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Intensive Care Unit–Acquired Weakness in Patients With Acute Kidney Injury: A Contemporary Review

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Abstract

Acute kidney injury (AKI) and ICU-acquired weakness (ICU-AW) are two frequent complications of critical illness which, until recently, have been considered unrelated processes. The adverse impact of AKI on ICU mortality is clear, but its relationship with muscle weakness – a major source of ICU morbidity – has not been fully elucidated. Furthermore, improving ICU survival rates have refocused the field of intensive care towards improving long-term functional outcomes of ICU survivors. We begin our review with the epidemiology of AKI in the ICU and of ICU-AW, highlighting emerging data suggesting that AKI and AKI-requiring kidney replacement therapy (AKI-KRT) may independently contribute to the development of ICU-AW. We then delve into human and animal data exploring the pathophysiologic mechanisms linking AKI and acute KRT to muscle wasting, including altered amino acid and protein metabolism, inflammatory signaling, and deleterious removal of micronutrients by KRT. We next discuss the currently available interventions that may mitigate the risk of ICU-AW in patients with AKI and AKI-KRT. We conclude that additional studies are needed to better characterize the epidemiologic and pathophysiologic relationship between AKI, AKI-KRT, and ICU-AW and to prospectively test interventions to improve the long-term functional status and quality of life of AKI survivors.

Keywords: acute kidney injury; acute renal failure; critical illness myopathy; ICU-acquired weakness; continuous kidney replacement therapy; continuous renal replacement therapy; post-intensive care syndrome; AKI; CRRT; PICS
Introduction

Acute kidney injury (AKI) is a common complication of critical illness, and up to 15% of patients with AKI in the intensive care unit (ICU) require kidney replacement therapy (KRT).\(^1\) Though further studies are needed, AKI and the need for acute KRT may contribute to skeletal muscle dysfunction through multiple mechanisms. The purpose of this article is to review the proposed pathophysiology of skeletal muscle loss and dysfunction in critical illness with a focus on patients with AKI requiring KRT (AKI-KRT). We describe pre-clinical and clinical data suggesting that AKI and AKI-KRT may independently contribute to ICU-acquired weakness (ICU-AW) (Figure 1), suggest interventions that may mitigate or prevent ICU-AW in AKI patients, and identify areas of uncertainty in need of future research. Despite many unanswered questions, we propose that nephrologists should recognize AKI as risk factor for long-term functional impairment after critical illness and learn to routinely consider referring AKI survivors to physical rehabilitation.

AKI in the ICU: incidence and outcomes

In contemporary international cohorts, the incidence of AKI ranges from 20% to >50% of all ICU admissions, with 5-15% of critically ill patients developing AKI-KRT.\(^2,3\) Moreover, the rates of AKI, AKI-KRT, and AKI-related mortality have increased substantially in the last 20 years.\(^4,5\) Recently, the COVID-19 pandemic has further increased KRT use in the ICU. AKI complicates 25-40% of all COVID-19 admissions and AKI-KRT develops in 20-45% of critically ill COVID-19 patients.\(^6\) AKI, especially AKI-KRT, carries a high short-term mortality of ≥50% across diverse ICU populations with or without COVID-19.\(^1,4,6-10\) Furthermore, observational studies
have increasingly linked AKI to long-term impairments in functional status, including limited mobility, worsened quality of life (QoL), and muscle weakness.\textsuperscript{11-13}

Despite chronic kidney disease (CKD) being a recognized risk factor for AKI, the relationship between AKI-on-CKD and outcomes of critical illness appears to be complex, with data suggesting mortality rates are higher in AKI-on-CKD patients than in patients with neither AKI nor CKD but lower than in patients with AKI in the setting of normal baseline kidney function.\textsuperscript{14,15} The interplay between AKI-on-CKD and long-term functional outcomes remains unknown.

**ICU-acquired weakness: definition, incidence, outcomes, and risk factors**

ICU-AW is defined as muscle weakness and wasting (atrophy) resulting from critical illness.\textsuperscript{16} The reported incidence of ICU-AW ranges from 40\% in systematic reviews\textsuperscript{17} to >80\% in individual studies.\textsuperscript{18} Muscle wasting occurs early and rapidly during critical illness.\textsuperscript{19} We and others have reported that 3-5\% of baseline rectus femoris muscle size is lost in the first day of ICU admission, with up to 30\% lost in the first 10 days.\textsuperscript{20-23} Importantly, ICU-AW may persist for years and is associated with mortality, hospital readmission, long-term functional impairment, and lower QoL.\textsuperscript{24-26} Traditional risk factors (Figure 2) for ICU-AW include preexisting comorbidity, high illness severity, sepsis, acute respiratory failure, prolonged immobilization, hyperglycemia, advanced age, and prolonged exposure to corticosteroids, sedatives, or paralytics.\textsuperscript{25,26}

Recent data suggest that ICU patients with AKI and AKI-KRT may also be at increased risk of ICU-AW. Specifically, a recent prospective multicenter cohort study of 642 intubated patients identified days on KRT as an independent risk factor for ICU-AW.\textsuperscript{27} Likewise, our group analyzed
a cohort of 104 ICU survivors and found that patients with stage 2 or 3 AKI had increased severity of muscle weakness, lower health-related QoL, and impaired ability to return to work or driving. However, additional data are needed to further investigate the link between AKI, KRT, potential confounding factors such as ICU length of stay (LOS) and overall illness severity, and the risk of ICU-AW.

**ICU-AW: diagnosis**

For this review, in concert with prior guidelines, we will use the term ICU-AW as a framework that encompasses muscle atrophy, weakness, and dysfunction in ICU patients. Muscle dysfunction (ie. impaired muscle performance) due to critical illness typically results from overlapping effects of myopathy and neuropathy; however, as outlined below, the studies linking AKI and ICU-AW are overwhelmingly centered on muscle rather than nerve function. Assessment of skeletal muscle in the ICU is influenced by a patient’s ability to engage and follow simple commands and the time course and severity of their illness. With the emerging data linking AKI to ICU-AW, nephrologists practicing in the ICU should have foundational knowledge of the diagnosis and measures of ICU-AW to be able to interpret results and communicate effectively with intensivists, interprofessional team members, patients, and their care partners as part of patient-centered care (Table 1).

ICU-AW is diagnosed by assessing global muscle strength testing using the Medical Research Council-Sum Score (MRC-ss) in the appropriate clinical setting. MRC-ss grades volitional strength in twelve predefined peripheral muscle groups (bilateral shoulder abductors, elbow flexors, wrist extensors, hip flexors, knee extensors, and foot dorsiflexors). Handgrip
dynamometry measures grip strength and has been proposed as a valid and reliable screening
tool for ICU-AW, but, like MRC-ss, requires patient participation.²⁹

Imaging permits muscle assessment in patients that are unable to follow commands,
potentially leading to earlier detection of ICU-AW. Computed tomography (CT) can quantify
muscle size and quality but is rarely performed clinically for this purpose. Muscle ultrasound
has similarly been proposed as a diagnostic tool to assess muscle size and quality, and has been
demonstrated in ICU patients to correlate well with CT-derived measures³⁰ and
immunohistochemical analysis of muscle biopsy specimens.²²,²³ However, whether ultrasound
reliably predicts patient-relevant outcomes including ICU-AW requires further study.

