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Sepsis-Associated Acute Kidney Injury

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Introduction

Sepsis-associated acute kidney injury (S-AKI) is a common, life-threatening complication in hospitalized and critically ill patients. S-AKI increases in-hospital mortality six to eight fold, [1] and the risk of developing chronic kidney disease (CKD) three fold.[2,3] Furthermore, up to a quarter of patients with S-AKI will require renal replacement therapy (RRT).[4]

The kidney is one of the earliest injured organs during sepsis. Acute kidney injury (AKI) develops in about two thirds of patients with septic shock,[5,6] and in half of them, AKI develops before presenting to the emergency department.[1] Therefore, it is reasonable to consider AKI as an early sign of sepsis. Importantly, patients who recover from S-AKI have similar 1-year mortality than patients with sepsis who never developed AKI in the first place, suggesting that the pathophysiologic processes leading to S-AKI are reversible to a certain extent.

The early presentation of S-AKI limits the impact of preventive interventions, but opens the door to the development of therapeutic strategies focusing on reversing cell injury and promoting adaptive repair. To embrace this change in paradigm, the mechanisms by which renal tubular epithelial cells (TEC) are injured during sepsis, the defense strategies that TEC employ to defend from such injury and the mechanisms by which defense strategies may become maladaptive need to be better understood.

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In this issue of *the Clinics*, we provide an overview of the current understanding of S-AKI, with emphasis on pathophysiology and biomarker development, and finalize with remarks on current preventive and therapeutic approaches.

Definitions

In 2016, sepsis was re-defined as a *'life-threatening organ dysfunction caused by a dysregulated host immune response to infection.'*[7] This new definition emphasizes the importance of organ dysfunction in the pathophysiology of sepsis, and underscores the preponderant role that organ dysfunction plays in mortality by sepsis. Despite broad tools to assess organ dysfunction, such as the sequential organ failure assessment (SOFA) score,[8,9] or more precise tools such as the Kidney Disease: Improving Global Outcomes (KDIGO) criteria for AKI, sepsis remains a clinical diagnosis, one that relies heavily on the experience of the clinician.

Similar to sepsis, ongoing efforts to unify the definition of AKI have yielded the three largest classification systems developed in the last two decades: the Risk, Injury, Failure, Loss of kidney function, and End stage kidney disease (RIFLE) criteria proposed by the Acute Dialysis Quality Initiative (ADQI)[10], the Acute Kidney Injury network (AKIN) criteria and the most recent KDIGO criteria (Table 1).[11] All three classification systems rely on an increase in serum creatinine (sCr) and/or a decrease in urinary output (UO) to establish the diagnosis of AKI.[11] Despite this, current sepsis guidelines still recommend the use of the SOFA score to define AKI, which is problematic because SOFA neither distinguishes between chronic and acute kidney disease, nor considers demographic differences in baseline sCr.

In the absence of a consensus definition and based on current clinical and pathophysiologic understanding, it is reasonable to define S-AKI as a clinical syndrome characterized by an abrupt deterioration of renal function manifested by an increase in sCr, oliguria, or both, in the presence of sepsis without other meaningful explaining factors.[4,12]

Epidemiology

Current estimates show that S-AKI affects 10% to 67% of septic patients.[13,14] More specifically, up to two thirds of patients with sepsis or septic shock will develop S-AKI.[6,15] With approximately 19 million cases of sepsis occurring globally every year,[16] it is reasonable to estimate that up to 11 million patients will develop S-AKI every year. Additionally, in comparison to AKI of other etiologies in critically ill patients, S-AKI carries an increased risk of death, fewer free-ventilator days and longer hospital stays.[17,18] An important feature is S-AKI is an early event in the progression of sepsis. Half of the patients with septic shock develop AKI before presenting to the Emergency Department.[15] In this context, AKI can play a fundamental role as a sepsis-defining event. Analogous to the canaries that would alert coal miners about the presence of lethal toxins in the air, AKI may be an early sign alerting of the presence of sepsis.

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Pathophysiology of S-AKI

Limitations to a better understanding of the pathophysiology of S-AKI

Advancing the understanding of S-AKI pathophysiology faces multiple limitations. The first limitation is establishing temporality in human S-AKI. Because more than 50% of patients with septic shock develop AKI before receiving medical attention,[15] it is difficult to establish which one came first.[19] This not only detracts from developing effective preventive therapies, but hinders the possibility of establishing temporality as a scientific principle of causality. Second, because patients with sepsis, and more so with S-AKI, are often in critical condition, the risk of obtaining tissue biopsies largely outweighs the benefit of establishing a pathologic diagnosis, and therefore data on the pathologic evolution of S-AKI is lacking. Furthermore, although some real-time monitoring techniques have been proposed, applicability remainslimited.[20] Third, despite recent progress made to unify the diagnosis of S-AKI, reliance on sCr and UO poses significant limitations to the timely diagnosis of AKI and provides no information about the specific cause of injury. The discovery of novel biomarkers of tubular injury[21] and non-invasive techniques to assess renal blood flow (RBF),[20] bare the promise of improving the diagnosis of S-AKI and hint toward possible causal mechanisms.

Because of these limitations, progress in understanding the mechanisms leading to S-AKI has relied largely on translational, *in vitro* and *in vivo* animal models. Although these studies have and continue to provide valuable mechanistic insight, there is a translational barrier that prevents direct extrapolation to human sepsis. Studies using post-mortem biopsies of patients dying with S-AKI have helped overcome this barrier and have revolutionized the understanding of the pathophysiology of S-AKI, as will be described in the next section. However, these studies focus on very late stages, and provide no insight into earlier stages of the disease. *The Kidney Precision Medicine Project (KPMP)* may offer a solution to further the understanding of human S-AKI and other forms of AKI. KPMP is a project created by The National Institutes of Health in the US that aims to ethically obtain and evaluate kidney biopsies from patients with AKI and CKD, therefore providing an unprecedented opportunity to investigate the evolution of human S-AKI. It is clear that a combination of research strategies that can move knowledge between the bench (*in vitro* and *in vivo* models) and the bedside (i.e., KPMP, observational and clinical trials) will be the most efficient approach to understand the mechanisms by which sepsis induces AKI.

