Review

Acute kidney injury after burn

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Abstract

Acute kidney injury (AKI) is a common and morbid complication after severe burn, with an incidence and mortality as high as 30% and 80%, respectively. AKI is a broad clinical condition with many etiologies, which makes definition and diagnosis challenging. The most recent Kidney Disease: Improving Global Outcomes (KDIGO) consensus guidelines defined stage and severity of AKI based on changes of serum creatinine and urine output (UOP) across time. Burn-related kidney injury is typically classified as early (0–3 days after injury) or late (4–14 days after injury). Early burn AKI is typically due to hypovolemia, poor renal perfusion, direct cardiac suppression from TNF-alpha, and precipitation of denatured proteins, while late AKI is often due to sepsis, multi-organ failure, and nephrotoxic drugs. Diagnosis can be difficult as UOP and biochemical markers can be relatively normal even with significant renal injury. A sensitive and specific biomarker for the early diagnosis of AKI is sorely needed, and multiple potential biomarkers are being investigated. For treatment, the reversal of the underlying cause is the first intervention. The advent of renal replacement therapy has significantly improved the mortality of burn patients with AKI and should be initiated early if injury progresses despite initial maneuvers. Unfortunately, no beneficial pharmacologic agents have been identified, despite multiple investigations. Of burn patients who survive AKI, the vast majority do not receive long-term hemodialysis and they are generally thought to have a good renal prognosis although this view is shifting. Preliminary data in the burn population suggest that AKI may confer an increased risk of end-stage renal disease and long-term all-cause mortality, but further research is needed.

Abbreviations: AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; CKD, chronic kidney disease; CRRT, continuous renal replacement therapy; CVVH, continuous venovenous hemofiltration; ESRD, end-stage renal disease; FeNa, fractional excretion of sodium; GFR, glomerular filtration rate; IHD, intermittent hemodialysis; KDIGO, Kidney Disease: Improving Global Outcomes; NGAL, neutrophil gelatinase-associated lipocalin; RIFLE, risk, injury, failure, loss, end-stage renal disease; RRT, renal replacement therapy; sCr, serum creatinine; SLED, sustained low-efficiency dialysis; TBSA, total body surface area; TNF, tumor necrosis factor; UOP, urine output.

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1. Introduction

Acute kidney injury (AKI) is a frequent and very serious complication of burns, with an incidence of up to 30% depending on the definition utilized. Even with the advent of continuous renal replacement therapy (CRRT), AKI in burned patients portends a poor prognosis with a mortality rate as high as 80% [1-4]. Before 1965, no survivors were reported from AKI after burns [5]. Advances have been made in the understanding of AKI pathobiology in these patients; however, this has not translated to significant advances in treatment or an improvement in mortality outcome until recently. Prevention and mitigation of nephrotoxicity are likely the best strategies to attenuate AKI risk or progression, although AKI is often unavoidable in severely burned patients. In this article, we will review the current definitions, etiology, pathophysiology, diagnosis, treatment, and long-term effects of AKI in burn patients.

2. Definitions and classification

AKI is conventionally defined as an abrupt decrease in kidney function [6]. This clinical syndrome has many etiologies and encompasses both direct injury to the kidney and acute impairment in kidney function, or either individually [7].

The early detection of AKI leads to effective avoidance of nephrotoxicity and adequate fluid management and therefore improvement in post-AKI outcomes, which highlights the importance of a standardized definition of AKI that incorporates both classic and novel markers of kidney function and damage [7]. For many years, no consensus existed for the definition of AKI. More than 30 different definitions have been used in the literature, making comparisons between studies and drawing conclusions from them extremely difficult [8]. The first combined effort to standardize the definition of renal insufficiency was the Risk, Injury, Failure, Loss, End-Stage Renal Disease (RIFLE) criteria that used absolute and relative changes in estimated glomerular filtration rate (GFR), serum creatinine (sCr) or urine output (UOP) to characterize AKI severity stages (Table 1). RIFLE has good prognostic accuracy for mortality as there is an independent and stepwise increase in mortality as AKI severity increases, but this classification system does have some major limitations. One is that a baseline sCr is necessary to define and classify AKI in this system. This baseline value is often unknown and then has to be estimated using age, gender, and race. The RIFLE criteria also does not account for patients receiving renal replacement therapy (RRT) and therefore has less accuracy in predicting mortality in this population [9]. Lastly, it may not identify patients with slight, but clinically significant, changes in sCr.

