Evolving Practices in Critical Care and Potential Implications for Management of Acute Kidney Injury

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Acute kidney injury (AKI) is a common complication in hospitalized patients, with an incidence of 3 to 10% (1–4). In-hospital mortality rates that are associated with AKI remain high, in the range of 30 to 70% (5–8), despite significant improvements in dialytic technology as well as important advances in critical care, which have resulted in improved survival for other critical illnesses, including acute lung injury and sepsis (9). These improvements include continuous renal replacement therapies, which allow for continuous removal of solutes and fluid and may be tolerated better from a hemodynamic standpoint, and biocompatible dialysis membranes, which are associated with reduced complement and granulocyte activation.

In general, indications for dialysis in the acute care setting have been extrapolated from those that are applied in chronic kidney disease, including volume overload that is refractory to diuretic therapy; electrolyte abnormalities (in particular hyperkalemia); uremic complications (pericarditis or pleuritis); severe acidosis (pH < 7.20); and selected toxic ingestions, such as methanol, ethylene glycol, and other water-soluble agents (10,11). However, the evidence base supporting specific dialysis practices in the acute care setting is limited. For example, several studies that were completed in the 1960s and 1970s compared “early” and “late” initiation of dialysis, using blood urea nitrogen (BUN) to define early and late (Table 1). These studies primarily were cohort studies that used historical controls, not randomized, clinical trials. The results of these investigations, along with extrapolation from the ESRD population, promoted recent practice patterns. Currently, many nephrologists often delay dialysis in the acute care setting until the patient has an impending complication of AKI, such as hyperkalemia leading to cardiac arrhythmias, acidosis resulting in hypotension, or oliguria leading to volume overload or hypoxemia, or until the BUN exceeds 100 mg/dl (18). Given differences in protein catabolism, diet, comorbid conditions, and severity of illness, it may be inappropriate to extrapolate any BUN or creatinine cutoff for dialysis initiation in the chronic setting to patients with AKI.

Practice patterns regarding decisions to initiate dialysis in the acute care setting have not been well described and have not been subjected to randomized trials. Further investigation is needed to describe and provide evidence for these clinical practices. However, nephrologists and intensivists should recognize that recent evidence-based changes in the practice of critical care medicine have significant effects on the parameters that trigger the decision to initiate dialysis. For example, aggressive volume resuscitation for sepsis will exacerbate volume overload in an oliguric patient; as a result that patient may require dialysis earlier in the course of AKI to avoid complications of volume overload, including hypoxemia. In this article, we review recent changes in critical care practice and the potential effects of these practices on metabolic factors that may influence dialysis practice. In so doing, we emphasize the need for randomized clinical trials to examine the optimal timing of dialysis after AKI.

Acute Respiratory Distress Syndrome, AKI, and Acidosis

Acute respiratory distress syndrome (ARDS) historically has been associated with a mortality rate of 40 to 50%. The ARDS Network demonstrated that a lung-protective, low tidal volume ventilation strategy markedly improves survival (19). In the ARDS Network trial, 861 patients who had acute lung injury and were mechanically ventilated were randomly assigned to either conventional tidal volumes of 12 ml/kg or to low tidal volumes of 6 ml/kg of predicted body weight. There was an 8.8% absolute reduction in death (31.0 versus 39.8%; P = 0.007) before discharge home or breathing without assistance with the low tidal volume ventilation strategy. A subsequent ARDS Network trial compared higher and lower levels of positive end-expiratory pressure (PEEP) (20) and found a further reduction in mortality (26%) in patients who were ventilated with the low tidal volume strategy. Therefore, the current standard of care for patients with acute lung injury is to use tidal volumes in the range of 4 to 6 ml/kg ideal body weight with a plateau pressure <30 cm H2O, maintaining acceptable oxygenation by modulating PEEP and fraction of inspired oxygen (21). However, the low volume ventilatory strategy can...
lead to acidemia, resulting from respiratory acidosis, a strategy that is known as permissive hypercapnia (22). In the original ARDS Network trial, 57 (14%) of 423 patients who were ventilated with low tidal volumes had a serum pH < 7.30 on day 1 of the trial, compared with 22 (6%) of 386 patients in the high tidal volume therapy arm of the trial despite no difference in the incidence of AKI in the two groups. In the face of respiratory acidosis, the functioning kidney generates bicarbonate to maintain pH balance. However, the renal capacity to compensate for respiratory acidosis is limited after AKI. Indeed, the mild metabolic acidosis that often accompanies early AKI will compound the respiratory acidosis of permissive hypoventilation. Without correction of the metabolic acidosis, hyperkalemia, hypotension, and other complications may ensue. Intravenous sodium bicarbonate may transiently correct the metabolic acidosis but may have adverse effects, including hypoxemia from volume overload as well as intracellular acidosis (23). Therefore, in the face of kidney injury, dialysis may be required for control of acidemia.

