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REVIEW ARTICLE

Recent Advances on Biomarkers of Sepsis-induced Acute Kidney Injury

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ABSTRACT

SEPSIS is a complex clinical syndrome involving both infection and a deleterious host immune response. Actue Kidney Injury (AKI) is a frequent and serious complication of sepsis in Intensive Care Unitpatient (ICU). Despite recent impressive advances in the pathophysiology, diagnostic procedures, and appropriate therapeutic interventions in sepsis, sepsis-induced AKI fails to reduce the overwhelmingly high mortality rate and longer hospital stay. A major obstacle for effective treatment of sepsis-induced AKI is the relative lack of specific early and effective diagnostic tools. Current clinical Serum Creatinine (Scr) is unable to detect the early AKI, in the past ten decades, studies have identified several biomarkers for the early diagnosis of AKI, but only limited information exists concerning their values in the diagnosis of sepsis-induced AKI. In this article, we have made a comprehensive review to discuss the clinical value of biomarkers in the diagnosis of sepsis-induced AKI.

Introduction

Sepsis, a complex clinical syndrome defined by the clinical response to a suspected or proven infection, is a leading cause of death worldwide. It is estimated that 18 million cases of sepsis occur each year in the world, with mortality rates ranging from 30% to 50% [1-3]. Sepsis affects persons of all ages [4], and is considered the 10th leading cause of death overall in the United States [5,6]. In the United States, approximately $24.3 billion is spent per year on the costs of hospitalization for septic patients [7]. AKI is very common in sepsis, and is associated with a higher risk of adverse outcomes [8]. AKI is a frequent and serious complication of sepsis in ICU patients [9], especially in the elderly [10]. Moreover, sepsis is the most important causes of AKI, accounting for 50% or more of cases of AKI in ICU, and associates with a very high mortality [11]. In adults, AKI occurs in approximately 19–23% of patients with moderate/severe sepsis, and in more than 50% in patients with septic shock [12]. The incidence of AKI increases with the severity of sepsis and estimates are that AKI develops within the first 24 hours in 64% of patients with severe sepsis and hypotension [13]. Strikingly, the mortality rate for septic patients with AKI is approximately doubled compared with sepsis alone [14]. Thus, early specific diagnostic tools, preclinical biomarkers, protecting the

Kidney could significantly reduce morbidity and mortality in patients with severe sepsis.

The pathophysiology of sepsis-induced AKI is complex and multi-factorial, including intra-glomerular thrombosis, obstruction of tubules, infiltration of inflammatory cells, endothelial dysfunction and so on [15] (Figure 1).

decrease in urinary output [29]. Accordingly, it is necessary to make a diagnosis of the suclinical sepsis-induced AKI by utilizing biomarkers. This review will focus on recent advances in biomarkers of sepsis-induced AKI and evaluation for their clinical value in the diagnosis of this disease.

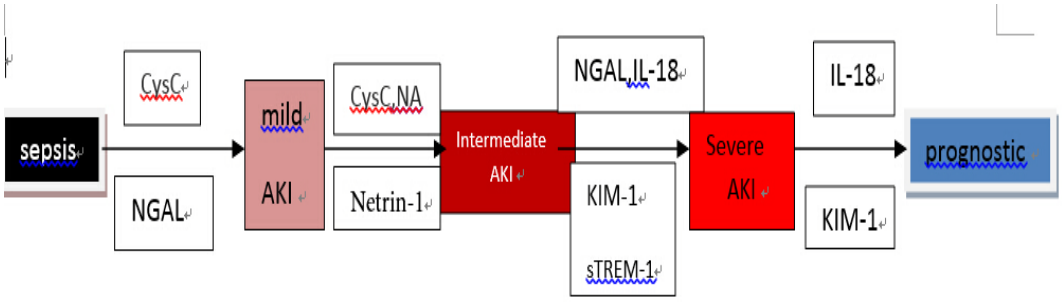

Figure 1: Sepsis-induced AKI biomarkers.

There is an increasing evidence that sepsis-induced immune responses involve the activation of both pro-and anti-inflammatory mechanisms [16,17]. Inflammatory cascades and oxidative stress with microcirculatory changes play an important role in sepsis-induced AKI [18-21].

