Renal Replacement Therapy

REVIEW

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Current therapeutic strategies for acute kidney injury

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Abstract

Acute kidney injury (AKI) is an emerging public health problem worldwide and is associated with high morbidity and mortality. The high mortality rate can be attributed to the lack of pharmacological therapies to prevent and treat AKI. Renal replacement therapy (RRT) plays a pivotal role in the treatment of patients with severe AKI. However, the mortality rate of patients with AKI requiring RRT exceeds 50%. Although studies on RRT for AKI have begun to resolve some of the associated problems, many issues remain to be addressed. Notably, the optimal timing of the initiation of RRT for AKI is still being debated. Recently, new therapeutic strategies for AKI have been developed. Angiotensin II and recombinant alkaline phosphatase treatment are expected to improve the clinical outcomes of patients with distributive and vasodilatory shock. Moreover, mitochondrial-targeted agents have been developed for the treatment of patients with AKI. This review is focused on the optimal timing of RRT for AKI and the new pharmacological interventions and therapies for AKI.

Keywords Acute kidney injury (AKI), Renal replacement therapy (RRT), Timing of RRT, Angiotensin II, Alkaline phosphatase (AP), Mitochondria

Background

Acute kidney injury (AKI) is one of the most common and serious complications that affects hospitalized patients, especially critically ill patients admitted to intensive care units (ICUs). The diagnosis of AKI is defined by an abrupt decline in glomerular filtration rate (GFR) with a retention of serum creatinine or a decrease in urine output. The incidence of AKI has been markedly increasing globally during the past few decades because of aging of the population; health complications such as hypertension, diabetes mellitus, chronic kidney disease (CKD), and cardiovascular diseases; and therapeutic interventions such as major surgeries, percutaneous coronary intervention, and chemotherapy. Despite significant advances in renal replacement therapy (RRT) and basic research, the mortality and morbidity of patients with AKI remain unacceptably high, particularly among critically ill patients with symptoms severe enough to require RRT in ICU settings. Since 2000, recently critically ill patients requiring RRT have accounted for 1.0–13.5% of patients in ICU settings [1–10]. The mortality rate of AKI patients requiring RRT is greater than 50%. The higher mortality rate of patients with AKI requiring RRT can be attributed to a lack of established pharmacological therapies for the prevention and treatment of AKI. Several studies have shown that AKI is strongly associated with increased long-term and short-term mortality. Moreover, patients with AKI are at a higher risk of progression to CKD and the development of end-stage kidney disease [11, 12]. New therapeutic strategies are currently being developed for AKI. This review focuses on treatment approaches for AKI including RRT. There is some consensus regarding RRT modality [13] (continuous, intermittent), and RRT dose [14–16]. We discuss the

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effort to determine the optimal timing for initiation of RRT for AKI in this review.

Epidemiology and outcomes of AKI

A recent systematic review of 312 cohort studies revealed that the overall incidence of AKI was 23.2% among 154 studies ($n=3,585,911$), based on the Kidney Disease: Improving Global Outcomes (KDIGO) criteria for AKI [17]. Approximately one in five adults (21.6%) and approximately one in three children (33.7%) in hospital settings had AKI. AKI-associated all-cause mortality was 23.0% (23.9% in adults and 13.8% in children). The incidence of AKI is higher among critically ill patients admitted to ICU. However, AKI incidence differs across countries, as does the definition of AKI. The Acute Kidney Injury- Epidemiologic Prospective Investigation [9] (AKI-EPI) and Beginning and Ending Supportive Therapy for the Kidney [1] (BEST Kidney) studies were representative multinational trials that investigated the occurrence of AKI and associated mortality in ICU settings. The incidence of AKI was 5.7% in the BEST Kidney study [1] and 57.3% in the AKI-EPI study [9]. Among patients with AKI, the overall hospital mortality rates were 60.3% (BEST Kidney study) and 26.9% (AKI-EPI study). The difference in AKI incidence may be explained by the definitions of AKI in the studies. According to reports since 2000, the incidence of AKI in the ICU settings has varied between 5.2 and 67.2% [1–10, 18–23] (Table 1). The mortality rates of patients with AKI in the ICU were approximately three-fold to five-fold higher than those of patients in the ICU without AKI. The highest rate of AKI, according to the RIFLE classification for AKI, was reported at 67.2% in Pittsburgh, USA [18].

