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Chapter 5

Sepsis-associated Acute Kidney Injury

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Abstract

Sepsis is a life-threatening condition caused by a dysregulated immune response to infection. Interestingly, sepsis mortality increases with acute kidney injury (AKI) and patients with AKI worsen with sepsis. It is interesting to note that most of the clinical trials on sepsis treatment that derived from the results of translational researches are a failure. This is, in part, because of the complexity of human sepsis in comparison with animal models. Another reason for the failure-translation might be the improper matching of the animal models to the individual patient. It is possible that the main mechanism of sepsis induction in each patient with the variety causes of sepsis might be different. Indeed, immune response to sepsis depends on genetic background, route of immune activation, and organisms. Thus, sepsis treatment classified by "mechanistic approach" to individual patient might be more proper than the classification with "sepsis severity". Specific treatment of sepsis in individual patient according to the specific immune response characteristic might be a more proper translational strategy. Indeed, the understanding in immune response pattern of sepsis and sepsis pathophysiology is necessary for "sepsis mechanistic approach". Then, we conclude most of the topics and our hypothesis regarding SA-AKI in this review.

Keywords: sepsis-acute kidney injury, immune responses, pathophysiology, sepsis mechanistic approach, individual treatment

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1. Introduction

Sepsis is a condition with life-threatening organ dysfunction caused by a dysregulated host response to systemic infection [1]. Sepsis is the leading cause of acute kidney injury (AKI) in critically ill patients especially in the intensive care unit (ICU). The morbidity and mortality of patients with sepsis-associated AKI (SA-AKI) is still high despite an advance in supportive care [2, 3]. Therefore, a well understanding of SA-AKI is essential not only for nephrologists but also for all physicians to enhance awareness and proper initiation of managements. In this chapter, we discuss several topics in SA-AKI, including the potential new therapeutic managements.

2. Definition and classification

Because SA-AKI definition follows the definition of AKI, in general, the understanding in AKI definition is necessary. Despite the heterogeneity in AKI definition with more than 35 equivalent terms within the last few decades [4], RIFLE (Risk, Injury, Failure, Loss of kidney function, End-stage kidney disease) and AKIN (Acute Kidney Injury Network) classification systems, published in 2004 and 2007, respectively, are widely accepted [5]. RIFLE classification stratifies AKI according to AKI severity as determined by serum creatinine (SCr) or glomerular filtration rate (GFR) and urine output (UO) into three categories; Risk (R), Injury (I), and Failure (F). In addition, RIFLE criteria also categorize advanced AKI into other two categories based on the duration of AKI, kidney function loss (L, persistent AKI > 4 weeks), and end-stage kidney disease (E, AKI > 3 months) [5]. In RIFLE classification, worsening of SCr must be over a 7-day period and persists for at least 24 h. In case of unknown data on previous SCr level, a baseline GFR between 75 and 100 ml/min/1.73 m^2 is assumed, and the modification of diet in renal disease (MDRD) equation is recommended for an estimation of baseline renal function. However, the poor prediction of clinical outcomes from renal function derived by MDRD equation is demonstrated [6]. Therefore, RIFLE and AKIN classifications are modified [7]. In modified AKIN classification, the diagnostic accuracy is improved by precluding either SCr or GFR which discards the requirement of baseline SCr for AKI classification. Despite the improved diagnostic sensitivity of AKIN in comparison with RIFLE classification, AKI outcomes are not in consideration of AKIN system [8]. And AKIN does not synergize with RIFLE criteria in predicting in-hospital mortality of patients with critical illness. Recently, the kidney disease improving global outcomes (KDIGO) work group merges the RIFLE and AKIN classifications in order to establish one AKI classification [9]. KDIGO system defines AKI as an increase in SCr ≥0.3 mg/dL within 48 h or an increase in SCr to ≥1.5 times of baseline SCr or a urine volume of <0.5 mL/kg/h for 6 h. Baseline SCr is the known or presumed value that has occurred within the previous 7 days. In addition, AKI staging of KDIGO follows the AKIN classification with a simplification. KDIGO system shows some advantages over the RIFLE and AKIN classifications in AKI identification and AKI-outcomes prediction. Moreover, KDIGO introduces a new term of "acute kidney disease, AKD" which means the slower increase in SCr or GFR, >7 days but <3 months. This is because renal injury in some

conditions progresses slowly and does not match with AKI definition where significant renal function declines within 7 days after the insults.

Regarding SA-AKI classification, Pereira et al. [10] demonstrate that SA-AKI with all of these three classifications—RIFLE, AKIN, and KDIGO—shows similar prediction ability (assessed by the area under the receiver operating characteristic (AUROC) curve) for in-hospital mortality (RIFLE 0.652, $p < 0.001$; AKIN 0.686, $p < 0.001$; KDIGO 0.658, $p < 0.001$). However, the study shows that RIFLE and KDIGO classifications identify AKI more than AKIN criteria. Thus, SA-AKI is AKI induced or enhanced by sepsis which could be classified with any of these three classification systems. It is also interesting to note that SA-AKI is another entity that should be separated from nephrotoxic and ischemic causes of AKI. In fact, inflammatory responses in SA-AKI seem to be more prominent than ischemic and nephrotoxic AKI [11].

3. Epidemiology

A longitudinal, 10 years, cohort with more than 20 ICUs and almost 90,000 patients demonstrates the increased incidence of AKI by 2.8% per year [12]. In parallel, the incidence of sepsis and septic shock is on the rise. In the United States, the retrospective data from 22 years of hospital records reveal 8.7% annual increase in diagnosis of sepsis [13]. Sepsis is the most common contributing factor for AKI. The incidence of SA-AKI is 10–45% based on etiology and population [14, 15]. In surgical condition, the incidence may be as high as 60–70% [16], especially in the ICU setting (>50%) [3]. The severity of SA-AKI also depends on the underlying diseases as well as causes of sepsis [17].

Populations with a high risk of SA-AKI are elderly patients, female gender, and medical comorbidities, including diabetes mellitus, chronic kidney disease (CKD), congestive heart failure, advanced liver disease, and malignancy [18, 19]. In addition, the source of infection and side effect of treatment also contribute as risk factors of SA-AKI. As such, intra-abdominal infection, urological sepsis, infective endocarditis, and blood stream infection are conditions that are susceptible to SA-AKI.

4. Immune responses in sepsis

Sepsis immune responses are very complex and possibly different among diverse etiologies. The progression of sepsis definition is parallel to the current understanding of sepsis pathophysiology in each period (**Figure 1**).

