Biomarkers, diagnosis and management of sepsis-induced acute kidney injury: a narrative review

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ABSTRACT
Sepsis is a leading cause of acute kidney injury in clinical practice. The diagnosis of sepsis-induced acute kidney injury requires the diagnosis of sepsis and subsequent occurrence of acute kidney injury. The current definition for acute kidney injury is based on Scr and urine output, which is limited by the delayed identification of such patients. Numerous novel biomarkers have been found to be up-regulated in kidney injury, among which cystatin C and neutrophil gelatinase-associated lipocalin are the most studied. In the management of sepsis-induced acute kidney injury, early goal directed therapy may be potentially useful, but requires further validation in large clinical trials. It is well known that fluid overload is harmful in septic patients with established acute kidney injury and should be avoided. Renal replacement therapy is the mainstay treatment for the severe form of sepsis-induced acute kidney injury. However, there is still no consensus on the definition of timing and dosing in clinical practice, and the optimal timing and dosing are still unknown.

Keywords: sepsis, acute kidney injury, review, diagnosis, management.

INTRODUCTION
Sepsis is a primary cause of mortality and morbidity worldwide, affecting more than 160,000 people in the United States alone in 1979, and the number increased to 659,000 in the year 2000 (1). The trend is expected to continue due to the aging population and increases in comorbidities (2). Kumar G et al. found that the incidence of severe sepsis keeps on rising from 143 in 2000 up to 343 per 100,000 persons in 2007 (3). Not only the quantity, but the severity of sepsis also accentuated as represented by the number of organ failure. In the same study, Kumar G et al. reported that the mean number of organ failure increased from 1.6 to 1.9 (p < 0.001) during study period (3). Sepsis is a systemic inflammatory disorder that will affect other organs, and the number of organ failure had additive effect on patients’ outcome. Following lung (18%), the kidney is the second most frequently involved organ in sepsis (15%). If a kidney is involved, the mortality rate will increase exponentially.

Acute kidney injury (AKI) is commonly seen in septic patients. It is estimated that more than 20% septic patients may show some degree of AKI, and mortality rate of this subgroup will increase up to 35% (4). Other causes of AKI include major surgery, heart failure, respiratory failure and hypovolemia, all of which associated with shock and hypoperfusion. Tissue
hypoperfusion is the main reason for the development of sepsis-induced AKI. Some authors believe that resuscitation aiming to restore tissue perfusion will minimize or even reverse the kidney injury (5). However, this paradigm has been challenged by evidences from clinical and experimental studies. AKI can develop in the setting of increased renal blood flow (6). In clinical setting, it is reported that only a very small proportion of patients after cardiac arrest showed signs of AKI (7). Only patients with cardiogenic shock after cardiac arrest are prone to the development of AKI (5). While there is an active research area on the mechanisms underlying AKI development in sepsis, but this is not the primary focus of current review. Readers who are interested in this topic are referred to another review (8).

The primary goal of the review is to summarize the diagnosis and the management of sepsis-induced AKI (SIAKI). The current guidelines for the diagnosis will be reviewed and incorporated together to reach the diagnosis of SIAKI. I will not limit my attention to the diagnosis of SIAKI, but I will extend the review to the prediction of SIAKI, because I believe that early identification of patients at increased risk of SIAKI will alert clinicians to adopt strategies to avoid this potentially deadly condition.

Identification of patients with sepsis

The earliest consensus achieved to define sepsis is done by American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) in 1991 (9). In this meeting, “systemic inflammatory response syndrome (SIRS)” was developed and the definition required at least two of the four clinical criteria: hyperthermia or hypothermia, tachypnea, tachycardia, and leukocytosis or leukopenia with immature neutrophils. However, this definition is criticized for its non-specificity that SIRS is not only specific to infection but can be caused by many other critical conditions including trauma, burn, pancreatitis and ischemia injury (10). In the conference held in 2001, sepsis was further stratified into four aspects: predisposing factors, infection, host response and organ failure (Figure 1) (11). This was deemed as the PIRO (predisposing, infection, response, organ dysfunction) system (10). The diagnosis of sepsis becomes more complex than the original one. In the new definition, some other important aspects of sepsis are incorporated such as the hemodynamics and organ dysfunction (Figure 2).

