

## VIEWPOINT

# Permissive hypofiltration

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### Abstract

Acute kidney injury (AKI) is a syndrome with a multitude of causes and is associated with high mortality and a permanent loss of renal function. Our current understanding of the most common causes of AKI is limited, and thus a silver bullet therapy remains elusive. A change in the approach to AKI that shifts away from the primary composite endpoint of death/dialysis, and instead focuses on improving survival and mitigating permanent renal damage, is likely to be more fruitful. We suggest that the current approach of augmenting renal function by increasing the renal blood flow or glomerular filtration rate during AKI may actually worsen outcomes. Analogous to the approach towards adult respiratory distress syndrome that limits ventilator-induced lung injury, we propose the concept of permissive hypofiltration. The primary goals of this approach are: resting the kidney by providing early renal replacement therapy, avoiding the potentially injurious adverse events that occur during AKI (for example, fluid overload, hypophosphatemia, hypothermia, and so forth), and initiating therapies focused on improving survival and mitigating permanent loss of kidney function.

### Introduction

Acute kidney injury (AKI) is a disorder that often complicates the hospital course of patients and is associated with a significant mortality risk. Those patients with the most severe forms of AKI, who develop such significant solute or fluid imbalance that they are usually treated with renal replacement therapy (RRT), experience a hospital mortality of approximately 60% [1]. In spite of improvements in care, the mortality of AKI remains unacceptably high [2].

AKI is a clinical syndrome that is associated with the acute loss of kidney function, as evidenced by a drop in the glomerular filtration rate (GFR). The most common causes of AKI in developed countries are sepsis, circulatory shock, major cardiovascular surgery, and heart and liver failure [1]. Because decreased renal blood flow (RBF) is usually assumed to play a role in each of these conditions, the traditional teaching approach for AKI is that restoration of RBF is critical. The focus of therapeutic intervention in AKI for the past 40 years has thus been to restore RBF and to minimize nephrotoxic exposure. Therapeutic clinical trials of AKI have focused on increasing the RBF and GFR by utilizing a variety of drugs (for example, dopamine, anaritide, fenoldopam) [3]. Unfortunately, this approach has yielded no successful therapy for the treatment of AKI.

### Our understanding of the pathophysiology of AKI is insufficient

AKI is a clinical syndrome with a multitude of causes. Like any syndrome, AKI can be separated into susceptibility and exposure. The most common susceptibilities for AKI are advanced age and chronic kidney disease (CKD). The most common exposure related to AKI is sepsis, which is associated with 45 to 50% of all cases of AKI [4]. Of note, available preclinical and human data suggest that septic-associated AKI is *not* associated with tubular necrosis [5,6]. These same studies demonstrate that RBF in sepsis is typically increased, and that, despite this augmented RBF, septic patients still experience a drop in GFR and develop AKI (reviewed in [6]). In addition, the few studies that have assessed histopathology in septic patients do not show evidence of tubular necrosis [7]. The failure to develop appropriate therapeutic agents for AKI may thus be due to the fact that the therapeutic agents being considered work via increasing the GFR by increasing RBF (for example, anaritide) – which is unlikely to benefit those patients with sepsis, the most common exposure associated with AKI.

It is logical to try and assist a failing organ by treating the underlying cause. Once an organ is injured, however, trying to force that organ to work harder may not be the best approach. In fact, this approach has been shown to be counter-productive in other areas of critical care. For

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example, the focus of therapy during myocardial infarction is twofold: treat the underlying cause and rest the injured organ. For example, when patients sustain a significant myocardial infarction, if ventricular function is inadequate after treatment (for example, angioplasty) then it is common to place an intra-aortic balloon pump (or in extreme cases a ventricular assist device) to decrease the workload on the heart [8]. Similarly, the therapeutic intervention in adult respiratory distress syndrome (ARDS) is to *decrease* the tidal volume, sometimes even to the point of allowing respiratory acidosis (permissive hypercapnia), in order to avoid exacerbating lung injury and thereby to improve outcomes [9].