Disruptive notions that have challenged existing paradigms

Although sublethal hypoperfusion may still play a role in certain cases of S-AKI, the concept that lethal cellular hypoxia leading to necrosis (i.e., acute tubular necrosis or ATN), like during ischemia reperfusion injury animal models or after aortic cross clamping during an abdominal aneurysm repair, causes S-AKI has been challenged. In an ovine model of gram-negative septic shock, Langenberg *et al.*[22] showed that S-AKI can occur in the setting of normal or increased RBF suggesting that decreased global perfusion to the kidney was not necessary for S-AKI to occur. In a similar model, Meiden *et al.*[23]. confirmed this finding, showing that S-AKI occurred without changes in RBF, oxygen delivery or renal histology. This is relevant to human sepsis because Prowle *et al.*[20] showed that patients with septic

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shock with preserved RBF still developed S-AKI, and Murugan *et al*.[24] demonstrated that a quarter of septic patients who never presented signs of hemodynamic instability still developed AKI. Importantly, Takasu and Hotchkiss[25] demonstrated in postmortem biopsies of patients dying with sepsis that S-AKI develops in the absence of overt TEC necrosis or apoptosis (less than 5% of renal tubules examined). Based on this, it is clear that S-AKI can occur in the absence of overt signs of global renal hypoperfusion and/or macrohemodynamic instability,[26] that S-AKI is not equivalent to ATN,[19,23,27] and that mechanisms other than hypoperfusion must be at play.

Microcirculatory dysfunction—Sepsis causes alterations in regional microcirculatory flow characterized by an increase in heterogeneity of blood flow, a decrease in the proportion of capillaries carrying stopped or intermittent (non-nurturing) blood flow and a decrease in the proportion of capillaries carrying sluggish and continuous (nurturing) flow.[26,28–30] This pattern of microcirculatory dysfunction is present in septic humans and in animal models across every vital organ, is independent of changes in macrohemodynamic parameters[28–34] and is associated with the development of organ dysfunction and worse outcome. Based on this, microcirculatory dysfunction has been proposed to be a key mechanism in the causal pathway of organ injury.[26]

Multiple mechanisms have been proposed that may lead to microcirculatory dysfunction. Endothelial injury, autonomic dysfunction, shedding of the glycocalyx, and activation of the coagulation cascade result in increased leucocyte and platelet rolling and adhesion, reduction in blood flow velocity, and microthrombi formation, ultimately disrupting microvascular flow (Figure 1).[17,29,35] As a consequence of altered renal peritubular capillary flow, the release damage associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) in the vicinity of TEC by slow moving leukocytes and platelets, may induce significant tubular injury.[36] Furthermore, microcirculatory dysfunction can lead to altered regional blood flow distribution potentially resulting in patchy areas of ischemia and loss of autoregulation, aggravating TEC injury and dysfunction.[26,37–39] In the kidney, peritubular capillary dysfunction can result in direct tubular epithelial injury. Tubular epithelial dysfunction can result in the loss of glomerular filtration rate (GFR) through the activation of the tubuloglomerular feedback by increasing non-reabsorbed chloride concentration to the macula densa. In this way, peritubular capillary dysfunction leading to renal tubular injury can result in decreased GFR and UO, and in increased sCr.

Loss of GFR during sepsis can also occur as a consequence of impaired microcirculatory hemodynamics at the glomerular level. Under normal physiologic states, GFR is tightly regulated to maintain a constant filtration rate over a wide blood pressure range, through dilation and contraction of the afferent and efferent arterioles. However, during sepsis, GFR control is impaired by at least two mechanisms. First, simultaneous constriction of the afferent arteriole and dilation of the efferent arteriole decreases glomerular hydrostatic pressure, and thereby GFR. Second, constriction of the afferent arteriole results in intrarenal shunting through extraglomerular capillaries, which bypass the glomerulus altogether and result in decreased GFR.[20,26,40–42]

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Inflammatory Response—The inflammatory response is the host's primary defense mechanism against infections, and is critical to initiating and mediating repair processes necessary to recover function after injury. However, a dysregulated inflammatory response may cause further injury and result in maladaptive repair. During sepsis, the recognition of released PAMPs and DAMPs[43] by pattern recognition receptors (i.e., Toll-like receptors or TLR) expressed on the surface of immune cells and renal TEC initiate intracellular molecular cascades that manifest phenotypically as the inflammatory response to infection.[44] In TEC, binding of DAMPs/PAMPs to TLRs (i.e. TLR2 and TLR4) triggers a downstream signaling cascade that activates nuclear factor kappa-light-chain-enhancer of activated B-cells (NF-κB), which upregulates the gene expression of inflammatory cytokines and is necessary for immune cell recruitment to the site of injury and bacterial clearance.[45] However, the exposure to these inflammatory mediators and the activation of innate immunity in TEC results in increased oxidative stress, reactive oxygen species production and mitochondrial injury, all of which exacerbate the TEC injury.[44,46–48] Released blood-borne PAMPs and DAMPs in renal peritubular capillaries can gain access to the interstitial space and the vicinity of the basolateral membrane of TEC. In addition, PAMPs/DAMPs can be filtered through the glomerulus, and can be recognized TLR4 receptors in the apical membrane of TEC initiating inflammatory responses and inducing inflammatory and oxidative injury (Figure 1). This double hit mechanism makes proximal TECs especially susceptible to injury. A critical question that remains unanswered is whether the shutdown of tubular function is an adaptive mechanism of the kidney to avoid further injury and cell death, or just an epiphenomenon of TEC injury.

