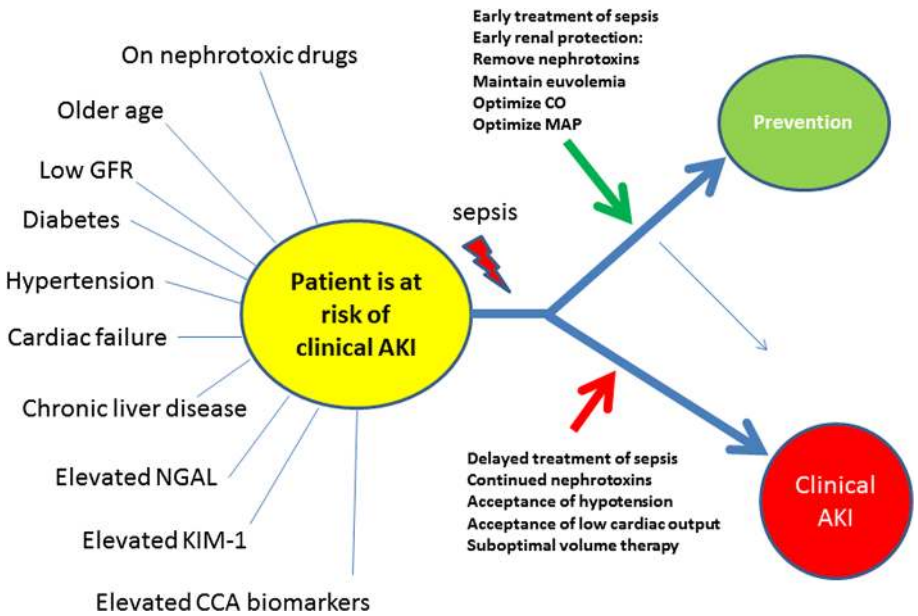

Fig. 2 Diagram illustrating how identification of a patient at risk of septic AKI can correctly inform all aspects of care

to norepinephrine infusion for hemodynamic support in septic shock was associated with reduced likelihood of worsening AKI, receipt of RRT, and mortality [54]. Recently, the VANISH trial found no significant differences in the rate of stage 3 AKI or kidney injury-free days among 409 septic shock patients randomized to either vasopressin or norepinephrine as initial vasopressor [21]. Fenoldopam, a selective dopamine receptor-1 agonist, was found to reduce the number of patients who reached a serum creatinine greater than 150 μmol/l in a randomized trial of 300 septic critically ill patients; however, this effect did not translate into decreased mortality [55] and has not yet been confirmed in subsequent studies.

Fluids

Traditional teaching suggests that aggressive fluid therapy is crucial to the successful management of both sepsis and AKI. However, as discussed above, septic AKI may not be characterized by hypoperfusion. Thus, aggressive fluid administration may be physiologically illogical and ineffective; it may contribute to renal edema which, in an encapsulated organ, may induce congestion and ischemia (Fig. 3).

Fluid bolus therapy (FBT), combined with the oliguria of AKI, is likely to lead to fluid accumulation in septic patients [56]. Fluid accumulation was associated with adverse outcomes and increased mortality from the Vasopressin versus Norepinephrine Infusion in Patients with Septic Shock [57] and in the Fluids and Catheters Treatment [58] trials, and in the Program to Improve Care in Acute Renal Disease group [59], with persistent and pervasive data demonstrating harm in a variety of patient populations including those with septic AKI. In contrast, the pilot Conservative vs. Liberal Approach to fluid therapy of Septic Shock in Intensive Care (CLASSIC) trial demonstrated that restricting resuscitation volumes in patients with septic shock is feasible and may improve renal outcomes [60]. In the CLASSIC study, a