It is interesting that recent animal and human studies have suggested that low tidal volume ventilation may be renoprotective. In several animal models, injurious ventilatory strategies have been shown to result in AKI (24–26). In the ARDS Network trial (19), patients who were ventilated with the low tidal volume strategy were slightly less likely to develop AKI (number of “renal failure–free days” 20 ± 11 versus 18 ± 11 in control subjects; \( P = 0.005 \)). Although low tidal volume may protect against AKI (a finding that will require confirmation), it is important to recognize that patients who develop AKI in the setting of acute lung injury may require dialysis earlier when low tidal volume ventilation is applied, to prevent the complications of a mixed metabolic and respiratory acidosis.

### Early Goal-Directed Therapy, AKI, and Volume Overload

Approximately 750,000 patients in the United States develop severe sepsis each year (27). Severe sepsis is associated with a mortality rate of approximately 30% (27). It has been recognized that patients with the sepsis syndrome may benefit from early goal-directed therapy, that is, early and aggressive volume resuscitation and vasopressor management (28). Indeed, the 2004 Surviving Sepsis Campaign guidelines (from organizations e.g., the American College of Chest Physicians, the American Thoracic Society, the European Society of Intensive Care Medicine, and the Society for Critical Care Medicine) recommend resuscitation of patients on the basis of the protocol described by Rivers et al. (29). In this protocol, tissue oxygen delivery is optimized in patients with early severe sepsis using a stepwise approach of goal-directed volume resuscitation (using a central venous catheter to guide management), followed by the use of vasopressors, transfusion, and inotropic agents to achieve and maintain a central venous oxygen saturation of >70%.

These strategies frequently result in the administration of several liters of crystalloid, usually 0.9% saline or other isotonic solutions, with the goal of maintaining a central venous pressure of 8 to 12 mmHg and sustaining organ perfusion (28). Indeed, the use of a central venous catheter per protocol to maintain central venous pressure resulted in a significant increase in crystalloid administration during the first 6 h of the protocol. Whereas volume expansion may abrogate prerenal azotemia, the effects of the Rivers et al. protocol on other causes of AKI and its complications remain untested. The recently completed Acute Respiratory Distress Syndrome Network Fluid and Catheter Treatment Trial (FACTT) study may shed important light on the effects of targeted volume resuscitation. However, when there is concomitant AKI, the capacity of the kidneys to maintain salt and water balance, as well as acid-base homeostasis, is reduced. In particular, in the setting of oliguria, patients with AKI may become rapidly volume overloaded. Moreover, the expansion of body water by crystalloid administration may mask the severity of AKI by increasing the total body water space, thereby diluting creatinine and other markers of kidney function (30).

In the setting of volume overload, diuretic agents can be used to augment urine output, although several observational studies and a large randomized trial (31–33) have indicated no benefit and even potential harm associated with the use of high-dose furosemide and other diuretic agents in the intensive care unit (ICU). Even in the setting of diuretic-responsive AKI, there is a diminished capacity to induce a large net negative fluid balance (which usually is required, given obligate fluid

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**Table 1. Timing of initiation of dialysis and its association with mortality**