Metabolic Reprogramming—Metabolic reprograming is a conserved defense mechanism that cells use to optimize and reprioritize energy expenditure,[17,49,50] and adapt to environmental or intracellular danger signals while preventing cell death.[25,50–52] In sepsis, this has been better characterized in T-cells and monocytes. In response to inflammatory signals, monocytes and T-cells characteristically shift metabolism from oxidative phosphorylation (OXPHOS) toward aerobic glycolysis during the acute phase of the syndrome, reminiscent of the switch toward Warburg metabolism in cancer cells.[50] Importantly, this metabolic shift is necessary for T-cells and monocytes to differentiate into pro-inflammatory phenotypes like Th-17 and M1 macrophages, respectively, and to mount an appropriate inflammatory response (Figure 2).[53] Inflammatory cells shift back to OXPHOS in order to 'turn off' inflammation, and return to an anti-inflammatory phenotype.[54,55] This switch back to OXPHOS is also necessary for animals to survive sepsis and recover organ function, because persistence of glycolysis results in increased death, and in survivors, in chronic inflammation, fibrotic repair and CKD.[56,57]

Experimental data suggests that a similar reprioritization of metabolism may occur in TEC during S-AKI.[49,58] Furthermore, this reprioritization might be the explanation of the dissociation that exists between function deterioration and structural changes. Using gas chromatography/mass spectrometry, we showed a decrease in the substrate flux through the tricarboxylic acid cycle, and a shift of metabolism toward glycolysis in kidneys of C57BL/6 mice 8 hours after inducing sepsis by performing cecal-ligation and puncture (CLP).[49] This supports the idea that, during the early phase of sepsis, TECs switch from a highly efficient

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(i.e. OXPHOS) to a less efficient energy producing mechanism (i.e. aerobic glycolysis).[50] Similar results have been demonstrated in *in vitro* studies, in which human kidney 2 cells exposed to Lipopolysaccharide (LPS) show an early increase in drivers of aerobic glycolysis and a switch back to OXPHOS.[59]

Metabolic reprogramming during sepsis may result in the reprioritization of TEC functions and in a decrease in ATP synthetic capacity. In support of this, CLP and human sepsis induce a decrease in ATP levels in different tissues and organs, including the kidney.[60–62] Inflammatory stimuli from cytokines or PAMPs results in the downregulation of the expression of TEC ion transporters and in shut down of tubular ionic transport,[17,63–67] thereby sacrificing 'non-vital' functions for cell survival (Figure 3). Pharmacologic manipulation of metabolic reprogramming impacts renal function and survival during sepsis in experimental models. For instance, stimulation of OXPHOS through pharmacologic activation of the metabolic master regulator AMP activated protein kinase (AMPK), results in prevention of AKI and increased survival after CLP.[59] Stimulation of other OXPHOS regulators such as Sirt1 or the peroxisome proliferator-activated receptor (PPAR)-γ coactivator-1α (PGC-1α)[68] also decrease mortality, supporting the notion of a protective effect of OXPHOS during sepsis.[69–71] Conversely, pharmacologic inhibition of AMPK during experimental sepsis increases mortality and may impair metabolic flexibility by limiting the capacity of TEC to recruit OXPHOS and glycolysis (i.e., metabolic fitness).[59] Whether protection is a direct consequence of restoring OXPHOS or other effects of these regulators on mitochondrial quality control processes such as mitophagy (recycling of dysfunctional mitochondria) or biogenesis (synthesis of new mitochondria), or on interference of cell signaling pathways like the mTORC1/HIF-1α pathway is still unclear[72]. Regardless, the availability of functional mitochondria is an essential component of cell metabolism, OXPHOS and metabolic reprogramming[72], and therefore it is possible that the benefits of promoting OXPHOS may be secondary to the effects of OXPHOS regulators on mitochondrial function.

Diagnosis

The diagnosis of S-AKI is based on sCr levels and UO in the framework of the KDIGO criteria in a patient with sepsis (Table 1).[11] However, the definition of sepsis is based on SOFA score, which is problematic when evaluating AKI. First, the renal SOFA score does not account for underlying CKD and thus, can't differentiate between new-onset AKI, underlying CKD or acute or chronic AKI. Second, SOFA relies on a discrete data point of creatinine, which is a delayed marker of renal dysfunction and provides no information about course. The assessment of renal function using the KDIGO criteria overcomes some of these limitations by detecting AKI earlier using urine output criteria, and by discriminating AKI from CKD by using the change in creatinine from baseline.[11] For instance, UO may be more sensitive than spot sCr levels in detecting changes in renal function during sepsis, as changes in UO can be detected as early as every 3–5 hours. [73,74] Furthermore, changes in UO and sCr are associated with the severity of injury and with short- and long-term outcomes like the need for dialysis and mortality[75], and rigorous monitoring of UO is associated with an improved survival.[76] Therefore, we propose an evaluation of renal

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function in patients with suspected or documented infection based on KIDGO criteria and not SOFA (Figure 4).

However, even with KDIGO criteria, the reliance on sCr and UO is problematic because of their lack of sensitivity and specificity and other several limitations.[77] For instance, UO is difficult to track outside of the ICU, where a significant proportion of patients with early sepsis are usually admitted.[78] In addition, aggressive fluid resuscitation of the septic patient may result in dilution of sCr, resulting in the underdiagnosis of S-AKI. Furthermore, decreased skeletal muscle perfusion during sepsis results in decreased creatinine production, leading once again to an underrepresentation of the alterations in glomerular filtration and tubular injury by sCr.[79] In addition, ascertaining baseline sCr values is sometimes difficult, making it challenging to define real changes from baseline and determining the presence of chronic renal injury prior to the septic insult. In contrast, diagnosing AKI may not be sufficient, however, because treatment options will depend on defining and identifying the mechanisms leading to AKI. For instance, differentiating contrast-induced AKI from S-AKI is important and influences therapeutic decision making as well as prognostication of outcome. Several techniques have been put forth to address the origin of renal injury. The score based on the number of renal tubular cells and casts found in the urinary sediment has been suggested to differentiate S-AKI from other causes of AKI. Using RIFLE criteria and the need for RRT as reference standards, a score ≥ 3 was associated with higher urine Neutrophil Gelatinase-Associated Lipocalin (NGAL) levels and with increased severity of S-AKI with a sensitivity and specificity of 67.0% and 95.0%.[80] Another example is the presence of de novo dipstick albuminuria within the first 24h of hospital admission, which has been associated with the development of S-AKI after adjusting for comorbidities, critical illness parameters, baseline renal function, demographics and exposure to nephrotoxins (Odds ratio [OR]:1.87, 95% Confidence Interval [CI] 1.21–2.89, $p<0.01$).[81]

A promising strategy to improve the diagnosis of S-AKI is the development of better kidney injury biomarkers. The ideal S-AKI biomarker should predict or diagnose S-AKI early in the disease course, provide information about the mechanism and location of renal injury, serve as a monitor for progression and recovery, and predict outcome. Although it is unlikely that a single biomarker will fit this profile, it is plausible that a combination of injury and functional biomarkers could fulfill these characteristics.[82] The most relevant available biomarkers, their physiologic function and performance in the diagnosis of S-AKI are summarized in (Table 2) and will be described below.