AKI definition and diagnosis

AKI is defined with respect to the increase in serum creatinine (Scr) and decrease in urine output: these parameters are widely available and intensively investigated. The two most widely used definition system for AKI is the RIFLE (risk, injury, failure, loss, end stage) and AKIN (acute kidney injury network) criteria (12). The RIFLE criteria uses the following categories: “Risk” is the least severe form, followed by “Injury”, “Failure”, ”Loss” and ”End-stage renal disease” (Figure 3) (13). AKIN criteria is slightly modified from the RIFLE to incorporate the finding that even small increase in Scr is associated with significantly elevated mortality rate (14). Historically, plasma urea nitrogen has been used as a marker of renal dysfunction before discovery of Scr. The value of plasma urea nitrogen, however, is discounted because there are numerous factors other than renal function that influences its concentration. These include diet, muscle mass, age, gender and medications (15).

The definition of AKI based on Scr has long been debated, mostly due to its shortcomings such as assay interference, dilution during fluid resuscitation, altered metabolism during critical illness and altered clear-
ance with drugs (16). Furthermore, Scr is a late and indirect reflect of renal damage. As a result, scientists are trying to discover and develop novel biomarkers to represent kidney injury, aiming to identify the injury timely. An ideal biomarker should be the one that is able to predict AKI and its outcomes, locate the site of injury (glomerulus vs tubule), determine the type of injury, and enable the initiation of therapeutic interventions (16). Several potential biomarkers have been identified and merit extensive researches to establish their role in the diagnosis of AKI.

**Figure 2** - Definition of sepsis from several aspects.

WBC = white blood cell count; CRP = c-reactive protein; GCS = Glasgow coma scale.
Figure 3 - Definition of acute kidney injury with RIFLE criteria.
RIFLE = risk, injury, failure, loss, end stage; AKI = Acute kidney injury;
GFR = glomerular filtration rate;
Scr = serum creatinine;
UO = urine output.

Cystatin C is a 13-kDa protein that is secreted from all nucleated cells and does not bind to plasma proteins. It is freely filtered by the glomerulus and it is subsequently re-absorbed and degraded in proximal tubule by the endocytic receptor. Since Cystatin C is not secreted into urine by the tubule in normal condition, its appearance in urine can reflect the impairment of tubule (15). Serum concentration of Cystatin C is dependent on the glomerular filtration rate (GFR) and it is more sensitive than Scr in detecting minor impairment in GFR (such as a GFR of 60-90 ml/min) (17). In clinical studies, more evidence is demonstrating the good diagnostic performance of Cystatin C in early diagnosis of AKI. In children undergoing cardiac surgery, Hassinger et al. (18) found that Cystatin C is a good predictor of “risk” of AKI with an area under receiver operating characteristic curve of 0.834-0.875. In another study conducted also in pediatric cardiopulmonary bypass surgery, the authors showed that the 12-hour Cystatin C strongly correlated with severity and duration of AKI (19). A systematic review and meta-analysis by our group demonstrated that the combined diagnostic odds ratio for cystatin C to predict AKI was 27.7 (95% confidence interval [12.8-59.8]), with the sensitivity and specificity of 0.86 and 0.82, respectively (20). The diagnostic performance of urine cystatin C, unfortunately, is less than satisfactory, with sensitivity and specificity of 0.52 and 0.70 respectively. Beyond its diagnostic value for AKI, our group has also demonstrated that cystatin C measured on initiation of continuous renal replacement therapy (CRRT) could predict the renal function recovery (21, 22). However, the value of cystatin C is criticized for some limitations. Royakkers AA et al. showed that in mixed intensive care unit (ICU) patients the diagnostic performance of serum cystatin C was fair on day-2 (area under the curve (AUC) 0.72) and was poor on day-1 (AUC 0.62) to predict AKI (23). These inconsistent results may be partly explained by different definitions for AKI.