Electromyography (EMG), nerve conduction velocity studies (NCV), and muscle biopsy may be
useful to diagnose ICU-AW but are relatively costly and invasive techniques typically reserved
for complex neuromuscular disorders and research. Ultimately, imaging, EMG/NCV, and muscle
biopsy are diagnostic adjuncts to strength testing by trained providers using MRC-ss; despite its
limitations, strength testing remains the gold standard and most practical method to diagnose
ICU-AW.

ICU-AW: pathophysiology

Multiple mechanisms have been proposed for ICU-AW (Figure 1). Critical illness is
associated with a significant inflammatory response, which has been demonstrated in
experimental studies to alter mitochondrial, myofibrillar, and collagen protein homeostasis and
to trigger myofibrillary oxidative stress.¹⁹ Additional animal, space flight, and human research
has shown that disuse or immobility lead to muscle atrophy through mechanical silencing—the
process of inducing myosin loss and atrophy through the removal or reduction of internal (i.e.,
muscle contraction) or external (i.e., loading or weight-bearing) stimuli. Patients requiring mechanical ventilation with deep sedation are therefore at the greatest risk of muscle dysfunction. We propose that AKI and acute KRT may independently contribute to ICU-AW.

Proposed mechanisms of muscle wasting in AKI

Though muscle wasting in CKD, including in kidney failure, has been studied for decades, less is known about muscle wasting in AKI. Some of the mechanisms underlying muscle wasting in CKD may apply to AKI, including systemic inflammation, metabolic acidosis, defective insulin signaling, and malnutrition stimulating mediators of muscle protein catabolism including the ubiquitin-proteasome system (UPS), caspase-3, lysosomes, and myostatin. However, unrelated mechanisms may contribute to muscle wasting in AKI, as AKI and CKD are distinct clinical processes, with AKI having drastically worse prognosis in the ICU.

The experimental data linking AKI to muscle wasting are summarized in Figure 3 and outlined in detail in Table 2. Collectively, animal studies suggest that AKI of multiple etiologies causes muscle wasting by rapid activation of protein degradation via UPS, subsequently followed by impaired protein synthesis via, in part, downregulation or disruption of activation/phosphorylation of the protein kinase mTOR (mammalian target of rapamycin) by the kinase Akt. The Akt-mTOR signaling pathway has been shown in other settings to promote muscle synthesis and inhibit muscle degradation in response to stimuli such as insulin and insulin-like growth factor-1. These studies also implicate roles for dysregulated autophagy, mitochondrial dysfunction, and inflammatory mediators, especially interleukin-6 (IL-6).

The ability of AKI to induce systemic inflammation and predispose to skeletal muscle wasting may be considered a form of organ “cross-talk.” Notably, such kidney-skeletal muscle
cross-talk has been proposed to mediate muscle wasting in CKD. AKI is increasingly recognized as a systemic inflammatory state associated with multiorgan dysfunction induced by TNF-alpha, interleukin-1, IL-6, and other mediators. These systemic effects are hypothesized to mediate the high mortality of critically ill patients with AKI and the worse outcomes of ICU patients with AKI-KRT versus ESKD. Specifically, renal ischemia-reperfusion injury has been shown in animal models to induce cardiac oxidative stress, amino acid (AA) depletion, cardiomyocyte apoptosis, and systolic and diastolic dysfunction. Similar effects of AKI on skeletal muscle may occur. IL-6 specifically has been shown in other animal models to induce or augment muscle catabolism, thereby providing another plausible mechanistic link between AKI and muscle breakdown. However, data to support the theory that direct inflammatory cross-talk between kidney and skeletal muscle mediates AKI-induced muscle wasting remain limited.

**Proposed mechanisms of muscle wasting in acute KRT**

While AKI itself may promote ICU-AW, AKI-KRT may compound muscle dysfunction by additional mechanisms (Figure 3).

The effects of KRT on muscle have been extensively studied in kidney failure, but far less is known about the impact of AKI-KRT on muscle. A recent systematic review on the acute effects of hemodialysis on skeletal muscle included 14 studies of patients with kidney failure and reported variable effects on muscle perfusion and function but consistently found that hemodialysis causes acute muscle protein breakdown and net protein loss, induces markers of muscle protein breakdown (caspase-3 activity and polyubiquitin), and triggers inflammation, especially IL-6.
Hemodialysis and hemofiltration remove unbound water-soluble molecules non-selectively. Therefore, the effects of KRT on muscle may be mediated by non-selective removal of AAs, peptides, or small proteins. Studies decades ago demonstrated substantial removal of AAs by intermittent hemodialysis (IHD) in the setting of kidney failure. Similar significant dialytic losses of AAs, peptides, and small proteins have subsequently been demonstrated in AKI-KRT (Table 3). The loss is most pronounced in continuous kidney replacement therapy (CKRT), followed by prolonged intermittent KRT, and lastly by IHD, paralleling the cumulative clearance (i.e., standardized Kt/V urea) typically provided by each modality.

While KRT clearly removes AAs, how significantly this contributes to negative protein or nitrogen balance is unclear. For example, a recent study of ICU patients with AKI, including 31 CKRT patients and 24 non-KRT patients, measured serum AA levels at days 1 and 6. Effluent levels of AAs were also measured in the CKRT group and all AAs were detected. However, significant depletion of serum AA levels was noted before CKRT initiation and glutamic acid was the only AA with significantly lower levels in CKRT patients than in non-KRT AKI patients. The authors concluded that these findings refute the hypothesis that losses during KRT are the main reason for altered micronutrient profile in AKI patients. However, serum levels of substances do not necessarily reflect total body levels. An alternative hypothesis is that, while AKI alone does indeed result in significant disruption in AA metabolism, the added non-selective clearance of AAs by KRT may aggravate catabolism and total body depletion of AAs as serum levels are maintained at the expense of muscle breakdown.
Similarly, we carried out an analysis of serum and effluent levels of 101 metabolites, including AAs, in 13 CKRT patients and, despite detecting AAs in the effluent with most dialyzer sieving coefficients approaching 1, we found reductions in serum levels of only 3 of 20 AAs.\textsuperscript{56} Notably, the reductions were seen at 24h relative to baseline, but thereafter no further reduction in AA levels was seen at 48h or 72h,\textsuperscript{56} again suggesting that serum AA levels may be maintained despite ongoing removal by CKRT at the expense of total body/muscle stores.

