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EDITORIAL

Newphrologist: The Intensive Care Kidney Specialist

The tsunami of CKD has now possibly generated an even greater wave of acute kidney injury (AKI) that is sweeping over the world. The causes and frequencies of AKI differ markedly between developed and developing nations, but the wave of AKI continues to rise.[1] The pre-eminent risk factor for the development of AKI is CKD, and older patients are at risk for multiple reasons.[2] The elderly have less kidney regenerative capacity and often have chronic medical conditions that render them more greatly susceptible to kidney insults, such as ischemic heart disease. Notably, an episode of AKI may follow several courses: (1) complete recovery, (2) progressive CKD, (3) worsening of the rate of progression of pre-existent CKD, and (4) evolution to ESRD.[2] In fact, the number one reason why a patient is initiated onto dialytic therapy today in the United States is AKI, and AKI is common in intensive care units, where nephrologists now spend an ever-increasing amount of time as consultants.

This issue of *Advances in Chronic Kidney Disease* underscores a call to action for nephrologists who ply their tools of trade in intensive care units. The average nephrologist devotes nearly half of the working day to hospitalized patients, and a disproportionate amount of this time is spent in intensive care units. The most common reasons for the appearance of kidney specialists in intensive care units include AKI, particularly in septic patients, hypertension, electrolyte and acid-base disturbances, and patients with ESRD and a host of distressing conditions, including hemorrhage, cardiac failure, myocardial ischemia, pulmonary edema, post-surgical recovery, and infection-related problems. As such, nephrologists must become facile with the tools of intensivists, whose numbers now include experts in infectious disease, neurology, surgery, anesthesiology, and emergency medicine. Moreover, nephrologists must collaborate with intensivists to provide cohesive and coherent care plans because critically ill patients cannot be treated in isolation, as a multitude of other factors impinge on their health.

Sepsis is the most common cause of AKI and AKI is a harbinger of sepsis.[3] Therefore, recognition of sepsis is paramount followed by its treatment with antibiotics. An accrual of knowledge about newer antibiotics and their respective dosing regimens, especially those reserved for more exotic infections and those that are intrinsically nephrotoxic, must be achieved firsthand. In addition, systematic avoidance of nephrotoxic antibiotics must be practiced, since such nephrotoxins may prove injurious when combined with other injurious renal exposures, such as radiocontrast media. Protocolized avoidance of nephrotoxins, especially iodinated radiocontrast media, requires collaborative leadership and input from nephrologists at pharmacy therapeutics committees. This knowledge must be judiciously distributed among other involved health care personnel, pharmacists, and the electronic health record, with fault-free dispersal through computerized order entry systems, given the emerging specter of stage 2 meaningful use criteria that begin in 2013.[4] These criteria encourage information technology in health care as a driver of continuous quality improvement at the point of care and information exchange in a highly structured format.

AKI runs rampant in intensive care units and has multiple and often overlapping causes. AKI is frequently complicated by a reduction of uremic solute clearance and/or urine output to the extent that renal replacement therapy is necessary. The intensivist-nephrologist must now be conversant in continuous renal replacement therapies because intermittent hemodialysis may not be feasible in hypotensive individuals, especially those who become vasopressor-dependent for several days or more. Whether using continuous venovenous therapy as purely hemofiltration or as hemodiafiltration, the

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critical care kidney specialist must appreciate not only the positive aspects of continuous therapy but also the negative ones, including net negative potassium and phosphorus balance,[5] as well as reductions in vasopressor concentrations and antibiotic concentrations. With regard to the latter, continuous venovenous therapy may offer the intensive care pharmacy an easier pathway to effective antibiotic dosing,[6] compared with intermittent dialysis or sustained low-efficiency dialysis, unless the latter modality is on a continuous basis as is possible with regional citrate anticoagulation.[7] Recently, sustained low-efficiency dialysis/regional citrate anticoagulation has been proved effective and safe in individuals with severely compromised hepatic function. Furthermore, patients with portal-systemic encephalopathy or cerebral edema from other causes who are at risk for impending cerebral herniation may benefit from continuous therapies.

The effective circulatory volume can be manipulated, as can the prevailing tonicity in which the swollen brain is bathed. The manipulation of serum sodium with renal replacement therapy[8] may now supplant or augment conventional osmotherapy[9] and is now within the purview of the nephrologist-intensivist who may now be called upon to enact treatments for brain shrinkage. Likely, consultations requesting these treatments will increase. Even if armed with more advanced techniques of renal replacement therapy, the nephrologist-intensivist must now acknowledge that the determination of "volume status" is ever more difficult in desperately ill individuals. Protocolized volume resuscitation algorithms have proved worthy but sometimes at a cost.[10]

Volume or fluid overload has become the rule rather than the exception. The nephrologist must exercise judgment jealously on behalf of the patient because fluid overload is associated with worse outcomes, including increased intubation and ventilator times, suboptimal recovery from AKI, and mortality.[11] However, this judgment must be annealed to more modern and sophisticated techniques of volume assessment, such as inferior vena cava ultrasonography that demonstrates luminal obliteration, central venous pressure monitoring in selected cases, and dynamic measurements of stroke volume changes during mechanical ventilation that use Doppler ultrasonography, pulse contour analysis, and bioreactance measurements.[12] These data, in combination with traditional measures of perfusion (vital signs, arterial blood gas and lactate measurements) may prove more informative than clinical "guesstimation." Finally, a simple maneuver such as the assessment of fluid responsiveness to passive leg raising may prove rapidly and clinically useful.[13] Unlike the aforementioned methods, this subtle and sublime technique is also exceedingly inexpensive.

Recognition of when fluid overload has occurred is a minimal requirement, but preventing it is better. Prevention requires not only an assessment of fluid inputs and outputs but also much more careful analysis: the calculus of mass balance and electrolyte–free water determination, with appropriate forecasting.[14,15] Notably, no large scale, commercially available electronic health care record carries out these calculations in a truly meaningful fashion that amplifies care of the patient. All account for fluid inputs and outputs, colloids, and blood products as equivalents, and 10 L of 5% dextrose in water is ranked equally with 10 L of 0.9 saline solution. Ionic compositions are systematically ignored, especially with regard to enteral and parenteral nutrition solutions, with brutal consequences for patients. Patients may be overly ultrafiltered by nephrologists who fail to perform such mass balance. Conversely, intensivists who ignore mass balance may induce dysnatremias with or without fluid overload. Lastly, simple clinical acuity cannot be forsaken. Otherwise, differentiation of AKI from an abdominal compartment syndrome[16] with elevated bladder pressure, right-sided heart failure, or hepatic sinusoidal hypertension will not occur.

Certainly, the nephrologist's scope of business has been forcefully expanded in conjunction with the enlarging critical care space. This has provoked the evolution of a new brand of nephrology and nephrologist. This discipline, "newphrology," welcomes and actively engages the nephrologist as an intensive care kidney specialist. These individuals will increase in number and take their place among those nephrologists who became disciples of other former "new" disciplines of nephrology, including kidney transplantation and interventional nephrologists. These "newphrologists" are favorably positioned to participate in and impact patient care and research in medical, surgical, neurosurgical, and pediatric intensive care units. These individuals will be dedicated to breaking the wave of AKI through the earlier recognition, mitigation of aggravating factors, and treatment of AKI—the selfsame mantra of nephrologists who treat CKD. In fact, they are already doing so as delineated by the series of articles in this issue of *Advances in Chronic Kidney Disease*, as collated by our Guest Editor, Kathleen Liu, herself a nephrologist-intensivist.

Jerry Yee, MD
Editor-in-Chief

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Critical Care Nephrology: Update in Critical Care for the Nephrologist

Like the tide, over the past 15 years critical care has changed—back and forth and back again. In 2001, the pivotal PROWESS (Protein C Worldwide Evaluation in Severe Sepsis) clinical trial led to the approval of the first targeted therapy in patients with sepsis and a high risk of death, activated protein C (APC).[1] However, subsequent negative studies led to the PROWESS-SHOCK trial,[2] a randomized clinical trial mandated by the European Medicines Agency, Europe's equivalent of the US Food and Drug Administration. The PROWESS-SHOCK study showed no benefit of APC therapy and resulted in the withdrawal of APC from the clinical market. Along the same lines, the landmark article of Van den Berghe and colleagues demonstrating significant benefit to intensive glycemic control in surgical intensive care unit (ICU) patients[3] resulted in the widespread implementation of intensive glycemic control, only to have a number of subsequent clinical trials suggest that there is no significant benefit and potential harm with intensive glycemic control.[4-6]

At the same time, the field of acute kidney injury (AKI) has flourished. The widespread adaptation of consensus definitions for AKI[7-9] has greatly improved the epidemiology of AKI. Furthermore, the increasing recognition of the close pathophysiologic and epidemiologic link between AKI and CKD and ESRD makes understanding AKI of significant relevance to all nephrology practitioners.

In this issue, we review recent updates in critical care as well as updates in ICU nephrology. With regard to the critical care setting, we first begin with a review of sepsis by Venkataraman and Kellum, which focuses on "best practices" in the care of the critically ill patient with sepsis. As will be the theme for a number of the critical care updates, this article also highlights the impact of AKI on mortality in patients with sepsis. Next, we turn to the acute respiratory distress syndrome (ARDS), in which large-scale clinical trials have led to significant improvements in ventilator management[10] and substantial reductions in mortality. Seeley reviews recent changes to the definition of ARDS[11] as well as current evidence-based management of the patient with ARDS. The third article, by Busse and colleagues, focuses on hemodynamic monitoring in the ICU, where it has become clear that interventions that were widespread in clinical practice several years ago, such as pulmonary artery catheterization, have limited benefit[12,13] and where a number of new technologies to provide relatively noninvasive hemodynamic monitoring are emerging.

Continuing on the critical care theme, we turn next to the role of transfusion in the ICU. As discussed by Afshar and Netzer, transfusions may have deleterious impacts on patients, including transfusion-related acute lung injury and transfusion-associated circulatory overload. Similarly, in the critical care context, no benefit and potential harm has been suggested with the use of erythropoiesis-stimulating agents; the data in support of these statements is reviewed here. Hirsch and Josephson review the rapidly growing field of neurocritical care, including acute electrolyte issues that may arise in neurologically injured patients and considerations for patients with ESRD, who are at higher risk for certain neurologic complications, including stroke.

The current issue turns next to fluid and diuretic management in patients with AKI. Recent data suggest that although patients with septic shock benefit from early fluid resuscitation,[14] patients with ARDS without shock benefit from a restrictive fluid management strategy.[15] Since many of these patients have concomitant AKI, the data for fluid and diuretic management in these patients are relevant and are reviewed by Nadeau-Fredette and Bouchard. Next, Cruz reviews the recently proposed classification scheme for cardiorenal syndromes,[16] which divides these syndromes based on the chronicity of the cardiac and renal conditions and the proposed directionality of the interaction. The overall intent of the new classification system is to refine the pathogenesis and treatment of these distinct conditions. The next review focuses on perioperative AKI, an entity associated with significant postoperative morbidity and mortality. Thakar succinctly reviews this large body of literature and cardiac surgery–associated AKI, which has been relatively well characterized and in which the major insult presumably occurs in the ischemic and proinflammatory milieu of cardiopulmonary bypass, making important distinctions throughout between other types of perioperative AKI, which are generally less well described in the literature.