Important differences exist in Sepsis -induced AKI characteristics with a distinct pathophysioloy between nonseptic origin patient [15,22-24] (Table1). Firstly, both renal medullar and cortical blood flow is maintained and even increased during severe septic shock [15]. Secondly, there is an important role for apoptosis rather than necrosis in sepsis -induced renal tubular cell death [25,26]. Thirdly, both afferent and efferent arterioles are the same as dilatation, with greater efferent than afferent dilatation, leading to decreased capillary pressure and subsequent decrease in filtration and AKI [27]. In addition, a hyperemic injury is also thought to involve in the sepsis-induced AKI [28].

In recent years, it has been put forward that there is a continuum between transient AKI without tubular damage, transient AKI with minor tubular damage, and intrinsic AKI in sepsis.Thus, there may be a new subgroup of AKI, namely subclinical AKI, which was defined as a rise in biomarker level without a rise in Scr or a

Sepsis-Induced Expression of AKI Biomarkers

An ideal kidney function biomarker should be constantly produced, freely filtered, neither secreted nor reabsorbed by the renal tubule [30]. Unfortunately, a lot of kidney filtration biomarker is influenced by many extra-renal factors (muscle mass, age, gender, and reduced production in sepsis-AKI) and tubular secretion [31]. An ideal sepsis-induced AKI biomarkers should be an early detection biomarker that is tightly coupled to GFR, enabling rapid detection after the insult and identifying patients that may be at a higher risk, meanwhile a prognosis biomarker that can predict severity or mortality. There are partial early detection biomarkers of sepsis-induced AKI as following (Table 2).

1. Cystatin C (CysC)

CysC is a proteinase inhibitor that prevents connective tissue destruction [32], **and** it's molecular weight is 13.3 kDa [33]. It is continously produced by nucleated cells in the body, is filtered by the glomerulus, and then is entirely reabsorbed in the proximal tubule [34,35]. Serum CysC (sCysC) is affected by age, gender, muscle mass, smoking, thyroid function, and malignancies [36]

Whether sCysC is a better biomarker of AKI is still controversy. [37,38], Several studies have suggested

that sCysC is an ideal endogenous biomarker of chronic kidney function [33,39-41].

Table 1: The different pathophysiology of early AKI.

Sepsis	Non-sepsis
Renal Blood Flow (RBF) increased	RBF decreased
(hyperemic)	(hypoperfusion)
Mechanism apoptosis and necrosis	necrosis
(inflammation, microvascular dysfunction, (cellular energy regulation)	
cellular energy regulation)	
Manifests dramatic decline in GFR, tubular dysfunction	variable tubular dysfunction.

[34,48,49]. SCysC is 3-fold higher than baseline while SCr is unchanged and BUN slightly changed at 3h after CLP mice. Thus, SCysC could meet the criterion of ideal biomarkers, SCysC is a better early detection biomarker than Scr in sepsis, and still influenced by non-renal factors that conspire to limit the accurate prediction of GFR during the evolution of sepsis -induced AKI .

2. Neutrophil gelatinase-associated lipocalin (NAGL)

NGAL is also known as lipid-transport protein 2 (lipocalin-2), one member of the lipocalin superfamily. It was initially found as an oncogene expressed by multiple human cells, including epithelial cells and neutrophils [50]. The major biological function of NGAL is its bacteriostatic feature related to iron-chelating properties [51].

Table 2: Apartial biornarkers list of sepsis -induced Al li.

Biomarker	Source of sample	Site of expression	Elevation in sepsis-inducedAKI	Proznostic value
Cystain C	plasma/urine	nucleated cells	SCysC changed at 3h after CLP mice Urinary Cys predicts AKI 48-72h before Scr	Urinary CystainC
NAGL	plasma/urine	epithelial cells and neutrophils PT>DT	Urinary NGAL 3 hours after injury peaking at 6 hours	Urinary NGAL
Netrin-1	Urine	PT, various organs	urine 1 hour after injury peaking at 3- 6 hours	NO
IL-18	Urine	PT, renal cortex	12-18 hours after injury	predict the therapy, mortality
KIM-1	Urine	PT	6 hours after injury peaking at 24 hours. remained until 48 h	predict the severe level
sTREM-1	Urine	monocytes, macrophages, and neutrophils	48 hours after injury	assess AKI severity