Indeed, the importance of hyperinflammation as a major component of sepsis is gradually altered by the progression in the understanding of sepsis-induced hypoinflammatory responses. The updated definition of sepsis focuses on organ dysfunction, host responses, and infection as an etiology [1]. This is due to the recognition that sepsis in the individual patient is different due to host factors (underlying disease, genetic susceptibility, duration of infection, and organ involvement) and organism factors (virulence and antibiotic susceptibility). Hence, the

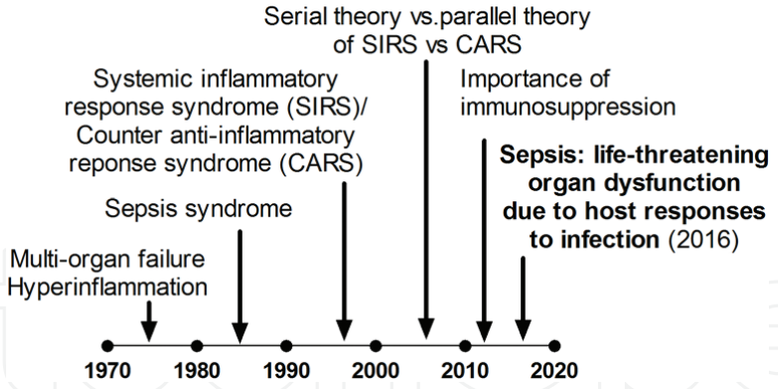


Figure 1. Summary of sepsis definition or main mechanisms in each period.

major mechanisms responsible for sepsis and the proper therapeutic strategies to encounter sepsis for each patient might be different. Indeed, several responsible molecular pathways of sepsis-induced hyperinflammatory response have been demonstrated (e.g., Toll-like receptor 4, Toll-like receptor 9, HMGB1, NF-κB, etc.) mostly in animal models with very rapid clinical progression [20]. These sepsis models enlighten us that the harness of innate immune responses in several processes with adequate organism control attenuates sepsis severity [21–29]. However, the control of innate immune-induced hyperinflammation results in only 50% survival. This demonstrates that other mechanisms might also contribute to the severity of sepsis. Indeed, the clinical observation from patients with sepsis demonstrates immunosuppression in sepsis as determined by (i) high susceptibility to secondary infection, (ii) defect in delayed-type hypersensitivity responses, and (iii) reactivation of dormant virus (e.g., herpes group) [30]. From these clinical observations, immunosuppressive phase of sepsis seems to occur at the late phase. However, Hotchkiss et al. nicely demonstrate the importance of sepsis-induced immune suppression and conclude that moribund stage of patients with sepsis could occur shortly after the onset of sepsis (either hyperimmune or hyporesponsive phase) [30].

As such, the rapid immune exhaustion after sepsis has been demonstrated in mice with the defect of immune inhibition (Fc gamma receptor IIb-deficient mice) [31]. These mice lack the inhibitory signaling with prominent immune responses to infection. The preconditioning with endotoxin induces immune exhaustion and blunt responses of subsequent infection. In translational aspect, this is an example of the rapid immune-suppressive phase that occurs shortly after the onset of sepsis due to the preconditioning in the susceptible host. Moreover, bacterial sepsis also enhances the susceptibility to secondary fungal infection [32]. Interestingly, *Candida albicans* intravenous injection alone and with sepsis causes candidemia after injection at 7 days and 6 h, respectively. Sepsis induces candidemia approximately 1 week faster than non-sepsis control group. This model is also demonstrated that immunosuppression after sepsis could be very rapid, and the host factors are important for the direction of immune responses.

In animal model, sepsis in the pre-conditioning models, pre-existing AKI or CKD or lupus manifestation, demonstrates the more severe hyperimmune responses as shown by the prominent cytokine storms [23, 26, 31, 33]. Then, the host factor is very important for inducing rapid progression due to hyper- or hypoimmune responses in sepsis. While several

therapeutic strategies from animal studies are available mostly for controlling hyperimmune responsiveness, the clinical study in sepsis categorizes patients according to the severity of sepsis but not by the characteristic of immune response. Therefore, it is not surprising that nearly all of the clinical studies fail and the difference between animal models versus patients is blamed for the translational failure. The mechanistic-oriented approach with patient characterization by molecular biomarkers, but not simply with sepsis severity, should be more appropriate. Biomarkers for differentiating the direction of sepsis immune response are urgently needed. The anti-inflammatory treatment should be appropriate for patients in hyperimmune response phase and *vice versa* for immunosuppression phage. Moreover, hyper- and hypoimmune response in sepsis is dynamic and the monitoring biomarkers are necessary.

In addition, the molecular-oriented treatment is also an interesting topic in sepsis. For example, anti-HMGB1 should be beneficial in sepsis condition with high HMGB1, and anti-TLR-4 should be appropriate for patients with increased TLR-4 expression on immune cells. Due to the possibility of heterogeneity pathways of sepsis immune responses, the tailor-made or individualized therapy might be the most suitable management of sepsis. However, the understanding in sepsis immune responses is still incomplete. Then, the current sepsis definition depending on sepsis-induced end-organ damage regardless of mechanistic responses is still fragmentary. More studies are needed to reach "sepsis mechanistic approach" in the future.

5. Pathophysiology of SA-AKI

Currently, the pathophysiology of SA-AKI is not completely known. Probably renal biopsy is rarely performed in SA-AKI. Hence, the basic knowledge of SA-AKI is based upon animal models which might be relevant only to a specific condition of SA-AKI in human [34]. For an example, AKI from cecal ligation and puncture model might be relevant to intra-abdominal sepsis but less appropriate representative of pneumonia-induced AKI. The interpretation and results translation from bench to bedside should be properly matched between models and sepsis conditions in patients. Hence, the experiments on the larger animals are performed but, unfortunately, the models might not represent all aspects of patient conditions. With the data gathering from patients and animal studies, the pathophysiology of SA-AKI is, at least in part, through overt inflammatory process-induced renal injury, tubular tight junction (TJ) injury, cell cycle arrest, cellular adaptation/apoptosis, and so on [35]. Perhaps, an alteration in microvascular oxygen transport during sepsis might be the major pathophysiology of SA-AKI. Here, we summarized the mechanisms of SA-AKI mentioned in the literatures (**Figure 2**).