In addition to AAs, KRT removes other nutrients, minerals, and metabolites that could potentially affect muscle function.\textsuperscript{54-56} Of these, the most studied is phosphate (\textbf{Table 4}). Though readily cleared from the vascular compartment by hemodialysis or hemofiltration, the kinetics of phosphate removal by IHD and CKRT differ dramatically. Because phosphate is primarily intracellular and slowly re-equilibrates with the extracellular compartment, IHD clears a relatively small amount of total-body phosphate with each treatment. CKRT, by virtue of being continuous, overcomes the slow re-equilibration between the intra- and extracellular compartments.\textsuperscript{57} CKRT ultimately removes phosphate so effectively that after 2-4 days, hypophosphatemia requiring repletion is a near-universal complication when using traditional phosphate-free CKRT solutions.\textsuperscript{57}

Phosphate depletion may lead to significant and long-term effects on muscle function. For example, phosphate depletion during CKRT has been linked with decreased erythrocyte levels of 2,3-diphosphoglycerate,\textsuperscript{58} which, especially if coupled with hypophosphatemia-induced cardiovascular dysfunction,\textsuperscript{59,60} could lead to impairment in oxygen delivery to skeletal muscle. Furthermore, phosphate depletion also could directly impair the function of kinases in
the Akt-mTOR pathway and other signaling pathways responsible for stimulating muscle protein synthesis.\textsuperscript{35,61-63}

Data linking hypophosphatemia directly to muscle weakness in general ICU populations are limited.\textsuperscript{64} However, multiple observational studies have found hypophosphatemia to be associated with worse outcomes in CKRT patients and suggest that it may contribute to respiratory muscle dysfunction. Specifically, CKRT-induced hypophosphatemia has been independently associated with prolonged mechanical ventilation or increased need for tracheostomy, and, to a lesser degree, with increased LOS, with variable but generally neutral effects on mortality.\textsuperscript{60,65-70}

As opposed to the situation with phosphate, most standard CKRT solutions contain physiologic or near-physiologic concentrations of potassium, calcium, and magnesium. As such, hypokalemia, hypocalcemia, and hypomagnesemia – though present in a substantial minority of CKRT patients – develop less frequently than hypophosphatemia\textsuperscript{9,10} and fewer data exist on the impact of depletion of these electrolytes on outcomes. CKRT specifically using regional citrate anticoagulation can cause hypocalcemia and hypomagnesemia,\textsuperscript{71} as citrate chelates magnesium and calcium, and both hypocalcemia and hypomagnesemia have been associated with respiratory muscle weakness in small studies.\textsuperscript{72,73} Furthermore, limited data have associated hypomagnesemia and hypocalcemia with increased ICU mortality and morbidity, including respiratory failure and/or need for mechanical ventilation,\textsuperscript{74-76} potentially implicating respiratory muscle dysfunction. In contrast, hypokalemia developing during CKRT was not associated with mortality in a recent single-center study of >1200 patients.\textsuperscript{77} The relative
impacts of CKRT-induced hypokalemia, hypocalcemia, or hypomagnesemia on ICU-AW remain unclear.

**Interventions to mitigate micronutrient loss during KRT**

Use of AA-containing dialysate has been studied in kidney failure, though the impact on outcomes and clinical uptake have been limited.\(^{41,42}\) There are no studies of AA-containing CKRT solutions for AKI-KRT. Studies of AA supplementation in CKRT have been performed but with limited impact on outcomes apart from maintenance of serum AA levels.\(^{49}\)

Based on the available data, prevention of hypophosphatemia is a reasonable intervention to mitigate ICU-AW in CKRT patients.\(^{57}\) Options include adding phosphate to CKRT solutions or using commercially available dextrose-free solutions containing phosphate. Multiple centers, including those using regional citrate anticoagulation, have reported that either option can effectively mitigate hypophosphatemia without effects on solute control apart from modest degrees of hypocalcemia, hypoglycemia, and metabolic acidosis.\(^{67,78,79}\) Moreover, in a retrospective before-and-after study at one of our centers, the use of phosphate-containing CKRT solutions was independently associated with decreased durations of mechanical ventilation and ICU and hospital LOS without impact on mortality.\(^{67,78}\) Though promising, prospective interventional data on phosphate-containing CKRT solutions and outcomes are needed. An alternative to adding phosphate to CKRT solutions to mitigate CKRT-induced hypophosphatemia is to implement preemptive enteral or intravenous phosphate replacement as soon as serum phosphate levels fall to within normal limits, often 24-48h after CKRT initiation.\(^{57}\)
The optimal approach to replacement of other electrolytes in CKRT patients appears less clear. Though typically standard of care, data on the benefits of treating or preventing CKRT-induced hypomagnesemia, hypocalcemia, or hypokalemia – beyond normalizing serum levels – are lacking.\textsuperscript{80,81} Interestingly, some animal and observational human data suggest harm from calcium supplementation in the setting of sepsis or general critical illness,\textsuperscript{82-84} but the relevance of these observations to KRT patients is unclear.

Similarly, though nutrition is essential supportive care in the ICU, the optimal nutritional approach to mitigate ICU-AW in patients with AKI or AKI-KRT is unclear. Despite some data suggesting that standard approaches to estimating nutritional needs perform poorly in critically ill AKI patients,\textsuperscript{85} guidelines recommend, based on low-quality evidence, that AKI patients receive the same targets as other ICU patients for protein (1.2-2 g/kg/day) and total calories (25-30 kcal/kg/day).\textsuperscript{86} In patients requiring CKRT or frequent KRT, additional protein supplementation up to 2.5 g/kg/day is recommended to counteract AA loss.\textsuperscript{86} Notably, secondary outcomes of some large RCTs of nutrition in the ICU suggest that earlier initiation of supplemental nutrition and/or higher caloric intake may be associated with prolonged need for KRT or delayed kidney recovery.\textsuperscript{87,88} Furthermore, higher protein intake has not been convincingly associated with improved outcomes in general ICU populations, with a recent meta-analysis demonstrating attenuation of muscle loss but no impact on measured muscle strength, QoL, discharge destination, or mortality.\textsuperscript{89} Likewise, a recent study of 15 ICU patients demonstrated impaired incorporation of nutritional AAs into skeletal muscle despite normal enteral protein digestion and absorption.\textsuperscript{90} High-quality prospective data on optimal nutrition for ICU patients with AKI or AKI-KRT are needed.
Physical rehabilitation/early mobilization to mitigate ICU-AW in patients with AKI

Early mobilization, physical rehabilitation, and exercise are the primary approaches to reducing the detrimental effects of prolonged immobilization or bedrest. Multiple factors have been proposed as barriers to early mobilization in the ICU including vasopressor and sedative use and, in AKI-KRT patients, the presence of vascular catheters and ongoing KRT. However, clinical practice and recent research have demonstrated that these barriers can be overcome. Strategies that we and others have reported include disconnection from the KRT circuit during mobilization, extensions placed on KRT lines, portable batteries to mobilize patients with KRT machines, and temporarily adjusting the KRT prescription (e.g., to recirculation mode or to pause net ultrafiltration) to facilitate rehabilitation.