For patients with AKI, "best practice" supportive care is critical. In this regard, Palevsky reviews the current evidence base for dose, timing, and modality in patients who have severe AKI requiring renal replacement therapy (RRT). Although we have excellent data from large multicenter clinical trials to inform our practice with regard to dose,[17,18] data for timing and modality are limited. The design of trials to inform these questions is complicated

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by our current inability to accurately predict those patients with AKI who will go on to "need" dialysis and those patients who will recover spontaneously. A previously underappreciated aspect of supportive care in AKI that is gaining rapid acceptance and exposure in the literature is the impact of RRT on medication dosing. In particular, there is concern that RRT may increase underdosing of critical medications such as antibiotics in the septic patient. Fissell uses antibiotics as a paradigm to discuss drug dosing in patients receiving RRT and offers a number of practical suggestions for medication dosing for the practitioner.

Along the same lines, another area of growing interest is the role of extracorporeal therapy in the treatment of overdose and intoxication. A number of nephrology societies (including the National Kidney Foundation) and critical care societies have constituted the Extracorporeal Treatments in Poisoning Workgroup to systematically review data in support of the use of extracorporeal therapy for intoxication. Here, Gosselin and Ghannoum[19] review both corporeal and extracorporeal methods to enhance poison elimination, a topic of significant relevance to nephrologists because we are frequently asked to prescribe extracorporeal therapy for critically ill intoxicated patients.

Finally, Szamosfalvi and Yee review the care of the critically ill patient with ESRD. Given the rapidly increasing number of prevalent ESRD patients in the United States and their relatively higher overall rates of hospitalization, this group constitutes another growing population of ICU patients.[20] They suggest a checklist of management issues that nephrologists should review closely with their intensivist colleagues and provide a review of newer techniques to monitor dialysis adequacy and clearance in this patient population.

In sum, the past 15 years have been an area of great evidence-based progress in critical care, albeit with some steps forward and some backward. The articles in this issue of *Advances in Chronic Kidney Disease* review recent evidence-based changes in critical care, current management challenges, and new technologies in use in the ICU. Given the widespread interest in this field, hopefully the next 15 years will bring even more evidence-based improvements to the ICU and reduce mortality in this high-risk patient population.

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Sepsis: Update in the Management

Ramesh Venkataraman and John A. Kellum

Sepsis and septic shock are syndromes that overlap between several disciplines and subspecialties. Emerging evidence suggests that sepsis may be associated with short- and long-term adverse outcomes, even when the syndrome does not appear to be severe and is not managed in the intensive care unit. Hence, all practicing clinicians need to be familiar with the fundamental principles of diagnosis and management of sepsis. In this review, we have summarized the key components in the management of sepsis/septic shock, including early recognition, early resuscitation, principles of antibiotic therapy, organ support, and role of adjunctive therapies.

Key Word: Sepsis

Early Recognition

The first essential step in the management of sepsis is early identification. Often the term systemic inflammatory response syndrome (SIRS) is used interchangeably with sepsis in the clinical setting. However, SIRS can arise from a noninfectious insult, and the term sepsis is reserved for systemic inflammation arising from infection. When sepsis results in organ dysfunction (including circulatory dysfunction), it is termed as severe sepsis. When there is evidence of circulatory dysfunction (eg, hypotension refractory to volume resuscitation, or evidence of end-organ hypoperfusion such as elevated blood lactate), the condition is termed as septic shock.[1]

However, it is important to recognize that most patients with sepsis will not be cared for in the intensive care unit (ICU). For example, in a landmark study, only 16% of patients hospitalized with severe community-acquired pneumonia and sepsis were ever admitted to the ICU.[2] However, a subsequent analysis of this same cohort revealed that a third developed acute kidney injury (AKI), half of these severe (RIFLE-I or F).[3] It is important to note that AKI was still common (24%) even in so-called "nonsevere" sepsis. Furthermore, survival to 1 year was significantly reduced in patients developing AKI (risk was nearly identical for RIFLE-I and F) even if they had no other evidence of organ failure.[2] It is important to recognize that sepsis is the most common etiology of AKI,[4] and AKI may increase the risk of sepsis. Thus, sepsis should always be suspected in patients with AKI.

Various biomarkers have been evaluated to help discriminate sepsis, early severe sepsis (ie, before clinical manifestations of organ failure), or septic shock from conditions that may mimic sepsis (with or without SIRS) (Table 1). Unfortunately, no biomarker to date has demonstrated sufficient predictive value to diagnose or exclude sepsis as a stand-alone test. Traditional biomarkers such as C-reactive protein start to rise and peak late in bacterial infections and have been shown to lack adequate sensitivity and specificity for the diagnosis of bacterial infections.[5,6] More recently, several studies have evaluated the role of serum procalcitonin (PCT) for the differentiation of sepsis from other conditions that may resemble sepsis. PCT is normally synthesized in the thyroid C cells, and a small amount leaks into the blood with serum levels usually less than 0.1 ng/mL.[7] However, in bacterial infection, PCT is synthesized in various extrathyroidal neuroendocrine tissues in response to bacterial toxins, leading to elevated serum levels. It is important to note that PCT levels in response to sepsis do not appear to be altered by the use of steroids.[8] Most studies that have looked into the discriminative ability of serum PCT in the diagnosis of sepsis have been small, with heterogeneity in the patients enrolled, and have used different cutoff values and hence have provided variable results.[9] A recent meta-analysis found 71% (95% confidence interval 67-76%) sensitivity and specificity for serum PCT as a marker of sepsis.[10] Therefore, it concluded that the diagnostic performance of PCT was low and that it cannot reliably differentiate sepsis from other conditions in critically ill adult patients. Moreover, a recent systematic review did not find any mortality benefit with PCT-guided antibiotic therapy compared with the control group in patients presenting with respiratory infections and sepsis.[11]

In summary, differentiating sepsis from conditions that may resemble it can be challenging, and integration of history, clinical, laboratory, and imaging data is often necessary to arrive at an accurate diagnosis. Although

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serum PCT can be used as a guide to diagnosis, it does not have enough positive or negative predictive value to rule in or rule out sepsis as a stand-alone test.

Volume Resuscitation

Sepsis may result in rapid loss of perfusion to tissues and life-threatening circulatory shock. Early management of a sepsis involves assessment and management of airway and breathing; oxygen saturation of more than 93% should be maintained for adequate oxygen delivery to tissues. Initial history, examination, and evaluation should be performed simultaneously with resuscitative efforts. Basic blood work and relevant cultures should be sent promptly, and the first dose of antibiotic should be administered as early as possible. Measurement of serum lactate at admission as a marker of tissue hypoperfusion has been recommended by the surviving sepsis campaign guidelines.[12]

After initial assessment, a jugular or subclavian central venous catheter (CVC) should be inserted in most patients with septic shock for rapid administration of fluids, initiation of medications, hemodynamic monitoring, and possibly to obtain central venous oxygen saturation (SCvO2). A single-center randomized study concluded that early resuscitation targeted to achieve and maintain certain physiological variables within the first 6 hours of septic shock improved survival compared with standard care.[13] Targets in this study included a central venous pressure (CVP) of 8-12 mmHg, a mean arterial pressure (MAP) of 65 mmHg or more, a urine output of 0.5 mL/kg/hour or more, and a SCvO2 greater than 70%. If SCvO2 was less than 70% after adequate volume resuscitation, interventions to improve global oxygen delivery such as transfusion of PRBC to achieve hemoglobin levels of greater than 10 g/dL and initiation of dobutamine infusion were undertaken sequentially in this study. However, this study has been criticized for several reasons.[14] First, the primary resuscitation target (SCvO2 > 70%) has been questioned because, in contrast to this study, other studies in septic patients found that only a small proportion of patients had low SCvO2 on admission. Second, the validity for the use of SCvO2 as a surrogate for mixed venous oxygen saturation (SVO2) is not widely accepted. Third, a normal SVO2 (>70%) does not always reflect adequate oxygen delivery because in septic patients tissue extraction and utilization of oxygen is also deranged. This may lead to near normal or even supranormal SVO2 despite active tissue dysoxia. Fourth, the rationale for red blood cell transfusion has been challenged because the improvement in oxygen-carrying capacity of transfused blood may be suboptimal because of several factors related to its shelf life. The risks incurred by the transfusion may also outweigh any benefits. Lastly, in this study dobutamine was used without measurement or documentation of cardiac contractility. Although multiple subsequent observational studies have found similar results compared with historical controls, this approach is yet to be validated in a large multicenter randomized controlled trial (RCT). Three such trials are currently underway in North America, Australia, and the United Kingdom with results expected sometime in 2013.

More recently, a randomized trial of 300 patients with severe sepsis evaluated clearance of serum lactate as a substitute for SCvO2 and found similar outcomes when resuscitation was targeted to either a lactate clearance of 10% or greater or a SCvO2 of 70% or greater.[15]

No specific cutoffs for "adequate" CVP and MAP can be universally recommended for all septic patients. CVP can be altered significantly by right ventricular compliance; tricuspid valve pathology; and intrathoracic, intra-abdominal, and pericardial pressures and hence do not always reflect the actual right ventricular preload in a given patient. Moreover, no value of CVP can predict whether a patient's cardiac output will improve with a fluid challenge. Despite all of this, a CVP of 8-12 is recommended by the Surviving Sepsis Campaign[12] in the expectation that at these levels of CVP most patients are unlikely to have significant intravascular volume depletion. Likewise, although the Surviving Sepsis Campaign[12] advocates a MAP of more than 65 mmHg, there exists large variation in the pressure-flow relationship between individuals and between various organs within the same individual. For example, a patient with end-stage liver disease may have adequate perfusion at a lower MAP, but a chronic hypertensive patient may need a much higher MAP for adequate perfusion. Hence, it is important to recognize that cutoffs recommended by guidelines only serve as benchmarks during resuscitation and should be used with clinical judgment in the resuscitation of all septic patients.

There has been no consensus on the type and amount fluid to administer during resuscitation of septic patients. There has been controversy regarding superiority of colloids in comparison to crystalloids as a resuscitation fluid. In a large multicenter RCT of patients in ICU, the use of either 4% albumin or 0.9% saline for fluid resuscitation resulted in similar 28-day outcomes.[16] However,

CLINICAL SUMMARY

- Early and appropriate management of sepsis significantly improves short-term and long-term mortality.
- Fluid resuscitation for shock and early appropriate antibiotic therapy have the most impact on survival.
- Source control should be accomplished within 24 hours where appropriate.

Table 1. Conditions that Commonly Mimic Sepsis in the ICU Setting

1. Neurologic conditions
   a. Intracranial hemorrhage and subarachnoid hemorrhage
   b. Brain stem stroke
2. Cardiovascular conditions
   a. Acute myocardial infarction
   b. Myocarditis—autoimmune, viral
3. Respiratory conditions
   a. Pulmonary embolism
   b. ALI from noninfective causes
4. Gastrointestinal conditions
   a. Acute severe Pancreatitis
   b. Acute Liver Failure
   c. Mesenteric Ischemia
5. Endocrine conditions
   a. Diabetic ketoacidosis
   b. Adrenal insufficiency
   c. Thyroid storm
6. Other systemic conditions
   a. Polytrauma
   b. Burns
   c. Acute vasculitides
   d. Acute cellular rejection
   e. Heat stroke
7. Drugs
   a. Drug fever
   b. Drug withdrawal—baclofen, opioids, benzodiazepines
   c. Neuromuscular malignant syndrome
   d. Serotonin syndrome
   e. Malignant hyperthermia

preplanned subgroup analysis found harm with albumin in traumatic brain injury patients, but there was a trend toward benefit with albumin in patients with sepsis. A subsequent meta-analysis of studies of fluids for fluid resuscitation in sepsis also favored albumin.[17]

A recent multicenter trial of 800 patients with sepsis found that compared with similar volumes of crystalloid, hydroxyl ethyl starch was associated with higher rates of AKI and greater risk of death by 90 days.[18] A similar signal was found in a trial using pentastarch[19] and hence we recommend avoiding hydroxyl ethyl starch for resuscitation in patients with sepsis.