Neutrophil Gelatinase-Associated Lipocalin (NGAL)

NGAL is expressed in many cell types, including prostate, uterus, salivary gland, lung, trachea, stomach, colon and kidney.[83] NGAL functions as an iron transporter into the renal tubular cells, and it is released in the serum primarily by TEC in the presence of ischemia.[84,85] Bagshaw et al, demonstrated that plasma and urinary NGAL levels are higher in S-AKI than in other AKI etiologies[86], however, despite similar sensitivity (plasma NGAL: 83.0% and urinary NGAL: 80.0%), urine NGAL has higher specificity than plasma NGAL for S-AKI (80.0% vs 57.0%).[87]

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Kidney Injury Molecule-1 (KIM-1)

KIM-1 is a type 1 glycoprotein expressed in the membrane of proximal renal tubules upon ischemic or inflammatory injury. A meta-analysis of 11 clinical studies suggested that urinary KIM-1 had a sensitivity of 74.0% (95% CI, 61.0–84.0%), a specificity of 86.0% (95% CI, 74.0–93.0%) and an AUC of 0.86 (95% CI, 0.83–0.89) for the diagnosis of AKI.[88] Despite its good performance in AKI, the evidence supporting its role specifically in S-AKI is scarce. A sepsis model in zebrafish found higher transcriptional levels of KIM-1 on the nephritic tubule at 24h in septic compared to non-septic fish.[89] In a cross-sectional study of 102 patients with different AKI etiologies including contrast induced and nephrotoxins, urinary KIM-1 levels were higher in S-AKI. [90] The performance of urinary KIM-1 in S-AKI has been evaluated in one prospective study in 150 patients with sepsis, which showed that urinary KIM-1 measured within the first 24h of admission had an AUC of 0.91 for the diagnosis of S-AKI.[91]

Liver-type fatty acid binding protein (L-FABP)

L-FABP is a part of the lipocalin protein family and is in charge of binding free fatty acid on the cytoplasm and transporting them to the mitochondria and peroxisomes for their metabolism.[92] Data on the performance of L-FABP in S-AKI is limited, in part because L-FABP is not expressed in mice, but it has shown promise in predicting severity of S-AKI. One study including 145 septic patients, demonstrated that a high urinary L-FABP level at admission to the ICU was associated with higher mortality, with higher AUC for predicting mortality than APACHE II or SOFA (0.99 vs 0.92 and vs. 0.81, respectively).[93]

Tissue Inhibitor of metalloproteinase 2 (TIMP2) and Insulin-Like Growth Factor Binding Protein 7 (IGFBP7)

TIMP2 and IGFBP7 are proteins involved in the induction of G1 cell cycle arrest, and the regulation of cell growth and apoptosis.[21,94,95] In the discovery and validation studies for TIMP2 and IGFBP7, which included 522 and 744 critically ill patients respectively, the combination of urine TIMP2 and IGFBP7 had the highest sensitivity and specificity for the prediction of AKI in comparison with any other biomarker including urine KIM-1, NGAL, L-FABP, and IL-18.[94,96] Importantly, the diagnostic performance of TIMP2/IGFBP7 was better in septic patients (AUC for any AKI: 0.80 vs S-AKI 0.84) and increased minimally in the presence of other causes of organ dysfunction.[94,971] In addition, an elevation in TIMP2 and IGFBP7 levels early in the course of septic shock was an independent predictor of the progression from mild/moderate (KDIGO stage 1 or 2) to severe AKI (KDIGO stage 3) over the next 24h.[98]

Recovery from S-AKI and long-term follow-up

The recognition that cell death alone is insufficient to explain the profound loss of renal function during S-AKI,[25] and that organ dysfunction may be a manifestation of cellular adaptive defense strategies,[59] has led to the consideration that S-AKI may be reversible. The progression of renal dysfunction and failure to recover has been attributed to maladaptive repair. Disordered regeneration in the tubular, vascular and interstitial compartments of the kidney in response to AKI results in vascular insufficiency, glomerular hypertension, and

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interstitial fibrosis leading to progression to CKD[99,100]. The evaluation of renal recovery after AKI has many pitfalls,[101] the most significant of which is the lack of a definition of recovery, until recently. The ADQI 16 consensus group recently defined AKI recovery as the absence of sCr and UO criteria (by KDIGO) within 7 days of AKI diagnosis.[102]

A prospective observational study including 1753 patients, found that S-AKI is associated with higher risk of death and longer hospital stay than non-septic AKI[18]. However, this study also showed that patients with S-AKI had lower sCr levels at hospital discharge compared to patients with non-septic AKI (median: 1.2 Interquartile range (IQR) [0.83–1.79] vs 1.37 IQR [1–2.08] mg/dl; p=0.01), suggesting that patients with S-AKI may have higher rates of recovery. Importantly, recovery from S-AKI improves short- and long-term survival of patients with sepsis. Kellum *et al.* [103] and *Fiorentino et al.* showed that patients who recover from S-AKI have similar one-year and three-year mortality as patients who never developed AKI in the first place[1103], supporting the theory that organ dysfunction during sepsis is not permanent.

Because of the importance to long term outcomes and the association with the development of life-threatening complications such as CKD, cardiovascular disease, bone fractures and proteinuria amongst others,[104,105] it is recommended that recovery from S-AKI is monitored during the hospital stay and beyond discharge if absent.[4,11,106]

Prevention and treatment of S-AKI

Most therapies for S-AKI remain reactive and non-specific, focusing on preventing secondary sources of injury like pre-renal injury, venous congestion and the use of nephrotoxins, and rely on the ability of the clinician to approach each individual case. Furthermore, due to the difficulties of establishing precise timing of injury, it has been challenging to develop preventive therapies for patients admitted with new onset sepsis. However, preventive strategies may still prove useful for hospitalized patients in whom timely diagnosis can be established.