Catheter type (i.e., non-tunneled vs tunneled) and access site (i.e., femoral vs jugular) may influence the perceived feasibility of mobilizing KRT patients. However, in one prospective study, 77 patients with a total of 92 femoral venous or arterial catheters suffered no catheter-related complications during mobility sessions including hip flexion. Another study of 101 ICU patients with femoral catheters receiving 253 therapy sessions, including standing, walking, sitting, supine cycle ergometry, and in-bed exercises, reported no catheter-related adverse events. Collectively, these data suggest that mobilization of ICU patients with femoral catheters is feasible and safe.

We recently performed a systematic review analyzing adverse events, both major (i.e., catheter dislodgement, accidental extubation, bleeding, fall, hemodynamic emergency) and minor (i.e., desaturation, hypotension, bradycardia, tachycardia), reported in 10 observational studies involving 840 mobility sessions during CKRT and found pooled rates of 1.6% and 0.2%
for minor and major adverse events, respectively. Finally, the 2014 expert recommendations on safety criteria for active mobilization of mechanically ventilated adults concluded that in-bed or out-of-bed exercises can be performed during CKRT with low risk of adverse events. Though it seems probable that early mobilization in CKRT patients would have a meaningful benefit on outcomes, randomized trials to prove this hypothesis are lacking.

**Post-discharge care for ICU-AW in AKI survivors**

Advancements in intensive care have led to increasing survival over the past two decades, but ICU survivors also often face significant impairments in cognitive, emotional, and physical health. Post-intensive care syndrome (PICS) encompasses the development or exacerbation of symptoms or impairments after critical illness in the cognitive, psychiatric, or physical domains and has become an increasing focus of post-discharge care being provided in multidisciplinary PICS clinics. Though some benefit in terms of decreased readmissions and PTSD has been demonstrated, no studies thus far have demonstrated improvements in functional status through rehabilitation provided by these clinics.

Similarly, dedicated post-AKI clinics have increased in number over the past decade, and tailored outpatient nephrology follow-up has been advocated as an intervention to improve post-AKI outcomes. Observational data suggest that early nephrology follow-up after AKI improves outcomes, though prospective studies thus far have been scarce and have produced mixed results, supporting the need for further interventional trials.

No data exist on how to best address persistent ICU-AW in AKI survivors, but we propose nephrologists providing post-AKI ambulatory care should, at a minimum, recognize these patients as being at high risk of long-term functional impairment and, where feasible,
consider referral to physical and occupational therapy for evaluation and treatment. Future studies should therefore investigate whether providing rehabilitation is useful in addressing long-term physical impairments in AKI survivors and, if so, how to best deliver such care. One novel model could be to provide post-AKI nephrology visits within or in coordination with multidisciplinary PICS clinics, which could potentially improve the feasibility of providing systematic post-AKI care. Alternatively, for AKI patients requiring post-discharge outpatient KRT, providing rehabilitation services or exercise training during hemodialysis, similar to interventions that have proven to some degree to be beneficial in kidney failure, could prove effective.

**Conclusions and Future Directions**

Critically ill patients who develop AKI are at high risk of skeletal muscle loss and dysfunction and associated long-term impairments in physical function and QoL. The need for acute KRT likely further exacerbates the risk of ICU-AW. Nephrologists must work with ICU teams to address potentially modifiable risk factors for ICU-AW and coordinate multidisciplinary care to optimize delivery of rehabilitation. The development of KRT quality assurance teams, which advocate for excellence in KRT and create protocols to prevent complications such as hypophosphatemia, optimize nutritional support, and enhance delivery of physical therapy, may mitigate the burden of ICU-AW in patients with AKI-KRT. Furthermore, though data to support such approaches remain limited, advances in proteomics and metabolomics may further enhance our understanding of how ICU patients adapt to extracorporeal therapies that non-selectively clear solutes. Specifically, improved characterization of the resulting metabolic derangements through analyses of tissue, blood, and effluent could promote the development
of precision medicine approaches to reestablishing homeostasis in critically ill patients with AKI-KRT. In conclusion, additional experimental research and clinical trials are direly needed to better understand the mechanisms that link critical illness, AKI, and KRT to ICU-AW and to ultimately develop and validate treatment strategies to prevent and mitigate ICU-AW in these high-risk patients.

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References


Figure 1: Framework for the relationship between critical illness, AKI requiring KRT, and ICU-associated weakness

AKI frequently complicates critical illness. In addition to the traditional mechanisms of AKI in critical illness such as ischemia, sepsis, and nephrotoxin exposure, AKI and critical illness have a bidirectional relationship mediated by systemic inflammation, organ cross-talk, and fluid overload, combining to produce the high rates of morbidity and mortality characteristic of AKI in the ICU. Muscle wasting is a well-known complication of critical illness mediated by immobility; systemic inflammation; altered myofibrillary, mitochondrial, and collagen protein homeostasis; and myofibrillar oxidative stress. Though not considered a traditional risk factor for ICU-AW, emerging data, both observational human studies and experimental animal data, strongly imply that AKI and KRT may directly contribute to the development of ICU-AW.

Abbreviations: AKI, acute kidney injury; ICU, intensive care unit; ICU-AW, ICU-associated weakness; KRT, kidney replacement therapy. Created with BioRender.com.

Figure 2: Risk factors for and management of ICU-associated weakness

In addition to emerging data linking AKI and KRT to ICU-AW, risk factors for ICU-AW include prolonged immobilization, need for mechanical ventilation, use of certain medications (especially prolonged treatment with corticosteroids, sedatives, or paralytic agents), sepsis and other forms of systemic inflammation, multiorgan dysfunction, and high severity of illness. Though additional data are needed to better delineate and validate interventions to prevent
and treat ICU-AW, early physical therapy and adequate nutritional support are felt to be the
cornerstones of prevention and management.

Abbreviations: AKI, acute kidney injury; ICU, intensive care unit; ICU-AW, ICU-associated
weakness; KRT, kidney replacement therapy; MOF, multiorgan failure. Created with
BioRender.com.

Figure 3: Potential mechanisms of muscle atrophy in critically ill patients with AKI and AKI
requiring KRT

Experimental data have demonstrated that AKI within 24h causes muscle wasting by rapid
activation of protein degradation via the UPS. This is followed as soon as 48h after AKI onset by
impaired protein synthesis which is mediated in part by downregulation of the Akt-mTOR
kinase pathway that normally functions to promote muscle anabolism in response to
physiologic stimuli such as leucine. Abnormal glucose metabolism and insulin response have
also been demonstrated in AKI, with AKI appearing to impair the normal ability of insulin to
stimulate muscle anabolism, glucose utilization, and glycogen synthesis. AKI itself induces an
intense systemic inflammatory response that has been shown to cause tissue damage,
inflammation, and dysfunction of multiple distant organs including the heart, and a similar
effect on skeletal muscle as has been demonstrated in cardiac muscle may partly mediate AKI-
induced muscle wasting. IL-6 in particular may be a central mediator of this effect, as this
cytokine has been shown to play a prominent role in the systemic inflammation and organ
cross-talk that follows AKI, to mediate muscle wasting in many other clinical settings, and to be
upregulated in muscle tissue after AKI. Likewise, AKI and ICU-AW may be linked by oxidative stress as AKI has been shown in animal studies to induce oxidative stress of distant organs, including the heart, and oxidative stress has been associated with skeletal muscle wasting and dysfunction in multiple non-AKI models of ICU-AW. Animal data also implicate possible roles for abnormalities in mitochondrial number and function and dysregulated autophagy. In addition to stimulating inflammation, KRT (especially CKRT) may directly contribute to ICU-AW via the non-selective clearance and the resulting depletion of muscle stores of amino acids, peptides, and small proteins as well as phosphate and other metabolites.