In an attempt to address these weaknesses and incorporate a time component for changes in sCr, the Acute Kidney Injury Network (AKIN) criteria were created with a classification of AKI based on sCr and UOP changes. The AKIN criteria do not include changes in GFR and do not need a baseline sCr. Instead, they define AKI as a sudden decrease (within 48h) of renal function defined by an increase in sCr by ≥0.3mg/dL or 1.5x initial value. They also classify injury into three stages. Stage 1 corresponds to the risk class in RIFLE (but considers a sCr increase of ≥0.3mg/dL). Stage 2 and 3 correspond to injury and failure classes, respectively. Stage 3 also includes patients receiving RRT independently of sCr or UOP prior to initiation [10]. The major criticism of the AKIN criteria is that they do not allow the identification of AKI when sCr elevation occurs in a time frame longer than 48h.

Both RIFLE and AKIN have been validated in multiple studies in both medical and burn ICUs, and both show that increased severity of AKI based on these criteria correlate closely with mortality and adverse renal outcomes [11-15]. Comparisons of these two definitions, in burn and non-burn patients, have not shown a clear benefit of one classification system over the other [14,16]. In 2010, in an attempt to combine these two criteria, increase sensitivity, and simplify the diagnosis and grading of AKI, The Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines established a consensus definition of AKI incorporating both sCr and UOP parameters, and staging the severity of AKI from 1 to 3 [6]. In this system, AKI is defined as any of the following: an increase in sCr ≥0.3mg/dL within 48h, an increase in sCr ≥1.5 times baseline (or first measurement), or a UOP <0.5mL/kg/h for 6h. The major advantages of these criteria is that they incorporate smaller sCr changes, which was the weakness of
the RIFLE system, and they liberalize the 48-h time frame, which was the weakness of the AKIN system.

This novel classification system has not yet been applied to the burn population but will hopefully aid in future observational and experimental designs due to its higher sensitivity and allow for enhanced comparisons between studies investigating burn-associated AKI outcomes.

3. Etiology

Burn-related AKI is traditionally classified as either early (post-burn day 0-3) or late (post-burn day 4-14) and both have differing etiologies. Early AKI is seen during the initial resuscitation phase after severe burn and is thought to be due to hypovolemia, increased inflammatory mediators, mechanical tissue destruction, release of denatured proteins, and cardiac dysfunction [1,17,18]. In the past, early AKI was attributed almost entirely to under-resuscitation, but recent studies have established that AKI is not dependent only on the quantity of fluid given, but also on the degree of shock after severe burn [19]. In contrast, late AKI is most commonly due to sepsis, multi-organ failure, fluid overload or nephrotoxic drugs, and it develops 3 to 14 days after resuscitation (Fig. 1) [20,21].

Substantial fluid loss from the burn wound and fluid shift from the intravascular space to the interstitial space cause hypovolemia and a decrease in cardiac output. This results in a decrease in renal blood flow leading to ischemia and cellular injury and death [1,22,23]. Additionally, the ischemic injury

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<th>Table 1 – RIFLE, AKIN, and KDIGO criteria for AKI [6].</th>
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<tr>
<td><strong>RIFLE criteria</strong></td>
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<tr>
<td>AKI definition</td>
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<tr>
<td>Staging Risk</td>
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<td>Injury Failure</td>
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<td>Loss</td>
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<td>End stage</td>
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Abbreviations: AKI (acute kidney injury), AKIN (Acute Kidney Injury Network), GFR (glomerular filtration rate), KDIGO (Kidney Disease: Improving Global Outcomes), RIFLE (risk, injury, failure, loss, end-stage renal disease), RRT (renal replacement therapy), sCr (serum creatinine).