Neutrophil gelatinase-associated lipocalin (NGAL) is another potential candidate for early detection of kidney injury. NGAL is a 25 kDa molecule composed of a single disulphide-bridged polypeptide. It is secreted by injured renal tubular epithelial cells (24). Experimental studies have shown that NGAL is one of the most increased
genes and proteins in early stage after renal insult, suggesting its potential role in predicting AKI (25). Later clinical observations confirmed its diagnostic performance. In patients undergoing cardiac surgery, the most important study is the multicenter TRIBE (Translational Research Involving Biomarkers and Endpoints). A total of 1219 adults and 311 children were included in the analysis. NGAL was measured in both serum and urine peaked within 6 hours after surgery. The diagnostic performance is only moderate with an area under curve (AUC) of 0.75 (26). A similar result was replicated in mixed critically ill patients (27, 28). Due to the large number of investigations in this area a systematic review and meta-analysis was conducted by the NGAL Meta-analysis Investigator Group. The diagnostic accuracy of serum and urinary NGAL was similar, with diagnostic odds ratio (DOR)/AUC of 17.9 (95% CI [6.0-53.7])/0.775 (95% CI [0.679-0.869]) for serum NGAL, and 18.6 (95% CI [7.2-48.4])/0.837 (95% CI [0.762-0.906]) for urinary NGAL (29). However, this study was done five years ago and numerous new studies have been published since then. Thus, an updated systematic review and meta-analysis is needed. With sufficient number of component studies, some statistical techniques such as cumulative meta-analysis and meta-regression can be incorporated into the analysis.

There are nearly 30 novel biomarkers being developed and are now under investigation for their role in diagnosing AKI. For instance, urinary interleukin-18 (IL-18) and kidney injury molecule-1 (KIM-1) have both been demonstrated to be satisfactory biomarkers of AKI (15). In a recent observational cohort study, we focused specifically on septic patients and found that increases in microalbuminuria is able to predict subsequent development of AKI, with an AUC of 0.86 (95% CI: [0.77-0.94]) (30). This is a single center study and it bears inherent limitations of such design, and the result requires further validation. Other candidate biomarkers include β2-microglobulin, Gamma glutamyl transpeptidase, Liver-type fatty acid-binding protein, N-Acetyl beta glucosaminidase, and plasminogen activator inhibitor 1. Comprehensive reviews of these biomarkers are out of scope of the current article.

A well written review of these biomarkers and their clinical usefulness has been published, and interested readers are referred to this article (15).

**Sepsis induced acute kidney injury**

Although sepsis is a leading cause of AKI (31), the framework for the definition and management of SIAKI has not been well established. For instance, the time interval required between the onset of sepsis and subsequent elevation of AKI biomarkers to define SIAKI has not been developed. Probably, the time interval between onset of sepsis and elevation of AKI biomarkers is important in that it helps to determine the underlying causes of SIAKI as well as to guide therapeutic decision. As for the definition of nosocomial pneumonia, it is required for the pneumonia onset to be lagged for over 48 hours after hospitalization. If the identification of pneumonia is within 48 hours after hospitalization, it is regarded as community acquired pneumonia and the pathogen as well as the choice of antibiotics can be quite different (32, 33). It is currently unknown whether the same situation exists in the field of AKI. Due to the lack of strong clinical evidence, I propose that the management of AKI caused by sepsis and hypovolaemia should be different. Antibiotics and inflammatory modulators can be beneficial in the former condition, whereas the latter may benefit from volume resuscitation to restore tissue perfusion.

Identification of SIAKI in clinical setting
is merely to identify patients meeting the diagnosis of both sepsis and AKI. The relationship between AKI and sepsis are bidirectional. While sepsis is a leading cause of AKI, patients with renal failure are also at an increased risk of developing sepsis during hospitalization.

**Management of SIAKI**

*Fluid.* AKI caused by sepsis is thought to be associated with inadequate intra-vascular volume (so called pre-renal failure), and thus fluid resuscitation is the indication for its initial treatment. The aim of the fluid resuscitation is to restore adequate renal blood flow. However, fluid resuscitation does not follow the rule “the more, the better”: administration of excessive fluid has been frequently proven to be harmful in the literature (34). The observation between fluid overload and adverse renal outcome was first described in children (35). In adults with AKI, Payen et al. showed that mean fluid balance was an independent risk factor for 60-days mortality (hazards ratio 1.21 for each 1 unit increase in L/24 hours), after adjusting for age, Simplified Acute Physiology Score II (SAPS II), heart failure, medical admission, mechanical ventilation and liver cirrhosis (36). Similar findings supporting the association between fluid overload and adverse outcome in patients with AKI have been reported (37).