Timing of RRT initiation in patients with AKI

Although many studies have evaluated the optimal timing of RRT for patients with AKI, no ideal timing has been established. It is widely recognized that emergent RRT should be initiated if life-threatening complications-such as fluid overload unresponsive to diuretics, rapid hyperkalemia, severe metabolic acidosis, or uremic manifestations such as pericarditis and encephalopathy-occur in patients with AKI. However, the optimal timing for initiation of RRT in the absence of such emergent indications of RRT remains poorly understood. Whether early initiation of RRT improves mortality in patients with AKI compared with late initiation of RRT is still up for debate. Early initiation of RRT is supposed to provide better control of fluid and electrolyte balance, but may needlessly expose patients with AKI to complications such as

Table 1 the incidence of AKI in selected studies

References	No. of subjects	Country	Center	AKI definition	AKI incidence (%)	Mortality (%)
Uchino et al. [1]	29,269	Multinational	Multiple	UO ≦ 200 mL/12 h and/or BUN ≧ 84 mg/dL	5.7	60.3 (Hospital)
Ostermann et al. [2]	41,972	UK, Germany	Multiple	RIFLE	35.8	28.4 (ICU), 36.1 (Hospital)
Andrikos et al. [3]	1076	Greece	Multiple	RIFLE	15.8	64.7 (Hospital)
Thakar et al. [4]	3,25,395	USA	Multiple	Cr > 0.3 mg/dL from baseline Cr values	22	49.8 (ICU)
Clec'h et al. [5]	8639	France	Multiple	RIFLE	32.9	27.6 (Hospital)
Piccinni et al. [6]	576	Italy	Multiple	RIFLE	65.8	28.8 (ICU)
Vaara et al. [7]	24,904	Finland	Multiple	RIFLE	26.6	35 (Hospital)
Gammelager et al. [8]	30,762	Denmark	Multiple	RIFLE	15.6	39.6 (30 day)
Hoste et al. [9]	1802	Multinational	Multiple	KDIGO	57.3	24.0 (ICU), 26.9 (Hospital)
Korula et al. [10]	715	India	Single	Cr > 1.6 mg/dL or 25% increase from baseline Cr values	16.1	49.5 (28 day)
Hoste et al. [18]	5383	USA	Single	RIFLE	67.2	17.1 (Hospital)
Bagshaw et al. [19]	91,254	Australia, New Zealand	Multiple	Cr ≧ 133 µmol/L or UO/24 h < 410 mL	5.2	42.7 (Hospital)
Bagshaw et al. [20]	1,20,123	Australia, New Zealand	Multiple	RIFLE	36.1	24.2 (Hospital)
Joannidis et al. [21]	14,356	Multinational	Multiple	RIFLE, AKIN	35.5 (RIFLE), 28.5 (AKIN)	36.5 (RIFLE), 36.4 (AKIN) (Hospital)
Medve et al. [22]	459	Hungary	Multiple	AKIN	24.4	39.3 (ICU), 49.1 (Hospital)
Kashani et al. [23]	10,283	USA	Single	ICD-9	16.9	15 (ICU), 24 (Hospital)

AKIN acute kidney injury network, *RIFLE* risk, injury, failure, loss, ESRD, *ICD-9* international classification of diseases, ninth revision, *KDIGO* kidney disease improving global outcomes, *UO* urine output

hypotension, bleeding due to anticoagulants, catheter-related infection, and hypophosphatemia. Moreover, early initiation of RRT may result in the administration of unnecessary RRT to AKI patients who would have recovered renal function.