Even more controversial is the use of fluid boluses outside of the ICU or modern emergency department. A large trial in Africa compared fluid boluses (20-40 mL/kg body weight) with saline or albumin solution to no boluses in 3141 children presenting with sepsis, many with malaria.[20] Children with severe hypotension or decompensated shock received boluses of either albumin or 0.9% saline. Fluid boluses significantly increased 48-hour mortality—10.6%, 10.5%, and 7.3% in the albumin-bolus, saline-bolus, and control groups, respectively ($P = 0.003$). The 4-week mortality was 12.2%, 12.0%, and 8.7% in the three groups, respectively ($P = 0.004$). However, no difference in mortality was observed in patients with decompensated shock. It is plausible that the increased mortality seen with fluid boluses could be related to several factors such as increased capillary permeability, increased interstitial edema (pulmonary and cerebral edema), and adverse effects related to fluid overload.

Thus, fluid resuscitation needs to be tailored to a patient's physiology, and frequent assessments of response and tolerance to fluid boluses are mandatory to balance under-resuscitation with fluid overload. Fluid responsiveness can be predicted better using dynamic indices of preload such as pulse-pressure or stroke volume variation[21] than static measures such as CVP. It is prudent to stop fluid administration once dynamic indices indicate a fluid-unresponsive patient, especially because the magnitude and duration of fluid overload have been shown to be associated with increases in mortality.[22,23]

Early and Appropriate Antibiotics

Identification of the source of sepsis and initiation of appropriate antibiotics are other vital steps in the initial management of septic shock. In an observational study, Kumar and colleagues demonstrated that effective antimicrobial administration within the first hour of documented hypotension was associated with increased survival to hospital discharge in adult patients with septic shock.[24] Each hour of delay in antimicrobial administration over the ensuing 6 hours was associated with an average decrease in survival of 7.6%. In multivariate analysis, time to initiation of effective antimicrobial therapy was the single strongest predictor of outcome in this study. The effect of timing seems to extend across all types of organisms including gram-positive, gram-negative, and *Candida* species.

Likewise, several studies have consistently shown that inappropriate initial empiric antibiotic therapy in septic shock is associated with reduced survival.[25,26] Hence, when prescribing empiric antibiotic therapy, it is imperative that the initial choice is broad enough to cover the organisms concerned. To get the initial choice of antimicrobial therapy right, the clinician must be able to accurately identify the source(s) of sepsis, predict the likely pathogens, know the local resistance patterns, and understand the pharmacokinetic and pharmacodynamic principles of the antibiotics used. Because volume of distribution, metabolism and clearance of antimicrobial drugs are unpredictably altered in septic shock, therapeutic drug-level monitoring must be used when available to titrate the subsequent maintenance doses for maximal efficacy. In short, an antimicrobial administration policy of "hit early, hit hard, and hit broad" is crucial in improving survival in patients with septic shock.

Source control is also important because antibiotics alone are often ineffective in patients with undrained abscesses or necrotic tissues. Identification of the source of infection and drainage and/or surgical debridement as indicated should also be undertaken early. Cultures

should be taken for later adjustment of initial antimicrobial regimen.

Organ Support in a Septic Patient

After initial stabilization and initiation of antimicrobial therapy, the subsequent goal of treatment is to provide organ support. The objectives of subsequent supportive critical care are to sustain and support organ function while attenuating and minimizing propagation of organ injury.

Lung-Protective Strategies

The airway must be secured when compromised and mechanical ventilation initiated. In patients with acute lung injury (ALI), overdistension of alveoli and repeated opening and closing of alveoli worsen lung injury further and increase mortality. Ventilation with low tidal volume (6 mL/kg of predicted body weight) and maintenance of airway pressures of less than 30 cm of water (to avoid alveolar overdistension) have been shown to improve survival.[27] Although maintaining adequate positive end expiratory pressure on the ventilator prevents alveolar collapse and improves oxygenation, it does not affect survival in patients with ALI.[28] In patients with ALI without shock (ie, without any evidence of end-organ hypoperfusion), a conservative fluid strategy (CVP $<$ 4 mmHg) achieved with fluid restriction and/or diuresis improves lung function and shortens the duration of mechanical ventilation and intensive care without increasing nonpulmonary organ failures compared with a liberal fluid strategy (CVP 10-14 mmHg).[29]

Management of Shock

For patients with septic shock who do not respond to fluid resuscitation alone or are hypotensive despite preload optimization, initiation of vasopressor support is recommended. As discussed earlier, although a MAP target of more than 65 mmHg is recommended by Surviving Sepsis guidelines,[12] this has to be individualized based on patient pathophysiology. Organs differ in their pressure-flow characteristics, and the kidneys are the most sensitive to pressure changes in states of shock. In a recent prospective observational study of 217 patients with sustained hypotension, Badin and colleagues have shown that in patients with septic shock and AKI at 6 hours, a higher MAP (72-82 mmHg) was associated with a reduced risk of AKI at 72 hours.[30] However, the observational nature of the study makes it impossible to determine whether increasing MAP has a salutary effect on kidney function or whether patients that can mount a better MAP have less risk of severe AKI.

Norepinephrine is the preferred initial agent. A recent RCT demonstrated no survival difference between patients with shock who were treated with dopamine as the first-line vasopressor agent and those who were treated with norepinephrine.[31] However, the use of dopamine was associated with increased adverse events in this study. If cardiac contractility is impaired, then adding an inotropic agent is also recommended. Addition of dobutamine as an inotrope to norepinephrine or using epinephrine as a vasopressor and an inotrope in such patients are equally acceptable options.[32]

In patients with septic shock, vasopressin, a potent vasoconstrictor hormone, is initially released into the circulation. However, subsequently vasopressin levels decline to inappropriately low levels rapidly because of depletion of stored vasopressin.[33] Thus, addition of low-dose vasopressin (0.01-0.03 units/minute) to patients with septic shock (already receiving at least 5 μg/minute of norepinephrine) may be helpful. However, a recent trial found no significant difference in the 28- or 90-day mortality rates when vasopressin was added to norepinephrine.[34] In a subsequent analysis of this study, the same authors found that low-dose vasopressin and corticosteroids favorably interacted to decrease mortality and organ dysfunction.[35]

Role of Steroids in Septic Shock

In critical illness including septic shock, cortisol production is suboptimal. This, along with tissue corticosteroid resistance, creates a state of relative adrenal insufficiency termed as critical illness-related corticosteroid insufficiency.[36] Critical illness-related corticosteroid insufficiency should be suspected in hypotensive patients who respond poorly to fluids and vasopressor agents. Earlier studies that used high doses of corticosteroids in septic shock did not show any survival benefit.[37,38] More recently, two large randomized trials evaluated the effect of low-dose corticosteroids in patients with septic shock. In the first study, patients were randomly assigned to receive placebo or hydrocortisone (50 mg intravenously every 6 hours) plus fludrocortisone (50 μg enterally once a day) within 8 hours of the onset of septic shock.[39] A high-dose adrenocorticotrophin hormone (250 μg) stimulation test was performed in all patients, and they were classified as responders (increase in serum cortisol of $>$ 9 μg/dL from baseline) and nonresponders (increase in serum cortisol $\leq$ 9 μg/dL from baseline). In the subgroup of nonresponders, there was a significant decrease in mortality with hydrocortisone that was not seen in the responders group. The vasopressor withdrawal rates were higher and faster in the hydrocortisone group. In a large study, the Corticosteroid Therapy of Septic Shock (CORTICUS) trial assigned 499 patients with septic shock to receive hydrocortisone (50 mg) or placebo intravenously every 6 hours for 5 days, followed by a tapering regime.[40] Similar to the previous study, high-dose adrenocorticotrophin hormone stimulation was used to differentiate nonresponders from

responders. Hydrocortisone did not improve survival in the overall patient population or in either subgroup. However, shock was reversed faster in the group of patients receiving hydrocortisone. The discordance in results of the these two studies could likely be due to the fact that the CORTICUS study evaluated less sick patients and enrolled patients up to 72 hours after shock onset, making the therapy less effective after such a delay.

On the basis of these data, our practice is to initiate norepinephrine infusion for vasodilatory shock in septic patients and consider initiation of hydrocortisone or low-dose vasopressin in patients with refractory shock. If shock is still refractory after 4-8 hours we will usually add both agents.

Kidney Support in Septic Shock

As discussed already, AKI is very common in patients with severe sepsis and septic shock and adds significant morbidity and mortality.[41] A comprehensive discussion on the prevention and treatment of AKI is beyond the scope of this article, but some basic principles will be discussed.

Adequate resuscitation and intravascular volume repletion, maintenance of adequate perfusion pressures, and avoidance of nephrotoxic agents are the only strategies currently available to prevent AKI.[41] There is no single value of MAP that is recommended as adequate to prevent AKI. MAP has to be titrated on the basis of individual needs, taking into account the patient's baseline blood pressure and clinical/laboratory evidence of end-organ perfusion. Low-dose dopamine does not decrease the incidence of AKI or AKI-associated mortality[42,43] and hence should not be used for kidney protection. Although commonly used in oliguric AKI, loop diuretics have not been shown to minimize the need for renal replacement therapy (RRT), decrease time on RRT, or reduce mortality.[44] Indeed there is some evidence, to suggest that they increase mortality.[45,46] Thus, diuretics should not be used to treat AKI per se, but they should be used only for the prevention and management of fluid overload. The time-honored approach of prescribing diuretics for patients with oliguria is not justified and may be harmful. However, judicious use of diuretics and other measures (RRT) to avoid volume overload is appropriate.

Once fully established, severe AKI will require support of kidney function using RRT. In patients with AKI whose care has not been limited as part of end-of-life directives, RRT is essential for clinical indications such as life-threatening fluid overload, hyperkalemia, and metabolic acidemia refractory to medical therapy. Whether initiation of RRT earlier offers any clinical benefit is unproven, and no clear cutoff value for the level of azotemia at which RRT must be initiated exists.[47] An additional consideration in patients with AKI and sepsis is the fact that antibiotic management can be very difficult with changing glomerular function and volume of distribution. Early initiation of RRT may allow for stabilization of drug dosing, but it has not been evaluated by randomized trials.