Abbreviations: AKI, acute kidney injury; CKRT, continuous kidney replacement therapy; ICU-AW, ICU-associated weakness; IL-6, interleukin-6; KRT, kidney replacement therapy; mTOR, mammalian target of rapamycin; UPS, ubiquitin-proteasome system. Created with BioRender.com.
<table>
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<th>Test or Modality</th>
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<th>Provider</th>
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| Medical Research Council-sum score (MRC-ss)²⁸ | • Standardized manual muscle strength testing of 12 pre-defined bilateral muscle groups:  
  • Shoulder abductors  
  • Elbow flexors  
  • Wrist extensors  
  • Hip flexors  
  • Knee extensors  
  • Foot dorsiflexors  
  • 6-point ordinal scale, ranging from 0 = no muscle contraction to 5 = normal strength against full resistance, with total score of 0-60  
  • Gold standard and clinical standard for diagnosing ICU-AW | • Requires patient engagement and cognitive function  
  • Ordinal scale may reduce sensitivity | • Physical Therapist  
  • Occupational Therapist  
  • Dietician  
  • Physiatrist* | • Upon ICU awakening and repeated serially  
  • Milestones† | • <48/60 with no other etiology of weakness constitutes a diagnosis of ICU-AW |
| Handgrip dynamometry (HGD)²⁹ | • Evaluates handgrip strength, i.e., concurrent strength of the elbow flexors and wrist extensors  
  • Standardized position recommended  
  • Continuous outcome in kilograms or pounds of force improves objectivity | • Requires patient engagement and cognitive function  
  • Requires equipment | • Physical Therapist  
  • Occupational Therapist  
  • Dietician  
  • Physiatrist* | • Upon ICU awakening and repeated serially  
  • Milestones† | • <7 kg for females and <11 kg for males suggests a diagnosis of ICU-AW |
<table>
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<th>Assessment Method</th>
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<tr>
<td>Handheld Dynamometry (HHD)</td>
<td>Evaluates strength (force generated) of a selected muscle group (e.g., knee extensors)</td>
<td>Requires patient engagement and cognitive function</td>
<td>Requires equipment</td>
<td>Physical Therapist, Occupational Therapist, Dietician, Physiatrist*</td>
<td>Rarely used in clinical practice, Commonly used in research</td>
</tr>
<tr>
<td>Muscle Ultrasound (US)</td>
<td>Ultrasonography to visualize and assess respiratory and peripheral skeletal muscles</td>
<td>Requires equipment, Requires training, Heterogeneity in reported techniques, positioning, and landmarking</td>
<td>Trained sonographer‡</td>
<td></td>
<td>20-30% reduction in muscle size in first 10 days of ICU admit is suggestive of ICU-AW</td>
</tr>
<tr>
<td>Computed Tomography (CT) or MRI</td>
<td>Imaging modalities with precise and accurate measures of muscle mass and composition</td>
<td>Expensive, Requires significant planning in ICU for scheduling and for patient safety</td>
<td>Radiologist</td>
<td>Rarely used for muscle assessment, Typically ordered for other purpose and muscle is a</td>
<td></td>
</tr>
</tbody>
</table>

Note: †Trained sonographer, ‡Heterogeneity in reported techniques, positioning, and landmarking, ¶Myofiber necrosis.
<table>
<thead>
<tr>
<th>Assessment Type</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Secondary Assessment</th>
<th>Patient Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electromyography (EMG) and Evoked Forces</td>
<td>• Non-volitional measurements of motor axon depolarization (evoked force) by either electrical or magnetic stimuli • Objective measure of evoked force using an ergometer</td>
<td>• Expensive • Requires training and equipment • Stimuli may cause discomfort • Physiatrist* • Neurologist • Physical therapist with training</td>
<td>Rarely used in clinical practice Primarily used in research</td>
<td>Compared to healthy controls or followed longitudinally No standardized values</td>
</tr>
<tr>
<td>Muscle biopsy</td>
<td>• Most commonly obtained from vastus lateralis and performed with local anesthesia • Immunohistochemical, histochemical, and biochemical examinations performed on tissue</td>
<td>• Expensive • Invasive • Risk of complications • Physician or advanced practice provider with training • Pathologist</td>
<td>Rarely used in clinical practice Occasionally used in research</td>
<td>Interpreted by pathologists Norms established for certain parameters</td>
</tr>
</tbody>
</table>

*Physiatrists are physicians specializing in Physical Medicine and Rehabilitation. †Patient milestones include any change in medical or functional status that requires re-evaluation (i.e., clinical decompensation or fall); ICU and hospital discharge; and 1, 3, 6 and 12 months after discharge. ‡Trained sonographer may be from any professional discipline that has received ultrasound-specific training; no current standard for muscle ultrasonography certification exists. Additional abbreviations: EI, echo intensity (a surrogate marker of muscle quality); L3, level of third lumbar vertebra.
Table 2: Studies in animal models investigating the mechanisms of muscle wasting in AKI.