5.1. Microscopic hemodynamic disturbances

The renal microcirculation is an important delivery system of blood and oxygen to kidney tissue. Decreased glomerular perfusion pressure in sepsis is due to microdynamic disturbance with approximately normal renal blood flow (RBF) [36]. However, reduced RBF in sepsis could be found only in some patients with the failure of cardiac output. In fact, sepsis induces hyper-dynamic cardiac responses with relatively high cardiac output. Although RBF is

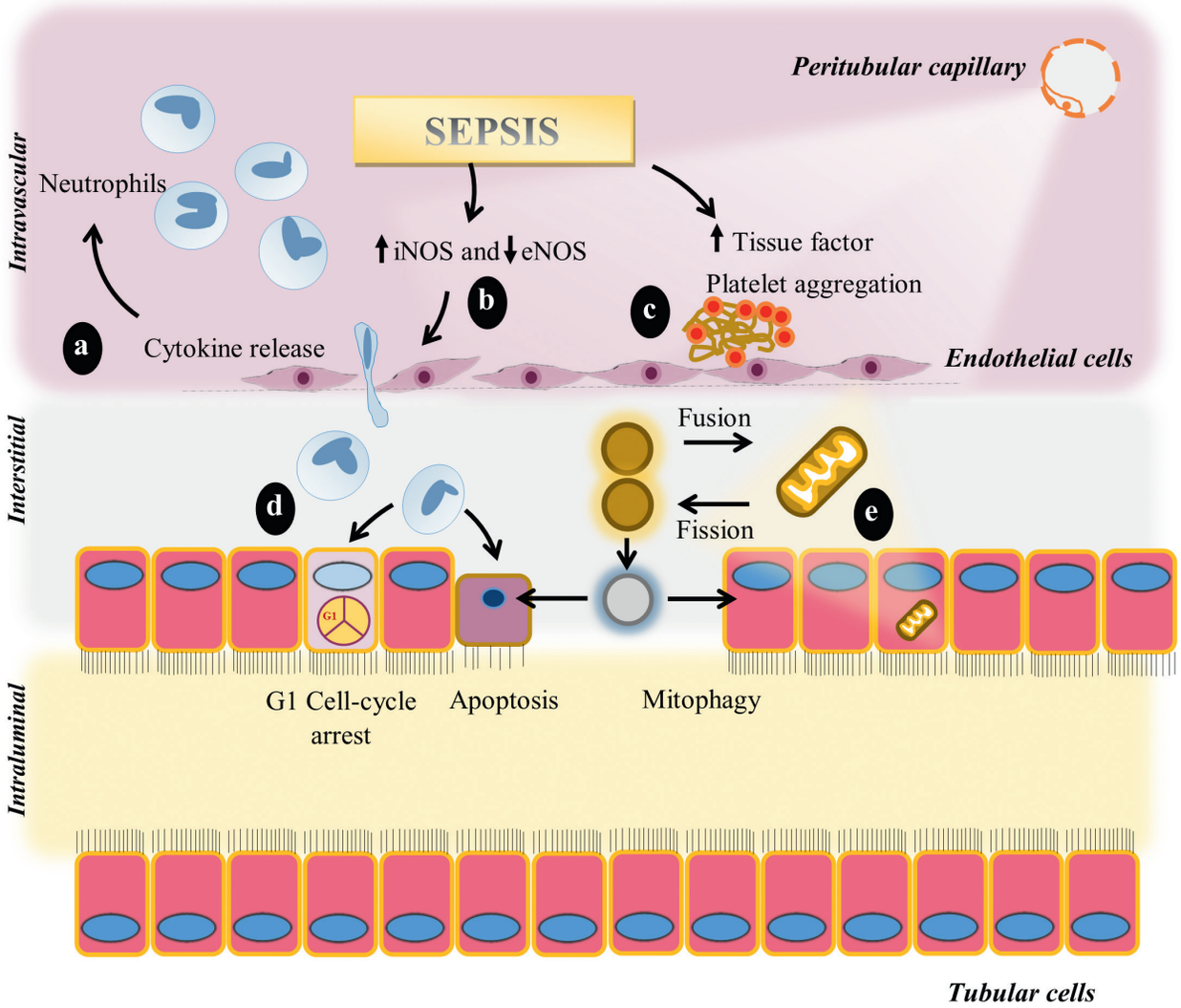


Figure 2. Immune responses in sepsis. Due to renal microcirculation dysfunction (glomerular and tubular capillary), sepsis induces chemotaxis of inflammatory cells and proinflammatory responses leading to endothelial injury (a). Vascular permeability increases due to the downregulation of endothelial nitric oxide synthase (eNOS) activity and induction of inducible nitric oxide synthase (iNOS) (b). In parallel, inflammatory responses increase tissue factor and induce the coagulation system as demonstrated by microvascular thrombosis (c). In addition, inflammatory responses induce tubular cell injury, activate cell cycle arrest at G1 phase and cell apoptosis (d). The insufficient cell energy induces the abnormality in fusion/fission mechanisms of mitochondria resulting in mitochondrial injury (e). The toxic cell environment induced predominant mitochondria fission and dysfunction mitochondria (gray circle). The successful or failure of mitophagy activates cell regeneration or cell apoptosis, respectively (e, lower part).

maintained or increased in sepsis, glomerular capillary hydrostatic pressure is insufficient to permit effective filtration because of efferent-afferent arteriolar imbalance function. Reduced GFR in persistent AKI is a result of several mechanisms including inappropriate activation of tubuloglomerular feedback (TG feedback) [37], tubular back-leak [38], tubular stasis/obstruction, nephrosarca, and altered glomerular permeability.

Normally, TG feedback is controlled by the concentration of chloride delivery to the distal nephron for the induction of afferent arteriole vasoconstriction. Its role is important to limit the hyperfiltration in case of high glomerular perfusion pressure. In SA-AKI, TG

feedback is inappropriate due to high chloride presentation at distal nephron because of decreased chloride reabsorption at the proximal renal tubule. This results in overt afferent arteriole vasoconstriction. Marked arteriole vasoconstriction in combination with systemic hypotension causes profound decline in GFR [37].