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>No. of Patients</th>
<th>Study Design</th>
<th>Predialysis Urea (mg/dl)</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parsons et al. (12)</td>
<td>1961</td>
<td>33</td>
<td>Cohort with historical control</td>
<td>Early: 120 to 150, Late: 200</td>
<td>Early: 25, Late: 88</td>
</tr>
<tr>
<td>Fischer et al. (13)</td>
<td>1966</td>
<td>162</td>
<td>Cohort with historical control</td>
<td>Early: 152, Late: 231</td>
<td>Early: 51, Late: 77</td>
</tr>
<tr>
<td>Kleinknecht et al.² (14)</td>
<td>1972</td>
<td>71</td>
<td>Cohort with historical control</td>
<td>Early: 93, Late: 164</td>
<td>Early: 29, Late: 42</td>
</tr>
<tr>
<td>Conger (15)</td>
<td>1975</td>
<td>18</td>
<td>Case-control</td>
<td>Early: 50, Late: 120</td>
<td>Early: 20, Late: 64</td>
</tr>
<tr>
<td>Gettings et al. (16)</td>
<td>1999</td>
<td>100</td>
<td>Retrospective cohort</td>
<td>Early: 42.6, Late: 94.5</td>
<td>Early: 61, Late: 80</td>
</tr>
<tr>
<td>Bouman et al. (17)</td>
<td>2002</td>
<td>65</td>
<td>Randomized trial</td>
<td>Early: 48, Late: 105</td>
<td>Early: 31.4, Late: 25</td>
</tr>
</tbody>
</table>

²Case patients and control subjects differed with respect to both the timing of initiation of dialysis and the dose of dialysis delivered.
requirements in the form of antibiotics, vasopressor agents, and parenteral or enteral nutrition) and may be limited further by hemodynamic effects (e.g., venodilation) and metabolic complications, including hypokalemia and hyponatremia (34). In the setting of acute lung injury, volume overload may be poorly tolerated because an increase in extravascular lung water and pleural effusions may impair oxygenation and ventilation further. Therefore, in the setting of oliguric AKI, aggressive fluid resuscitation may necessitate earlier initiation of dialytic support for control of volume status and to remove extravascular fluid.

In addition, depending on the choice of intravenous fluids administered, the patient may develop a hyperchloremic metabolic acidosis, exacerbating the acidemia described in the previous section. Hyperchloremic metabolic acidosis is more likely to occur when 0.9% saline is used. In the Rivers study (28), patients in the early goal-directed therapy arm received an average of 4.9 L of fluid during the first 6 h of their hospital course. The effects of crystalloid administration on acid-base balance have not been studied carefully in the critically ill. In the Saline versus Albumin Fluid Evaluation (SAFE) trial, patients received relatively little crystalloid by post-Rivers standards (1565 ± 1526 ml during the first 24 h) and equal amounts of nonstudy fluids, rendering evaluation of the intervention on acid-base balance difficult (35). Furthermore, the SAFE study, along with recent meta-analyses, demonstrated that there is no benefit to colloid administration in the critically ill, compared with crystalloid administration. This also may result in increased crystalloid administration to critically ill patients, which, in the presence of kidney injury and depending on the choice of intravenous fluid, may worsen acidosis. In a randomized clinical trial from the surgical literature, Scheingraber et al. (36) randomly assigned 24 women who were undergoing gynecologic surgery to receive 0.9% saline or Ringer’s lactate solution. These patients received an average of 5 L of crystalloid during the first 2 h of surgery, approximately the same volume of fluid that patients in the Rivers study received during the first 6 h of resuscitation. Women who received 0.9% saline had a reduction in pH from 7.41 to 7.28, with no associated change in PaCO2 but with an increase in serum chloride from 104 to 115 mmol/L. Therefore, rapid infusion of chloride-containing solutions may have significant effects on pH, in particular in the setting of other therapeutic interventions such as permissive hypercapnia (Figure 1).

Corticosteroids, AKI, and Azotemia

Recent studies suggest that relative adrenal insufficiency may be underrecognized in critically ill patients. The diagnosis (and therefore the incidence) of relative adrenal insufficiency remain controversial, but it has been estimated that 10 to 30% of critically ill patients have relative adrenal insufficiency (37,38). Annane et al. (39) reported in a randomized clinical trial that low-dose hydrocortisone (50 mg, four times per day) and fludrocortisone (50 µg, once a day) for 7 d enhanced survival with no increase in complications among ICU patients with septic shock; a large multicenter clinical trial is ongoing. Meta-analyses of recent studies also have suggested that low-dose corticosteroids may have survival benefit (40,41). Although the survival benefit of steroids remains an area of clinical debate, these studies have led to wider recognition of relative adrenal insufficiency and treatment of more critically ill patients with low-dose corticosteroids.