Fig. 1 – Common causes of early and late AKI after severe burn.

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yields oxygen free radicals that cause tubular damage and a disturbance of tight junctions, resulting in obstructing cellular casts, causing urine backflow which further lower GFR. Due to these mechanisms, burn size is an independent predictor of AKI [24]. Although early aggressive fluid resuscitation cannot completely prevent AKI, it does have a protective effect [25,26]. The time to initiation of resuscitative fluids is also directly related to the incidence of renal dysfunction and overall mortality [20]. Unfortunately, timely and aggressive resuscitation cannot completely alleviate AKI, and over-resuscitation from excess volume carries its own complications. It was previously shown that patients who are given more fluid than recommended by the Parkland formula (4cc/kg/%TBSA) and who are not oliguric can still develop AKI [19]. Furthermore, over-resuscitation leads to intraabdominal hypertension, abdominal compartment syndrome, extremity compartment syndrome, pneumonia, acute respiratory distress syndrome, and increased mortality [21,26,27].

Cardiac dysfunction is another contributor to AKI in the burn population. Historically, low cardiac output after burn was thought to be due only to decreased preload and hypovolemia, but evidence suggests that a component of direct myocardial suppression may be involved [28]. Multiple mechanisms have been proposed to explain the decreased cardiac output associated with severe burn including increased sympathetic activity paired with insufficient adrenal response, hypovolemia resulting in myocardial ischemia, and direct myocardial suppression by tumor necrosis factor (TNF)-alpha or some other factor [29,30]. TNFα is released from myocytes in response to endotoxin or direct thermal injury and the effects of TNFα include decreased ejection fraction, reversible biventricular dilation, and decreased response to catecholamines [30-33]. The management of cardiac dysfunction by both correcting diminished preload and providing inotropic support, if needed, are important to reduce inadequate renal perfusion and mitigate AKI.

The development of early AKI in burned patients has also been ascribed to denatured proteins from rhabdomyolysis and free hemoglobin. Direct thermal or electrical injury or resultant compartment syndrome can cause muscle damage with a dissolution of skeletal muscle fiber. Rhabdomyolysis induces muscle fluid sequestration, intrarenal vasoconstriction, and the release of toxic intracellular components into the systemic circulation, which contribute to oxidative injury and inflammation leading to ischemic tubular injury and AKI [34,35]. The released myoglobin precipitates in renal tubules causing afferent renal arteriolar vasoconstriction and the generation of oxygen free radicals [36]. Myoglobinuria (Fig. 2) is evident when serum myoglobin levels rise above 1500-3000ng/mL and creatinine kinase levels rise over 500U/L and is associated with both ischemic tubular injury (proximal tubules) and tubular obstruction (distal tubules) and therefore AKI development [35,37]. Management is focused on intravenous fluid resuscitation to correct hypovolemia and acidosis and treating any ongoing processes, such as a compartment syndrome [38]. Some clinicians favor using sodium bicarbonate in an effort to alkalize the patient’s urine, but this has not been shown to have any benefit over saline alone, particularly if urine pH is >6.5. Similarly, mannitol was proposed as a possible protective agent as it causes a diuresis, theoretically minimizing intratubular heme pigment deposition and cast formation and acting as a free radical scavenger. It has no additional benefit over adequate hydration alone and is not recommended for use in patients with myoglobinuria and acute kidney injury [37,39].

