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REVIEW ARTICLE

Sepsis and Renal Replacement Therapy

Sarinya Boongird, Supawadee Suppadungsuk, Sarassawan Kananuraks and Arkom Nongnuch*

Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Renal Unit, Mahidol University, Bangkok, Thailand

***Corresponding author:** *Arkom Nongnuch, Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Renal Unit, Mahidol University, Bangkok, Thailand, E-mail: oatega@yahoo.com*

Introduction

Sepsis-associated acute kidney injury

Sepsis has long been recognized as the most common cause of Acute Kidney Injury (AKI), present in approximately 11-40% of patients who are admitted to intensive care units [1,2]. Sepsis-Associated Acute Kidney Injury (SA-AKI) is associated with worsened outcomes including longer hospital stays, greater disturbance in hemodynamics and laboratory parameters, and higher healthcare costs when compared to septic patients without kidney injury [3,4]. The severity of sepsis increased the incidence of AKI in a stepwise pattern [5,6]. In comparison with non-septic AKI, patients with SA-AKI carries greater severity of illness, indicating by higher Sequential Organ Failure Assessment (SOFA) scores [1], and require more hemodynamic supports with vasoactive agents and more aggressive fluid resuscitation [1,7,8].

Conversely, acute kidney injury itself is also a risk factor for developing sepsis [9]. The current AKI diagnostic criteria and staging system based on acute changes in urine output and serum creatinine level, proposed by Kidney Disease Improving Global Outcomes (KDIGO) group in 2012 [10], modified form Acute Kidney Injury Network (AKIN) and RIFLE criteria [11,12], is well-accepted among nephrology and critical care communities. These diagnostic criteria and staging system are applicable to AKI from any causes, including sepsis (Table 1).

Despite improvements in new interventions and supportive treatments in the last decade, the mortality rate from SA-AKI remains unacceptably high, around 40% [9]. Not only associated with detrimental short term outcomes, survivors from sepsis induced acute kidney injury also have an increased risk of developing progressive long-term renal function decline, resulting in chronic kidney disease. In this review, we aim to

Table 1: KDIGO, RIFLE, and AKIN AKI diagnostic criteria.

	Serum creatinine criteria			Urine output
AKI stage	**KDIGO**	**RIFLE**	**AKIN**	
1 (R)	Increase ≥ 0.3 mg/dl within 48 h or ≥ 1.5- to 2-fold from baseline	Increase × 1.5 baseline or GFR decrease > 25%	Increase 1.5-1.9 times from baseline or ≥ 0.3 mg/dl increase within 48 h	< 0.5 ml/kg/h for 6-12 h
2 (I)	2.0-2.9 times from baseline	Increase × 2 from baseline or GFR decreased > 50%	Increase > 2- to 3-fold from baseline	< 0.5 ml/kg/h for 12 h
3 (F)	3.0 times from baseline or increase in serum creatinine to ≥ 4.0 mg/dl or initiation of renal replacement therapy or, in patients < 18 years, decrease in eGFR to < 35 ml/min per 1.73 m^2	Increase × 3 from baseline, or serum creatinine > 4 mg/dl) with an acute rise > 0.5 mg/dl or GFR decreased > 75%	Increased > 300% (> 3-fold) from baseline, or ≥ 4.0 mg/dl with an acute increase of ≥ 0.5 mg/dl or on renal replacement therapy	< 0.3 ml/kg/h for 24 h or anuria for 12 h

R: Risk; I: Injury; F: Failure; KDIGO: Kidney Disease Improving Global Outcomes; RIFLE: The Risk, Injury, Failure, Loss, End-Stage; AKIN: Acute Kidney Injury Network.

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Table 2: Sequential or Sepsis-related Organ Failure Assessment (SOFA score).