It is well established that steroids contribute to the hypercatabolism of critically ill patients. Slotman et al. (42) reported a significant increase in BUN over the entire first 7 d in critically ill patients who had sepsis and were treated with methylprednisolone for a 24-h period, when compared with patients who were treated with placebo (26 versus 11%; P < 0.01). There was no associated increase in serum creatinine, suggesting that the increase in BUN primarily was the result of increased protein catabolism and not AKI. Therefore, patients who are treated with steroids and who have AKI are likely to experience an abrupt increase in nitrogenous waste products, which may result in uremic complications and also diminish the ability to provide nutritional support. Hypercatabolism will be exacerbated further by acidosis, as a result of the effects on acidosis on the ubiquitin-proteasome pathway (43). Finally, the mineralocorticoid effects of methylprednisolone, prednisone, or fludrocortisone will promote fluid retention and volume overload by increasing sodium reabsorption in the distal tubule. Therefore, patients who are treated with glucocorticoids may require earlier dialytic intervention primarily for azotemia but also for volume overload (Figure 1).

Future Directions

Randomized trials that focus on several aspects of the dialysis prescription, including the preferred modality of dialysis in the critically ill and the optimal method of nutrition support for AKI, should be designed and carried out. The optimal dose of dialysis is the focus of the ongoing Acute Renal Failure Trial Network study (44), a multicenter, randomized trial to compare intensive versus conventional dialysis dose for treatment of severe AKI.

Recent changes in clinical practice in the ICU highlight the need for clinical trials to determine the optimal timing of the
initiation of dialysis after AKI. Earlier provision of dialysis may be associated with increased risks (11); these include an increased risk for infection from an indwelling dialysis catheter, hypotension associated with therapy, and leukocyte activation from contact with dialysis membranes, although some of these factors may be attenuated by the use of biocompatible membranes and extended treatment duration, either in the form of slow low efficiency dialysis or continuous renal replacement therapy. Moreover, earlier provision of dialysis might result in procedures’ being performed on patients who otherwise eventually would have recovered kidney function. The effects of dialysis on recovery of kidney function are unclear. Animal studies have suggested that autoregulation of blood flow is impaired after ischemic injury; whether this applies to human disease is unclear but cannot be excluded by current data. Although continuous or hybrid dialysis modalities have not been shown definitively to enhance survival or recovery of kidney function after AKI, these modalities tend to be associated with less intradialytic hypotension than intermittent hemodialysis. However, continuous and hybrid therapies are relatively new methods of renal replacement, and the full spectrum of their effects has not been characterized fully.

Ultimately, whether the hypothetical risks are outweighed by potential benefits of earlier dialysis initiation will require a rigorously conducted randomized clinical trial. Early intervention will require careful consideration of patients’ inclusion criteria; for example, patients might be enrolled after experiencing a 200% increase in serum creatinine (the “injury” criteria of the new Acute Dialysis Quality Initiative RIFLE criteria for acute renal failure) and randomly assigned to start dialysis when prespecified levels of BUN are attained. Biomarkers that better predict the course of AKI would be helpful to incorporate into clinical trial design, although reliable, valid biomarkers may not be available for several years or more. Pilot studies will be needed to test feasibility and acceptance by nephrologists and non-nephrologists alike.

Conclusion
Randomized clinical trials are urgently needed with the goal of reducing the exceptionally high mortality rates that are associated with AKI. While awaiting the results of randomized clinical trials, nephrologists and other intensivists should recognize that changes in evidenced-based ICU practice may necessitate earlier initiation of dialysis in selected circumstances, particularly among patients who are treated with low tidal volume ventilation, early goal-directed therapy for sepsis, and corticosteroids for adrenal insufficiency.

References