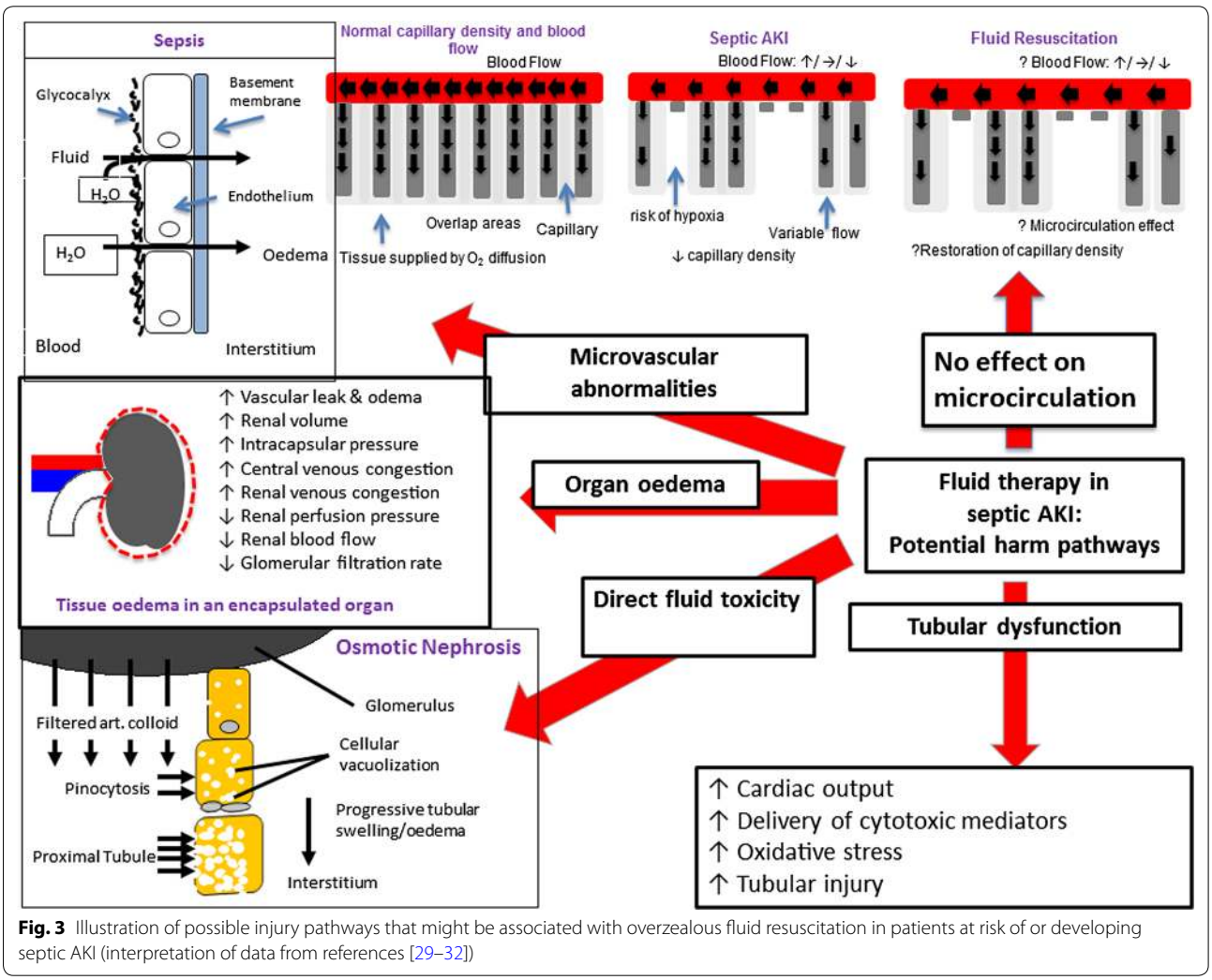

Fig. 3 Illustration of possible injury pathways that might be associated with overzealous fluid resuscitation in patients at risk of or developing septic AKI (interpretation of data from references [29–32])

pilot assessment of more restrictive fluid therapy, AKI was more likely to worsen in patients receiving standard care (restrictive: 37% vs. standard: 54%, $P = 0.03$). Other recent studies have shown lack of effect of FBT on renal function or urinary output [61–63].

Fluid type

A preference for balanced crystalloid solutions is emerging, with observational evidence linking chloride loading with AKI and mortality [64, 65]. However, a recent multicenter, cluster-randomized, double-crossover randomized controlled trial (RCT) demonstrated no such toxicity in an undifferentiated population of critically ill patients or, on subgroup analysis, in those with sepsis ($n = 84$) [66]. However, in such a study the amount of trial fluid administered was limited, making assessment of an effect problematic. In a prospective, open-label, cluster-randomized, multiple-crossover trial comparing the use of saline and balanced crystalloids in a single medical ICU where the type of fluid administered alternated monthly after random allocation, no difference was seen between groups in the rate of major adverse kidney events at 30 days. However, on analysis of the 260 patients with sepsis, balanced solution led to a significant reduction in the risk of the composite outcome (odds ratio 0.56) [67]. These variable effects may be related to the dose of exposure to exogenous chloride.