Organ system	Score				
	0	1	2	3	4
Respiration: PaO_2/FiO_2 (mmHg)	≥ 400	< 400	< 300	< 200	< 100
Coagulation: Platelets (× 10^3/μL)	≥ 150	< 150	< 100	< 50	< 20
Liver: Bilirubin (mg/dl)	< 1.2	1.2-1.9	2.0-5.9	6.0-11.9	> 12.0
Cardiovascular:	MAP ≥ 70 mmHg	MAP < 70 mmHg	Dopamine < 5 or dobutamine (any dose)[a]	Dopamine < 5.1-15 or epinephrine ≤ 0.1 or norepinephrine ≤ 0.1 (any dose)[a]	Dopamine > 15 or epinephrine > 0.1 or norepinephrine > 0.1 (any dose)[a]
Central nervous system: Glasgow Coma Scale score	15	13-14	10-12	6-9	< 6
Renal: Creatinine (mg/dl) or	< 1.2	1.2-1.9	2.0-3.4	3.5-4.9	> 5.0
Urine output (mL/d)				Urine < 500	Urine < 200

[a]Catecholamine doses are given as μg/kg/min for at least 1 hour.

summarize recent advances on different aspects of Sepsis-Associated AKI focusing on a new sepsis and roles of renal replacement therapy in Sepsis-Associated AKI.

New definition of sepsis

Recognizing several limitations of the previous definitions of sepsis, the Society of Critical Care Medicine and the European Society of Intensive Care Medicine have recently redefined sepsis in the year of 2016 as "life-threatening organ dysfunction caused by a dysregulated host response to infection" [13]. The first definition and clinical criterion of sepsis developed in 1991 by the same groups [14] focused mainly on systemic inflammatory response or the host compensatory anti-inflammatory response syndrome triggered by infection [15], which is a misleading concept and unable to predict a transition point in the risk of death [16]. In fact, sepsis is a clinical syndrome involving a complex interplay between a "dysregulated" systemic host response to an infection and pathogen factors. The consequences of the uncontrollable host's systemic response to infecting pathogen have resulted in distant organ dysfunctions such as depressed cardiac function, activation of coagulation cascades, and acute kidney injury [17]. Given the simplicity and widespread use of the Sequential [Sepsis-Related] Organ Failure Assessment Score (SOFA) in determining the extent of organ dysfunction, the task force recommends using an increment in baseline of the total SOFA score of 2 points or more to represent organ dysfunction (Table 2).

Renal Replacement Therapy

Renal Replacement Therapy (RRT) has been frequently used to support critically ill patients with SA-AKI. There are several aspects to consider before commencing and writing a prescription for RRT in any patients. Here, we will discuss current evidence regarding the timing of RRT initiation, the selection of the specific modality of RRT, and the intensity of RRT.

Timing of renal replacement therapy initiation

The optimal time to start Renal Replacement Therapy (RRT) in the setting of SA-AKI is still unknown. The conventional indications for commencing RRT in patients with AKI (refractory acidosis, severe hyperkalemia, uremia, oliguria/anuria, and volume overload unresponsive to diuretic therapy) have long been recognized and universally accepted by nephrologists. However, many believe that awaiting those life-threatening complications to evolve before commencing RRT are too late or relatively delayed for the disease process. Volume overload, electrolyte and acid-base derangements, and increment in inflammatory cytokines commonly occur in most SA-AKI patients. These insults cause further damage to the kidney and lessen the chance of renal recovery [18]. On the other hand, adopting the early initiation of RRT strategy on every case may expose patients whose their kidney function would recover spontaneously to the risks of unnecessary RRT and its inherent complications [19]. To deepen this issue, researchers have defined "early" initiation of RRT differently in each study. Despite conflicting results from observation studies on beneficial effects of early RRT approach [13,14], there are increasing trends toward earlier or pre-emptive use of RRT well before the development of advanced complications. The conundrum regarding the benefits of early RRT strategy and risks of unnecessary treatment will be unsolved research questions until we can find reliable methods or robust predictive markers to predict renal recovery.