Tubular cell tight junction disturbance (tubular back-leak) is in the leak-back of non-selective ultrafiltration and ions from renal luminal site into basolateral portion. In SA-AKI, TJ is one of the target actions of endotoxin. Eadon et al. demonstrates direct structural damage of LPS at TJ. The injury of TJ, as determined by the injury at zonula occludens-1 (ZO-1) and claudins, is too severe to explain with LPS-induced-hemodynamic disturbance alone [38]. The tubular back-leak from TJ damage reduces UO by (i) reduced urine volume due to the leaking back of urine into circulation, (ii) increasing intra-renal pressure (renal intracapsular pressure or nephrosarca) [39], and (iii) cell debris-induced tubular lumen obstruction, tubular TJ damage, and abnormal TG feedback mechanisms. The reduction of GFR in SA-AKI also associates with altered glomerular permeability due to inflammation and endotoxins-induced direct glomerular endothelium damage [40, 41]. Nevertheless, the exact mechanisms of glomerular endothelium injury in human remain unknown.

Additionally, an alteration of renal microcirculation might be a physiologic mechanism that aims to limit oxygen and nutrition of organisms. Melican et al. [42] demonstrated, in a urosepsis model, that renal ischemia facilitates bacterial isolation and defends against organisms in sepsis. The suppression of intravascular coagulation by heparin causes fatal urosepsis despite improved microvascular architectures.

5.2. Renal endothelial cells injury

Renal endothelial cells and its function play a central role in microcirculatory dysfunction during sepsis. Sepsis-induced systemic inflammatory cytokines activate endothelium cells and initiate the inflammatory process [41]. Moreover, sepsis induces hypercoagulable state in vessels at both micro- and macroscopic levels. In animal SA-AKI model, Drake et al. demonstrates an increased expression of tissue factor by glomerular endothelial cells in *Escherichia coli* sepsis [43]. The hypercoagulable state in SA-AKI also contributes to localized ischemia and hypoxia in the related intravascular thrombosis area, even though GFR is preserved [42].

Endothelial nitric oxide (NO) synthase (eNOS) induces NO which inhibits platelet aggregation and leukocyte activation. During sepsis, there is depletion of eNOS and activation of inducible NO synthase (iNOS). While eNOS has been shown to attenuate tissue ischemia, iNOS released from activated leukocytes and vascular smooth muscle cells causes vascular dysfunction [44, 45]. Langenberg et al. has recently demonstrated that NOS isoforms increase significantly in SA-AKI, particularly in renal cortex more than in medulla [46]. This may potentially lead to medullary ischemia due to intrarenal shunting.

5.3. Mitochondrial cell dysfunction, autophagy, and apoptosis

Mitochondria are organelles found in every cell and are very prominent in cells of energetic organs including kidney. They are known as the powerhouses of cells. Renal mitochondria are

most densely concentrated due to the high and constant demand for adenosine triphosphate. Indeed, lack of cell energy and mitochondrial injury is demonstrated in several organs in sepsis [47]. Normally, mitochondrial dynamics is described as characteristics of "fission"and "fusion."The mitochondrial fission, a cleavage of the defective parts of a mitochondrion, may be important for the maintenance of healthy organelles and necessary for mitochondria distribution to daughter cells during cell division. On the other hand, mitochondrial fusion is the multiple steps fusion between adjacent mitochondria to improve their functions. Both mitochondrial fission and fusion facilitate inter-mitochondria exchanges of metabolites and substrates to maintain the optimal functions that are essential to cell viability [48].

Autophagy is a cellular process by which cytoplasmic organelles are sequestered and delivered to lysosomes for the proper degradation. Therefore, it plays a crucial role in intracellular nutrient turnover, cell differentiation, cellular homeostasis, and viability [49]. But the overactivity of autophagy, however, may cause cell injury or death. In mouse models of SA-AKI, autophagy is rapidly induced and plays important roles in renoprotection [50]. Because mitochondria are prokaryote inhabited inside eukaryotic cell in symbiosis relationship, the breakdown of mitochondria will release several prokaryotic molecules that are capable of inflammatory activation as other pathogen-associated molecular patterns (PAMPs). Hence, the autophagy on mitochondria, as referred to mitophagy, protects unnecessary inflammatory responses and recycles nutrients from the injured mitochondria. In the same line with apoptosis, autophagy is the process that requires enough cell energy. In the condition with the excess injured-mitochondria for autophagy, some mitochondria rupture and mitochondrial cytochrome C further activate cell apoptosis. As such, if there are too many apoptotic bodies to clear by phagocytic cells, apoptotic cells will progress into secondary necrosis where the rupture of its membrane induces prominent inflammation. Hence, mitophagy is also postulated to be another cytoprotective process to control cellular metabolism through the balance in number of mitochondria. Mitophagy is linked to mitochondrial dynamics—fission and fusion—through the surveillance and clearance mechanisms [51].

Taken together, it is conceivable that during the early phase of SA-AKI, mitophagy is increased to control and clear the damaged mitochondria. However, as sepsis progress, the autophagy may be overwhelmed by injured mitochondria, and/or the autophagic processes are disrupted, leads to the abnormal cell functions. Therefore, well homeostasis of intracellular mitochondria to restore healthy mitochondrial mass may be essential for renoprotection and the recovery of renal function in SA-AKI.

5.4. Cell cycle arrest

Cell cycle arrest is a protective mechanism to avoid entering the cell cycle during injury [52], thereby temporarily arresting cell cycle at G_1 stage for reducing cell damage. In cecal ligation and puncture septic model and folic acid-induced AKI, cyclosporine A, a known cell cycle arrest inducer attenuates AKI [53, 54].

In human, Kashani and colleagues propose biomarkers of cell cycle as an early biomarker of AKI [55]; tissue inhibitor of metalloproteinases-2 (TIMP-2), a natural inhibitor of the group of matrix metalloproteinase, and insulin-like growth factor-binding protein 7 (IGFBP7). IGFBP7

regulates the availability of insulin-like growth factor and stimulates cell adhesion. In addition, both TIMP-2 and IGFBP7 are responsible for several molecular pathways, including oxidative stress, detoxification, and inflammatory responses. Therefore, they represent the early stage of any stresses that affect kidney. After tubular cells injury, IGFBP7 directly increases the expression of p21 and p53. Simultaneously, TIMP2 enhances p27 expression through an autocrine and paracrine manners. All of these p-proteins block the functions of the cyclin-dependent protein kinase complexes (CyclD-CDK4 and CyclE-CDK2) during the cell-cycle promotion process. G1 cell-cycle arrest occurs momentarily for avoiding cell division during the injury, and this alarm could send to adjacent cells as paracrine effect. This mechanism needs further exploration. More recently, a new interesting hypothesis mentioned that all of the injuries are the results of the cell maladaptation to an insufficient energy condition [56]. More studies are needed to support this interesting hypothesis.