### Lessons from ARDS and potential for harm

AKI and ARDS are syndromes that have much in common. Both have multiple etiologies; and the most common cause for both ARDS and AKI is sepsis. Both syndromes are associated with increased mortality; and both affect critically ill patients, contributing to an increased risk of death. In addition, both syndromes typically involve a mechanical intervention for organ support, RRT and mechanical ventilation, respectively. However, the clinical trial endpoints of focus are quite different for AKI and ARDS. In ARDS, the endpoints utilized in clinical trials are most often both short-term disability (30-day mortality, ventilator-free days) and long-term disability. For AKI, however, the endpoints are typically only short term: 30-day mortality and need for RRT. The need for RRT is akin to the need for intubation and mechanical ventilation in ARDS and yet the two endpoints are treated very differently. *This difference is critical.* The notion that a drug or intervention can prevent the need for mechanical ventilation in a patient with severe ARDS is not realistic. ARDS causes rapid deterioration in pulmonary function and organ support (for example, mechanical ventilation) is instituted early. Because the endpoint in AKI is need for RRT, there is an implicit expectation that a drug or intervention can alter the clinical trajectory of severe AKI within a few days and furthermore that RRT can be safely delayed awaiting renal recovery. With the advent of more biologically compatible membranes and physiologic RRT fluids, there has been a secular trend of initiating RRT sooner. Therefore, even if diagnostic techniques improve our time to diagnosis of AKI, do we expect a therapeutic drug or intervention to forestall the need for organ support within a short time frame (that is, 2 to 3 days)? Unlike opening an artery for the treatment of myocardial infarction, the kidney's response to injury is more complex; the renal vasculature, glomeruli, renal tubules, and interstitium do not respond monolithically. To expect an intervention or drug to heal the kidney and all its complex components in a few days is not biologically plausible.

One of the lessons of ARDS is thus to focus on realistic endpoints. Instead of short-term mortality and need for RRT, we propose that the more appropriate short-term endpoints in studying AKI should be short-term mortality and RRT-free days, or even AKI-free days (similar to the endpoints in ARDS).

Another critical lesson from ARDS is the potential to do harm. The mainstay of treatment for ARDS is to avoid ventilator-induced lung injury [9]. A key advance in the treatment of ARDS was the recognition that mechanical ventilation performed incorrectly can be injurious [9]. Similarly, the way that patients with AKI are treated can also be injurious. RRT must be prescribed in a thoughtful fashion to avoid significant adverse events. For instance, the use of intermittent hemodialysis in critically ill patients can result in significant hypotension and persistent intestinal ischemia [10,11].

### Fluid overload in acute kidney injury

Because classic teaching states that hypovolemia is the most common reversible cause of AKI, the standard treatment for AKI is a trial of volume (for example, crystalloid infusion). For the vast majority of clinicians, the standard approach to AKI once it is recognized is as follows: rule out reversible causes of AKI, discontinue diuretics, administer a trial of volume, stop any nephrotoxic drugs, and rule out obstructive nephropathy. Once the patient is deemed optimally resuscitated, a trial of loop diuretics is usually conducted. This approach is reasonable and represents the recommended approach [12]. However, this approach also offers the opportunity to do harm.

A trial of volume administration is a core feature of most empiric AKI treatment. Not surprisingly, fluid overload is common in patients with AKI [13]. Fluid overload has been shown to be associated with increased mortality and increased length of stay in multiple studies, and has an independent effect on mortality even after the severity of illness and the degree of AKI are taken into account [13-15]. This association has been shown in adults and children, and prospective trials have shown that interventions which reduce fluid overload lead to more rapid liberation from mechanical ventilation and *less* renal failure [16,17].

### Renal replacement therapy in acute kidney injury

For those patients with AKI who require RRT, the technical aspects of RRT have become increasingly important. Contemporary RRT is associated with higher dosing of RRT as compared with historical controls. When patients are subjected to higher doses of RRT, they experience improved solute clearance and faster resolution of electrolyte and acid-base imbalances. However, these patients may have a higher incidence of inadequate plasma antibiotic levels, hypophosphatemia and hypothermia.

Pharmacology studies assessing antibiotic levels in patients undergoing continuous renal replacement therapy (CRRT) with contemporary dosing found that antibiotic levels were inadequate for up to 75% of the antibiotics tested [18]. Appropriate and adequate antibiotics has been a cornerstone of sepsis therapy [19,20], and studies such as these endorse the notion that antibiotics can be rendered less useful if the CRRT and the drug dosing are not harmonized. Similarly, patients undergoing CRRT are susceptible to hypophosphatemia [21]. Hypophosphatemia can have multiple negative consequences including, but not limited to, hemolysis, respiratory failure, rhabdomyolysis, delirium and neutrophil dysfunction [22,23]. Another potential complication of RRT is hypothermia. Because of the extracorporeal circuit, inadequate warming of replacement fluid/dialysate can lead to hypothermia [24]. In a large multicenter study of more than 10,000 patients, hypothermia has been shown to be a major risk factor associated with increased risk of mortality in critically ill patients [25]. Large well-powered clinical trials of increased doses of RRT did not protocolize these aspects of RRT [21,26], and some investigators have suggested that inadequate control of these parameters may have had a significant negative impact.