The main causes of late AKI in burned patients are nephrotoxic drugs, sepsis, and multi-organ failure. Nephrotoxic agents such as aminoglycosides, some cephalosporins, and intravenous contrast agents are often given to burn patients. Sepsis and septic shock are the leading cause of death in the ICU and may account for up to 87% of AKI cases in the burn ICU [40,41]. The pathophysiology of sepsis-related AKI is

Fig. 2 - Myoglobinuria.
multifactorial but it starts with systemic arterial vasodilation due to decreased vascular resistance (a high-flow, low-pressure state) [42]. Bacteria activate sepsis-associated cytokines, which then cause endothelial damage, vasoparalysis, and a procoagulant state. The vasoparalysis leads to profound hypotension, which activates the sympathetic nervous system and the renin-angiotensin-aldosterone response causing an increased cardiac output state. Late sepsis is mediated by inflammatory tubular and microvascular injury leading to progressive afferent renal arteriolar vasoconstriction and increased tubular pressure, which decrease GFR until tubular epithelium regenerates and increased interstitial pressure resolves [42-44]. The contribution of inflammatory mediators to renal function is becoming an active area of research and new therapeutic approaches, such as anticytokine therapy and immune targeting, for kidney disease are focusing on the immune system and inflammation [45].

A special population to be considered are patients with preexisting chronic kidney disease (CKD). These patients are at increased risk of developing AKI and should be monitored closely. The KDIGO guidelines should still be used for diagnosis of acute-on-chronic kidney injury and treatment is largely the same as patients without CKD, although fluids should be used judiciously when possible and RRT should be considered early in their course. Another special population to mention is patients with inhalational injury. Approximately 6% of burn patients are diagnosed with concomitant inhalational injury, which confers a greatly increased risk of multiorgan failure, renal failure, and mortality [46]. One study found that rate of multiorgan failure, including renal failure, increased tenfold in burn patients with an inhalational injury and another found that patients with inhalational injury (with or without multiorgan failure) trended toward higher incidence of AKI, although it was not statistically significant [19,47]. Early recognition and intervention is important for patients with AKI and both of these populations must be carefully monitored due to their increased risk.

4. Diagnosis

The diagnosis of AKI after thermal injury can be challenging as UOP and sCr can be relatively normal even with significant renal injury. Physicians should continually reevaluate the patient’s overall physiological condition and anticipate events that might affect the kidney. The development of standardized definitions and grading of AKI severity (RIFLE, AKIN, KDIGO) has aided in making the AKI diagnosis more objective and homogeneous. These classifications have also been shown to carry prognostic value, although KDIGO has yet to be applied to burn patients [16].

Decreased UOP is often the first physiologic sign of renal injury in burn patients and although it is very specific, it is not sensitive [48]. UOP is based on the difference between the glomerular filtration rate and tubular reabsorption, making it possible for patients with kidney injury to still have a normal UOP, particularly in early stages of injury.

Microscopic and biochemical urine sediment analyses can aid in the evaluation of AKI and the underlying etiology. A prerenal condition is suggested by a combination of normal urinary sediment or hyaline casts in an oliguric patient. Findings of tubular epithelial cells, granular casts, and epithelial cell casts are highly characteristic of acute tubular necrosis [49]. Myoglobinuria, likely due to rhabdomyolysis, causes pigmented casts on microscopic evaluation and the classic dissociation between positive blood in dipstick urinalysis with absent red blood cells on microscopy [50,51]. Urine electrolytes and osmolarity can also be used to help determine the renal pathophysiology of AKI. Prerenal etiologies are associated with concentrated urine (osmolarity >400 mmol/kg), decreased urinary sodium concentration, and a fractional excretion of sodium (FENa) <1%. A FENa of >1% is typically associated with intrinsic renal pathology. However, it is important to recognize the limitations of FENa in patients who do not have a marked reduction in GFR or have underlying chronic kidney disease (CKD), sodium wasting states, diuretic exposure, or other causes of renal damage with low FENa, particularly rhabdomyolysis-induced AKI, which is very common in burn patients. Other measurements that can be used to evaluate renal causes of AKI include specific gravity and fractional excretion of urea [52].