In the real clinical situations, multiple mechanisms in combination might be responsible for the individual patient. Therefore, a mechanistic approach to patients with SA-AKI needs the integration and understanding of these mechanisms. The biomarkers for detecting these events might be helpful for sepsis mechanistic approach in the future.

6. Clinical approach to SA-AKI

Clinical presentation of SA-AKI is completely uncertain especially in the early phase of sepsis. SA-AKI may develop simultaneously with sepsis or follow by sepsis. Therefore, physicians must be alert of SA-AKI when encountering with sepsis patients and *vice versa*—during evaluation of patients with AKI. In clinical practice, the individual baseline characteristics of patients are very useful for the proper SA-AKI management. Signs and symptoms of sepsis in individual patients depend upon individual susceptibilities and are usually masked by the organ involvement. As mentioned earlier, the SA-AKI diagnosis depends on SCr (absolute increase of SCr concentration of 0.3 mg/dL over 48 h or a relative change in SCr concentration of 1.5- to 1.9-fold to baseline over 7 days) or UO (less than 0.5 mL/kg/h for 6 h). SCr measurement, however, is insensitive indicator of AKI due to the time dependence accumulation. In mice with bilateral nephrectomy, SCr increases from baseline as late as 12–18 h after surgery [33]. According to SCr half-life ($t_{½}$), increments in SCr concentration lag the decrements in GFR by an hour. In addition, sepsis leads to the reduction in muscular production of creatinine from inflammatory process. And diuretic administration in AKI for promoting the non-oliguric phase results in the unreliable UO criteria. Thus, other biomarkers in addition to SCr and UO are required. Urine analysis and urine biochemistry indices may be useful as adjunctive biomarkers to support or differentiate SA-AKI. The presence of urine granular cast and renal epithelial cells is not only for the differentiation between pre-renal AKI and ATN but also for SA-AKI versus non-septic AKI [57]. Urinary sediment examination remains a classic, cost-effectiveness, and worthwhile method for the differentiation of AKI etiologies. By contrast, urine chemistry indices including urine sodium (U_{Na}), fractional excretion of sodium (FE_{Na}), and fractional excretion of urea (FE_{urea}) are beneficial for the differentiation of pre-renal AKI from acute tubular necrosis (ATN) but unfortunately unable to differentiate between SA-AKI

versus non-septic AKI. However, Vanmassenhove et al. [58] demonstrates that low FE_{Na} and low FE_{urea} are predictive of transient AKI and oliguria is predictive for impending AKI in early sepsis. Although some studies demonstrate the benefit of urine chemistry indices in SA-AKI, there is still no established urine chemistry test to differentiate SA-AKI from non-septic AKI.

As such, the quest for novel biomarkers as an earlier assessment tool for detecting SA-AKI is crucial. Such biomarkers are categorized into two groups: (i) the determination of renal functions and (ii) the detection of renal cell injury. Some lists of candidate new biomarker of SA-AKI are cystatin C (Cys-C), neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), interleukin-18 (IL-18), liver-type fatty acid-binding (L-FABP), soluble-triggering receptor expressed on myeloid cells-1 (sTREM-1), and activating transcriptional factor 3 (ATF-3). The sensitivity and specificity of these biomarkers vary depending on the timing of measurement and clinical samples. Generally, blood (serum) biomarkers show a lower sensitivity for AKI diagnosis than urinary biomarkers [59, 60]. NGAL is currently the most considered biomarker in AKI. However, it is non-specific to AKI and may be increased by activated neutrophils due to the response of systemic infection. We have demonstrated the benefit of NGAL and Cys-C in SA-AKI with bilateral nephrectomy and bilateral ureter obstruction models [33, 61]. Cys-C is generated from all nucleated cells and NGAL produced from several organs (lung, heart, kidney, and spleen). Because NGAL is reabsorbed from proximal tubules but produced from distal renal tubules [62], NGAL is not only a biomarker of proximal tubular function but also a biomarker of renal injury. Although both molecules are not specific for kidney, NGAL and Cys-C increase more rapidly than SCr after bilateral nephrectomy, possibly due to the more intrinsic sources in the body than SCr. While SCr is generated from muscle due to the utilization of creatine, these molecules are generated from several organs including muscle. It is interesting to note that renal NGAL, as determined by Western blot analysis, after bilateral ureter obstruction, does not increase as rapidly as serum NGAL [33]. This implies the possible limited utilization of kidney-specific NGAL (monomeric form of NGAL) for SA-AKI diagnosis. It is also interesting to note that sepsis does not enhance the production of creatinine, NGAL and Cys-C. SCr and Cys-C after CLP in bilateral nephrectomized mice are lower than CLP in normal mice. And serum NGAL in bilateral nephrectomized mice is not different to the level of CLP in normal mice [33]. In this aspect, among these biomarkers, SCr has several limitations and NGAL is the best representative for SA-AKI in these mouse models.

For other biomarkers, urine IL-18 is a cytokine that respond not only to AKI but also to inflammation and infection. Urine L-FABP has been reported as a good predictor of mortality in patients with sepsis in ICU and shows the significant higher level in SA-AKI in comparison with sepsis-non-AKI [63]. In addition, urine exosome is another interesting source of candidate AKI biomarkers. Exosome is the nanosize vesicle containing molecules from cytoplasm or nuclei surrounded by some parts of cell membrane [62, 64–66]. Exosome is another mechanism of cell-cell communication possibly aiming to deliver non-soluble molecules and/or ligands of cell membrane receptor. As such, MHC-containing exosome could activate other immune cells in a distance without the necessary for the close proximity activation [64]. Moreover, several rapid-degradable molecules (RNA, miRNAs) or molecules of intra-nuclei (e.g., transcriptional factors) could be protected and delivered by exosome. Likewise, our group recently demonstrates the role of urine exosomal ATF-3 as a good additional biomarker

for determining the onset of AKI in sepsis [62]. The summary of promising urine and serum biomarkers for SA-SKI is shown in **Table 1**. Although only a single biomarker might be already useful for SA-AKI determination, the combination would be even more beneficial in the clinical practice. For examples, an increase in biomarkers of injury but not biomarkers of renal function could represent subclinical AKI (normal SCr). And an increase in functional biomarkers but not biomarkers of cell injury may represent CKD. More studies are needed.