<table>
<thead>
<tr>
<th>Author(s), Year</th>
<th>AKI Model and Timing</th>
<th>Findings</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitch, 1981; Clark &amp; Mitch, 1983; May et al., 1985&lt;sup&gt;112-114&lt;/sup&gt;</td>
<td>Rat, 24-48h after bilateral ureteral ligation</td>
<td>● Lower serum AA levels  &lt;br&gt;● AA release from perfused rat hindquarter  &lt;br&gt;● Findings exaggerated in rats deprived of foot and water  &lt;br&gt;● Increased protein degradation without changes in synthesis at 24h  &lt;br&gt;● Increased degradation and impaired synthesis are present by 48h  &lt;br&gt;● Changes in protein metabolism correlate with changes in insulin-mediated protein synthesis, glucose utilization, and glycogen synthesis</td>
<td>● AA release in AKI is of peripheral/non-hepatic source  &lt;br&gt;● Muscle protein degradation occurs soon after AKI, with impaired synthesis occurring later  &lt;br&gt;● Dietary changes may exacerbate AKI-induced AA release  &lt;br&gt;● Suggests role of defective insulin-induced muscle synthesis and glucose utilization</td>
</tr>
<tr>
<td>Flugel-Link et al., 1983&lt;sup&gt;115&lt;/sup&gt;</td>
<td>Rat, 30h after bilateral nephrectomy</td>
<td>● Greater net urea generation  &lt;br&gt;● Lower plasma/muscle levels of most AAs  &lt;br&gt;● Increased muscle protein degradation  &lt;br&gt;● Unchanged or slightly decreased muscle protein synthesis  &lt;br&gt;● Net release of phenylalanine, tyrosine, alanine, total AAs, potassium, and phosphate from perfused hemicorpus</td>
<td>● Replicates prior studies with a nephrectomy model of AKI</td>
</tr>
<tr>
<td>Study</td>
<td>Model, Time Point</td>
<td>Findings</td>
<td></td>
</tr>
<tr>
<td>-----------------------</td>
<td>------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
</tbody>
</table>
| Baliga & Shah, 1991   | Rat, gentamicin-  | ● Net muscle protein degradation significantly increased in AKI rats, but only those fed a high-protein diet  
● Muscle protein synthesis not affected  
● Insulin reduced net protein degradation in AKI rats fed low- or normal-protein diet but protein degradation continued despite insulin in AKI rats on high-protein diet |
|                       | induced AKI,      |                                                                                                                                                                                                       |
|                       | assessed on day 8 |                                                                                                                                                                                                       |
|                       | after 7d of      |                                                                                                                                                                                                       |
|                       | gentamicin       |                                                                                                                                                                                                       |
|                       | exposure         |                                                                                                                                                                                                       |
| Price et al., 1998    | Rat, 40h after   | ● Lower or unchanged serum plasma levels of BCAA  
● Activity of BCKAD (mitochondrial enzyme and rate limiting step in BCAA catabolism) in muscles increased by >17-fold  
● Increase in BCKAD activity partly suppressed by correction of acidemia with supplemental sodium bicarbonate  
● Change in BCKAD activity not due to changes in muscle BCKAD mRNA or protein content |
|                       | bilateral ureteral ligation |                                                                                                                                                                                                     |

| Andres-Hernando et al., 2014 | Mice, 7d after bilateral IRI (22 min of renal pedicle clamping) | ● Using serum glutamate levels as a marker, demonstrated increase muscle catabolism at 7 days after IRI                                                                                                                                 |

| McIntire et al., 2014 | Rat, 44h after bilateral ureteral ligation | ● Disrupted phosphorylation of mTOR protein by the kinase Akt (which normally stimulates muscle anabolism induced by the BCAA leucine)  
● Increased muscle levels of IL-6 mRNA, LC3B-II (marker of autophagy), and UPS components (atrogin-1, MuRF) |

|                       |                                                             | ● Replicates possible role of insulin in AKI-induced muscle wasting in nephrotoxic AKI  
● Confirms changes in net muscle protein balance in early AKI are due mostly to increased degradation rather than impaired synthesis  
● Suggests dietary protein intake may increase risk of AKI-induced muscle wasting in nephrotoxic AKI (not replicated in other models) |

|                       |                                                             | ● Suggests that AKI-induced catabolism of BCAA is partly but not fully mediated by acidosis  
● Suggests (as serum levels of BCAAs decreased or remained unchanged despite significant increase in BCAA catabolism by BCKAD) that serum AA levels can change independently of muscle AA levels in AKI |

|                       |                                                             | ● Demonstrates AKI-induced muscle catabolism for the first time in ischemic AKI and in a mouse model  
● Muscle catabolism persists up to 7 days after AKI |

|                       |                                                             | ● Possible mechanism for why AKI results in muscle wasting resistant to nutritional supplementation  
● Suggests roles for IL-6-mediated inflammation, autophagy, Akt-mTOR |
Aniort et al., 2016[^62]

| Rat, gentamicin-induced AKI, assessed at day 7 after 7d of gentamicin exposure |
| ● Muscle atrophy (decreased muscle weight) in extensor digitorum longus but not soleus |
| ● Activation of UPS components (MuRF-1, atrogin-1) |
| ● Downregulation of Akt-mTOR pathway |

- Replicates roles of UPS and Akt-mTOR pathway in nephrotoxic AKI
- Suggests AKI may preferentially affect phasic muscles rather than postural muscles

Nagata et al., 2020[^63]

| Mice, 7 days after IRI [15 min of renal pedicle clamping in contralateral nephrectomized rats (AKI + uremia) or 35 min of clamping in rats with intact contralateral kidney (AKI without uremia)] |
| ● Muscle wasting (decreased weight, myofiber cross-sectional area, and mitochondrial density) and decreased maximal running time in AKI + uremia |
| ● Increased muscle tissue expression of mediators of muscle wasting (myostatin, atrogin-1) in AKI + uremia |
| ● Decreased Akt phosphorylation in AKI + uremia |
| ● Changes in AKI + uremia partially prevented by regimen of regular treadmill exercise and BCAA supplementation |
| ● In AKI without uremia, atrogin-1 expression increased on day 1 but not day 7, and muscle weight was same as control |

- Replicates roles of Akt-mTOR pathway and UPS in ischemic AKI
- Suggests role of disordered mitochondrial function/number in AKI-induced muscle wasting
- First study to relate biochemical or structural changes to measurable deficit in function
- Implies exercise and nutritional supplementation with BCAAs may mitigate muscle wasting in AKI
- Implies uremia may be necessary for induction of muscle wasting in AKI

Note that atrogin-1 is also known as muscle atrophy F-box (MAFbx). Abbreviations: AA, amino acid; AKI, acute kidney injury; AMP, adenosine monophosphate; BCAA, branched chain amino acid; BCKAD, branched-chain ketoacid dehydrogenase; IL-6, interleukin-6; IRI, ischemia-reperfusion injury; mTOR, mammalian target of rapamycin; MuRF, muscle RING-finger protein; UPS, ubiquitin-proteasome system.
Table 3: Studies in humans with AKI requiring KRT demonstrating depletion of amino acids, peptides, proteins, and/or other nutrients.