To date, several randomized controlled trials (RCTs) have examined the effects of early initiation of RRT over late initiation in patients with AKI [24–37]. The four latest RCTs have revealed conflicting results [34–37] (Table 2). Only the Early versus Late Initiation of Renal Replacement Therapy In Critically Ill Patients With Acute Kidney Injury (ELAIN) trial demonstrated that the early initiation of RRT significantly reduced the mortality of patients with AKI requiring RRT compared with the mortality of those treated with late-initiation RRT [33]. However, there were several differences among the other three RCTs in the definitions of the early and late initiation, patient characteristics, and the modality of RRT. The ELAIN trial was conducted with the target patients in KDIGO stage 2. Therefore, the levels of serum creatinine and BUN at the time of the initiation of RRT in the ELAIN trial were lower than those in the other trials (Table 3). The largest multinational RCT, the Standard versus Accelerated Initiation of Renal Replacement Therapy in Acute Kidney Injury (STARRT-AKI) trial, failed to show lower 90-day mortality in patients with AKI treated with accelerated RRT [37]. STARRT-AKI was conducted in 168 hospitals in 15 countries, with patients requiring RRT randomly assigned to accelerated initiation or standard initiation. In the accelerated-initiation group, patients were started on RRT as soon as possible and within 12 h after randomization. On the contrary, patients in the standard-initiation group were started on RRT at the time of emergent indications of RRT or at 72 h after randomization. No significant difference in 90-day mortality was observed between the accelerated-initiation and standard-initiation groups (accelerated group: 43.9% and standard group: 43.7%). Moreover, among survivors at 90 days, there were no significant differences in RRT dependence between the two groups.

The latest RCT, the Artificial Kidney Initiation for Kidney Injury 2 (AKIKI 2) trial, was conducted in 39 ICUs in France to investigate whether more delayed initiation of RRT would reduce the number of patients who received RRT [38]. In particular, this trial examined the benefit of initiating RRT even later than in the late or standard groups in the previous trials. The patients with severe AKI (defined as KDIGO stage3) who had oliguria for more than 72 h or a serum urea concentration ≧112 mg/dL were randomly assigned to either the delayed RRT strategy group or the more-delayed group. In the delayed RRT group ($n=137$), RRT was started within 12 h after randomization. In the more-delayed RRT group ($n=141$), RRT was not initiated until the urea concentration reached 140 mg/dL or the emergent indications of RRT were observed. AKIKI 2 revealed no significant difference in RRT-free days between the delayed group (12 days, interquartile range [IQR]: 0–25) and the more-delayed strategy group (10 days, IQR: 0–24). Moreover, 60-day mortality did not significantly differ between the two groups (delayed group: 44% and more-delayed group: 55%). However, multivariable analysis indicated that the

Table 2 Four latest RCTs

Study	Country	Design and setting	No of patients	Primary outcome	Result	*p* value
ELAIN	Germany	Single-center surgical population	231	60-day mortality	eRRT:dRRT = 39.3%:54.7%	0.03
AKIKI	France	Multicenter mixed population	619	90-day mortality	eRRT:dRRT = 48.5%:49.7%	0.79
IDEAL-ICU	France	Multicenter mixed population	488	90-day mortality	eRRT:dRRT = 58%:54%	0.38
STARRT-AKI	Multinational	Multicenter mixed population	2927	90-day mortality	eRRT:dRRT = 43.9%:43.7%	0.92