Recently, there are 3 randomized controlled trials examining the optimal timing of RRT initiation published in major medical journals. Wald, *et al*. conducted a randomized open-label pilot trial comparing accelerated (12 hour or less once fulfilling the criteria for KDIGO stage 2 AKI) to standard RRT initiation in critically ill adults suffering from volume replete AKI [20]. There was no significant difference in 90-day survival or RRT-related complications between groups. Owing to a relatively small number of patients included in this pilot study (n = 101), the trial was underpowered to detect differences in mortalities or clinical outcomes. However, Wald and colleagues demonstrated the feasibility of implementing a protocol for design of a larger definitive trial. In early 2016, Zarbock and colleagues reported finding from their studies of "Effect of early vs. de-

Table 3: Theoretical advantages and disadvantages of different renal replacement modalities.

Techniques	Solute transport	Duration of therapy/session (hr.)	Advantages	Disadvantages
IHD	Diffusion	4	- Rapid removal of uremic toxins and small molecule clearance - Technically simple - Relatively low cost - Patients mobility	- Increased risk of hypotension and disequilibrium - Require vascular access and anticoagulant
PD	Diffusion	24	- Technically simple - Require less infrastructure - No anticoagulation required - Less hemodynamic instability - Relatively low cost	- Slow small molecule and uremic toxin clearance - Unpredictable fluid removal - Risk of peritonitis - May compromise respiratory function
PIRRT	Diffusion	6-12	- More rapid solutes and uremic toxin removal than CRRT, but slower than IHD - More hemodynamically stable than IHD - Technically simple - Relatively low cost - Patients mobility	- Require vascular access and anticoagulant - Risks of hypotension and disequilibrium
CVVHF	Convection	24	- Increased middle molecule and cytokines removal from convective technique - Continuous removal of uremic toxins and fluid - More hemodynamically stable than IHD	- Complex circuit - High cost - Require vascular access and anticoagulant and prolonged use of anticoagulant - Patient immobility
CVVHD	Diffusion	24	- Continuous removal of uremic toxins and fluid - More hemodynamically stable than IHD	- Complex circuit - High cost - Require vascular access and anticoagulant and prolonged use of anticoagulant - Patient immobility
CVVHDF	Diffusion and convection	24	- Increased middle molecule and cytokines removal from convective technique - Continuous removal of uremic toxins and fluid - More hemodynamically stable than IHD	- Complex circuit - High cost - Require vascular access and anticoagulant and prolonged use of anticoagulant - Patient immobility

IHD: Intermittent Hemodialysis; PD: Peritoneal Dialysis; PIRRT: Prolonged Intermittent Renal Replacement Therapy; CVVHF: Continuous Venovenous Hemofiltration; CVVHD: Continuous Venovenous Hemodialysis; CVVHDF: Continuous Venovenous Hemodiafiltration.

layed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury: the ELAIN study" [21]. This was a single-center randomized clinical trial conducted in Germany, comparing effects of Early (within 8 hours of reaching KDIGO stage 2 AKI; n = 112) to delayed (within 12 hours of stage 3 AKI or no initiation; n = 119) initiation of RRT to 90-day all-cause mortality in 231 critically ill patients. Patients in the early group had significantly lower 90-day mortality compared with the delayed group (an absolute risk reduction of -15.4% [95% CI, -28.1% to -2.6%]; P = 0.03). The early group also had more favorable secondary outcomes than the delayed group, including shorter duration of RRT, shorter hospital length of stay, and higher rate of renal recovery by day 90. Noticeably, this study not compare early RRT with conventional criteria leading to the incidence of RRT in this study are incredibly high as 90%, thus the certain number of patients might receive unnecessary dialysis. Surprisingly, Gaudry, *et al.* reported conflicting results of early-strategy compared with delayed-strategy RRT a month later. Gaudry and colleagues conducted a multicenter randomized trial in France, involving 620 patients with KDIGO stage 3 AKI who required mechanical ventilation, vasopressor, or both but did not develop life-threatening complications requiring immediate RRT. Gaudry assigned patients into either an early (RRT initiated immediately after randomization) or a delayed strategy of RRT (RRT initiated if reaching one of the following criteria: severe hyperkalemia, metabolic acidosis, pulmonary edema, blood urea nitrogen level higher than 112 mg per deciliter, or oliguria for more than 72 hours after randomization). The primary outcome, survival at day 60, was similar between groups (48.5% in the

early-strategy group and 49.7% in the delayed-strategy group, P = 0.79). Interestingly, about half of the patients in the delayed group did not receive RRT but had similar outcomes compared to those of patients who received it. More recently meta-analysis showed no benefits of early RRT on mortality and renal recover [22].