The KDIGO Bundle

The KDIGO guidelines have suggested a bundle of selected supportive strategies to prevent AKI (Figure 4). This strategy, despite not being specific to any mechanism, appears promising as the application of the KDIGO bundle in patients undergoing cardiothoracic surgery has already demonstrated benefit in reducing the frequency and severity of AKI.[107] To our knowledge, the only randomized clinical trial addressing the effectiveness of the KDIGO bundle in patients with sepsis is underway in Alicante, Spain, and started recruitment in January 2020 (ClinicalTrials.gov, NCT04222361). This study will specifically assess if the implementation of the KDIGO bundle can reduce the occurrence and severity of AKI in high-risk abdominal post-surgical septic patients.

Antibiotics, source control and nephrotoxins

Whether infection is suspected, or sepsis is diagnosed, early and appropriate initiation of antibiotic treatment and identification of septic source is crucial to prevent AKI and reduce mortality. Delays in initiating appropriate antimicrobial therapy from the time of onset of

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hypotension in septic shock are associated with early AKI development.[108,109] However, caution should be used when prescribing and monitoring antibiotic therapy, as many of the antibiotics used to treat the infection leading to sepsis are also nephrotoxic. Medications like vancomycin, particularly in combination with other antimicrobials like piperacillin-tazobactam, aminoglycosides or amphotericin B, or with other nephrotoxins like intravenous radiocontrast media should be used with caution.[11]

Types of Intravenous Fluids

The evidence is now clear that in critically ill and especially in septic patients, the use of hydroxyethyl starch and gelatin based solutions increases the risk of AKI and mortality[110,111], and that balanced crystalloids are the fluid of choice[112,113]. Furthermore, the use of saline should be abandoned based on large RCTs that have now confirmed the findings of observational[114,115] studies showing that the use of fluids with high chloride concentration increases the risk of AKI.

The most recent SALT-ED [116] and SMART[112] trials were carried out to compare balanced crystalloids against 0.9% saline on different clinical outcomes in non-critically and critically ill patients, respectively. Both studies favored the use of balanced crystalloids demonstrating a protective effect major kidney adverse events (MAKE) at 30 days. Furthermore, the SMART trial demonstrated a larger protective effect of balanced crystalloids in septic patients than in the general population (OR: 0.80 (95%CI) vs 0.90 (95%CI), respectively.[113]

Although albumin-based solutions have been shown to be safe in recent multicenter RCTs[117,118] dissipating concerns about renal toxicity, albumin has not been found to be superior to balanced crystalloids[117] and thus, current recommendations still favor the use of balanced crystalloids for the resuscitation of patients with sepsis.

Hemodynamic Support

Fluid resuscitation followed by vasopressor agents is the cornerstone treatment in septic shock. In 2001, Rivers *et al.*[119] published a landmark study demonstrating that Early Goal Directed Therapy (EGDT) decreased mortality of patients with septic shock. Although this was a single center trial and had limitations that have been eagerly criticized throughout the past two decades, this study changed the approach to the resuscitation of the septic patient, setting a new standard of care and probably saving many lives. This may be one of the reasons why more recent trials analyzing the effect of EGDT, have shown no benefit in terms of S-AKI, use of RRT or mortality.[120]

The SEPSISPAM multicenter, RCT showed that, demonstrated that the mean arterial (MAP) pressure target in sepsis must be 65–70 mmHg, because except for patients with underlying hypertension, a higher MAP (80 – 85 mmHg) did not improve survival.[121] Currently, norepinephrine is the recommended first-line agent for treatment of septic shock[122], whereas the use of vasopressin has been discouraged based on its cost and the confirmation in a multicenter RCT and patient-level meta-analysis that although safe, vasopressin does not improve survival as compared to norepinephrine.[123124]

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Conclusions

S-AKI is defined as the abrupt renal function deterioration in the presence of sepsis, is an early, common, life-threatening complication and an independent risk factor for mortality. The early presentation of renal dysfunction in the course of sepsis suggests AKI may well be one of the earliest markers of the presence of sepsis and in the context of the new definition of sepsis, a sepsis-defining event. Although the pathophysiology of S-AKI remains incompletely understood, it is clear that S-AKI is not equivalent to ATN, and that, in addition to hypoperfusion, other mechanisms are at play. The interplay between microcirculatory dysfunction, inflammation and metabolic reprogramming of the TEC in response to sepsis are candidate mechanisms that, if better understood, can open doors to specific therapies to prevent or reverse S-AKI. In parallel to understanding specific mechanisms, the identification of better biomarkers to enhance early and mechanism-sensitive detection of S-AKI remains a critical step in improving outcomes.

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Abbreviations

AKI	Acute kidney injury
ATN	Acute tubular necrosis
CKD	Chronic kidney disease
DAMPs	Damage-associated molecular patterns
GFR	Glomerular filtration rate
IGFBP7	Insulin-Like Growth Factor Binding Protein 7
ICU	Intensive care unit
KDIGO	Kidney Disease: Improving Global Outcomes
KIM-1	Kidney Injury Molecule-1
L-FABP	Liver-type Fatty Acid Binding Protein
NGAL	Neutrophil Gelatinase-Associated Lipocalin
OXPHOS	Oxidative phosphorylation
PAMPs	Pattern-associated Molecular Patterns

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RBF	Renal blood flow
RRT	Renal replacement therapy
S-AKI	Sepsis-associated acute kidney injury
sCr	Serum creatinine
TEC	Tubular epithelial cells
TIMP2	Tissue inhibitor of metalloproteinase 2
TLR	Toll-like receptors
UO	Urinary output

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Synopsis

Sepsis associated acute kidney injury (S-AKI) is a common and life-threatening complication in hospitalized and critically ill patients. It is characterized by rapid deterioration of renal function associated with sepsis. The pathophysiology of S-AKI remains incompletely understood and thus, most therapies remain reactive and non-specific. Several pathogenic mechanisms have been described to explain S-AKI, such as microcirculatory dysfunction, a dysregulated inflammatory response and cellular metabolic reprogramming. Additionally, several biomarkers have been developed in an attempt to improve diagnostic sensitivity and specificity of S-AKI. In this clinic, we will provide an overview of the current understanding of S-AKI, with particular attention to recent advances in the pathophysiology and biomarkers development and finalize with remarks on current preventive and therapeutic approaches.