sCr is the standard biomarker used for estimating GFR. sCr is freely filtered across the glomerulus and is neither absorbed nor metabolized by the kidney, making it a practical indicator of GFR [53]. Although sCr does lag behind the actual degree of renal dysfunction and recovery, especially in critically ill patients, it remains a suitable tool, especially when looking at the trajectory change over time [48]. It is important to note that sCr mandates a time-dependent cumulative increment of creatinine which may be impaired in patients with sarcopenia and prolonged ICU stay [54,55]. sCr is also affected by multiple factors, including hepatic insufficiency, fever, and immobilization (Table 2). In addition, sCr identifies functional changes in renal function but not necessarily renal injury in early stages of AKI, a condition now call subclinical AKI [56].

Fluid overload also influences sCr as fluid distributes into both the intra- and extracellular fluid compartments and therefore dilutes sCr in patients with significant positive fluid balance. Because of this, some clinicians propose that sCr should be adjusted for daily fluid balance when evaluating for AKI in critically ill patients after fluid resuscitation. A study of 1000 acute lung injury patients found that patients with “unrecognized” AKI (patients with AKI unveiled only after adjusting for positive fluid balance) had high mortality rates similar to the group of patients with “recognized” AKI before fluid balance adjustment. Patients who had AKI before but not

<table>
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<th>Table 2 – Factors affecting sCr measurements in burn patients.</th>
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<tr>
<td>Factor</td>
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<tr>
<td>Decreased muscle mass</td>
</tr>
<tr>
<td>Hepatic insufficiency</td>
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<tr>
<td>Fluid overload</td>
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<tr>
<td>Sepsis</td>
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<tr>
<td>Trauma</td>
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<tr>
<td>Fever</td>
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<td>Immobilization</td>
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Abbreviations: sCr (serum creatinine).
after adjustment for fluid balance had low mortality rates comparable to patients without AKI [57]. Burn patients receive large volumes of fluid and the impact of fluid balance on AKI diagnosis warrants further study in this susceptible population.

The search for earlier and more sensitive biomarkers of AKI development has led to the study of cystatin C and neutrophil gelatinase-associated lipocalin (NGAL), which have shown some initial promise as early markers of AKI [58-60]. Cystatin C is a protease inhibitor located in nucleated cells that is freely filtered through the glomeruli but not actively secreted (in contrast to creatinine). When GFR is impaired, it causes increased plasma levels of cystatin C even at early stages. Another possible benefit of cystatin C measurements is that normal plasma concentrations do not depend on age, gender, or muscle mass [61]. NGAL is a protein expressed at very low concentrations in several human tissues including the kidney, lung, stomach, and colon, and it is produced rapidly in the renal tubules in response to acute injury and is easily detected in plasma and urine. Multiple studies have shown both elevated cystatin C and NGAL to be associated with the development of AKI, but results are conflicting [60-63]. Yang et al. measured levels of sCr, cystatin C, urine and plasma NGAL every two hours from admission to 48h in 90 severely burned patients and found that all four measures were predictive of early AKI and early death at all time points. The NGAL levels, however, were increased earlier after admission, while sCr and cystatin C increased only after 12h from admission [63]. Conversely, Rakkolainen et al. serially measured sCr, cystatin C, and plasma NGAL for a week in 19 burn patients and found that sCr and cystatin C identified patients at risk for AKI earlier than did NGAL [61]. More study is warranted to determine if cystatin C or NGAL can be a valuable clinical tool in burn patients. Recently, a pair of cell cycle arrest biomarkers, tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP7), were FDA-approved to diagnose AKI 12h after measurement in critically ill patients [64]. To our knowledge, these markers have not been yet measured in burn patients.