The discovery of early biomarker of SA-AKI not only improves the clinical management strategies but also adds up the understanding in the pathophysiology of SA-AKI. Unfortunately, SA-AKI pathophysiology in patients is not straightforward. Several comorbidities and the exposure to other AKI inducers (radiologic contrast-media (contrast-induced nephropathy), antibiotics (nephrotoxic ATN or acute interstitial nephritis), and hypotensive state (ischemic ATN) enhance the complexity of sepsis in patients. Hence, the major molecules responsible for SA-AKI in each patient might be different and the different approach and therapies might be necessary. For an example, SA-AKI with the predominant of HMGB1 versus high activated protein C might require the different managements. Therefore, it might be difficult to recognize the molecular responses of SA-AKI only by patient history or current biomarkers. More serum, urine, or tissue biomarkers should be beneficial. Thus, appropriate techniques of renal biopsy in an appropriate time point of SA-AKI might be helpful for an early diagnosis and exploration of the individual molecular responses. This approach could be one of the strategies for "sepsis-individualized therapy." As such, numerous renal biopsy techniques have high yields, safe and effortless [67, 68]. The studies of renal biopsy in the selected case of patients with AKI will be very interesting.

In addition, the interpretation of some non-renal biomarkers in AKI should be cautious. For examples, cardiac troponin I, a biomarker of cardiac muscle injury, is usually high in patients with abnormal renal function [69]. Troponin I of >0.8 ng/dL or the alterations from baseline level or additional use of other biomarkers (e.g., myocardial creatinine kinase; CKMB) might be helpful to determine cardiac cell injury. Fluid status in SA-AKI could affect N-terminal pro-B-type natriuretic peptide (NT-BNP) and troponin T [70]. We also explore microRNA-122 (miR122), a new liver injury biomarker, in several mouse models including sepsis [71]. We found that miR-122 is not superior than alanine transaminase (ALT) for the detection of sepsis-induced liver injury.

Indices	Timing of measurement	AUROC	Threshold values	Sensitivity	Specificity	References (year)
Urine biomarker(s)						
NGAL[a] (ng/mg creatinine)	12-h following septic shock	0.86	>68	0.71	1.0	Martensson et al. [72] (2010)
sTREM-1[a] (pg/mL)	48-h before AKI diagnosis*	0.92	69.04	0.94	0.76	Su et al. [73] (2011)
Cys-C[a] (mg/L)	Within 8 days after admission	0.86	0.106	0.85	0.80	Aydoğdu et al. [60] (2013)
NGAL[a] (ng/mL)		0.80	29.5	0.88	0.73	

Indices	Timing of measurement	AUROC	Threshold values	Sensitivity	Specificity	References (year)
NGAL[a] (ng/mL)	7 days after onset of sepsis	0.86	402	0.89	0.74	Fan et al. [74]
NGAL[a] (ng/mL)	24 h after admission	0.78	350	0.75	0.82	Matsa et al. [75] (2014)
α1m[a] (mg/L)	24 h before AKI onset	0.74	47.9	0.88	0.62	Terzi et al. [76] (2014)
Cys-C[a] (mg/L)	24 h before AKI onset	0.74	N/A	N/A	N/A	Dai et al. [77] (2015)
NGAL[a] (ng/mL)		0.88	N/A	N/A	N/A	
sTREM-1[a] (pg/mL)		0.78	N/A	N/A	N/A	
ATF3[b] (ng/mL)	24 h before AKI onset	0.84	12	0.93	0.85	Panich et al. [62] (2017)
NGAL[b] (ng/mL)		0.64	150	0.98	0.44	
Serum or plasma biomarker(s)						
NGAL (ng/mL)	12 h following septic shock	0.67	>120	0.83	0.50	Martensson et al. [72] (2010)
Cys-C (mg/L)	Within 8 days of admission	0.82	1.5	0.73	0.68	Aydoğdu et al. [60] (2013)
NGAL (ng/mL)		0.44	N/A	N/A	N/A	
NGAL (ng/mL)	24 h after admission	0.88	400	0.79	0.75	Matsa et al [75](2014)
Presepsin (pg/mL)	Within 24 h of admission	0.70	670	0.70	0.81	Nakamura et al. [78]
Procalcitonin (ng/mL)	Within 24 h of admission	0.88	0.42	0.95	0.65	Nakamura et al. [79] (2015)
Cys-C (mg/L)	24 h before AKI onset	0.74	N/A	N/A	N/A	Dai et al. [77] (2015)
NGAL (ng/mL)		0.83	N/A	N/A	N/A	
sTREM-1 (pg/mL)		0.75	N/A	N/A	N/A	

α1m, alpha-1-microglobulin; AKI, acute kidney injury; ATF3, activating transcriptional factor 3; AUROC, area under the receiver operating characteristic curve; Cys-C, cystatin-C; N/A, data not available; NGAL, neutrophil gelatinase-associated lipocalin; sTREM-1, soluble-triggering receptor expressed on myeloid cells-1.

*No data were available 24 h before AKI onset.

[a]Detection from urinary soluble fraction part.

[b]Detection from urinary exosomal part.

Table 1. Summary of the published studies in early urine and plasma biomarkers for detecting SA-AKI.

7. Managements

Similar to general managements in sepsis, SA-AKI treatment bases upon the rapidly appropriate antibiotic administration and best supportive cares. Here, we summarized the important points in SA-AKI management.

7.1. Fluid therapy

Fluid administration is the corner stone of resuscitation especially in sepsis. Theoretically, fluid responder defines by a patient whose stroke volume (SV) increases by 10–15% after a fluid challenge (250–500 mL) [80], but less than 40% of septic patients are fluid responders [81]. According to Frank-Starling principle, as the preload increases, SV increases until the optimal preload is achieved. Thus, if the fluid challenge does not increase SV, the amount of volume loading would be harmful from the increase in arterial pressure, venous pressure, and, in the end, pulmonary hydrostatic pressures. Moreover, these responses stimulate the release of natriuretic peptide that induces fluid shift from intravascular portion into interstitial space. Of note, kidney is also particularly affected by increased venous pressure resulting in increased renal subcapsular pressure and decreased GFR.