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Key Points

- Sepsis-associated acute kidney injury (S-AKI) is a life-threatening complication characterized by an abrupt deterioration of renal function, manifested by increased serum creatinine, oliguria, or both, associated to infection or sepsis.
- Sepsis is the most common cause of AKI, and AKI is a sepsis-defining event by virtue of being one of the earliest manifestations of sepsis.
- Although the pathophysiology of S-AKI remains incompletely understood, the interplay of microcirculatory dysfunction, dysregulated inflammation and metabolic reprogramming in the context of tubular dysfunction are important contributors to S-AKI.
- Novel biomarkers of tubular stress and damage recently validated for risk prediction and early diagnosis of AKI, promise to provide the next step in the evolution of strategies to diagnose and monitor therapy.
- Recovery from S-AKI is possible, and it is associated with a decline in mortality. Thus, unraveling mechanisms that promote renal recovery and restore function should be a priority in developing treatment strategies for S-AKI.

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Clinics Care Points

- Diagnosis and definition of S-AKI primarily rely on the KDIGO criteria and SOFA score; however, these tools present many limitations and pitfalls. Therefore, a high clinical suspicion of S-AKI is needed for early diagnosis and treatment initiation.
- Newer kidney injury biomarkers, with higher sensitivity and specificity, are necessary for the early diagnosis and prevention of S-AKI.
- S-AKI is considered a sepsis-defining event and AKI may be one of the earliest complications of sepsis. Therefore, sepsis must be suspected in AKI with unknown origin.
- Therapies for S-AKI remain reactive and non-specific. Early initiation of antibiotics, adequate hemodynamic support and avoidance of nephrotoxins remain as pillars of therapy.

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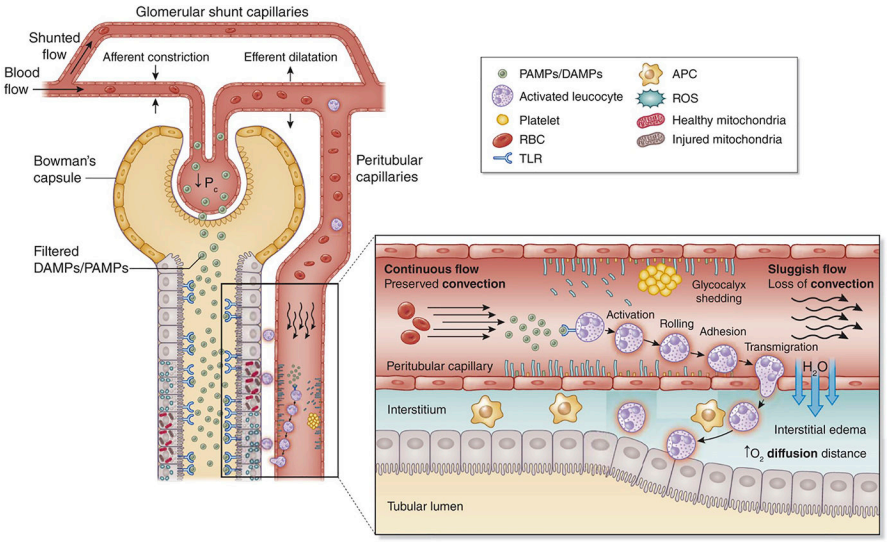

Fig. 1.

Inflammatory response and microcirculatory dysfunction. Pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) are inflammatory mediators derived from bacteria and host immune cells, respectively. These inflammatory mediators bind to pattern recognition receptors (PRRs) expressed on the surface of innate immune cells, endothelial cells, and renal TECs initiating a downstream cascade of signals. This cascade increases the synthesis of proinflammatory cytokines, reactive oxygen species (ROS), oxidative stress, and endothelial activation by nitric oxide and nitric oxide synthase (iNOS) upregulation. During inflammation, DAMPs and PAMPs are filtered in the glomeruli. Once in the tubule, these bind the Toll-like receptor (TLRs) present in the apical membrane of the TEC. In addition, some evidence suggests that TECs are also exposed to the inflammatory mediators present in the peritubular circulation, creating a double-hit effect. Moreover, the inflammatory response can also injure the TECs by increasing the oxidative stress and producing ROS. Microcirculatory dysfunction is the result of a series of events that lead to an impaired delivery of oxygen and nutrients to the tissue. Endothelial activation provoked by the inflammatory response results in a cascade of events that lead to shedding of the glycocalyx, increased leukocyte migration, and endothelial permeability. In addition, microcirculatory dysfunction is characterized by a heterogeneous flow, reduced number of capillaries with continuous flow, with an associated increase of capillaries with sluggish or no flow. Sluggish and no flow, a result of the increased expression of adhesion molecules on the inflammatory and endothelial cells, facilitate the migration of neutrophils and macrophage to the interstitial space. Furthermore, the areas with sluggish flow have increased production of ROS and oxidative stress, manifested by TEC apical vacuolization.16,35,49 APC, antigen-presenting cell; RBC, red blood cell. (Adapted from: Peerapornratana, S., Manrique-Caballero, C. L., Gó mez, H. & Kellum, J. A. Acute kidney injury from sepsis: current concepts, epidemiology, pathophysiology, prevention and treatment.
Kidney international 96, 1083–1099, https://doi.org/10.1016/j.kint.2019.05.026 (2019).)