eRRT early renal replacement therapy, *dRRT* delayed renal replacement therapy

Table 3 Serum Cr values and BUN values at the initiation of RRT

Studies	Year	Serum Cr values (mg/dL)		*p* value	BUN values (mg/dL)		*p* value
		Early initiation	Late initiation		Early initiation	Late initiation	
ELAIN	2016	1.9 ± 0.6	2.4 ± 1.0	< 0.001	38.5 ± 15.5	47.5 ± 21.6	0.001
AKIKI	2016	3.27 ± 1.37	5.33 ± 2.33	< 0.001	52 ± 24	90 ± 34	0.001
IDEAL-ICU	2018	3.21 ± 1.51	4.56 ± 1.72	< 0.001	58.9 ± 27.7	87.1 ± 35	0.001
STARRT-AKI	2020	3.7 ± 1.7	4.9 ± 2.1	NA	63.7 ± 49.8	85.3 ± 51.3	NA

Data are described as means ± standard deviations

more-delayed strategy was statistically significantly associated with 60-day mortality (hazard ratio [HR] 1.65, 95% CI 1.09–2.50). However, the reasons for this discrepancy are unclear.

Several meta-analyses of RCTs have compared early RRT initiation with late RRT initiation. Three recent meta-analyses that include the latest RCTs have shown that early RRT initiation has no significant beneficial effect on patient survival compared with late initiation of RRT [39–41]. In the Japanese clinical practice guidelines for AKI, early initiation of RRT is not recommended [42]. The appropriate time to start RRT for AKI should be decided after consideration of individual clinical symptoms and disease conditions, as no optimal timing for RRT for patients with severe AKI has been established. There is insufficient evidence to recommend the early initiation of RRT. However, excessive delay of RRT initiation may lead to high mortality.

Angiotensin II

Sepsis is one of the most common contributing factors to AKI in critically ill patients. AKI related to septic shock is associated with higher mortality than that without septic shock. However, despite advances in our understanding of AKI, we only incompletely understand the pathophysiological mechanism of sepsis-associated AKI (S-AKI). The hypodynamic hypotensive animal model of sepsis revealed that renal ischemia together with a decrease in renal blood flow (RBF) leads to AKI in sepsis. However, several studies have shown that RBF is preserved and increased, not decreased, in animal models of hyperdynamic sepsis, which is typically seen in critically ill patients with sepsis [43, 44]. Efferent arteriolar vasodilation is assumed to result in a decline in GFR in S-AKI. Angiotensin II has a powerful effect on renal microcirculation, causing more constriction of the efferent arteriole than the afferent arteriole. Wan et al. showed that angiotensin II infusion increased creatinine clearance and urine output in experimental hypotensive hyperdynamic sepsis using adult ewes [45]. These effects were attributed to greater constriction of the efferent arteriole than the afferent arteriole of the nephron.

Two recent RCTs have shown a clinical benefit of angiotensin II in patients with vasodilatory shock [46, 47]. The phase 3 Angiotensin II for the Treatment of High-Output Shock (ATHOS-3) trial examined the effect of angiotensin II on the mean arterial pressure (MAP) of patients with vasodilatory shock [47]. ATHOS-3 enrolled 321 patients with vasodilatory shock, who were then randomly assigned to either the angiotensin II group ($n=163$) or the placebo group ($n=158$); in these patients, angiotensin II treatment significantly increased MAP. No significant difference in 28-day mortality was observed between the two groups. However, a responder analysis showed that the 28-day mortality rate of responders to angiotensin II was significantly lower than that of non-responders [48] ($p<0.0001$). A multicenter, retrospective trial demonstrated that two-thirds of patients with refractory vasodilatory shock who were treated with angiotensin II exhibited a favorable hemodynamic response [49]. Moreover, patients who responded to angiotensin II had a lower rate of 30-day mortality.