Early institution of RRT is likely to have multiple positive effects in AKI, including improved fluid balance and the capacity to rest the injured kidney. However, the manner in which RRT is conducted in the ICU appears to be important. RRT must be conducted with the appropriate management of drug dosing, thermal control, volume and electrolyte balance.

### **Interplay of acute kidney injury and chronic kidney disease**

Classic teaching regarding patients who survive an episode of AKI – in particular, acute tubular necrosis – states that these patients achieve full or nearly full recovery. This notion was based on multiple studies that followed survivors of AKI after hospital discharge [27]. More recently, from 2008 through 2012, multiple studies assessing unique cohorts of patients demonstrated that patients who survive an episode of AKI have a significant risk for progression to advanced CKD (stage 4/5) [28-33]. Moreover, there are multiple studies that have linked severity of AKI with increased risk of CKD progression [29,30,34]. In short, patients who experience a severe episode of AKI are at risk for incident CKD, and those patients with pre-existing CKD are at risk for accelerated progression of CKD.

### **Choice of endpoints for clinical trials in AKI**

As discussed earlier, the short-term composite endpoint of death/RRT may not be appropriate. Because subsets of

AKI patients tend to progress to CKD, medium-term outcomes in AKI should also be assessed. Similar to the pathophysiology of ARDS, wherein a fibroproliferative phase follows the initial exudative phase, subsets of patients with AKI experience ongoing fibrosis that tends to persist after injury. Clinical epidemiologic studies confirm that about 15 to 20% of patients who experience AKI rapidly progress to advanced-stage CKD within 20 to 24 months [28]. Given that CKD is a significant risk factor for cardiovascular events, patients who survive AKI and progress to CKD are more likely to experience cardiovascular events [35].

In aggregate, we propose that endpoints for clinical trials of AKI should be short term and medium term. The primary short-term endpoints should be 30-day mortality and AKI-free days. Medium-term endpoints should include 90-day to 180-day outcomes to determine whether permanent loss of renal function and associated cardiovascular events can be mitigated. The composite endpoint of major adverse kidney events has been proposed to include each of these end points.

### **Hypothesis: permissive hypofiltration**

The approach we propose is based on four broad themes: (1) focus on the underlying process causing AKI, since there are many different mechanisms that cause AKI; (2) when a patient is experiencing AKI, augmenting the GFR and RBF may not be helpful and may in fact be harmful; (3) current and recommended interventions for AKI have the capacity to do harm; and (4) interventions should be focused on *durable* renal recovery and improving survival.

The first theme is obvious of course, but has important consequences when enacted. This theme recognizes that septic-associated AKI is different from nephrotoxic AKI, which is different from ischemic AKI caused by profound global hypotension (for example, cardiac arrest). The treatment for all AKI is therefore not necessarily about augmenting RBF, but rather restoring RBF when it is persistently inadequate.

The second theme is based on the notion that increasing the work of an injured organ may worsen outcomes. As in the example of myocardial infarction and ARDS, organ support during injury is a key approach to improving outcomes. Consistent with this concept, early institution of RRT has the capacity to rest the injured organ by limiting the solute load and mitigating fluid overload. As an example, much of the progress in abrogating the progression of CKD is focused on treating presumed hyperfiltration using renin-angiotensin-aldosterone system blockade to lower the GFR and prevent fibrosis, thereby improving organ survival. Similarly, we believe that the utilization of early RRT and avoidance of GFR augmentation via hyperemia during

AKI may have the same effect as angiotensin-converting enzyme inhibitors have on patients with CKD to preserve long-term renal function.

The third theme is based on recognizing that thermal control, antibiotic dosing and maintenance of electrolyte and volume balance must be carried out carefully during RRT to avoid harm. This is one of the core lessons from the experience of ARDS therapy; limiting the harm of the device–patient interaction. In order to improve outcomes, these aspects of the care of the patient with AKI must be improved.