In summary, we need to interpret findings from these studies carefully before applying the results to real-world clinical practice by taking the study designs, baseline characteristics of participants, feasibility of implementing those protocols into consideration. Currently, the early initiation of dialysis is not recommended. Some ongoing clinical trials (NCT01682590, NCT02568722) may shed some light on this controversy.

Mode of renal replacement therapy

Hemodialysis (HD) and Peritoneal Dialysis (PD) have been primarily used to support SA-AKI patients for years. Diffusion is the main mechanism for uremic toxin and excess small solute removal for intermittent hemodialysis and peritoneal dialysis. In the past three decades, there have been several new evolving modalities of renal replacement therapy developed to overcome limitations or disadvantages of those main methods. The current dialysis armamentarium has expanded to various modalities of Continuous Renal Replacement Therapy (CRRT), intermittent hemofiltration/hemodiafiltration, and Prolonged Intermittent Renal Replacement Therapy (PIRRT). Hemofiltration and hemodiafiltration techniques rely on convective clearance and combination of convective and diffusive clearance, respectively, for solute and uremic toxins elimination.

CRRT *vs.* IHD: Applying convective solute transport to dialysis therapy enhances middle to large molecule solute clearance, pro and anti-inflammatory cytokine removal that play significant roles in sepsis. In addition, CRRT may seem more suitable for unstable critically ill patients than intermittent HD because of its longer operating time allowing greater fluid control, and better hemodynamic stability. The caveat of CRRT is anticoagulants usage to prolong circuit survival may aggravated bleeding in critically ill patients, thus regional anticoagulant may be the alternative options [23]. These notions have resulted in increased use of Continuous Venovenous Hemo Filtration (CVVHF) and Hemodiafiltration (CVVHDF) technique for potential immunomodulatory effect in hemodynamically unstable SA-AKI patients. Retrospective and observational studies from Europe and the United States reported a beneficial effect of CRRT on promoting renal recovery [24,25]. To date, the ideal modality to support SA-AKI remains controversial since prospective randomized controlled trials or meta-analysis trials have not shown a survival advantage with one particular modality [26-29]. Nevertheless, these data must be interpreted with caution due to wide heterogeneity of inclusion criteria, definition of AKI and selection bias among included studies. KDIGO has supported using CRRT as a preferable modality in patients with acute brain injury and hemodynamically unstable patients with AKI.

CRRT *vs.* PIRRT: Prolonged Intermittent Renal Replacement Therapy (PIRRT) is an extended hemodialysis treatment frequently performing over 6-12 hours per day. Since its longer operating time, this dialysis modality offers the opportunity to remove excess fluid more gradually with less hemodynamic instability comparing to conventional intermittent hemodialysis. Whereas CRRT is routinely operated continuously 24 hours a day, compromising patient's mobility and investigation, PIRRT provides a down time from dialysis facilitating rehabilitation and other aspects of care.