On the other hand, some studies have shown the superiority of sCysC as an early biomarker of AKI [42]. Urinary CysC predicts AKI 48-72h before Scr, while serum CysC may detect AKI one to two days earlier than Scr in Intensive Care Unit (ICU) patients who developed AKI [43]. Urinary CysC can be used for the diagnosis of kidney injury and sepsis, and predicts mortality in the intensive care unit [44]. SCysC also outperforms Scr as an early biomarker of AKI in the emergency patients [45], and in children after cardiopulmonary bypass [46]. Recently, a study by Asada et al [47] supposed that sCysC outperforms Scr and BUN as a renal function biomarker early in the course of sepsis-AKI. SCysC production is not largely affected by acute inflammation, including sepsis- induced inflammation, AKI

NGAL, a 24-kDa protein consisting of 178 amino acid residues, is freely filtered by the glomerulus, and largely reabsorbed in the proximal tubules by efficient megalin-dependent endocytosis [52].The half-life of NGAL is estimated at 10–20minutes [53], It is postulated that increased serum and urinary NGAL are a sensitive marker of AKI, predominantly of damage to tubular cells, but do not reflect the decline of GFR. [54]. Several results showed that plasma NAGL might be able to detect not only AKI, but also sepsis [55,56].

Emerging evidence supports NGAL as a valuable biomarker of AKI and chronic kidney disease (CKD). Recently two trials initiated by Goldstein et al, and Ricci et al [57] showed that NGAL is a biomarker in predicting fluid accumulation and kidney injury in

paediatric AKI. Hur at al, demonstrated that plasma NGAL was a biomarker for AKI in critically ill patients with suspected sepsis, Cantaluppi et al, further showed that plasma NGAL was an early biomarker of DGF in kidney transplantation from extended criteria donors, Cruz DN provided that NGAL was a biomarker of cardiovascular disease beyond the kidneys, Damman et al. assumed NGAL as a biomarker in heart failure [58].

However, plasma NGAL can increase not only in sepsis - induced AKI, but during sepsis in the absence of AKI, this has been proved by Müge et al [59]. Plasma NGAL can be freely filtered by the glomerulus, and is largely reabsorbed in the proximal tubules by efficient megalin-dependent endocytosis [52]. It is possible that the patho-physiology of inflammatory response, with increased release of neutrophils, will have the effect on serum total NGAL concentration. Current results strongly pointed to NGAL as a marker of endothelial injury and neutrophil activation, rather than solely AKI, especially in sepsis - induced AKI patients [54]. All of these authors recently described increases in serum NGAL in septic patients without correlation to AKI [59-63]. Thus there is need to use other biomarkers in conjunction with both serum and urinary NGAL to accurately identify patients with both sepsis and AKI. Thus, Katagiri demonstrates that a biomarker panel consisting of plasma NGAL and EA assay can detect sepsis with high accuracy in AKI patients, both biomarkers can be evaluated in less than an hour from the time the patients enter the ICU, and significantly improved their detection performance incomplicated conditions of septic AKI [62].

On the basis of current criteria, Martensson [56] and Aydogdu [59] concluded that urine NGAL is probably a more robust marker of AKI than plasma NGAL in patients with sepsis -induced AKI, since urine NGAL levels remain within normal limits even when plasma levels are high and signs of AKI are absent. They thought that any urinary excretion of NGAL is likely only when there complies with proximal renal tubular injury. In sepsis, although plasma NGAL levels increase due to inflammation, urine NGAL (uNGAL) increase only in the presence of AKI [52], Thus, in sepsis -induced AKI, both urine and plasma NGAL can increase, with uNGAL being more useful for the early diagnosis of AKI, as NGAL protein is detectable in the urine as early as 3 hours after injury, although the peaks of concentration of urine NGAL at 6 hours after injury. uNGAL is also independently associated with subsequent sepsis - induced AKI [64]. Changes in uNGAL excretion during sepsis-induced AKI closely correlate with the severity and the progression of the disease [65].