<table>
<thead>
<tr>
<th>Authors, Year</th>
<th>N</th>
<th>Nutrition and other patient characteristics</th>
<th>KRT modality and approximate dose</th>
<th>Key Study Features and Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davenport &amp; Roberts, 1989&lt;sup&gt;43&lt;/sup&gt;</td>
<td>8</td>
<td>On TPN and mechanical ventilation</td>
<td>High-flux CVVH (1 L/h)</td>
<td>• Approximately 2-4 mmol/day of AAs lost in effluent</td>
</tr>
<tr>
<td>Davies et al., 1991&lt;sup&gt;44&lt;/sup&gt;</td>
<td>8</td>
<td>6/8 on TPN</td>
<td>CAVHDF (Qd 1-2 L/h; variable UF)</td>
<td>• Total effluent losses represented about 10% of daily protein input and up to 112% of AA input for specific AAs (e.g., tyrosine)</td>
</tr>
<tr>
<td>Frankenfield et al., 1993&lt;sup&gt;45&lt;/sup&gt;</td>
<td>17 (+15 controls not on KRT)</td>
<td>Trauma with SIRS on TPN</td>
<td>CAVHDF or CVVHDF (Qd 15 or 30 mL/min; variable Qr)</td>
<td>• AA losses (mean 6.6 g/12h) were 2-3 times higher in CKRT patients than controls and increased with higher Qd and higher AA serum levels but did not correlate with AA intake</td>
</tr>
<tr>
<td>Mokrzycki &amp; Kaplan, 1996&lt;sup&gt;46&lt;/sup&gt;</td>
<td>7 patients (22 effluent samples)</td>
<td>12 samples during TPN infusion; 1 during enteral feeding</td>
<td>CVVH and CVVHDF</td>
<td>• Protein loss of 1.2-7.5g per day</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Protein loss higher with CVVH than CVVHDF despite lower total effluent dose (mean of approximately 1400 mL/h vs. 1800 mL/h)</td>
</tr>
<tr>
<td>Kihara et al., 1997&lt;sup&gt;47&lt;/sup&gt;</td>
<td>6</td>
<td>On TPN receiving 40 g/day of AAs</td>
<td>PIKRT (slow HD with Qd 20 mL/min for 10h daily)</td>
<td>• Mean of 6.2g of AAs eliminated in dialysate per treatment, corresponding to 16% of daily intake and accounting for 43% of the daily negative nitrogen balance</td>
</tr>
<tr>
<td>Novak et al. 1997&lt;sup&gt;48&lt;/sup&gt;</td>
<td>6 (+16 healthy controls)</td>
<td>On TPN; 4 with multiorgan failure; 2 with isolated AKI</td>
<td>CVVHDF (Qd 1 L/h)</td>
<td>• Daily AA nitrogen loss of 0.6 g daily or 4.5% of daily input (including 0.2 g daily of nitrogen as glutamine)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Serum levels of most AA were lower than controls though were stable throughout 5 days of CKRT except for glutamine (whose levels dropped on day 2 but subsequently returned to baseline)</td>
</tr>
<tr>
<td>Study</td>
<td>Number of Patients</td>
<td>Type of Nutrition</td>
<td>Treatment Details</td>
<td>Results/Findings</td>
</tr>
<tr>
<td>-------------------------------</td>
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<td>---------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| Scheinkestel et al., 2003<sup>49</sup> | 11                 | Anuric; on TPN and mechanical ventilation | CVVHD (with Qd 2L/h) | • 17% of infused AAs lost in the dialysate  
  • With protein intake <2.5 g/kg/day 14-57% of serum AA levels were below the normal range, but all levels were within normal limits with protein intake increased to 2.5 g/kg/day |
| Chua et al., 2012<sup>50</sup>   | 7                  | 4/7 on enteral nutrition; 0/7 on TPN | PIKRT (EDHDF, 8h/day with Qb 100 mL/min, Qr 21 mL/min, and Qd 280 mL/min) | • AA loss of 4.2 g/day or 4.5% of intake in patients on enteral nutrition, accounting for 6.5% of negative nitrogen balance of 10.7 g/day |
| Schmidt et al., 2014<sup>51</sup> | 10 KRT sessions in 5 patients | 3/5 on TPN | PIKRT (extended dialysis, 10h per treatment with Qb and Qd of 150 mL/min) | • 10.5g of AAs removed in effluent per each 10h treatment, with glutamine accounting for 30% of the AAs removed  
  • Despite removal, pre- and post-KRT serum AA levels did not differ significantly |
| Umber et al., 2014<sup>52</sup>  | 5                  | 2/5 on IV nutrition | PIKRT (12h SLED sessions with low-flux dialyzer and Qb 200 mL/min and Qd 100 mL/min) | • Mean AA loss of 15.7g (range of 10-57g), including mean of 5.3g of glutamine, per treatment  
  • Albumin loss negligible |
| Stapel et al., 2019<sup>53</sup> | 10                 | 8 on enteral nutrition, 1 on parenteral nutrition | CVVH (high-flux membrane, Qb 180 mL/min, predilution Qr 2.4 L/h) | • 13.4 g day of AA lost per day, including 10.4 g in effluent and 2.9 g assumed to be lost by adsorption  
  • Degree of adsorption varied by AA, with some appearing to be “generated” (i.e., levels higher in effluent than in post-filter blood) |
| Oh et al., 2019<sup>54</sup>    | 60                 | Mix of ward and ICU patients; majority malnourished but nutritional input not recorded | 27 on IHD (2-3h, Qb 200-250 mL/min; Qd 400-500 mL/min); 12 on PIKRT (SLEDf, 6-8h daily, Qb 200 mL/min, effluent 200 | • First 1-2 sessions of KRT studied  
  • Micronutrient loss was generally greater for CVVH >> SLEDf > IHD (e.g., mean total AA loss of 18.7, 8.2, and 5.1g, respectively, per 24h of CVVH or per IHD/SLEDf treatment) |
<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Dialysis Modality</th>
<th>Flow Rate (L/min)</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Griffin et al., 2020</td>
<td>13 (11 AKI, 2 ESKD)</td>
<td>CVVH (35 mL/min)</td>
<td>Differences in modality persisted when correcting for AA plasma concentration and KRT dose; authors attributed differences to modality (i.e., convection v. diffusion v. both) rather than dose ● Serum AA levels dropped with KRT, but rebounded within 2h of stopping ● Variable but marked loss of non-AA trace elements (e.g., copper, zinc) ● B vitamins were undetectable in effluent</td>
<td></td>
</tr>
<tr>
<td>Ostermann et al., 2020</td>
<td>55 AKI patients (31 treated with CKRT)</td>
<td>CVVHD (25 mL/kg/h)</td>
<td>● 22 of 101 metabolites measured decreased in serum by day 2 ● Serum levels were reduced for only 3 of 20 AAs (alanine, proline, and cysteine); other metabolites with significant serum reductions included phosphate and lactate ● AA levels in ef- fluent in all patients with most sieving coefficients approaching 1 ● Re- ductions were largely seen at 24h relative to baseline, but no further reduction was seen beyond 48h, suggesting serum levels of AAs or other metabolites are maintained despite removal by CKRT at the expense of muscle or total body stores</td>
<td></td>
</tr>
</tbody>
</table>

Note: TPN = total parenteral nutrition; AA = amino acid; ESKD = end-stage kidney disease; CVVH = continuous venovenous hemofiltration; CVVHD = continuous venovenous hemodiafiltration; KRT = kidney replacement therapy.
patients and only the difference in glutamic acid levels persisted to day 6