The type of fluid is also important for the management of AKI. Hydroxyethyl starches (HES) have been frequently proven to be harmful. A systematic review and meta-analysis performed by Serpa Neto A et al. showed that patients receiving HES for resuscitation were at significantly increased risk of AKI development (relative risk (RR) 1.24; 95% CI [1.13-1.36]) and need of RRT

| Table 1 | Commercially available solution formulas for renal replacement therapy. |
|---------|---------------------------------------------------------------------|
| Calcium formula | Calcium-free formula | Dextrose free |
| Plasma | PrismSol BGK/2.5 | PrismSol BGK/3.5 | PrismSol BGK0/2.5 | PrismSol BGK4/0/1.2 | PrismSol BGK2/0 | PrismSol B22GK/4/0 | PrismSol BK0/0/1.2 |
| Potassium (mEq/l) | 3.5-5.0 | 4 | 2 | 0 | 4 | 2 | 4 | 0 |
| Calcium (mEq/l) | 2.3-2.6 | 2.5 | 3.5 | 2.5 | 0 | 0 | 0 | 0 |
| Magnesium (mEq/l) | 1.4-2.0 | 1.5 | 1 | 1.5 | 1.2 | 1 | 1.5 | 1.2 |
| Sodium (mEq/l) | 135-145 | 140 | 140 | 140 | 140 | 140 | 140 | 140 |
| Chloride (mEq/l) | 100-108 | 113 | 111.5 | 109 | 110.5 | 108 | 120.5 | 106.2 |
| Bicarbonate (mEq/l) | 22-26 | 32 | 32 | 32 | 32 | 32 | 22 | 32 |
| Lactate (mEq/l) | 0.5-2.2 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Dextrose (mg/dl) | 70-110 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| Osmolarity (mOsm/l) | 280-296 | 300 | 296 | 292 | 295 | 291 | 296 | 282 |

BGK = Bicarbonate glucose potassium.
(RR, 1.36; 95% CI [1.17-1.57]), as compared to those receiving crystalloids (38). The same result was replicated by another group (39). In the systematic review, a total of 31 trials are eligible for analysis and 8725 patients were eligible for endpoint of AKI. The results showed an increased rate of renal failure with the use of Hydroxyethyl starches (RR, 1.27; 95% CI [1.09 to 1.47]; I², 26%; AR, 5.45%; 95% CI, 0.44% to 10.47%).

The adverse effect of HES is associated with its localization to circulatory system and deposition to the muscle, skin, liver, endothelial cells and kidneys. The toxic effect on renal function has been demonstrated in animal and clinical studies, which may be attributable to the volume and molecular weight of HES.

**Systematic resuscitation protocol**

Sepsis is a multifaceted disorder that requires management within a multidisciplinary framework. Resuscitation bundle is defined as quantitative administration of serial strategies aiming to achieve pre-specified goals. The 2012 Surviving Sepsis Campaign guideline recommends standard, quantitative resuscitation of patients with sepsis-induced tissue hypoperfusion to achieve goals during the first 6 h of resuscitation:

1. Central venous pressure 8–12 mmHg;
2. Mean arterial pressure (MAP) ≥65 mmHg;
3. Urine output ≥0.5 mL kg⁻¹ h⁻¹;
4. Central venous (superior vena cava) or mixed venous oxygen saturation 70 or 65 %, respectively. These recommendations, however, are not well validated by clinical trials and the best recommendation grade is 1C (40).