3. Netrin-1

Netrin-1 is a laminin-like related family of axon guidance molecule. The netrins were discovered in the early 90s as neuronal guidance cues [66]. Netrin-1, initially described in central nervous system (CNS) during neurogenesis [67], is also expressed in various organs like intestine, pancreas, mammary glands, lung, kidney, blood vessels, etc. The major biological function of Netrin-1 is involved in angiogenesis, cell migration, tissue morphogenesis, tumor progression and growth, and regulation of inflammation. The kidney is one of organs expressing the highest levels of Netrin-1. It prominently locates in the interstitium in normal kidney, consistent with expression in peritubular capillaries [68]. Preclinical studies performed in murine models indicated that Netrin-1 is markedly induced in kidney tubule cells and excreted in the urine. It appears in the urine, as early as 1 hour after renal ischemic injury, increasing approximately 30-fold by 3 hours and peaking at 6 hours [69].

Recently, clinical study result shown that urinary netrin-1 levels increased significantly as early as 1h, peaked at 3-6 h and remained elevated up to 48 h of ICU admission in septic AKI patients [70], similar to its profiles in the preclinical studies Therefore, Netrin-1 may be a clinically useful biomarker in the early diagnosis of sepsis -induced AKI.

4. Interleukin-18 (IL-18) L-18

IL-18, a 22-kD proinflammatory cytokine, is expressed in the renal cortex , peritubular capillaries and interstitium [71]. IL-18 is translated as a procytokine subsequently cleaved bycaspase-1 [72]. It promotes inflammation by signaling through the IL-18 receptor–

a/accessory protein–like heterodimer [73]. Urinary IL-18 has elevated within the first 6 hours after renal injury, but does not peak until after12–18 hours, the excretion of IL-18 is higher in sepsis -induced AKI than in nonseptic AKI, IL-18 also predicted deterioration in kidney function, with increased values preceding clinically significant kidney failure by 24-48 h [74]. Recent studies have shown that urinary IL-18 levels can be used for the early diagnosis of AKI. Urine IL-18 levels also predict the mortality of patients who have ARDS and are in the intensive care unit [75].

5. Kidney injury molecule-1 (KIM-1)

KIM-1 is a 38.7-kD type 1 transmembrane glycoprotein that contains extracellular mucin and Ig domains [76]. It expression is markedly up-regulated in proximal renal tubular cells in response to ischaemic or nephrotoxic AKI [77]. KIM-1 increased significantly by 6h, peaked at 24h and remained significantly elevated until 48h of ICU admission. These results suggest that KIM-1 is clinically useful as an early biomarker in the diagnosis of sepsis-induced AKI. In addition, persistent elevation of urinary KIM-1 level may be associated with poor prognosis [70].

6. Soluble triggering receptor expressed on myeloid cells-1 (sTREM-1)

sTREM-1, a 27-kD protein, can be excreted by the kidney. In the presence of kidney injury,asoluble form of TREM-1 can be released into body fluids. TREM-1 is a member of the immunoglobulin superfamily expressed mainly on mature monocytes, macrophages, and neutrophils [78]. Endothelial cells or the infiltrating inflammatory cells could produce sTREM-1, which measured in the urine, was able to predict the development of AKI. The AKI patients' urine sTREM-1 levels at 48 h before diagnosis were significantly higher than those for the non- AKI patients [79]. If these results were to be confirmed by larger studies, urinary sTREM-1 would possibly become a new biomarker for sepsis-induced AKI.

Summary and Perspective

The ideal biomarker in sepsis-induced AKI would have several characteristics, including reliable detection of AKI; being sufficiently sensitive to detect early subclinical injury; reflecting the location of kidney injury; reflecting time dependent changes in the severity of injury; and being simple, cheap and easy to measure.

This review highlights the major studies that have characterized the diagnostic and prognostic predictive power of sepsis-induced AKI biomarkers. Serum and urine CysC, NGAL, urine Netrin-1 biomarkers can be used in the early diagnosis of sepsis-induced AKI. In addition, KIM-1 and IL-18, have function in prognostic predictive power.

Currently, the clinical use of novel AKI biomarkers is still unclear, and biomarker in sepsis-induced AKI is poorly studied. Since large, prospective, multicenter trials failed to show the value for early diagnosis of AKI using currently available biomarkers, it is necessary to further search for the ideal marker of sepsis-induced AKI has clearly not been completed yet.

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