In patients who can receive either intermittent hemodialysis (IHD) or continuous renal replacement therapy (CRRT), including those with sepsis, no clear advantage has been found with one modality over the other.[48] A meta-analysis was performed by the Cochrane Collaboration, analyzing 15 RCTs in 1550 AKI patients, and it concluded that outcomes were not different for critically ill AKI patients treated with CRRT versus IHD for hospital mortality, ICU mortality, length of hospitalization, or kidney recovery (free of dialysis on discharge) in survivors.[49] However, most trials excluded patients with hypotension, and high rates of crossover between the treatment modalities also complicates the interpretation of these studies. The Kidney Disease Improving Global Outcomes AKI guideline[50] recommends use of continuous and intermittent RRT as complementary therapies, recognizing that although local practice varies, most centers use IHD and CRRT for patients with AKI. However, CRRT is preferred over standard IHD for hemodynamically unstable patients and for AKI patients with acute brain injury or other causes of increased intracranial pressure or generalized brain edema.[50]

Glycemic Control

Hyperglycemia associated with critical illness (stress hyperglycemia) is a consequence of an increase in hormones that induce hyperglycemia, such as cortisol, catecholamines, glucagon, and growth hormone, and a simultaneous increase in resistance to insulin. Recent evidence suggests that uncontrolled hyperglycemia is associated with poor outcomes in critically ill patients.[51] Subsequently, several studies have evaluated the optimal level of glucose in critically ill patients that favorably affects outcome.[19,52,53] Randomized trials in medical,[53] septic[19] and mixed medical and surgical patients[54] have clearly demonstrated that glucose values of less than 180 mg/dL have similar outcomes compared with tighter glucose levels of 80-100 mg/dL. The tighter glucose control had a much higher incidence of hypoglycemia in all of these studies, which could have negated any beneficial effect conferred by the glycemic control. Hence, most experts recommend reducing blood glucose to less than 180 mg/dL in all septic patients but to avoid overly "tight" control. Avoidance of hypoglycemia and huge fluctuations of glucose levels also seem to favorably affect outcome.

Adjunctive Therapies

Several novel approaches have been evaluated to modulate the inflammatory response and alter outcomes in

Table 2. Summary of the Key Principles in the Management of Patients With Septic Shock

Goals to be accomplished within first 6 h of ICU admission
1) Measurement of serum lactate at baseline and at 6 h
2) Early stabilization and titrated fluid resuscitation to achieve oxygenation and tissue perfusion
3) Administration of first dose of appropriate antibiotics within 4 h of presentation or 1 h of ICU admission
4) Addition of norepinephrine to patients who remain in vasodilatory shock after fluid optimization
Goals to be accomplished within first 6-12 h of ICU admission
1) Adequate source control
2) Administration of corticosteroids and/or vasopressin in patients with refractory shock
3) Ventilation with lung-protective strategy—low tidal volume (6 mL/kg)
4) Glycemic control—target blood sugar 80-150 mg/dL
Strategies not recommended
1) Low-dose dopamine for kidney protection
2) Use of rhAPC
Strategies of unclear benefit (considered experimental)
1) IVIG therapy
2) HVHF
3) Hemoperfusion through polymyxin-coated column

patients with septic shock. Although activated protein C has been extensively evaluated, others still remain experimental.

Recombinant Activated Protein C

A recent RCT, the PROWESS-SHOCK trial,[55] enrolled 1696 patients with vasopressor-dependent septic shock and randomly assigned them to receive recombinant activated protein C (rhAPC) or placebo. The study found no mortality benefit with rhAPC, prompting withdrawal of this drug from the market.

Intravenous Immunoglobulin

Polyclonal intravenous immunoglobulin (IVIG) has been hypothesized to benefit patients with sepsis by binding endotoxin; hence, their use in patients with sepsis has been evaluated. The results of studies are conflicting, with one RCT showing no mortality benefit[56] and a few meta-analyses demonstrating benefit with IVIG therapy.[57,58] However, all of the meta-analyses had significant heterogeneity and failed to show a benefit when restricting analysis to high-quality trials.[57,58] On the basis of the existing evidence, IVIG cannot be routinely recommended for the management of patients with severe sepsis and septic shock.

Extracorporeal Blood Purification

The inflammatory response occurring in sepsis is complex and redundant; hence, targeting any specific molecule in the inflammatory cascade is unlikely to attenuate this response or affect outcomes. This understanding has led several investigators to attempt extracorporeal blood purification techniques in an effort to nonspecifically remove the inflammatory mediators and attenuate the entire inflammatory process.

Overall, increasing the intensity of RRT in patients with AKI beyond conventionally recommended levels (eg, ultrafiltrate rates of 20-25 mL/kg/hour for CRRT) is not effective for improving survival or kidney recovery,[59,60] and preplanned subgroup analyses did not find any benefit specifically for patients with sepsis either. Small trials in patients with sepsis without AKI also found no benefit for "renal-intensity" CRRT compared with standard care.[61,62] However, they also could not show modulation of inflammatory mediators. These observations led to the development of high-volume hemofiltration (HVHF) using rates greater than 60 mL/kg/hour. Although initial small trials demonstrated improvement in hemodynamics and other physiological parameters with HVHF in septic patients,[63,64] these results have yet to be confirmed by subsequent large randomized trials.

Much greater efficacy has been seen in terms of inflammatory mediator removal using hemoperfusion, and animal studies show improved survival and reduced organ injury using this technique.[65,66] A special form of hemoperfusion removes endotoxins by use of polymyxin-bound fibers. Sixty-four patients with severe sepsis or septic shock who underwent emergency surgery for intra-abdominal infection[67] were randomized to conventional therapy or conventional therapy plus 2 sessions of polymyxin B hemoperfusion. The trial was terminated early because polymyxin B hemoperfusion appeared to reduce 28-day mortality; however, the results were not conclusive. Ongoing trials of blood purification including HVHF and hemoperfusion should improve our understanding of these therapies and their potential role in the management of sepsis in the near future. However, at the present time these therapies are only used in clinical trials or for "rescue" therapy.

Conclusions

The key principles of management of sepsis include early recognition, early and titrated fluid resuscitation, adequate source control, prompt and broad antibiotic therapy, and organ support (Table 2). Differentiating sepsis from conditions that resemble it remains a challenge. Targeting specific physiological parameters such as CVP, MAP, urine output, and SCvO2 are often recommended to assess the adequacy of perfusion. However, these end points should not be viewed as substitutes for clinical judgment.

Antibiotics should be administered early and must be broad enough to cover all likely pathogens for the suspected source of infection. Norepinephrine should be initiated if hypotension persists after adequate fluid resuscitation. Vasopressors and/or corticosteroids should be

considered in patients with refractory shock. There is no role for dopamine as a kidney-protective agent. Organ-specific goals should be adhered to while providing organ support. Adjunctive therapies such as hemofiltration, hemoperfusion, or IVIG will need further study before routine use in patients with septic shock.

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Updates in the Management of Acute Lung Injury: A Focus on the Overlap Between AKI and ARDS

Eric J. Seeley

Acute respiratory distress syndrome (ARDS) is a major cause of hypoxemic respiratory failure in adults and can result from several predisposing factors, such as sepsis and trauma, which also predispose patients to acute kidney injury (AKI). Animal models of AKI and ARDS suggest that AKI increases inflammatory cytokines in the circulation such that IL-6 may be a direct mediator of AKI induced lung injury. When ARDS and AKI overlap, intensive care unit length of stay, resource utilization, and mortality increase dramatically. New evidence suggests that the prevalence and clinical implications of even mild AKI in patients with ARDS is likely underestimated. The cornerstone of therapy for ARDS continues to be low tidal volume ventilation, and more recent trials illustrate that diuretic administration to shock-free ARDS patients may help them avoid the deleterious effects of volume overload. This review focuses on new developments in the care of ARDS patients with a specific focus on interactions between the lungs and kidneys in patients with overlapping ARDS and AKI.

Key Words: Acute kidney injury, Acute lung injury, Sepsis, Critical care, Acute respiratory distress syndrome

Introduction

Acute respiratory distress syndrome (ARDS) afflicts nearly 200,000 people in the United States each year.[1] Predisposing illnesses such as sepsis and trauma damage endothelial cells, and this insult can lead to ARDS and acute kidney injury (AKI). Indeed, 35% of patients with ARDS develop AKI, and this secondary insult dramatically increases mortality.[2,3] Consequently, it is imperative that intensivists and nephrologists understand the key pulmonary-renal interactions that occur during the resuscitation, supportive care, and weaning phases of critical illness for patients with ARDS and AKI. The objective of this article is to review the definitions, epidemiology, incidence, pathophysiology, and treatments for ARDS with a special focus on the therapeutic interplay between intensivists and nephrologists in patients suffering from ARDS and AKI.

Definitions

Petty and Ashbaugh first described the syndrome of "acute respiratory distress in adults" in their landmark 1967 *Lancet* publication.[4] This seminal work recognized that ARDS could result from various direct or indirect insults (Table 1) that lead to bilateral pulmonary infiltrates, hypoxemia, and decreased pulmonary compliance. The definition of ARDS has evolved since 1967. Until recently, the most widely accepted definition was the 1994 American/European Consensus Conference definition,[5] which defined acute lung injury (ALI) as the acute onset of hypoxemia ($PaO_2/FiO_2 < 300$ mm Hg) in the setting of bilateral airspace opacities without clinical or invasive hemodynamic signs of left atrial hypertension or volume overload. Peripheral edema, elevated brain natriuretic peptide, a history of congestive heart failure, or signs of left atrial hypertension on echocardiography may suggest cardiogenic pulmonary edema. This definition distinguished ALI ($PaO_2/FiO_2 < 300$ mm Hg) from ARDS ($PaO_2/FiO_2 < 200$ mm Hg); however, the durability and prognostic value of this distinction remained unclear.

A new definition of ARDS, titled the Berlin definition, was recently published.[6] This new definition was created by a consensus process and is unique in that diagnostic categories were tested for reliability and validity against a large database of ARDS demographic and physiologic data. The Berlin definition partitions patients by PaO_2/FiO_2 ratio into mild (PaO_2/FiO_2 200-300), moderate (PaO_2/FiO_2 100-199), and severe ARDS (PaO_2/FiO_2 <100) and no longer includes the term "acute lung injury". In addition, this definition clarifies several areas of uncertainty left by the American/European Consensus Conference definition, including onset, which must be within 1 week of a known clinical insult or new or worsening respiratory symptoms; chest imaging, which must include bilateral opacities that are not fully explained by effusions, lobar collapse, or nodules; and origin of edema, which cannot be fully explained by cardiac failure or fluid overload and must be objectively evaluated (eg, by echocardiography) if no clear predisposing factor for ARDS is present. The Berlin definition also sets a minimum positive end-expiratory pressure (PEEP) level of 5 cm H_2O during PaO_2/FiO_2 determination because it has been recognized that changes in PEEP may reclassify patients from the current definition of ALI to ARDS. For the sake of clarity, throughout this review the term ARDS will include all patients with a PaO_2/FiO_2 less than 300,

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and the terms mild, moderate, and severe as defined by the Berlin definition will be used.

Epidemiology, Incidence, and Outcomes

Despite advances in understanding of the pathophysiology and treatment of ARDS, the worldwide incidence of ARDS is still debated. The largest study of ARDS incidence is the Kings County Lung Injury Project (KCLIP) study in Kings County, Washington.[1] This prospective cohort study captured ARDS patients in academic and community hospitals in western Washington over a 16-month period and found the incidence of mild ARDS to be 78.9 per 100,000 person-years and of moderate/severe ARDS to be 58.7 cases per 100,000 person-years with an overall mortality of 40%. On the basis of these data, there are 200,000 cases of ARDS in the United States per year, leading to 75,000 deaths. More recent studies suggest that the incidence of ARDS in the United States may be decreasing. An 8-year observational study of patients in Olmsted County, Minnesota showed a decrease in the incidence of ARDS from 81 cases per 100,000 person-years in 2001 to 38.3 cases per 100,000 person-years in 2008.[7] This drop in ARDS incidence occurred during numerous interventions, including a decrease in blood transfusions, an increase in intensive care unit (ICU) staffing, and implementation of a sepsis team,[7] suggesting that risk factor modification might decrease the risk of developing ARDS.

CLINICAL SUMMARY

- AKI is common in patients with ARDS.
- Patients with both AKI and ARDS have increased mortality.
- A low tidal ventilation strategy is the cornerstone of treatment of ARDS.
- A fluid conservative protocol does not increase the risk of AKI and may expedite the resolution of ARDS.