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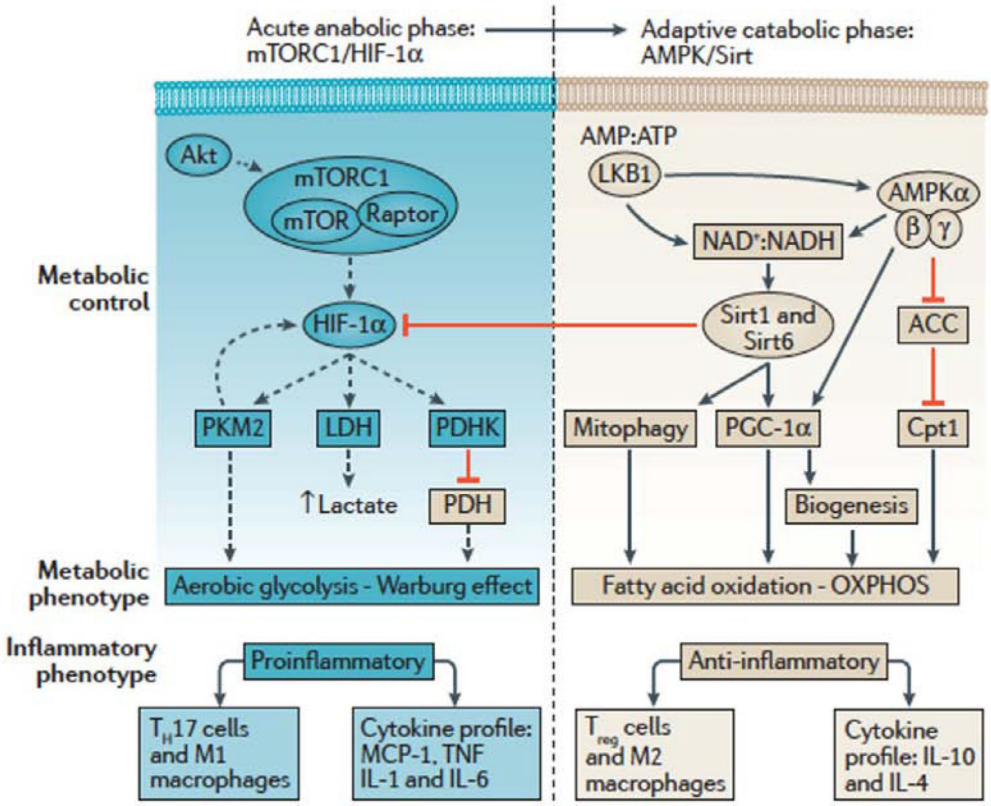

Figure 2. Metabolic Reprogramming

In the early metabolic response to S-AKI, renal tubular epithelial cells undergo a proinflammatory phase (acute anabolic phase) metabolism in which the Akt/mammalian target of rapamycin complex 1 (mTORC1)/Hypoxia Inducible Factor (HIF)-1α complex drives the induction of aerobic glycolysis by increasing the expression of glycolytic enzymes (e.g. lactate dehydrogenase [LDH], PKM2 and pyruvate dehydrogenase kinase [PDHK]). HIF-1α promotes the conversion of pyruvate to lactate and, along with PDHK, inhibit the conversion of lactate into acetyl-CoA hindering the induction of the Krebs cycle and decreasing OXPHOS. In the late anti-inflammatory (adaptive catabolic phase) OXPHOS, metabolic pathways are reestablished. This is driven by adenosine monophosphate-activated protein kinase (AMPK) activation, Sirt1 and Sirt6. AMPK activates Sirt1 and Sirt6. Sirt6 will block the activity of HIF-1α switching back from aerobic glycolysis to OXPHOS. is induced by the decrease in ATP levels. AMPK activates peroxisome proliferator-activated receptor (PPAR) γ coactivator-1α (PGC)-1α and with CPT-1 will stimulate fatty acid oxidation and oxidative metabolism. Furthermore, PGC1α along with AMPK will induce mitochondrial biogenesis.[17,36,50]

Adopted and adapted from: Gómez, H., Kellum, J. A. & Ronco, C. Metabolic reprogramming and tolerance during sepsis-induced AKI. Nature Reviews Nephrology **13**, 143, doi:10.1038/nrneph.2016.186 (2017).

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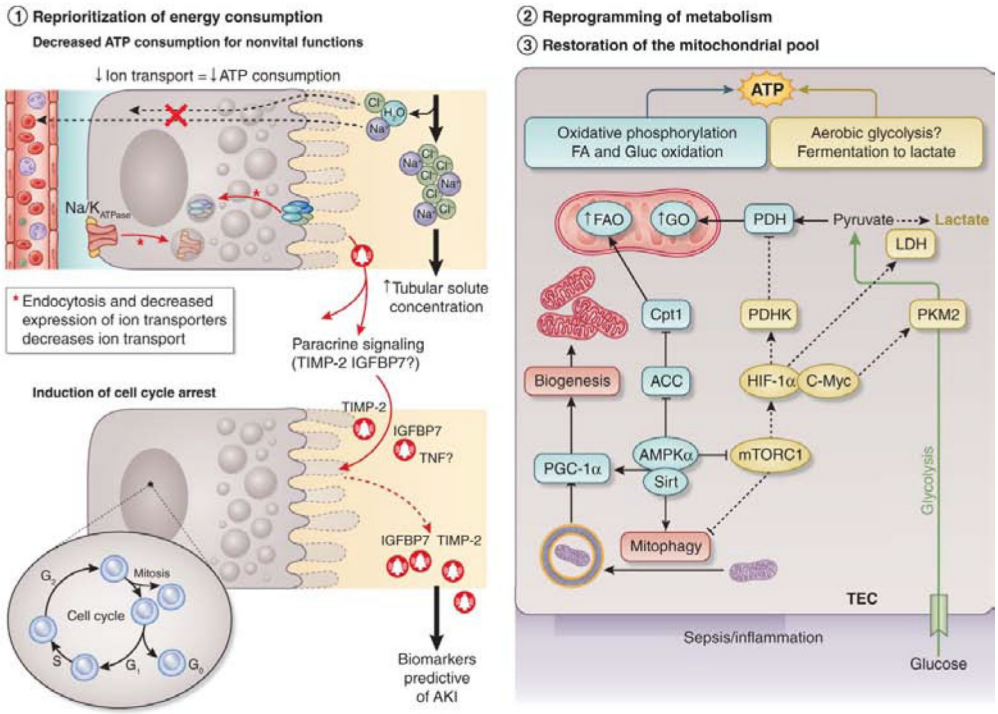

Figure 3. Metabolic Adaptive Response to Sepsis: Prioritizing Cell Survival

As consequence of the early metabolic reprogramming that TEC undergoes during sepsis, non-vital functions such as cell replication, protein synthesis and ion transportation are put in 'stand-by', and the limited amount of ATP available is redirected toward vital functions, prioritizing cell survival at the expense of cell function. Active transport pumps such as Na^+/K^+ ATPase are engulfed by the cell to limit the spend of ATP. Additionally, one of the most cell energy-consuming processes is cell replication. TEC have intrinsic mechanisms that allow to detect if the cell possesses enough ATP to undergo a complete cell cycle. If this is not the case it would shut down cell replication, resulting in elevation of cycle arrest biomarkers (i.e. IGFBP7 and TIMP2). Finally, to restore TEC oxidative metabolism and normal TEC metabolism, a healthy pool of mitochondria is required. During sepsis, mitochondrial population is severely injured. As a protective mechanism, mitochondrial quality control processes such as mitophagy and biogenesis are activated as a mechanism to restore the mitochondrial pool and switch back to OXPHOS.