The fourth theme is based on the preclinical and epidemiology data that show AKI is associated with progression to CKD. We posit that interventions initiated at the time of AKI may have durable long-term effects, particularly on retarding the progression of incident CKD. The improvement long-term outcomes include, but are not limited to, improvement in survival, a decreased incidence of CKD and fewer cardiovascular events.

### Testing the hypothesis: trial design

We suggest a conceptual trial design to test our hypothesis. The study population would consist of patients with RIFLE/Acute Kidney Injury Network stage 2 or greater AKI who also have evidence of an elevated AKI biomarker that predicts a high likelihood of persistence or progression of AKI. Patients would then be randomized to one of three arms: standard care, protocolized AKI management, and protocolized AKI management plus experimental agent.

The standard care arm would involve conservative management and monitoring for a need to begin RRT. If required (as assessed by routine clinical judgment), CRRT should be delivered at a dose of 20 to 25 cm<sup>3</sup>/kg/hour for patients on vasopressors. Patients not requiring vasopressors should receive thrice-weekly hemodialysis with weekly Kt/V  $\geq 3.6$ . Additional management should be as per clinical judgment.

The AKI protocolized management arm would consist of early initiation of RRT based on the criteria presented in Table 1, and then protocolized CRRT management would be as follows: CRRT delivered at a dose of 20 to 25 cm<sup>3</sup>/kg/hour for patients on vasopressors, or thrice-weekly hemodialysis with weekly delivered Kt/V  $\geq 3.6$  for patients not requiring vasopressors; maintenance of normothermia unless otherwise indicated; avoidance of hypophosphatemia; antibiotic dosing based on delivered RRT dose; and maintenance of volume and electrolyte balance.

Multiple candidate agents could be tested in the protocolized AKI management plus therapeutic agent arm of the study. The goal of the therapeutic agent would be to decrease mortality, enhance renal recovery and decrease the incidence of long-term loss of renal

**Table 1. Entry criteria for early initiation of renal replacement therapy**

Inclusion criteria	
1.	Age $\geq 18$ years
2.	Assessed to be adequately resuscitated
3.	Evidence of acute kidney injury. Defined by RIFLE/Acute Kidney Injury Network stage 2 or greater (creatinine or oliguria) and elevated acute kidney injury biomarker (precise cutoff determined by biomarker selected)
Exclusion criteria	
1.	Patient deemed moribund
2.	Any history of renal allograft
3.	Presence or clinical suspicion of glomerulonephritis, renal obstruction, vasculitis or acute interstitial nephritis
4.	Prehospitalization advanced chronic kidney disease, defined by an estimated glomerular filtration rate $< 15$ ml/minute/1.73 m <sup>2</sup>
5.	Any dialysis conducted within the previous 3 months (either acute or chronic renal replacement therapy)

function. As an example, preclinical models show that angiotensin-converting enzyme inhibition given at the time of AKI decreases the incidence of renal fibrosis during recovery [36]. Other agents that may prove successful include those that modulate the cell cycle or agents that block transforming growth factor beta or that target a variety of inflammatory pathways. Pilot and feasibility studies could start with variations of the approaches proposed.

### Conclusion

AKI is a syndrome with a multitude of causes and is associated with a high risk for mortality or permanent loss of renal function. Our current understanding of the most common causes of AKI is limited. A change in the approach to AKI that shifts away from short-term endpoints such as death or dialysis and instead focuses on improving longer-term survival and mitigating permanent renal damage is likely to be more fruitful. In addition, we suggest that augmenting renal function via increasing the RBF or GFR during AKI may actually worsen outcomes. Resting the kidney and providing early RRT analogous to the approach in the treatment of ARDS may prove to be a more effective strategy to improve survival and decrease permanent loss of kidney function for patients with AKI.

### Abbreviations

AKI, acute kidney injury; ARDS, adult respiratory distress syndrome; CKD, chronic kidney disease; CRRT, continuous renal replacement therapy; GFR, glomerular filtration rate; RBF, renal blood flow; RIFLE, Risk, Injury, Failure, Loss and End-stage kidney disease; RRT, renal replacement therapy.

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#### Competing interests

All authors participated in the concept and writing of the manuscript. LSC has links with Gambro Medical, Nxstage Medical, Alere, Astute Medical and Abbott Medical. JAK has links with Gambro Medical, Alere Medical, Abbott, Fresenius, Baxter and Astute. CR has links with Gambro, Merck, Alere, Astute, Abbott and GE.

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