Estimates of the incidence of and mortality from ARDS in Australia and Europe have been lower than in the United States.[8] A 2-month observational study in Australian ICUs found an incidence of mild ARDS and moderate/severe ARDS of 34 and 28 cases per 100,000 person-years with a mortality of 32% and 34%, respectively. In contrast, the incidence of ARDS in Spain was 7.2 cases per 100,000 person-years, several times lower than in the United States and Australia.[9] Geographic differences in the incidence of ARDS may be due to regional genetic variation, differences in hospital processes of care, methodologic differences (including diagnostic criteria or reporting), or worldwide variation in treatment preferences that predispose patients to ARDS, including choice of chemotherapy or transfusion thresholds.

Although many observational and treatment trials have focused on ARDS mortality, it is now clear that patients who survive ARDS go on to suffer enduring physical, psychological, and cognitive dysfunction.[10,11] Although pulmonary function tests in survivors of ARDS frequently return to normal within 1 year, physical impairment, as measured by a 6-minute walk distance, remains, on average, 30% lower than predicted even 5 years after hospital discharge.[10] Only half of patients who survive ARDS return to work at 1 year, and quality-of-life measures are persistently reduced in ARDS survivors. Cognitive impairment is also common in survivors of ARDS. In one study, 50% of ARDS survivors demonstrated cognitive dysfunction with impairments in memory and attention 2 years after ARDS resolution.[12] In addition, family members of critically ill patients may also experience depression and decreased productivity.[13] Unlike critical care physicians, nephrologists may be more intimately involved in the recovery of patients who survive ARDS but require prolonged hemodialysis, and they may witness the long-term decrease in the physical, emotional, and cognitive health of ARDS survivors.

Overlapping ARDS and AKI: Prognosis and Diagnosis

Patients with ARDS frequently develop AKI, and this second insult dramatically increases overall mortality (Fig 1).[3,14] During the ARDSnet trial of low tidal volume (TV) ventilation, 24% of the patients developed AKI during the first 4 days of mechanical ventilation and 35% developed AKI during their hospitalization.[14] Patients with ARDS had a mortality of 28%, but patients who developed AKI, in addition to ARDS, had a mortality near 60%.[14] The KCLIP study showed that patients who develop oliguric kidney failure (defined as urine output < 500 mL in a 24-hour period and a serum creatinine > 2.0 mg/dL) had a 60-day mortality of 85%, much higher than the 60% mortality of the entire cohort (Fig 1).[3] The causal relationship between AKI and increased mortality is not entirely clear, but a common theme from multiple studies is that the combination of ARDS and AKI increases the duration of mechanical ventilation and hospital length of stay. Thus, patients with ARDS and AKI require close attention and clear communication between critical care practitioners and nephrologists.

The incidence and importance of AKI in patients with ARDS is likely underestimated because of vigorous fluid administration during the resuscitation phases of ARDS. A secondary analysis of data from the FACTT study evaluated the effect of volume administration on the classification and outcome of patients with AKI and ARDS. This study is based on the concept that creatinine is

Table 1. Clinical Conditions Associated With ARDS

Direct Pulmonary Injury	Indirect Pulmonary Injury
Pneumonia	Shock
Aspiration of gastric contents	Sepsis
Trauma with pulmonary contusion	Transfusion
Drowning	Pancreatitis
Toxic inhalation (smoke, gas)	Reperfusion

distributed among all body compartments and thus is susceptible to dilution during aggressive volume resuscitation. In this study, AKI was defined as an increase in serum creatinine of 0.3 mg/dL or more or a relative change of more than 50% over 48 hours. Patients were classified as AKI present or AKI absent on the basis of serum creatinine. The same group of patients was then reclassified as AKI present/absent on the basis of serum creatinine corrected for the volume of fluid administered during resuscitation. Mortality was then compared between patients who were reclassified and those who were not.[15] Impressively, patients who were reclassified had mortality rates that were more concordant with their reclassified AKI status than with their initial status, suggesting that clinical phenotypes are more similar after correcting serum creatinine for the volume of fluid administered during resuscitation (Fig 2). These data highlight that AKI is underdiagnosed in the ICU and may have an important effect on mortality in patients with ARDS, even when the degree of AKI does not necessitate continuous renal replacement therapy (CRRT).

Pathophysiology: Pulmonary-Renal Interactions During AKI and ARDS

Although the exact mechanisms mediating pulmonary-renal interactions during critical illness have not been elucidated, emerging basic and clinical studies indicate that ARDS can incite kidney injury whereas AKI can alter leukocyte trafficking and pulmonary vascular permeability. Thus, injury to the lung may precipitate injury to the kidney and vice versa (Fig 3). The lungs and kidneys are exposed to a high circulating volume of blood each minute—the lungs receive the full cardiac output (CO) and the kidneys receive 22% of CO. In addition, both organs share an extensive capillary network that is exposed to circulating inflammatory mediators and circulating neutrophils and monocytes, putting both organs at risk for injury during the inflammatory insults of sepsis or trauma.

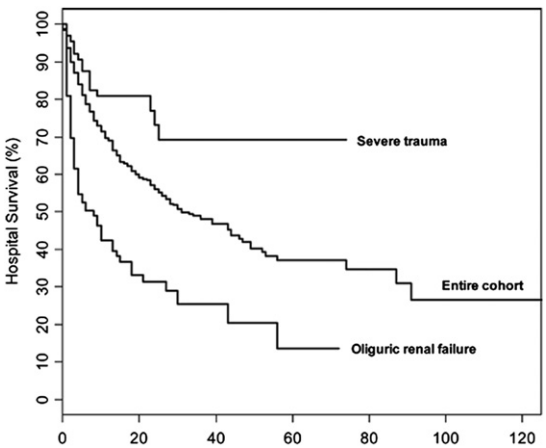

Figure 1. Patients with ARDS and severe AKI have a dramatic increase in mortality. Reproduced with permission from Cooke et al.[3]

The pathophysiologic link between AKI and ARDS has been investigated in animal models of organ injury. Kidney injury appears to affect pulmonary function through two main mechanisms: increased inflammatory cytokine production and downregulation of pulmonary ion and water transport channels.[16] Kidney dysfunction, mediated by ischemia reperfusion or bilateral nephrectomy, leads to an increase in circulating inflammatory cytokines, including interleukin (IL)-1-β, IL-6, and tumor necrosis factor, and a decrease in their clearance.[17] These inflammatory cytokines can lead to an increase in pulmonary neutrophil accumulation and pulmonary capillary permeability.[17-19] IL-6 appears to be a central mediator of lung injury during kidney dysfunction because IL-$6^{-/-}$ mice or mice treated with anti-IL-6 antibodies do not develop pulmonary impairment after kidney injury.[19] In addition to increased neutrophil infiltration and increased pulmonary vascular permeability, in rat models of kidney injury there is a dramatic downregulation of the key ion transport (ENaC, Na,K-ATPase) and water transport (aquaporin-5) channels in the lungs.[20] Thus, on the basis of these animal models, kidney injury leads to inflammatory changes in the lungs that may predispose patients to lung injury; furthermore, kidney injury may impair the compensatory mechanisms that remove solute and water from injured alveoli.

Treatment

Ventilator Management

The foundation of therapy for patients with ARDS is a lung-protective ventilation strategy and appropriate supportive measures for critically ill patients. The National Heart Lung and Blood Institute (NHLBI)-sponsored ARDSnet clinical trials group has conducted a set of pivotal trials that form an evidence-based framework to care for patients with ARDS.[21-23] In 2000, the ARDSnet compared ventilation with low-TV (6 mL/kg TV based on ideal body weight [IBW]) to ventilation with traditional TV (12 mL/kg IBW). The low-TV strategy specified that plateau airway pressures should remain below 30 cm H_2O, which in some cases required permissive hypercapnia and TVs as low as 4 mL/kg. This protocolized ventilator strategy (http://www.ARDSnet.org/node/77466) includes a matched escalation of PEEP and FiO_2 that

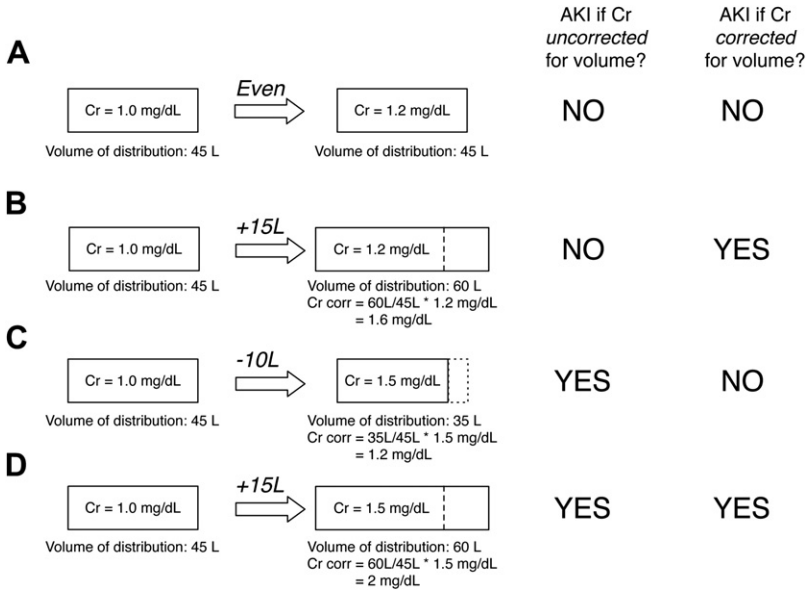

Figure 2. The incidence and effect of AKI in patients with ARDS is likely underestimated because of aggressive volume resuscitation. Reassignment from AKI absent to AKI present identifies a group of patients with increased hospital mortality. Reproduced and adapted with permission from Liu et al.[14]

was based on measures of oxygenation and was different from prior strategies in that it used lower TVs and higher PEEP. Low-TV ventilation decreased mortality from 40% to 31% ($P = 0.007$), and patients in the low-TV group had a shorter duration of ventilation, fewer ICU days, and fewer nonpulmonary organ failures. The subsequent ALVEOLI trial tested the optimal PEEP level and found no difference in mortality between FiO_2/PEEP tables that used higher versus lower levels of PEEP.[23] However, this trial did show an overall decrease in mortality when compared with previous ARDSnet trials, indicating that changes in supportive care, in addition to low-TV ventilation, have decreased the mortality of patients with ARDS.

Ventilator Management: Effect on the Kidney

A lung-protective ventilation strategy based on the ARDSnet protocol has been widely adopted by critical care physicians and has important implications for nephrologists.

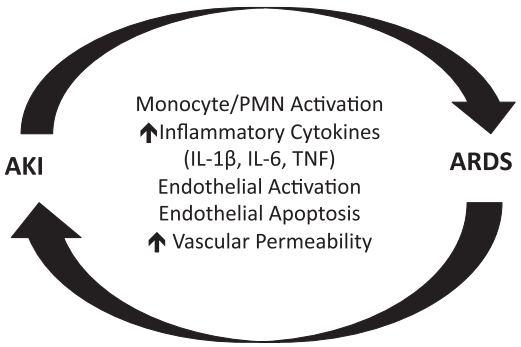

Figure 3. Interactions between the injured lung and injured kidney during critical illness can lead to an inflammatory loop that worsens kidney injury and increases pulmonary vascular permeability. PMN, polymorphonuclear leukocyte.