While 4% albumin does not appear injurious to the kidney [68], artificial colloids have been demonstrated to be nephrotoxic. Hydroxyethyl starch [69] and gelatin solutions [70] have been associated with an increased risk of AKI in septic patients and an increased risk of mortality in patients with septic AKI. Given the lack of a survival advantage, the risks associated with their use, their accumulation in tubular cells (Fig. 3), and their elevated cost in comparison to crystalloid solutions, it is difficult to see a role for artificial colloids in the modern management of septic AKI. In contrast, in many patients with septic AKI, another key intervention, often combined with fluid therapy and perhaps more physiologically rational, is the use of vasoactive drugs.

Vasoactive drugs

In patients with sepsis-induced AKI, vasoactive drugs remain the cornerstone of hypotension management and can restore adequate organ perfusion pressure [71, 72]. The most commonly used vasoactive drugs are norepinephrine, epinephrine, vasopressin, dopamine, and phenylephrine. However, new evidence from clinical and experimental studies suggests that angiotensin II may also be effective in septic shock [71]. In the setting of septic AKI, it is unclear whether any one vasopressor drug confers better renal protection than another. Nevertheless, norepinephrine can restore blood pressure and transiently improve renal function, with fewer side effects than alpha dose dopamine [73].

However, recent studies suggest that tissue ischemia and hypoxia may occur in the medulla, but not the cortex, before the development of septic AKI [34]. In such experimental models, restoring blood pressure with norepinephrine further exacerbates the degree of medullary ischemia and hypoxia (Fig. 4) [34]. These intrarenal changes occur independently of changes in global RBF and oxygen delivery and suggest that, while treatment with norepinephrine has beneficial effects on the systemic circulation and transiently increases renal function, it may also enhance medullary hypoxia and lead to long-term injury. These results suggest the need to carefully study different types of vasopressor drugs with or without fluid therapy in order to better define the optimal approach to preserving medullary oxygenation. Further studies of the renal microcirculation in septic AKI are therefore required to determine the causes of the reduced medullary perfusion and the effects of the subsequent medullary hypoxia. At this time, it is unclear whether norepinephrine-induced changes of medullary perfusion carry clinical implications and consequences. However, identifying whether vasoactive drugs, other than norepinephrine, have the potential to preserve, or even improve, regional kidney oxygenation and perhaps modify the shunting that is likely to take place in septic AKI appears important. However, not only the type of vasoactive agent but also the target mean arterial pressure may be important. In this regards, increasing mean arterial pressure to levels above 80 mmHg with greater norepinephrine dosage [74] appears to have potential beneficial effects on renal function in patients with premorbid hypertension. If these hemodynamic interventions fail, clinicians are then faced with the need to consider RRT.

Renal replacement therapy

A proportion of septic patients ultimately receive RRT due to severe AKI. However, very few RCTs [75–78] of RRT (excluding reports related to immunomodulation) have included only septic patients (Table 3). Nonetheless, in septic AKI patients timing, dose, and modality are key RRT-related issues. When assessing the timing of RRT, one should consider both the phase of sepsis and AKI. Commencing RRT early in the disease process of both sepsis and AKI could improve outcomes by limiting fluid overload, organ injury, and by removing inflammatory mediators. However, it may also expose patients to inadequate dosing of antibiotics and the adverse effects of an extracorporeal circuit. An RCT of non-oliguric severe sepsis patients with mean baseline creatinine