Adopted and adapted from: Peerapornratana, S., Manrique-Caballero, C. L., Gómez, H. & Kellum, J. A. Acute kidney injury from sepsis: current concepts, epidemiology, pathophysiology, prevention and treatment. Kidney international 96, 1083–1099, doi:10.1016/j.kint.2019.05.026 (2019).

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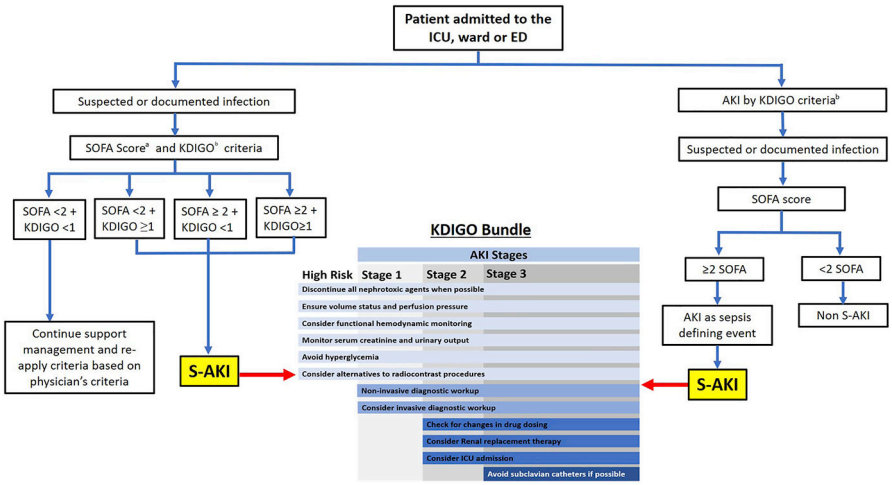

Fig. 4.

Proposed diagnostic approach to S-AKI and AKI as a sepsis-defining event. aSepsis-3 Q18 criteria7: patient with suspected or documented infection who has a total SOFA score greater than or equal to 2. bKDIGO criteria.11 Stage 1 AKI: increase in serum creatinine level 1.5 to 1.9 times baseline or increase in serum creatinine level greater than or equal to 0.3 mg/dL within 48 hours or urine output less than 0.5 mL/kg/h for 6 to 12 hours. Stage 2 AKI: increase in serum creatinine level 2.0 to 2.9 times baseline or urine output less than 0.5 mL/kg/h for greater than or equal to 12 hours. Stage 3 AKI: increase in serum creatinine level greater than or equal to 3.0 times baseline, or increase in serum creatinine level greater than or equal to 4.0 mg/dL, or urine output less than 0.3 mL/kg/h for greater than or equal to 24 hours, or anuria for greater than or equal to 12 hours, or need for initiation of RRT. ED, emergency department; ICU, intensive care unit.

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Table 1.

KDIGO Criteria for Acute Kidney Injury (AKI)

KDIGO Criteria for Acute Kidney Injury (AKI)		
Stage	**Serum Creatinine (sCr)**	**Urine Output (UO)**
1	1.5–1.9x baseline *OR* ≥ 0.3mg/dl (>26.5 μmol/l) increase	<0.5 ml/kg/h for 6–12 h
2	2.0–2.9x baseline	<0.5 ml/kg/h for 12 h
3	3x baseline *OR* Increase in SrCr ≥ 4.0 mg /dl (353.6 μmol/l) *OR* Initiation of RRT *OR* In patients < 18 years, decrease in eGFR to <35 ml/min per 1.73m^2	<0.3 ml/kg/h for ≥ 24 h *OR* Anuria for ≥ 12 h

Adopted and adapted from: Khwaja, A. KDIGO clinical practice guidelines for acute kidney injury. Nephron. Clinical practice 120, c179–184, doi:10.1159/000339789 (2012).[11]

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Table 2.

Biomarkers for S-AKI

Biomarker	Sample Source	Primary tubular release location	Physiologic Function	Use in S-AKI
NGAL	Plasma/ Urine	Thick ascending limb and collecting duct	Anti-inflammatory and antiapoptotic protein that is involved in the synthesis and transport of iron into the renal tubular epithelium. [21,125,126] NGAL confers a bacteriostatic effect limiting bacterial iron uptake. [126]	Urine NGAL is more specific than plasma NGAL. [87,127] However, plasma NGAL has been shown to predict S-AKI recovery.[128]
KIM-1	Plasma/ Urine	Proximal tubules	Type 1 transmembrane glycoprotein that has an anti-inflammatory effect on the kidney. Participates in renal recovery and tubular regeneration [21]	In one prospective study, KIM-1 in the first 24h after admission had an AUC of 0.91 for the diagnosis of S-AKI. Non survivors had higher level of urinary KIM-1 at 24 and 48 hours than survivors.[91]
L-FABP	Urine	Proximal tubules	From the lipocalin family, involved in binding and transportation of longchain fatty acids to the peroxisome and mitochondria to be metabolized. Plays a role as antioxidant reducing cellular oxidative stress due to the binding of fatty acid oxidation products.[92]	In a cohort of 145 patients with S-AKI, urinary levels of L-FABP at admission were higher in non survivors with S-AKI and had a higher AUC score than APACHE II and SOFA score.[93] It has also shown to be a predictor of mortality in septic children.[129]
TIMP 2-IGFBP7	Urine	Proximal tubules	Both proteins regulate cell growth and apoptosis. In the presence of cell injury, TIMP 2 and IGFBP7 are upregulated and may lead to G1 cell cycle arrest through the induction of p27 and p21, respectively. [21,94,95]	FDA approved biomarker for risk assessment tool of AKI in sepsis. Urine TIMP2/IGFBP7 has the highest specificity for renal injury, as there is minimal elevation in the presence of other organ injury.[97] High TIMP2 and IGFBP7 levels in the early phase of septic shock are independent risk factors for progression to severe AKI in the next 24h.[98]