First, and most importantly, lung-protective ventilation decreases the risk of nonpulmonary organ injury including AKI, resulting in a decreased risk of severe AKI requiring CRRT.[24,25] One potential undesired consequence of lung-protective ventilation is the development of a hypercarbic respiratory acidosis. This effect of low-TV ventilation is generally well tolerated, and a mild hypercapnic acidosis may have anti-inflammatory and cytoprotective effects.[26,27] However, when hypercapnia is compounded by a severe anion-gap acidosis, which frequently occurs during sepsis or trauma, then arterial pH may dive unacceptably low, predisposing patients to hemodynamic instability and arrhythmias. Attempts to correct this mixed acidemia through bicarbonate administration may worsen arterial and intracellular pH as bicarbonate is converted to CO_2, diffuses intracellularly, and accumulates in the lungs.[28] An alternative to bicarbonate in nonoliguric patients is THAM (tromethamine, tris-hydroxymethyl aminomethane), which is a chemically inert base that facilitates the kidney excretion of protons. In oliguric patients, CRRT with a high bicarbonate bath may also be considered to increase arterial pH and ameliorate the hemodynamic instability and potential arrythmogenic effects of severe acidosis. Lastly, extracorporeal CO_2 removal devices, which are currently under investigation, may be an alternative to CRRT in patients with a severe hypercapnic respiratory acidosis due to noncompliant lungs.[29]

Lung-protective ventilation, on the basis of the ARDSnet protocol, may also have important hemodynamic ramifications. High levels of PEEP can impair CO and kidney blood flow.[30] In one study, increasing PEEP from 0 to 10 cm H_2O in mechanically ventilated patients decreased CO by 15% despite having no effect on mean arterial

pressure. In addition, increasing PEEP led to a 34% reduction in urinary output, a 19% reduction in glomerular filtration rate, and a 32% decrease in kidney blood flow.[30] This same study also found that PEEP led to a significant increase in the plasma levels of renin and aldosterone that may further impair kidney function.[30] Thus, patients with severe ARDS who require PEEP more than 10 cm H_2O may have dramatic alterations in kidney hemodynamics and the renin-angiotensin-aldosterone axis, especially if these patients are not adequately volume resuscitated.

Fluid Management

Patients often develop ARDS in the context of severe medical illnesses, such as sepsis, trauma, or pancreatitis. The acute phases of these conditions require aggressive volume resuscitation.[31] However, continued volume administration after the return of hemodynamic stability is likely detrimental.[32,33] The ARDS Network tested the balance between kidney perfusion (fluid liberal) and ARDS resolution (fluid conservative) in ARDS patients during the FACTT study. In this multicenter trial, which enrolled 1000 patients and was published in 2006, patients were randomized to a liberal or conservative fluid administration protocol for the first 7 days of ARDS. The primary end points were 60-day mortality, duration of mechanical ventilation, and ICU length of stay. After resolution of shock, patients in the conservative fluid management group received diuretic therapy with a goal central venous pressure (CVP) less than 4 or pulmonary artery occlusion pressure of less than 8. Notably, the achieved CVP in the fluid conservative group was approximately 8, not less than 4, because of provisions in the protocol that guarded against end-organ hypoperfusion. For example, diuretics were not given with a CVP of 4-8 if the average urinary output was less than 0.5 mL/kg/hour or the mean arterial pressure was less than 60. In the liberal fluid therapy group, fluids were administered to keep the CVP at 10-14 or pulmonary artery occlusion pressure at 14-18. There was no difference between groups for the primary end point of mortality. However, patients randomized to the conservative therapy group had improved measures of oxygenation, increased ventilator-free days (14.6 vs 12.1, $P < 0.0001$), and shorter ICU lengths of stay (13.4 vs 11.2, $P < 0.001$).

Fluid Management: Effect on the Kidneys

Although fluids are commonly administered to critically ill ARDS patients with the goal of minimizing kidney hypoperfusion, the FACTT study and other studies indicate that continued administration of intravenous fluids to shock-free patients does not improve kidney function and may delay the resolution of lung injury. In the fluid conservative group of the FACTT study, in which there was concern that aggressive diuresis might lead to kidney hypoperfusion and AKI, there was actually a trend toward decreased dialysis (10% vs 14%, $P = 0.06$). A comparison of fluid administered over the first week of the trial showed that patients in the fluid conservative group were net fluid whereas patients in the fluid liberal group were 7 L net positive (Fig 4). These data suggest that aggressive diuretic use in shock-free patients with ARDS does not predispose them to AKI. Instead, it may expedite the resolution of lung injury and facilitate extubation. Importantly, the total volume of fluid received by the fluid liberal group was similar to the volume administered in previous ARDSnet trials, suggesting that the fluid liberal group was comparable to usual practice (Fig 4). Other studies also suggest that patients who are net volume positive during their ICU stay have worse outcomes including a longer duration of mechanical ventilation and longer ICU stays.[33,34] These observational studies may identify patients with persistent vascular leak and shock and further studies will be needed to dissociate cause from effect. Despite these compelling data, a fluid conservative therapy in shock-free ARDS patients has not been universally adopted, potentially because of lingering concerns that a fluid conservative therapy may predispose patients to AKI.

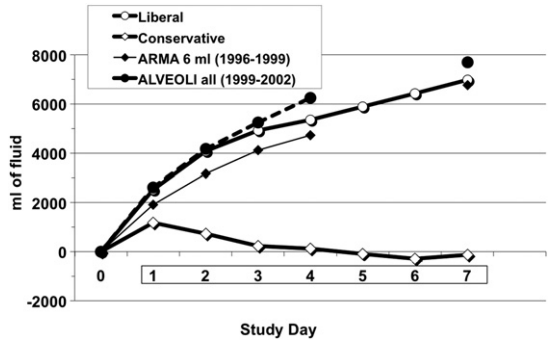

Figure 4. Patients randomized to the conservative fluid therapy arm of the FACTT study were net fluid even by the end of the 7-d trial compared with those in the liberal arm, who were approximately 7 L positive. Fluid administered to the liberal group was comparable to standard practice on the basis of two previous ARDSnet trials—the ARMA and ALVEOLI trials. Reproduced with permission from Wiedemann et al.[22]

Sedation, Analgesia, and Paralytics for ARDS

Sedation practices for critically ill patients have changed dramatically over the past 10 years, and these changes have been used in patients with ARDS. Shortly after the adoption of lung-protective ventilation, concerns arose that ventilating patients with lower TVs would lead to patient discomfort requiring higher doses of sedation. However, observational studies failed to show increased opiate or sedative use during low-TV ventilation.[35] In fact, recent studies have led to a movement away from deep sedation in critically ill patients. This movement started with the hypothesis that daily interruption of

sedation might decrease the duration of mechanical ventilation and empower physicians to more effectively evaluate the neurologic status of critically ill patients. In 2000, Kress and Hall published a landmark study illustrating that daily interruption of sedative infusions decreased the duration of mechanical ventilation and decreased ICU length of stay.[36] The Awake and Breathing Controlled trial, a multicenter trial of paired sedation interruptions and spontaneous breathing trials, showed similar results.[37] As a consequence of these trials, the continuous infusion of benzodiazepines should be avoided in favor of intermittent as-needed dosing based on standardized sedation scales such as the Richmond Agitation Assessment Scale. The development of new sedative agents may also decrease the need for deep sedation. Several recent studies have shown that dexmedetomidine,[38] a selective α_2-agonist that does not cause respiratory depression, is safe and effective in ICU patients, may facilitate extubation in agitated patients[39] and can shorten the duration of mechanical ventilation and improve patient-hospital staff communication when compared with other commonly used sedative medications.[38,40] Importantly, dexmedetomidine is hepatically metabolized to an inactive metabolite, which is then excreted by the kidneys. Thus, it is safe to use in patients with impaired kidney function.

Although there was a strong trend away from paralytic use in patients with ARDS because of a fear of the resulting myopathy of critical illness, a recent trial found that early neuromuscular blockade with Cisatracurium in patients with severe ARDS ($PaO_2/FiO_2 < 150$ mm Hg) improved adjusted 90-day mortality without increasing the risk of neuromuscular weakness.[41] Cisatracurium is enzymatically degraded through Hoffman elimination, and impaired kidney function or CRRT does not alter its pharmacokinetics. Thus, although early paralytics may improve outcomes in severe ARDS, when these patients are recovering, efforts should be made to minimize sedation.

Adjunctive Therapies

Recent trials have evaluated pharmacologic and nutritional therapies for ARDS. The ARDSnet consortium and other groups have performed large multicenter trials of the treatment of ARDS with glucocorticoids, surfactants, inhaled nitric oxide, antioxidants, protease inhibitors, and recombinant human activated protein C.[42,43] Unfortunately, none of these interventions consistently decreased mortality, days of mechanical ventilation, or ICU length of stay. On the basis of compelling animal data showing that β_2-adrenergic agonists increased the resolution of alveolar edema and a small human trial (BALTI-1) showing that intravenous β_2-agonists decreased extravascular lung water, the ARDSnet sponsored a multicenter trial of the inhaled β_2-albuterol.[44] This trial failed to show an increase in the primary outcome of ventilator-free days or the secondary outcome of mortality. In addition, the BALTI-2 trial, a European multicenter study of the intravenous β_2-agonist salbutamol failed to show improvements in any of the study end points, and patients receiving salbutamol showed an increase in overall mortality.[45] Thus, neither inhaled or intravenous therapy with a β_2-agonist can be recommended for ARDS. Several recent studies have also focused on nutrition for patients with ARDS.[46,47] The EDEN trial compared lower volume enteral trophic feeding with full-volume enteral feeding during the first 6 days of ARDS, and the OMEGA trial compared dietary supplementation with omega-3 fatty acids, antioxidants, and γ-linolenic acids with isocaloric feeds. Neither of these studies showed an improvement in the primary end point of ventilator-free days or the secondary end point of mortality. Studies of statins, inhaled heparin, and adoptive cellular therapy for ARDS are ongoing.

Conclusions

ARDS continues to be a major contributor to ICU morbidity, mortality, and resource utilization. When patients develop ARDS and AKI, the duration of hospitalization and mortality increase dramatically. Thus, this vulnerable patient population requires effective communication among all medical providers, and nephrologists and intensivists in particular must communicate effectively to manage the complex pulmonary-renal interactions during critical illness. To date, lung-protective ventilation is the only lung-centric therapy to decrease mortality from ARDS. Despite several recent trials, no pharmacologic agent, including intravenous or inhaled β_2-agonists, recombinant human activated protein C, or nutritional therapies, has been shown to decrease the duration of mechanical ventilation or improve mortality. However, supportive therapies, including a conservative fluid management strategy, minimization, and interruption of sedation and early mobilization have contributed to an overall decrease in mortality from ARDS. Future studies that focus on the pathophysiology of death in patients with ARDS and AKI as well as the timing, dosage, and method of CRRT may further improve the care of patients with overlapping AKI and ARDS.

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Hemodynamic Monitoring in the Critical Care Environment

Laurence Busse, Danielle L. Davison, Christopher Junker, and Lakhmir S. Chawla

Hemodynamic monitoring is essential to the care of the critically ill patient. In the hemodynamically unstable patient where volume status is not only difficult to determine, but excess fluid administration can lead to adverse consequences, utilizing markers that guide resuscitation can greatly affect outcomes. Several markers and devices have been developed to aid the clinician in assessing volume status with the ultimate goal of optimizing tissue oxygenation and organ perfusion. Early static measures of volume status, including pulmonary artery occlusion pressure and central venous pressure, have largely been replaced by newer dynamic measures that rely on real-time measurements of physiological parameters to calculate volume responsiveness. Technological advances have lead to the creation of invasive and noninvasive devices that guide the physician through the resuscitative process. In this manuscript, we review the physiologic rationale behind hemodynamic monitoring, define the markers of volume status and volume responsiveness, and explore the various devices and technologies available for the bedside clinician.