The idea of systematic resuscitation comes from a landmark study by Rivers et al. (41). In the study, patients with sepsis and septic shock were randomly assigned to the 6-hour early goal directed therapy (EGDT) group or control group. Patients in EGDT group received a central venous catheter that was capable of measuring central venous oxygenation. Serial strategies including fluid bolus, use of vasopressors and red blood cell transfusion were initiated with the target to achieve a central venous oxygenation of more than 70%. The results showed that the mortality rate was significantly reduced as compared with standard therapy, but the renal function was not assessed (42). A recent large clinical trial called ProCESS (Protocol-Based Care for Early Septic Shock) showed that EGDT-based protocol was associated with marginally significant reduction in the risk of new-onset AKI as compared to the standard protocol care group (3.1% vs 6%, p=0.04). However, the EGDT-based protocol was harmful in terms of new-onset AKI as compared to the usual care group (43).

**Renal replacement therapy (RRT)**

Substantial proportion of SIAKI requires RRT to avert deadly complications such as severe hyperkalcemia, acidosis and volume overload. Depending on different criteria to initiate RRT, however, the reported rate of RRT in AKI varies greatly across institutions. In general, about 5% of AKI patients require initiation of RRT (44). Hsu RK et al. reported that RRT-requiring AKI increased from 222 to 533 cases/million person-years from 2000 to the year 2009, with an average 10% increase per year (incidence rate ratio = 1.10, 95% CI [1.10-1.11] per year) (45).

RRT comprised two important aspects when given to SIAKI patients. One refers to the dose or intensity of RRT. In the literature, the intensity of RRT may be referred to as high-flow and slow-flow. There is no consensus on the definition of dose for RRT. Currently, the most widely used definition is the normalized effluent rate,
which has been incorporated into many clinical trials (46). This definition has the advantage of simplicity, but our subsequent work has demonstrated that it underestimates the real dialysis dosage and the gap between actually delivered dose and estimated dose become progressively larger with prolonged use of the filter (47). A meta-analysis by our group showed that intensive dose RRT had no additional benefit for the overall AKI patients (RR 0.91, 95% CI [0.77-1.08]), as well as for the subgroups with SIAKI (RR 0.99, 95% CI [0.90-1.09]) (48). We proposed that the turning point for CRRT dose to be beneficial is below 25 ml/kg/hr (46). There are varieties of solutions available for RRT as the replacement fluid. Seven formulas, varying in calcium, potassium, bicarbonate and dextrose levels, are commercially available (Table 1).

Since the mortality rate of sepsis increases dramatically when the sepsis is complicated by AKI, it is intuitive to postulate that early initiation of RRT may confer beneficial effects on SIAKI. The clinical question is the timing of CRRT, which has received much interest in the scientific community. A retrospective study conducted by Oh HJ et al. showed that the early use of CRRT could significantly reduce the risk of death within 28 days (p = 0.034) (49). A recent study, unfortunately, failed to identify any benefit from early initiation of RRT in patients with SIAKI (50). The inconsistent results may be due to the fact that there is no consensus on the timing of RRT. The criteria used to classify “early” and “late” are generally arbitrary. For instance, in Oh HJ’s study timing of CRRT application is based on the interval between the start time of vasopressors use and CRRT initiation, and “early” was defined as a time interval between vasopressor use and CRRT of more than two days. In contrast, in Shum HP’s study timing is based on the magnitude of Scr rise according to RIFLE criteria (50), and “early” was defined as the initiation of CRRT at the risk stage of RIFLE list.

CONCLUSION

Sepsis is a leading cause of AKI, and thus SIAKI requires special attention as its diagnosis and treatment may have some distinctive features. The diagnosis of SIAKI requires the determination of sepsis and subsequent occurrence of AKI. The current definition for AKI is based on Scr and urine output, and is limited by their delayed identification of patients with AKI. Numerous novel biomarkers have been found to be upregulated early after renal insult, and these include cystatin C, IL-18, KIM-1 and NGAL. In the management of SIAKI, the early goal directed therapy may be useful, but requires further validation in large clinical trials. It is well known that fluid overload is harmful in septic patients with established AKI and should be avoided. RRT is the mainstay treatment for the severe form of SIAKI. However, the best timing and dosing of RRT is still under debate, and there is still no consensus on the definition of timing and dosing in clinical practice.

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Sepsis-induced acute kidney injury

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