There is an urgent need to identify biomarkers that are sensitive and specific to provide accurate early AKI diagnosis and post-AKI risk stratification and aid the implementation of cost-effective surveillance strategies and therapeutics that could attenuate AKI, promote AKI recovery, and reduce the burden of CKD post-AKI.

Colloids, such as albumin or fresh frozen plasma, improve intravascular osmotic pressure, expand intravascular volume, and limit edema in unburned tissue [66]. Because of these beneficial effects, colloids can be used either early in resuscitation as an immediate dedicated strategy or to introduce colloids later in resuscitation as a responsive approach if the volume of crystalloid being used to maintain UOP is excessive. Multiple studies have found that the use of either immediate or responsive colloid reduces the resuscitation volume and most these studies used albumin as it is less expensive and has less risk of viral transmission or acute lung injury [67-71].

Other volume expanding synthetic colloids such as hydroxyethyl starch (HES) and gelatin have also been used in the early post-burn period and have demonstrated decreased edema and improved hemodynamics [72]. HES is inexpensive and has longer volume expansion effect than albumin and gelatin, however, starch has been linked with serious complications including coagulation impairments, kidney injury, and increased mortality [73,74]. Proponents of HES argue that newer, lower molecular weight starch is safer, but data is conflicting and further research into these newer formulations is needed [75,76]. Gelatins is a degradation product or collagen and it is thought to have less harmful renal and coagulation effects, but data on its safety and effectiveness as a volume expander is extremely limited. A large, prospective, double-blind randomized control trial (NCT02715466) is currently underway to investigate the efficacy and safety of gelatin in patients with sepsis [77,78].

Maintaining adequate renal perfusion pressure is important to mitigate damage to the kidneys an if these initial maneuvers do not maintain a mean arterial pressure over 60mm Hg, norepinephrine can be used to support blood pressure and renal perfusion [79]. Vitamin C has recently gained attention as a possible adjunct during burn resuscitation because of its antioxidant effects. Capillary permeability is significantly increased after burn, resulting in decreased intervascular volume, and although the mechanism underlying this increased permeability is complex, damage from reactive oxygen species plays a major role. Vitamin C is a scavenger of reactive oxygen species and has shown efficacy in reducing resuscitation volumes after burn, although this was only in two small studies [80,81]. Despite the possible fluid volume benefits of high-dose vitamin C therapy, it can cause secondary calcium oxalate nephropathy which has the potential to cause or worsen acute kidney injury [82]. Further investigation into the benefits and possible complications of vitamin C therapy after burn is needed.

Late AKI is often multifactorial and associated with sepsis and multi-organ failure. Early recognition and intervention in sepsis is extremely important, especially in the burn population. Early signs of sepsis such as increasing insulin resistance, feeding intolerance, or elevation of acute phase reactants should be carefully monitored so that goal-directed therapy can be started in a timely manner [83]. When a clinically relevant infectious organism is identified, appropriate antibiotics should be initiated and dosed accordingly to renal function status [84]. The goal is to treat a local infection and gain source control before it spreads systemically and causes septic shock and end-organ damage, such as AKI. Nephrototoxic

5. Treatment

The most important aspects of AKI therapeutics are timely identification, reversal of the underlying cause, and correction of electrolyte and fluid derangements. If the injury continues to progress despite conventional therapy, RRT should be judiciously initiated to prevent complications [65].

Early AKI, primarily due to poor renal perfusion, should induce early and aggressive crystalloid resuscitation utilizing the Parkland (or another resuscitative) burn formula. Adjustments to fluid administration rates and solutions should be made based on the individual patient’s physiologic status in order to give enough fluid to optimize renal perfusion without over-resuscitation.
Table 3 – Modalities of renal replacement therapy.