Key Words: Cardiac output, Hemodynamics, Stroke volume variation, Pulmonary artery catheter

Introduction

The goal of hemodynamic monitoring in the care of critically ill patients is to assess and ensure adequate tissue oxygen delivery and end organ perfusion. This is accomplished by thoughtful management of cardiac output (CO) and systemic vascular resistance (SVR). Often it is difficult to ascertain whether a strategy of volume expansion, vasopressor use, inotropic support, or diuresis is the most appropriate strategy. Moreover, inappropriate volume expansion can lead to volume overload, pulmonary edema, worsening gas exchange, and acidosis. In the setting of chronic kidney disease, volume management is further complicated by impaired kidney autoregulation as well as compromised free water and solute elimination. Several tools have been developed for use in clinical practice that may aid in determining hemodynamic status as well as estimate the effect of volume, diuresis, or manipulation of systemic vascular resistance (from vasopressors). This review article will provide a physiologic basis for hemodynamic monitoring as well as discuss many of the hemodynamic parameters and devices used in the care of the critically ill patient.

Physiology

The relationship among CO, mean arterial pressure (MAP), and SVR (Equation 1) plays an important role in the management of the hemodynamically unstable patient with the goal of optimizing organ perfusion. Clinicians often use systolic blood pressure or MAP as a crude measure of end organ perfusion and central venous pressure (CVP) as a measure of volume status; from a practical perspective, this is an appropriate place to start. However, it is important to note that MAP and CVP are affected by the manipulation of CO and SVR. The manipulation of SVR (via vasopressors or vasodilators) has its limitations because high vasopressor doses ultimately decrease tissue perfusion and increase myocardial oxygen demand.[1,2] Therefore, it is imperative that a clinician be able to assess CO and its components (Equation 2) to optimize perfusion.

$$(MAP - CVP) * 80 = CO * SVR \qquad \text{(Equation 1)}$$

$$CO = HR * SV \qquad \text{(Equation 2)}$$

Whereas heart rate is easy to determine, stroke volume is more difficult to measure directly. Stroke volume may be described by its relationship to cardiac filling pressure whereby increases in filling pressures, or preload, potentially correspond to a greater stroke volume. The Frank-Starling curve illustrates this relationship between pressure and volume. Traditionally, cardiac preload has been measured with CVP and pulmonary artery occlusion pressure (PAoP). It is important to recognize that this relationship is not linear because a complex set of factors can alter this relationship (ie, cardiomyopathy). Moreover, preload measurements can actually lead to incorrect assumptions regarding stroke volume, depending

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on where a patient lies along the Frank-Starling curve (Fig 1).

Disease-specific states can confound the relationship between pressure and volume, making volume status difficult to determine accurately. Patients with pulmonary hypertension or right ventricular dysfunction can generate CVPs that are not indicative of left atrial pressures or volume status but rather only reflect the failing right ventricle.[3]

Septic patients and patients with acute respiratory distress syndrome (ARDS) can also have misleading cardiac filling pressures despite being intravascularly depleted.[4] The presence of positive end-expiratory pressure may also be implicated in erroneous CVP and PAoP measurements.[5] All of this may be further complicated by acute or chronic kidney disease, whereby fluid management is an issue of its own.

To optimize end organ perfusion, clinicians have developed a myriad of specialized parameters and devices aimed at monitoring and guiding fluid management. These parameters can be broken down into static measurements that measure CO by exploiting its relationship to pressure and/or volume at one particular point in time. Static measurements include CVP and PAoP as described above briefly. Alternatively, dynamic tools predict a change in CO over time in response to a fluid bolus as a consequence of pressure changes within the respiratory cycle. A discussion of these techniques and their respective measurement devices is provided in the following section.

CLINICAL SUMMARY

- The goal of hemodynamic monitoring is to ensure adequate tissue oxygen delivery and end organ perfusion.
- Static measurements of volume status, including CVP and PAoP, lack accuracy and precision.
- Dynamic markers, including pulse pressure variation and stroke volume variation, are based on the principle of pulses paradoxus and are valid predictors of volume responsiveness.
- Cardiac performance can be evaluated at the bedside with good clinical judgement, appropriate interpretation of values, and judicious use of technological devices.

Hemodynamic Measurements of Volume Status and Fluid Responsiveness

Static Measurements

Static measurements of volume status include CVP and PAoP as well as left ventricular end diastolic area (LVEDA). CVP and PAoP are typically measured through a central line or a pulmonary artery (PA) catheter, which is inserted via the internal jugular or subclavian vein. The assumption behind CVP as a determinant of volume status is that CVP estimates right atrial pressure and correspondingly right ventricular end diastolic volume. In theory, a higher CVP signifies greater blood volume in the right atrium and thus higher right ventricular preload (a relationship that is questionable in cases of altered ventricular wall compliance). PAoP utilizes the same set of assumptions for the left side of the heart. PAoP is measured by a PA catheter, which has a balloon tip as well as a distal pressure transducer. When the balloon is inflated and wedged inside of one of the pulmonary arteries, the pressure transducer will measure pressure distal to this balloon (specifically the pressure of the pulmonary capillary bed, which is open to the left atrium). Similar to CVP measurement, left atrial pressure in theory corresponds to left ventricular end diastolic volume, which, according to the Frank-Starling relationship, is related to stroke volume. A schematic of PA catheter tip positions and the corresponding pressure tracings are provided in Figure 2.

Like CVP and PAoP, LVEDA is a static marker used to approximate the volume status of a patient. LVEDA is measured by transthoracic or transesophageal echocardiography. In principle, an increase in LVEDA signifies greater ventricular myocardial stretch and therefore the potential for a larger CO. As explored above, this assumption does not always hold true because myocyte stretch and corresponding myocardial wall tension depend on the shape of the Frank-Starling curve and the position on the curve.

An increasingly large body of evidence suggests that the static markers CVP, PAoP, and LVEDA are poor surrogates for volume status. Despite the classic teaching about the "wedge" pressure (PAoP), this indicator is not an accurate marker of volume status. Moreover, PaOP does not predict whether a fluid challenge will lead to an improvement in cardiac performance (also known as "fluid responsiveness").[3-5] CVP and LVEDA are similarly poor predictors of fluid responsiveness. A systematic review by Michard concluded that these static measures did not adequately predict or discriminate responders (as defined as an increase in SV or CO to a fluid bolus) from nonresponders.[5] Even in presumably fluid-responsive patients, evidence suggests poor correlation between cardiac filling pressure and volume status. In a trial of 44 healthy volunteers, initial CVP, PAoP, and LVEDA did not correlate with volume responsiveness. Moreover, changes in CVP and PAoP after a 3-L saline bolus failed to result in changes in cardiac index (CI) or stroke volume index (SVI). However, changes in LVEDA as measured by echocardiography did correlate with changes in SV.[3] In comparison to CVP and PAoP, LVEDA is a more accurate measurement of

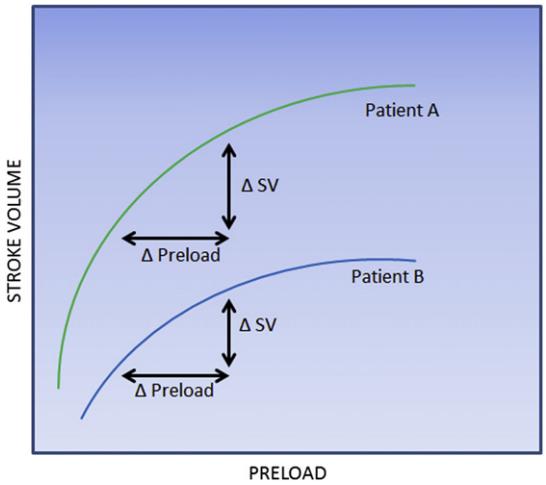

Figure 1. Patient A has a steeper starling curve than patient B. Both patients have identical changes in preloads. Administration of a volume challenge will yield different changes in stroke volume. Patient A is more "volume responsive" than patient B.

volume status but is difficult to measure continuously because of its reliance on echocardiogram. Finally, a systematic review of 803 patients concluded that CVP poorly correlated with blood volume, SV, and CO.[4] Despite this mounting body of evidence, CVP and PAoP are still widely used to guide fluid management in the critical care setting.

Dynamic Measurements

Because static measures do not predict volume responsiveness well, many clinicians have adopted the use of dynamic measures in an effort to predict fluid responsiveness and cardiac performance. These dynamic measures establish a relationship between fluid responsiveness and variations in various cardiac performance measures over time. Dynamic markers are based on the principle of *pulsus paradoxus*, or the variation of stroke volume and blood pressure with respiration. Physiologically, this occurs because blood flow return to the heart varies with the undulation of intrathoracic pressure caused by breathing. In patients who are mechanically ventilated (more specifically, synchronous with the ventilator and/or paralyzed) and who are in normal sinus rhythm, similar respiratory-cycle variations in SV and pulse pressure (SBP-DBP) can be seen. Specifically, positive pressure ventilation causes an increase in intrathoracic pressure, which in turn causes decreased venous return and increased right ventricular afterload. This correlates to a decreased right ventricular and subsequently left ventricular output, which is manifested as a relative decrease in SV or pulse pressure. Because of blood transit time, this decrease is usually seen 2 seconds later, after the cessation of a delivered positive pressure breath (Fig 3).[6] The variation in SV or pulse pressure (calculated as the maximum pulse pressure minus the minimum pulse pressure divided by the average of the two values) is exaggerated in periods of relative volume depletion. Specifically, a wide SV or pulse pressure variation indicates that a fluid challenge will result in an increase SV and better cardiac performance.

Many studies have demonstrated that the dynamic parameters of stroke volume variation (SVV) and pulse pressure variation are valid predictors of volume responsiveness. By way of example, a systematic review by Marik highlighted the results of 29 studies in which dynamic changes in arterial waveform outperformed static markers in predicting fluid responsiveness.[7]

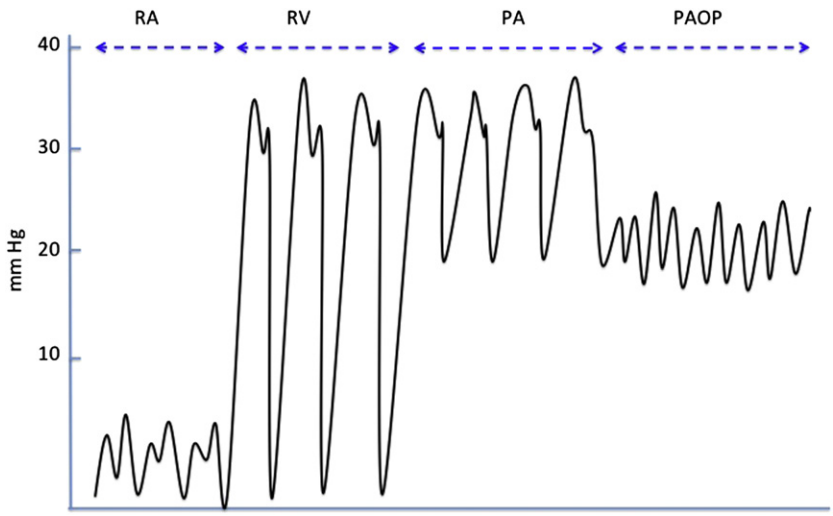

Figure 2. Schematic of the distal portion of a PA catheter and corresponding pressure tracings as the catheter travels through the heart. The PAoP reflects left atrial pressure. RA, right atrium; RV, right ventricle; PA, pulmonary artery.