"Fluid expansion as supportive therapy" (FEAST) is the most explicit study that demonstrates the harmful of fluid loading in sepsis [82]. In this randomized study, aggressive fluid loading is associated with an increased risk of death. After the concept of early aggressive fluid resuscitation—"early goal directed therapy" (EGDT)—published in 2001 [83], a number of studies using EGDT protocol have been published subsequently [84–86]. Interestingly, these studies show an obvious reduction in mortality rate, especially during 2010–2015, which associates with the decline in the volume of fluid resuscitation in the first 72 h. Although the fluid resuscitation in an early phase of sepsis with a significant decrease in effective circulatory volume sounds reasonable, the ongoing fluid maintenance therapy remains in trouble, particularly in SA-AKI [87]. Fluid therapy, moreover, is not only incapable of effective reverse septic shock but also contribute to the more renal dysfunction through several mechanisms. For instance, an increased venous pressure following fluid therapy directly increases pressure in renal interstitium and peritubular area in animal models [88]. Because a large fluid bolus (20–30 mL/kg) is associated with volume overload, the approach with the less volume of fluid bolus (200–500 mL) is currently recommended [89]. Acute dialysis quality initiative (ADQI) suggests the approach of fluid therapy in sepsis by dividing into four stages: rescue, optimization, stabilization, and de-escalation [5]. High-volume resuscitation is needed during the rescue stage followed by optimization and stabilization protocol depending on the individual patient. After that, the de-escalation consists of reduced total fluid water in patients where diuretics and/or renal replacement therapy (RRT) might be necessary. Regarding fluid therapy monitoring, passive leg-raising maneuver (PLR) after fluid bolus combined with the real-time SV measurement is the only procedure with a high clinical accuracy of fluid status [80, 89]. Due to the availability of ultrasonography in most of the ICUs, the exclusion of fluid overload by the real-time detection of B-line and abnormal curtain sign in the lung, the vena cava collapsibility by M-mode ultrasonography, and the abnormalities in cardiac function is noninvasive

and might be helpful as the additional information in the real clinical situation. But these procedures are operator dependent that need a special training. Nevertheless, physical examination, central venous pressure (CVP), central venous oxygen saturation ($ScvO_2$), chest radiography, and the vena-caval collapsibility index by ultrasonography show limited value in fluid monitoring and is not generally recommended for fluid challenge purpose [90–92]. It might be important to note that in patients with previous normal blood pressure, the mean arterial pressure (MAP) at 65–70 mmHg might be adequate for maintaining renal perfusion. But MAP at 80–85 mmHg might be needed in patient with a history of hypertension [93]. Moreover, serum lactate should be less than 2 mmol/L. The new definition of septic shock from the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3), the stage with the need of vasopressor from maintaining MAP ≥65 mmHg and serum lactate more than 2 mmol/L, implies the importance of serum lactate and vasopressor in clinical practice [1].

In addition to the amount of volume, fluid composition is another issue that must be considered in SA-AKI. Normal saline (0.9% NaCl), a non-physiologic solution, is possibly less beneficial in SA-AKI than other new fluid preparations. Normal saline causes a hyperchloremic metabolic acidosis resulting in decreased renal blood flow (by activation of TG feedback mechanisms and afferent vasoconstriction) and increases the risk of further renal injury [94, 95]. Moreover, normal saline is associated with an increased risk of death in comparison with physiologic salts solution. Similarly, synthetic hydroxyethyl starch is potentially nephrotoxic and not recommended in SA-AKI patients [96]. Blood transfusion is used to improve microcirculatory hemoglobin and tissue oxygenation. However, the results of blood transfusion in reducing morbidity and mortality remain inconclusive [96, 97]. Despite theoretical disadvantage of normal saline in SA-AKI, the result from randomized control trial is still controversy. Moreover, normal saline is generally available in a reasonable price worldwide. Thus, normal saline should still be a main fluid replacement used in SA-AKI. However, the alternative administration of normal saline with other fluid preparations or the limited volume of normal saline might be more beneficial. Recently, Steward approach on acid-base proposed the ratio of serum chloride/sodium (S_{Cl}/S_{Na}) at higher than 0.76 as the indication of chloride access and the timing for the replacement of normal saline into other solutions [98]. More studies are needed.

7.2. Control of acidosis

Acidosis is common in patients with sepsis which might be due to lactic acidosis, respiratory acidosis, and/or hyperchloremic metabolic acidosis from high volume of normal saline. But bicarbonate treatment is not recommended unless blood pH is lower than 7.15. Sodium bicarbonate infusion leads to hypernatremia, hypervolemia, intracellular shift of calcium-induced hypocalcemia, intracellular acidosis, and impaired oxygen delivery [99]. Improved tissue perfusion, proper respiratory machine adjustment, and balance administration of high-volume normal saline with other fluid therapy (e.g., other balance solutions) should be helpful. Tris-hydroxy methyl amino methane (THAM), a weak base with intracellular diffusion, might be beneficial due to the lower intracellular acidosis in comparison with bicarbonate infusion. However, THAM causes hyperkalemia, hypoglycemia, pseudohyponatremia, and increased osmolol gap in patients with preexisting renal dysfunction due to the excretion through kidney [100].

7.3. Antibiotics and other nephrotoxic

The rapid control organism is still the main theme of sepsis treatment. The survival rate of patients with sepsis declines 7.6% for every hour of delayed appropriate antibiotic treatment [101]. Regarding AKI from antibiotic, vancomycin is reported to induce AKI despite appropriate therapeutic level (15–20 mg/dL; the recommended level for the treatment of methicillin-resistance *Staphylococcus aureus* (MRSA)). Vancomycin is also reported to enhance nephrotoxic of piperacillin-tazobactam [102]. Although these events might be due to the contaminants, vancomycin administration in a high dose should be careful and blood level monitoring might be helpful. Other unnecessary nephrotoxic substances, such as amphotericin B, iodinated contrast agents, and so on, should be avoided. In addition, there is only a report of gadolinium (a contrast for MRI)-induced AKI [103] but several reports on increase incidence of nephrogenic systemic fibrosis in gadolinium injection in patients with preexisting renal injury.

7.4. Vasopressors

In SA-AKI, the alteration of vascular tone is a major cause of hypotension and renal injury. Norepinephrine maintains mean arterial pressure and increases renal medullary circulation without RBF alteration leading to improved renal function both in animal models and in human [93, 104–106]. Norepinephrine also restores normal capillary velocity and filtration pressure [107]. Thus, norepinephrine is the first-line drug for septic shock. On the other hand, iloprost, a vasodilatory prostacyclin, has been considered to reduce cortical microcirculatory hypoxia and preserve renal function in animal model of SA-AKI [108]. But the clinical data on the efficacy and safety of iloprost administration are still limited.