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<th>IHD</th>
<th>SLED</th>
<th>CRRT</th>
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<tr>
<td>Name</td>
<td>Intermittent hemodialysis</td>
<td>Sustained low efficiency dialysis</td>
<td>Continuous renal replacement therapy</td>
</tr>
<tr>
<td>Blood flow</td>
<td>300-400 mL/min</td>
<td>200-300 mL/min</td>
<td>50-200 mL/min</td>
</tr>
<tr>
<td>Dialysate flow</td>
<td>500-800 mL/min</td>
<td>1-2L/h</td>
<td>2-3L/h</td>
</tr>
<tr>
<td>Hemodynamic stability</td>
<td>Poor (hypotension common)</td>
<td>Good</td>
<td>Good</td>
</tr>
<tr>
<td>Duration</td>
<td>3-4L, 3x/week</td>
<td>6-12h daily</td>
<td>Continuous</td>
</tr>
<tr>
<td>Access</td>
<td>Fistula or vas cath</td>
<td>Fistula or vas cath</td>
<td>Vas cath only</td>
</tr>
<tr>
<td>Anticoagulation use</td>
<td>None</td>
<td>Rare</td>
<td>Always</td>
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Abbreviations: CRRT (continuous renal replacement therapy), IHD (intermittent hemodialysis), SLED (sustained low-efficiency dialysis).

There is no consensus regarding which mode is superior, but many clinicians argue that CRRT is most appropriate for severely burned patients as they often have significant hemodynamic instability, ongoing severe metabolic acidosis, and benefit from the removal of large amounts of fluid [79]. Chung et al. investigated the role of continuous venovenous hemofiltration (CVVH) in burn patients by comparing a population of patients treated with high-effluent CVVH to historical controls and found that both 28-day mortality and overall mortality were improved by 50% with this treatment [4]. There is no defined criteria or threshold for when RRT should be initiated in critically ill burn patients, but evidence suggests a timely and early start may be superior [4,87]. A multicenter randomized controlled trial comparing early high-volume CVVH to standard care in burn patients with septic shock is currently undergoing (ClinicalTrials.gov ID: NCT01213914).

Unfortunately, once AKI has occurred, there is no pharmacologic agent to improve renal blood flow or reverse kidney injury. Dopamine and other similar agents were previously used in an effort to dilate renal arterioles and increase renal blood flow, but these have been shown to be ineffective [91]. The use of fenoldopam, a potent dopamine-1 receptor agonist used for treatment of hypertensive emergencies, was studied in a meta-analysis of randomized controlled trials and found to reduce the incidence of RRT and hospital mortality in septic ICU patients [92]. However, these results have not been confirmed in large and properly designed randomized controlled trial. Bove et al. performed a randomized control trial of patients with AKI after cardiac surgery and found that fenoldopam did not reduce the need for RRT or 30-day mortality but was associated with increased rate of hypotension [93]. A retrospective study of low-dose fenoldopam use in critically ill burn patients suggested improvement in renal function, based on UOP and sCr, without a decrease in systolic blood pressure or increase in vasoactive medication use [94]. Further investigation is indicated to fully delineate its efficacy and safety in the burn population.

6. AKI recovery and long-term consequences

 Patients with severe burn who develop AKI have a higher mortality than burn patients without AKI and mortality increases with the severity of AKI (based on either RIFLE or AKIN criteria) [19,95]. In patients who develop burn-related AKI, other factors that independently increase mortality are...
older age, larger % total body surface area, and higher incidence of inhalational injury [40,96].

Clinicians previously considered AKI and CKD as two distinct syndromes, but recent evidence challenges this assumption. It is now believed that AKI does confer an increased risk of developing CKD and progressive renal failure, although data in the burn AKI population are scarce [97]. In burn-related AKI survivors, the need for long-term dialysis is very rare and historically these patients were considered to have an excellent renal prognosis [98]. This is a critical distinction because burn patients who suffered from AKI may represent a distinct AKI phenotype that may be less susceptible to either recurrent AKI or AKI progression into CKD, which may be related to patient-specific but also disease-specific factors.