Abbreviations: AA, amino acid; AKI, acute kidney injury; CAVH, continuous arterio-venous hemofiltration; CAVHDF, continuous arterio-venous hemodiafiltration; CKRT, continuous kidney replacement therapy; CVVH, continuous veno-venous hemofiltration; CVVHD, continuous veno-venous hemodialysis; CVVHDF, continuous veno-venous hemodiafiltration; EDHDF, extended daily hemodiafiltration; ESKD, end-stage kidney disease; HD, hemodialysis; IHD, intermittent hemodialysis; KRT, kidney replacement therapy; PIKRT, prolonged intermittent kidney replacement therapy; Qb, blood flow rate; Qd, dialysate flow rate; Qr, replacement fluid rate; SIRS, systemic inflammatory response syndrome; SLED, sustained low-efficiency dialysis; SLEDf, sustained low-efficiency diafiltration; TPN, total parenteral nutrition; UF, ultrafiltration.
<table>
<thead>
<tr>
<th>Authors, Year</th>
<th>N</th>
<th>Patient characteristics and KRT modality</th>
<th>Key Findings</th>
</tr>
</thead>
</table>
| Demirjian et al., 2011 | 66 | AKI treated with CVVHD for >2 days | ● Hypophosphatemia (<2 mg/dL) in 27%  
● Decline in serum phosphate was independently associated with higher rate of prolonged respiratory failure requiring tracheostomy (OR 1.81) but not 28-day mortality |
| Yang et al., 2013 | 760 | AKI treated with CVVH | ● Incident hypophosphatemia (<2.5 mg/dL) not associated with outcomes in overall cohort  
● In subgroup of 521 (69%) patients with hypophosphatemia, ratio of total days with hypophosphatemia over total CVVH days was independently associated with 28-day mortality (OR 1.45, p = 0.008) |
| Bellomo et al., 2014 | 1441 | CVVHDF, with either 25 or 40 mL/kg/h of total effluent dose, with ratio of Qd and post-filter Qr of 1:1 | ● Post-hoc analysis of the RENAL trial (comparing two doses of CKRT for AKI in ICU)  
● Hypophosphatemia (<0.6 mmol/L) developed in 32%, with peak incidence on CKRT days 2 and 3  
● Hypophosphatemia was not independently associated with 90-day mortality |
| Sharma et al., 2015 | 20 CKRT patients (+10 controls) | 19/20 CKRT patients on mechanical ventilation; 4 CKRT patients on parenteral nutrition, 10 on enteral nutrition; controls were surgical patients mostly without AKI | ● Mean RBC 2,3-DPG level decreased after 2d of CKRT and was associated with lower oxygen carrying capacity (i.e., mean oxygen partial pressure required for 50% hemoglobin saturation)  
● Reduction in 2,3-DPG levels reached 29% in the 3 patients still on CKRT at day 7  
● Reductions in 2,3-DPG correlated with negative phosphate balance despite maintenance of normal serum phosphate levels  
● Greater reduction in 2,3-DPG associated with increased hazard ratio for death |
| Lim et al., 2017 | 96 acute KRT patients | 64 (67%) on mechanical ventilation; 44 patients received CKRT only, 28 IHD only, and 24 both | ● Secondary analysis of single-center cohort study  
● 25 patients developed hypophosphatemia and had longer duration of vasopressor support and mechanical ventilation, with the latter persisting on multivariable analysis (adjusted OR 14); no difference in ICU mortality |
<table>
<thead>
<tr>
<th>Study</th>
<th>Number</th>
<th>Description</th>
<th>Findings</th>
</tr>
</thead>
</table>
| Hendrix et al., 2020[^68]   | 72     | 60 with AKI; 12 with ESKD; all treated with ≥12h of CKRT                   | ● Hypophosphatemia (<2.5 mg/dL) in 45 (63%)  
● Hypophosphatemia associated on univariable analysis with increased ICU LOS (p = 0.014) but not with hospital LOS, AKI recovery, duration of mechanical ventilation, or ICU mortality |
| Sharma et al., 2020[^65]    | 907    | Subset of patients in ATN trial on mechanical ventilation, with 80% starting KRT with CVVHDF, 15% with IHD, and 4.5% with SLED | ● In a post-hoc analysis of the ATN trial[^10] of KRT intensity in AKI, compared to patients assigned to less-intensive KRT, patients randomly assigned to more-intensive KRT had a lower rate of successful extubation (HR 0.67, p <0.001), corresponding to 1 fewer ventilator-free day over 14d  
● More intensive KRT resulted in more hypophosphatemia  
● Statistically significant interaction between effect of treatment group on extubation rates and tertiles of baseline phosphate levels, with patients in lowest tertile of baseline phosphate (≤4.3 mg/dL) having a 43% lower hazard rate of successful extubation if assigned to intensive group  
● Effect of treatment intensity was statistically significant in patients treated with CKRT and SLED but not in those treated with IHD |
| Thompson-Bastin et al., 2021[^78] | 1396   | 511 treated with CKRT using phosphate-free solutions; 885 treated with CKRT with phosphate-containing solutions | ● Single-center retrospective before-and-after study  
● Hypophosphatemia (<2.5 mg/dL) occurred in 21% of those treated with phosphate-containing CKRT solutions vs. 62% of those treated with phosphate-free solutions, with phosphate-free solutions associated with 8-fold higher adjusted incidence of hypophosphatemia (p < 0.001)  
● Phosphate supplementation requirement higher in non-phosphate group (p < 0.001) |
| Thompson-Bastin et al., 2022[^67] | 992    | All intubated; 343 treated with only phosphate-free CKRT solutions; 649 only with phosphate-containing solutions | ● Single-center retrospective before-and-after study of only mechanically ventilated patients  
● Treatment with phosphate-containing CKRT solution independently associated in multivariable analysis with 12% more ventilator-free days, 17% fewer ICU days, and 20% fewer hospital days  
● Reduction in ventilator-free days reproduced in propensity score analysis of 303 patient pairs  
● No impact on mortality |
Abbreviations: 2,3-DPG, 2,3-diphosphoglycerate; AKI, acute kidney injury; CKRT, continuous kidney replacement therapy; CVVH, continuous veno-venous hemofiltration; CVVHD, continuous veno-venous hemodialysis; CVVHDF, continuous veno-venous hemodiafiltration; ESKD, end-stage kidney disease; ICU, intensive care unit; IHD, intermittent hemodialysis; KRT, kidney replacement therapy; LOS, length of stay; OR, odds ratio; Qd, dialysate flow rate; Qr, replacement fluid rate; RBC, red blood cell; SLED, sustained low-efficiency dialysis; TPN, total parenteral nutrition.
Critical Illness

Organ Cross-Talk

Fluid Overload

Sepsis & Systemic Inflammation

Shock & Nephrotoxins

AKI & KRT

Observational Human Data

Animal Data

ICU-AW

Immobility

Disrupted Myofibrillary, Mitochondrial, & Collagen Homeostasis

Myofibrillatory Oxidative Stress

Systemic Inflammation
Mechanical ventilation & immobilization

Systemic Inflammation

AKI-KRT

Rehab & Early Mobility

Nutritional Support

Medications

MOF
Akt-mTOR↓

↑ UPS

Mitochondrial dysfunction

Glucose & insulin dysregulation

ROS

Autophagy

Removal of micronutrients (amino acids & phosphate)

Inflammatory response

Kidney-skeletal muscle cross-talk

Journal Pre-proof