A prospective, randomized study from Japan comparing post-dilution Sustained Hemodiafiltration (SHDF) using acetate-free bicarbonate dialysate to Continuous Venovenous Hemodiafiltration (CVVHDF) with effluent rate of 25 ml/kg in critically ill patients with AKI, they found that patients in SHDF group had greater renal recovery rate and shorter length of hospital stay when compared with CVVHDF group. However, good outcomes in SHDF group, particularly better renal recovery, could be due to either dialysis strategy (SHDF *vs.* CVVHDF) or beneficial effects of acetate-free bicarbonate dialysate [30]. Schwenger, *et al.* conducted a prospective, randomized, interventional study comparing a 12 hr. Sustained Low Efficiency Dialysis using a Single-Pass Batch Dialysis system (SLED-BD) to a 24 h predilutional CVVH in renal replacement therapy dependent AKI patients admitted to a surgical intensive care unit in Germany. Whereas there was no difference in 90-day mortality between groups (SLED: 49.6% *vs.* CVVH: 55.6%, P = 0.43), patients in the SLED-BD group had significantly fewer days of mechanical ventilation (17.7 ± 19.4 *vs*. 20.9 ± 19.8, P = 0.047) and shorter time for renal recovery (P = 0.049) resulting in lower cost [31]. Meta-analysis study by Zhang, *et al.* comparing Extended Daily Dialysis (EDD), defined as HD or hemodiafiltration between 6 to 24 hours per session, versus CRRT in AKI patients also confirmed similar mortality rates between EDD and CRRT (relative risk, 0.90; 95% CI, 0.74-1.11; P = 0.3) [32] (Table 3).

CRRT, HD *vs.* PD: PD is an effective yet underused modality of renal replacement therapy for septic patients suffering from AKI, particularly in low-resource settings. PD actually has many potential advantages over extracorporeal RRT including its simplicity, low cost, no need for anticoagulation, and relatively good hemodynamic stability. On the contrary, risk of peritonitis, unpredictable fluid and solute clearances account for its unpopularity among nephrologist's community.

With regard to peritoneal dialysis efficacy in AKI setting, good quality studies are scarce. Phu NH, *et al.* reported a superior outcome in infection associated AKI patients treated with hemofiltration as compared with PD. Patients treated with hemofiltration in Phu NH, *et al.* study had lower mortality rate, better control of aci-

dosis and shorter dialysis-dependent duration [33]. Nevertheless, this study has been criticized for flaws in several points such as probable non-adequate dosing in PD group, the use of rigid catheters and manual exchanges which may contribute to high peritonitis rate and poor outcome in PD group. Chionh CY and colleagues performed a systemic review comparing all-cause mortality outcome in patients with AKI treated with PD to extracorporeal blood purification. Even though, there was a significant heterogeneity among studies, no difference in all-cause mortality was detected from both randomized trials and observational studies [34].

Dose of dialysis for patients with sepsis and AKI

The optimal intensity of renal-replacement therapy in critically ill patients with acute kidney injury remains controversial. The notion of applying convective strategy in renal replacement therapy in SA-AKI patients is appealing for many reasons. In sepsis, the toxins and inflammatory cytokines are accumulated leading to disturbance of defensive cellular activity as well as phagocytic response. As such, the removal of soluble toxins and cytokines by using of convective therapy may contribute to lower inflammatory mediators and improve phagocytic activity, leading to resolution of sepsis and organ injuries. Several large, multicenter, well-designed, randomized controlled studies have attempted to prove this concept by investigating clinical outcomes, specifically mortality, in intensive/higher-volume hemofiltration or hemodiafiltration versus less-intensive volume (20-40 mL/kg/hr) in septic patients. Overall, there was no significant survival advantage or renal benefits of intensive volume over conventional volume demonstrated by these high-quality trials [35-38].

Conclusion

Sepsis-associated acute kidney injury is an epidemic problem, posing short-and long-term morbidity and mortality. The new definitions of sepsis and septic shock, recently proposed by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine, are intended to guide and help clinicians identify patients with or at risk of developing sepsis in a timely manner. Although there have been several new dialysis technologies developed in the past three decades, the mortality rate from sepsis-associated kidney injury remains unchanged. Currently, no specific dialysis modality or timing of RRT initiation confers survival advantage over the others. Hence, clinicians need to apply understanding in sepsis pathophysiology, current evidenced-based strategies for prevention and dialysis treatment, patient's condition, and costs into consideration before prescribing dialysis and other supportive treatments.

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