A post hoc analysis of ATHOS-3 was conducted for patients with AKI severe enough to require RRT ($n=105$) at the time of drug initiation [50]. Angiotensin II treatment ($n=45$) was associated with a significant improvement in 28-day survival rate compared with placebo treatment ($n=60$) (53% vs. 30%, respectively; unadjusted HR 0.52, 95% CI 0.30–0.87; $p=0.012$). With respect to renal function, patients treated with angiotensin II had greater RRT independence within 7 days (adjusted HR 2.90, 95% CI 1.29–6.52; $p=0.007$), and angiotensin II treatment improved 28-day mortality (unadjusted HR 0.52, 95% CI 0.30–0.87; $p=0.012$). Angiotensin II was approved by the US Food and Drug Administration in 2017 and the European Medicines Agency in 2019 for the treatment of hypotension in patients with septic or other distributive shock.

Alkaline phosphatase for patients with S-AKI

Alkaline phosphatase (AP) is an endogenous, membrane-bound enzyme found in multiple cells and organs. AP mediates detoxification through the dephosphorylation of various compounds, including lipopolysaccharide endotoxins and pro-inflammatory mediators such as extracellular adenosine triphosphate (ATP); it is thought to play a pivotal role in sepsis. However, the precise mechanism through which AP treatment improves S-AKI remains unclear.

ATP is released from damaged cells into the extracellular space during sepsis, where it causes inflammation and tubular damage. The two small RCTs that evaluated bovine intestinal AP treatment for patients with S-AKI demonstrated significantly improved kidney function [51, 52]. Following these trials, the therapeutic efficacy of human recombinant AP was investigated in a randomized phase 2a/2b clinical trial (STOP-AKI trial) [53]. This RCT examined the optimal dose, the effect on kidney function, and the adverse effects of a recombinant human AP in critically ill patients with S-AKI. The optimal dose was determined as 1.6 mg/kg of recombinant human AP. Although the STOP-AKI trial showed that recombinant human AP did not significantly improve short-term kidney function, it found that endogenous creatinine clearance was higher in the treatment group than in the placebo group on days 21–28 of treatment.

All-cause mortality at day 28 was significantly different in the two groups (treatment group: 14.4% and placebo group: 26.7%, $p=0.02$). To date, there is insufficient evidence to recommend the use of AP in patients with S-AKI. Further well-designed, large RCTs are needed to confirm the utility of AP treatment for patients with S-AKI. Currently, a larger phase 3 clinical trial (REVIVAL TRIAL) is evaluating the effect of AP treatment in patients with S-AKI. This study may provide new evidence to guide clinicians in the treatment of S-AKI.

Other new therapies for AKI

The role of mitochondria in AKI

The kidney is among the most energy-demanding organs because of its tubular sodium reabsorption function. The renal tubules, especially proximal tubules in the cortex and the thick ascending limb in the outer medulla, are rich in mitochondria and vulnerable to ischemic injury because of the low blood flow in these segments. Emerging evidence has suggested that mitochondrial dysfunction is associated with the development and progression of AKI and the AKI-to-CKD transition [54, 55]. Mitochondria are multifunctional organelles that not only produce cellular energy, but also affect numerous cellular functions. Mitochondrial dysfunction includes the alterations of mitochondrial structure, dynamics, biogenesis, mitophagy, and reactive oxygen species production. Structural changes, such as mitochondrial swelling and disruption of cristae, have been observed during the early stages of AKI [56]. The opening of mitochondrial permeability transition pores (mPTPs) caused by mitochondrial swelling leads to the release of cytochrome c and other mediators that induce apoptotic cell death. Mitochondria are highly dynamic organelles regulated by the balance between fission and fusion. The disruption of this balance is associated with AKI progression. During AKI, dynamin-related protein 1, which regulates mitochondrial fission, is activated [57], and mitofusin 1 and 2 (Mfn 1/2) and optic atrophy 1 are suppressed. These changes cause mitochondrial fragmentation due to excessive fission and the inhibition of fusion. Fragmentation has been shown to release cytochrome c and other mediators of apoptotic cell death. Moreover, decreased mitochondrial biogenesis has been observed in AKI. Peroxisome proliferator-activated receptor γ (PPARγ) coactivaor-1α (PGC1α) is a master regulator of mitochondrial biogenesis. In a mouse model of AKI in sepsis, PGC-1α expression in tubular cells was suppressed proportionally to the degree of renal injury [58]. PGC-1α may be necessary for recovery from AKI through mitochondrial biogenesis.