AKI may lead to more than just adverse renal outcome. Patients who survived and recovered from an episode of dialysis-requiring AKI were found to have an increased risk of stroke, coronary events, and all-cause mortality. In these studies, an episode of AKI conferred a similar risk for coronary event or stroke as did having diabetes [99,100].

Six epidemiologic studies of AKI in burn patients did not find any patients who underwent long-term dialysis after hospitalization, although a small percentage did receive IHD for less than six months after discharge [3,8,20,41,96,101]. Those studies, however, did not follow patients more than a year after discharge. A study of Finnish burn survivors found that their long-term risk of end-stage renal disease (ESRD) increased 2.5-fold compared to the general population. Importantly, the majority of the burn survivors identified with ESRD were also diagnosed with a specific kidney disease (e.g., diabetic nephropathy, polycystic kidney disease, IgA nephropathy) as the cause of ESRD, but 5 patients had an unknown cause of renal failure and the authors commented that a causal association between burn and ESRD could be plausible. They also speculated that burn might contribute to an accelerated deterioration of kidney function in patients with underlying CKD, which might explain the increased incidence of ESRD in the burn survivors [98]. Important to note is that the examination of ESRD risk in burn-related AKI survivors has not been done in reference to other critically ill AKI survivors without burns, which is necessary to further investigate the putative causal relationship between burn and long-term renal outcome. Another study in Australia found a 1.4-fold greater long-term all-cause mortality rate in burn patients compared to a non-burn cohort randomly selected from Australia’s electoral roll. Interestingly, the mortality risk was increased for both severe and minor burns [102].

Multiple studies performed in non-burn AKI survivors have shown a link to the later development of CKD, ESRD, and even increased long-term mortality [103-106]. AKI may lead to CKD regardless of the cause of the acute injury. Animal models propose a few causal pathways for the ongoing organ dysfunction, including maladaptive repair, disordered tubular regeneration, and persistent interstitial inflammation [97,107,108]. Current data are not adequate to ascertain if this is a causal relationship or whether AKI is a surrogate indicator for comorbidity or the later adverse renal outcome.

Appropriate treatment of AKI survivors consists of avoidance of nephrotoxins and optimal management of other CKD risk factors such as diabetes and hypertension [97]. Close observation within 1 to 3 months after discharge is necessary in severe AKI cases. This is critical to prevent recurrent AKI or attenuate transition to CKD. Future studies are needed to investigate whether novel biomarkers of AKI could augment the ability to risk-stratify patients for AKI development or recovery, whether AKI portends an independent increased risk of CKD and mortality, and whether interventions for AKI can prevent or mitigate long-term adverse events. Furthermore, novel therapies to prevent AKI, attenuate injury, and promote adaptive recovery are much needed, particularly in susceptible populations such as burn patients.

7. Conclusions/summary

AKI is a common and morbid complication after severe burn. It is a broad clinical condition, which makes its definition and diagnosis challenging. A new KDIGO consensus definition has been issued that will hopefully aid with staging of AKI, but it has yet to be applied to the burn population. Creatinine is a useful measure, but a biomarker that is sensitive and specific for the early diagnosis of AKI is much needed. The most important aspects of therapy are timely identification, the reversal of the underlying cause, the mitigation of nephrotoxicity, and the correction of electrolyte and fluid derangements. The advent of RRT has significantly improved the mortality of burn patients with AKI and should be initiated early if renal injury progresses despite initial maneuvers. Unfortunately, no beneficial pharmacologic agents for this condition have yet been identified, despite multiple investigations. There is mounting evidence that an episode of AKI may have lasting effects and increase the risk for CKD, ESRD, cardiac events, stroke, and long-term mortality. Although the vast majority of burn AKI survivors do not receive extended hemodialysis, further research is needed regarding possible long-term consequences.

Conflicts of interest

Dr. Steven Wolf is the Editor of Burns. No other authors have conflict of interest.

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