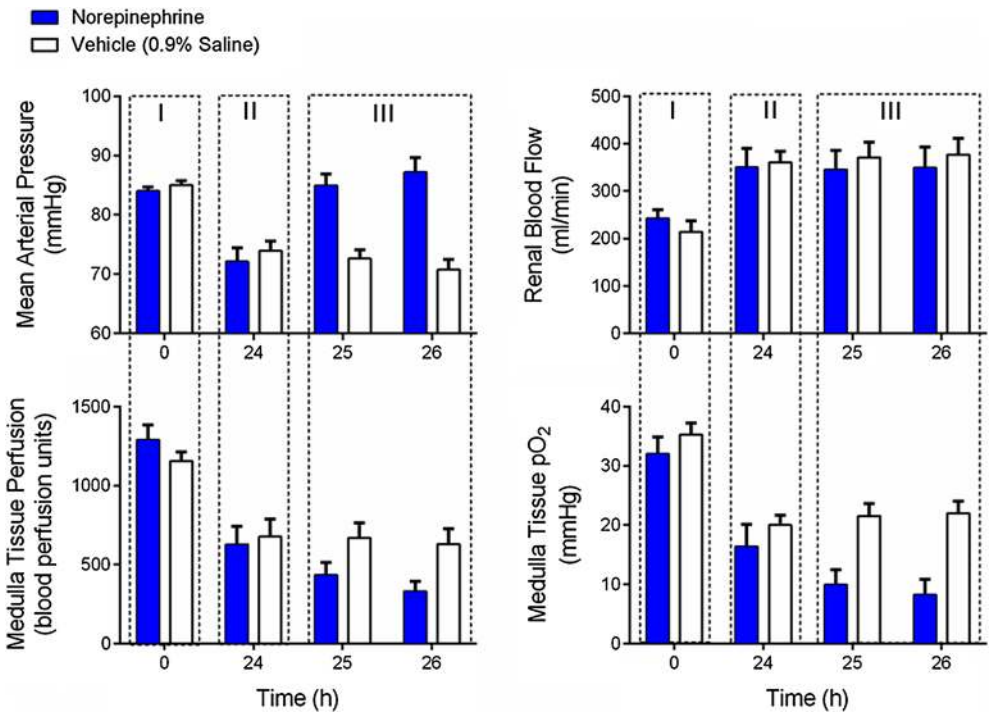

Fig. 4 Histograms summarizing the effects of norepinephrine in an experimental model of septic acute kidney injury in sheep using data from reference [34]. Even though mean arterial blood pressure and global renal blood flow increase, medullary perfusion and oxygenation decrease. *Phase I* indicates baseline, *phase II* indicates infusion, *phase III* indicates post infusion status

around 190 µmol/l (suggestive of KDIGO stage 2 AKI) found that early RRT increased the degree of organ failures [75].

In contrast, a single-center RCT among mainly surgical patients found that early RRT improved survival [79]. A third RCT with almost 80% septic patients found no difference in survival between early and delayed RRT [80]. These differences reflected variation in design, population, and choice of RRT modality. Two much larger RCTs studying the timing of RRT are underway, one among septic patients (IDEAL-ICU, NCT01682590) and one among mixed septic and non-septic ICU patients (STARRT-AKI, NCT02568722).

Once a decision is made to start RRT, continuous RRT modalities are more frequently used and recommended for hemodynamically unstable patients. However, there is no clear evidence that choice of modality alters outcome in this patient population. Subgroup analyses among septic patients in the RENAL [81] and ATN [82] trials also found no significant difference between different levels of treatment intensity. Subsequent trials investigating high-volume hemofiltration among septic patients have failed to show any benefit (Table 3). Thus, a delivered dose of 20–25 ml/kg/h is recommended. Notably, in a substudy of the RENAL trial, a quarter of patients receiving CRRT were outside target antibiotic concentrations regardless of continuous RRT dose, highlighting the need for improving the prescribing and monitoring of antibiotic levels during RRT [83]. Once septic patients have developed severe AKI and RRT is started a remaining key issue is that of prognosis and recovery.

Clinical implications of trials

Available trials as described above provide clinicians with several reference points which can then be applied and adjusted to individual situations in patients with or at risk of septic AKI. They indicate that early goal-directed therapy is not beneficial to renal function, that aggressive fluid loading with a positive fluid balance is not beneficial to renal function and may be injurious, and that artificial colloids are injurious to the kidney but that 4% albumin is not as shown in the SAFE and 20% is also safe as shown in the ALBIOS study [84]. They suggest that balanced solution may be safer than saline. They suggest that in patients with a history of hypertension, a higher blood pressure may protect renal function and that achieving blood pressure targets with the addition of vasopressin may improve renal function compared with norepinephrine alone. Moreover, they indicate that RRT intensity of 20–25 ml/kg/h of solute clearance is the current standard of practice. However, the optimal timing and cessation of such RRT remain uncertain.