Mitochondria-targeting agents are being developed, some of which are expected to prevent the development and progression of AKI in the future. These drugs are classified as cardiolipin-protective compounds, mitochondrial biogenesis activators, mPTPs inhibitors, fission inhibitors, and antioxidants [59]. Cardiolipin is a phospholipid that is localized and synthesized in the inner mitochondrial membrane. Its deficiency is associated with mitochondrial dysfunction.

Vagus nerve stimulation

Vagus nerve stimulation (VNS) is a treatment option for patients with refractory epilepsy and depression. Accumulating evidence suggests that VNS exerts a protective effect against rheumatoid arthritis, Crohn's disease, and sepsis. This neuroimmune system-mediated suppression of inflammation is regulated by the cholinergic anti-inflammatory pathway through the α7 nicotinic acetylcholine receptor (α7nAChR). Recently, researchers have discovered renal protective effects of VNS. Inoue et al. showed that VNS attenuated kidney injury in an ischemia/reperfusion injury-induced AKI model [60]. This renal protective effect required α7nAChR-positive splenocytes [61, 62]. However, it is still unclear how the kidney receives VNS and the signals from splenic macrophages. VNS is expected to develop as a new treatment for AKI in clinical practice.

Conclusions

The clinical outcomes of AKI remain poor despite important advances in management. Although no specific pharmacological interventions for AKI have been established, several new treatment options, including angiotensin II and AP, are being developed and applied in clinical practice. The standard treatment for AKI is currently RRT, but there are still several issues to be resolved around its use. Accumulating evidence suggests that early initiation of RRT does not reduce AKI-associated mortality compared with late initiation. The optimal timing for RRT for patients with severe AKI remains controversial. New pharmacological interventions and therapies for AKI are expected to prevent its development and improve the clinical outcomes of patients with AKI.

Abbreviations

AKI	Acute kidney injury
AKIKI	Artificial kidney initiation in kidney injury
AKIKI-EPI	Acute kidney injury-epidemiologic prospective investigation
AP	Alkaline phosphatase
α7 nAChR	α7 Nicotinic acetylcholine receptor
ATHOS	Angiotensin II for the treatment of high-output shock
ATP	Adenosine triphosphatase
BEST Kidney	Beginning and ending supportive therapy for the kidney
CKD	Chronic kidney disease
ELAIN	Early versus late initiation of renal replacement therapy in critically ill patients with acute kidney injury
GFR	Glomerular filtration ratio
HR	Hazard ratio

ICUs	Intensive care units
IQR	Interquartile range
KDIGO	Kidney disease: improving global outcomes
MAP	Mean arterial pressure
mPTPs	Mitochondrial permeability transition pores
PGC	Peroxisome proliferator-activated receptor γ coactivator
PPARγ	Peroxisome proliferator-activated receptor γ
RCTs	Randomized controlled trials
RBF	Renal blood flow
RRT	Renal replacement therapy
STARRT-AKI	Standard versus accelerated initiation of renal-replacement therapy in acute kidney injury
S-AKI	Sepsis-associated acute kidney injury
VNS	Vagus nerve stimulation

Acknowledgements
We thank Amanda Holland, PhD, from Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript.

Author contributions
SN planned and wrote the review, searched the literature.TW, NM and JM searched the literature and assisted in writing the article. TS assisted in planning and writing the article. All authors read and approved the final manuscript.

Funding
No funding has been received.

Availability of the data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
Takashi Shigematsu is an editor-in-chief of journal of Renal Replacement Therapy.

Received: 21 July 2023 Accepted: 11 September 2023
Published online: 18 September 2023

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