7.5. Renal replacement therapy

The general four concerning aspects of renal replacement therapy (indications, timing, modality, and delivered dose) and the traditional clinical indications of RRT ("A-E-I-O-U"; A-acidosis, E-electrolyte disturbance, I-intoxication, O-fluid overload, and U-uremia) should be applied to SA-AKI as other causes of AKI. Indeed, severe metabolic acidosis, fluid overload, and uremia are the top three common indications for RRT in SA-AKI.

Regarding the timing of RRT initiation, the data are heterogeneous, inconclusive, and centers dependence. Although adverse effect of delayed RRT initiation has been reported with a higher mortality rate and worse renal outcome in SA-AKI [109], many consensus guidelines remain set as individual timing based on the only published randomized controlled trial. Bouman et al. [110] demonstrated non-significant differences in renal outcomes or patient survival between early and late initiation of hemofiltration. As such, the recently two large, high-profile randomized trials, specifically designed for the determination of RRT initiation in patients with AKI and critically ill condition, show the discordant conclusions [111, 112]. Single-center early versus late initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury (ELAIN) demonstrates the benefit of an early strategy of RRT initiation over a delay strategy in the mortality rate of critically ill patients [113]. Although eligible patients are at KDIGO stage 2, they have high sequential organ failure assessment

(SOFA) score at 15.6–16.0. On the contrary, the artificial kidney initiation in kidney injury (AKIKI) study shows a negative result for early strategy of RRT initiation [114]. But patients enrolled in the AKIKI trial are at KDIGO stage 3 with SOFA score at 10.8–10.9 which is lower than the patients in ELAIN study. In addition, SOFA score in the renal component in AKIKI trial is also less than ELAIN study. Therefore, these two studies may have come to different conclusions because of the different inclusion criteria. The patients enrolled in the ELAIN trial are at an earlier AKI stage but more severe sepsis. Nevertheless, another trial for answering the optimal RRT timing is now ongoing—STARRT-AKI (standard vs. accelerated initiation of renal replacement therapy in acute kidney injury) study; *clinicaltrial.gov* NCT02568722.

The choice of hemodialysis (HD) modality for patients with SA-AKI is also important to mention. Although the best choice of HD modality in SA-AKI remains inconclusive, only some studies showed the benefit of continuous renal replacement therapy (CRRT) over intermittent hemodialysis (IHD) in survival and duration before renal recovery [115, 116]. Regarding CRRT in SA-AKI setting, continuous venovenous hemofiltration (CVVH) has recently demonstrated the promising results in comparison with extended daily hemofiltration (EDHF) [115]. Despite more severe sepsis (oliguria and severity of metabolic acidosis) of patients in CVVH group, they have a superior renal outcome on 60-day dialysis independence periods. However, a retrospective cohort study by AlEnezi et al. showed that CVVH does not attenuate mortality and length of hospital stay in comparison with continuous venovenous hemodiafiltration (CVVHDF) [116].

Although the benefit of renal recovery is superior in CRRT, over IHD, owing to the better fluid control with the fewer hypotensive episodes, CRRT is more expensive. On the other hand, on-line hemodiafiltration (Ol-HDF), an intermittent hemodialysis modality that increase mid-to-large molecular clearance by combining diffuse and convective transport with ultrapure dialysate, is a promising alternative modality for SA-AKI. Data from our study demonstrated that Ol-HDF not only benefits in renal support but also offers a potential role in immune modulation in SA-AKI [117]. The comparison of beneficial effects on renal outcomes and patient survival between CVVH and Ol-HDF in SA-AKI patients is ongoing in our center.

In addition, optimal CRRT dose is evaluated in two clinical trials with nonspecific causes of AKI at an effluent rate of 25–30 and 40 mL/kg/h [118–120]. Although there is a tendency toward the reduced mortality rate in the higher dose of CRRT (40 mL/kg/h), it is not enough to reach a significant level. Likewise, the CRRT prescription dose at 30–35 mL/kg/h or 25% addition to the usual dose of CRRT is recommended by some centers to ensure an adequate delivered dose [121]. By theory, delivered CRRT dose over 35 mL/kg/h as known as "high-volume hemofiltration" may remove systemic inflammation and improve septic shock survival, but it is not supported by several clinical studies.

It seems that CVVH has more benefit than IHD only in limited parameters with a significantly higher cost. Hence, we recommend IHD or sustained/slow low-efficiency dialysis (SLED) as a first choice of RRT modality followed by standard dose of CVVH (20–25 mL/kg/h) in SA-AKI depending on patient conditions. In addition, in the area with the limited resources, with less severe sepsis, and/or without other choices of RRT, peritoneal dialysis (PD) might be an alternative RRT modality [122]. However, the adequacy of PD in sepsis and the high

glucose level in peritoneal dialysate is the major limitation of PD in sepsis. On the other hand, extracorporeal blood purification (EBP) is currently considered as one of the treatments for balancing homeostasis of sepsis immune responses. The absorption therapy with polymyxin B or other cytokine absorbents shows benefit in hemodynamic parameters and mortality rate in some studies [123] but still inconclusive. Therefore, the specific indication and/or proper biomarkers (i.e., stress-, injury-, functional loss-, and recovery biomarkers) to select patients with the highest probability to be beneficial from any treatment methods are urgently in need [124].

8. Conclusions

Sepsis is often accompanied by acute renal failure, also called sepsis-associated acute kidney injury. The mechanisms by which sepsis and endotoxemia lead to SA-AKI are incompletely understood. However, growing evidences suggest that SA-AKI is a result of sustained renal microvascular hypoperfusion, insufficient cell energy, mitochondria dysfunction, endothelial injury, and cell cycle arrest. SA-AKI is associated with normal or even elevated renal blood flow, which is, at least in part, due to redistribution of blood flow from cortical to medullary region. Fluid therapy and proper antibiotics are crucial managements. Because too much fluid administration in sepsis increase organ dysfunction, hemodynamic-guided approach of fluid therapy and early vasopressor administration in SA-AKI would be beneficial. Currently, the role of renal replacement (RRT) in SA-AKI for renal support and immunomodulation has been evaluated. Although there is no consensus guideline, retrospective clinical studies have suggested that the early initiation of RRT and the use of continuous methods are associated with a better hemodynamic tolerance and renal outcome. Timing and dose of RRT are ongoing debate, yet recently randomized clinical trials remain unable to demonstrate any beneficial impacts of early RRT. In the future, we propose "sepsis mechanistic approach" as an individualized therapy for sepsis and the better matching between the results from the translational researches and the specific patient characteristics.

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