Table 3 Randomized trials investigating timing or intensity of renal replacement therapy in septic patients

Trial	Study population	Intervention	Timing	Results	Exploratory outcomes
Payen et al. [75][a]	80 with severe sepsis/shock	Early CVVH 25 ml/kg/h vs. no RRT	Within 24 h of first organ failure	CVVH did not limit organ failure	Cytokine levels not lower in the CVVH group
Zhang et al. [76]	280 with severe sepsis and conventional indication to RRT	CVVH 85 vs. 50 ml/kg/h	ICU stay 5–6 days pre-enrollment	28-day mortality 57.4 vs. 58.3%, $P = NS$	Norepinephrine requirements after 24 h of treatment not different
IVOIRE [77][a]	137 with septic shock and severe AKI (RIFLE I or F)	CVVH 70 vs. 35 ml/kg/h	Duration of shock no more than 24 h pre- enrollment	28-day mortality 37.9 vs. 40.8%, $P = 0.94$	Similar hemodynamics or acid–base balance greater clearance of antibiotics with 70 ml/kg/h
HICORES [78]	212 with sepsis and severe AKI (RIFLE I or F) and for RRT	CVVHDF 80 vs. 40 ml/kg/h	No data on duration of sepsis	28-day mortality 65.7 vs. 64.5%, $P = 0.5$	Similar cytokine levels but lower compared to baseline at 24 h in 80 ml/kg/h group

AKI acute kidney injury, *CVVH* continuous veno-venous hemofiltration, *CVVHDF* continuous veno-venous hemodiafiltration, *RRT* renal replacement therapy

[a] Prematurely stopped because of slow recruitment

Ongoing phase II trials dealing with the potential value of alkaline phosphatase to protect the kidney from inflammation [85], and phase III trials dealing with the potential value of angiotensin II [86] as a vasopressor agent in sepsis and addressing the issue of timing of RRT (STARRT-AKI, NCT02568722) will likely provide more level 1 information to assist clinicians with their decisions.

Prognosis of septic AKI

Compared with other AKI etiologies, septic AKI may have specific prognostic implications. In most reports, it is associated with a higher short-term mortality rate. In a subgroup analysis of the BEST Kidney trial [16], the odds of dying in hospital were 50% higher in septic AKI compared with non-septic AKI. Obviously, the different prognosis between septic and non-septic AKI is largely influenced by the composition of the non-septic group and its proportion of conditions with poor prognosis (such as cardiogenic shock). In addition, the role of confounding in the association between septic AKI and mortality needs to be addressed as all studies consistently report higher illness severity at onset and more frequent need for RRT in such patients.

In contrast, for those patients who survive to hospital discharge, septic AKI has been associated with improved renal recovery compared with other AKI etiologies. In the BEST Kidney study [16] there was a trend for a lower serum creatinine and RRT dependence (9 vs. 14%, $P = 0.052$). Obviously, numerous other factors are likely to play a role in renal recovery such as RRT modality, timing of RRT, and further nephrotoxic or ischemic insults. Renal recovery is also highly influenced by premorbid conditions as illustrated by a French multicentric observational study, which suggested that diabetic patients with septic AKI who survived to hospital discharge were more likely to require long-term RRT and had higher serum creatinine levels [87]. Irrespective of short-term recovery, however, it is now clear that even a single episode of AKI is associated with a greater risk of subsequent CKD and even end-stage kidney disease [88].

Conclusions

In critically ill patients, AKI is a common complication of sepsis, and sepsis is the most common trigger of AKI. Consensus criteria for both sepsis and AKI now exist and can be used to more clearly define its epidemiology. However, the development of novel biomarkers of AKI may soon lead to modifications in the definition of septic AKI. Irrespective of its epidemiology, our understanding of its pathophysiology remains limited and mostly based on animal models. Such models suggest that, at least in the first 24–48 h, septic AKI may be a unique form of

AKI with increased RBF, intrarenal shunting, and limited histological changes. Partly because of this limited understanding, our ability to prevent and treat septic AKI is also limited. In this regard, reliance on aggressive fluid-based therapy may be unwarranted and perhaps injurious. The use of vasoactive drugs to support blood pressure is warranted, but blood pressure targets may depend on premorbid blood pressure. If renal protection fails and RRT becomes necessary, the best timing and modality of such intervention remain uncertain. In contrast, dose of RRT is currently robustly based on findings from two large trials. If patients survive sepsis, recovery occurs in the majority, but our understanding of the mechanisms behind renal repair or failed renal repair remains poor and the lifetime risk of CKD and end-stage kidney disease is higher. Finally, the research agenda remains large, as recently reviewed [89], and should be a major focus for all clinicians dedicated to improved outcomes in this field.

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Compliance with ethical standards

Conflicts of interest
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