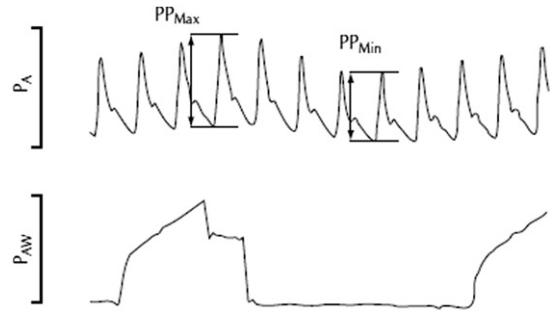

Figure 3. Illustration of pulse pressure variation. PA, arterial pressure; PAW, airway pressure; PPmax, maximum pulse pressure; PPmin, minimum pulse pressure. Note that tracing occurs during positive = pressure ventilation. Reprinted with permission from Gunn SR, Pinsky MR. Implications of arterial pressure variation in patients in the intensive care unit. *Curr Opin Crit Care*. 2001;7(3):212-217.[19]

Inferior Vena Cava Diameter

Inferior vena cava diameter (IVCd), or more specifically the variation in vena cava diameter during respiration as seen by echocardiography, is another valid dynamic mechanism by which fluid responsiveness can be measured. Much like SVV, IVCd variation during respiration is a function of increasing and decreasing intrathoracic pressures during respiration and has proven to be an accurate metric of volume responsiveness in mechanically ventilated and spontaneously breathing patients.[8-10] IVCd is measured subcostally, approximately 0.5-4 cm below the junction of the IVC and the right atrium, in the longitudinal direction at a perpendicular angle to the IVC.[11-15] Variation in IVCd is calculated as "the change" in IVCd during inspiration as compared with baseline (during expiration). Normative values for IVCd have been described in several studies, and, depending on the clinical scenario, range from 8 to 40 mm.[14,16] Variation of greater than 10-18% in IVCd during a respiratory cycle has been shown to be predictive of volume responsiveness in several studies, (sensitivity ranging from 50% to 100%; specificity ranging from 53% to 100%, predefined variation).[11,13,15] By way of example, Barbier and colleagues calculated the IVC distensibility index (calculated as the ratio of Dmax-Dmin/Dmin, expressed as a percent) in ventilated septic patients before and after volume challenge.[11] The authors demonstrated that using an IVC distensibility threshold of 18% differentiated responders (predefined as an increase in CI $>$ 15% after volume expansion) and nonresponders with 90% sensitivity and 90% specificity.[11] IVCd is measured at the bedside using echocardiography in M-mode during a respiratory cycle.

Determination of vena cava diameter using echocardiography requires operator skill and thus is subject to error. Additionally, interpretation may be difficult in patients with ascites, morbid obesity, and in patients with intra-abdominal hypertension.[11,13,15]

Passive Leg Raise

In the passive leg raise (PLR) test, the lower extremities are elevated above the heart of a recumbent patient mimicking the effect of a large fluid bolus on the central circulation. The postural maneuver is seen in Figure 4. Static and dynamic measures of CO are evaluated during this maneuver to determine if there is evidence of volume responsiveness. This may include changes in pulse pressure or SV, changes in MAP, or increases in CO or PAoP.

Evidence suggests that the PLR maneuver in critically ill, nonintubated patients not only predicts volume responsiveness but can also serve as a therapeutic intervention. A study by Maizel found that the PLR test induced changes in SV and CO (as measured by echocardiography and Doppler analysis) and was highly predictive of central hypovolemia (sensitivity 63-89% and specificity of 89%). Changes in CO witnessed during the PLR compared with that of a fluid bolus of 500 cc of normal saline correlated well.[17] A study by Preau concluded that changes in stroke volume, pulse pressure, and femoral artery flow velocity as a result of a PLR were all highly predictive of fluid responsiveness (sensitivity of 79-86% and specificity of 80-90%).[18] The straight leg raise is limited to those patients who can lay flat and can be put in the appropriate position. It is interesting to note that the PLR position is commonly seen in dialysis units in an effort to alleviate symptoms that arise in patients being dialyzed up to and perhaps beyond their dry weight. However, to date no studies have examined

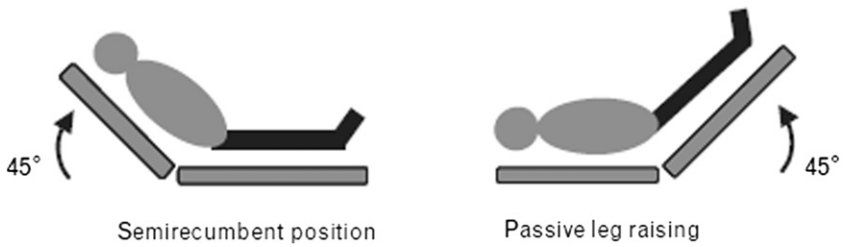

Figure 4. A PLR in a semirecumbent patient. Reproduced with permission from Teboul JL, Monnet X. Prediction of volume responsiveness in critically ill patients with spontaneous breathing activity. *Curr Opin Crit Care*. 2008;14(3):334-339.[41]

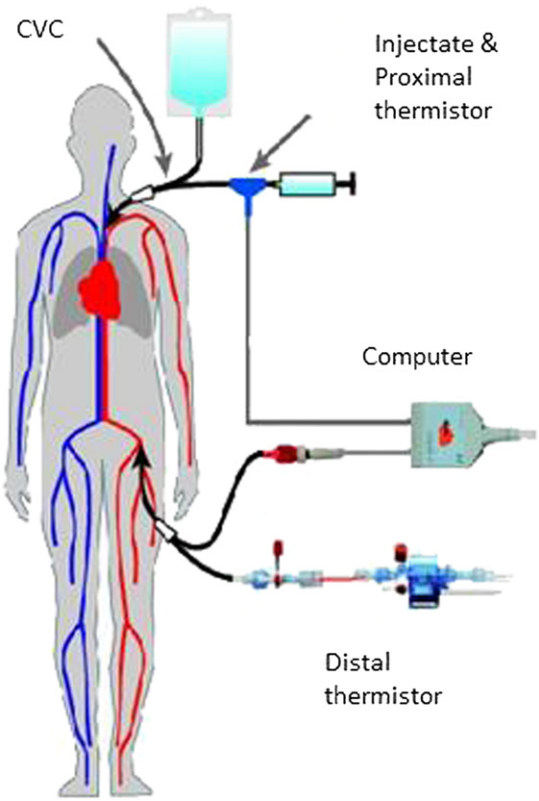

Figure 5. A schematic of a TPTD setup. Reproduced with permission from Pulsion Medical Inc., 2445 Gateway Drive, Suite 110, Irving TX, 75063, USA.

PLR in the dialysis setting as a tool to optimize volume status.

It should be mentioned that the administration of a fluid bolus for diagnostic purposes (ie, indiscriminately giving a fluid bolus to a patient to determine a patient's fluid responsiveness) is commonly done in clinical practice. However, this intervention is not always benign. One study by Michard found that 50% of hypotensive, critically ill patients are not fluid responsive.[5] Moreover, the consequences of fluid administration to an unresponsive patient can be deleterious, affecting gas exchange and acid base status.[19] Dynamic markers provide the clinician with the information to determine if a patient will or will not respond to volume before the fluid challenge, thereby helping to avoid situations of unnecessary and imprudent resuscitation.

Hemodynamic Monitoring Methods and Devices

Thermodilution

Advancements in PA catheter technology have allowed clinicians to calculate CO on the basis of flow of blood through the right ventricle. Thermodilution (TD)-measured CO is based on the Stewart-Hamilton equation (Equation 3).

$$Q = \frac{(V1 * (Tb - T1) * K1 * K2)}{(Tb(t)dt)} \qquad \text{(Equation 3)}$$

where Q = CO, $V1$ = injectate volume, Tb = blood temperature, $T1$ = injectate temperature, $K1$ = density factor, $K2$ = constant, and $Tb(t)dt$ = change in blood temperature as a function of time. CO correlates with the temperature gradient between the injectate and the patient's blood and is inversely related to the change in blood temperature over time. The smaller the temperature change (ie, a higher volume of warm blood mixes with the cold injectate), the higher the CO. In practice, CO is determined after a known volume and temperature of fluid is injected into the proximal end of the PA catheter, which then mixes with the patient's blood at a known temperature before entry into the right ventricle. Downstream at a given time interval, the blood-injectate temperature is measured again, allowing for an estimation of CO. Newer PA catheters are capable of continuous CO calculation using the same technique by virtue of an embedded proximal heating filament and distal thermistor built into the catheter. Several studies have demonstrated that TD is an accurate and valid way to measure CO.[20,21] TD using the PA catheter has emerged as the gold standard in estimating CO and is the method against which all other devices are measured.

A large body of evidence suggests that the use of the PA catheter itself is controversial. A landmark study by Connors showed that for a large population of critically ill patients, PA catheterization resulted in an increased 30-day mortality, increased cost of health care, and a greater length of stay.[22] A later trial by Sandham of surgical patients found no difference in mortality or length of stay between patients with and without PA catheters.[23] More recently, a Cochrane Database systematic review of PA catheterization found no difference in mortality or length of stay in critically ill or surgical patients, but it did find increased health care costs associated with PA catheters.[24] Theories as to why these outcomes exist include direct deleterious effects of the PA catheter itself (ie, arrhythmia, PA rupture, increased incidences of pulmonary embolism), or the harmful effects of the therapies implemented based on inappropriate interpretation of data.[22]

Transpulmonary Thermodilution

The transpulmonary thermodilution (TPTD) technique utilizes a standard central venous catheter and a thermistor, which is inserted in the femoral artery (Fig 5). A TD analysis, similar to the PA catheter TD methodology, can be generated by using the Stewart-Hamilton

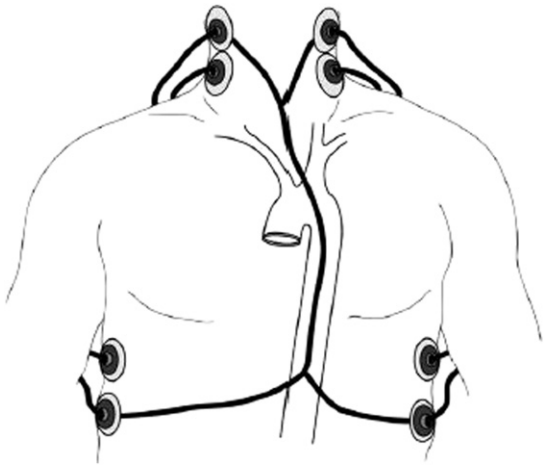

Figure 6. Schematic of an external electrode thoracic electrical bioimpedance setup. Impedance is tracked on a recording device (not shown). Reprinted with permission from Tang WH, Tong W. Measuring impedance in congestive heart failure: Current options and clinical applications. *Am Heart J*. 2009;157(3):402-411.[42]

equation (Equation 3). This method is potentially as accurate at PA catheter TD technique, provided that there is (1) constant blood flow, (2) minimal loss of injectate, (3) complete mixing of the injectate with blood, and (4) only one pass from the proximal thermistor on the central line to the distal thermistor in the aorta.[25] The TPTD is slightly less invasive than the PA catheter TD method and therefore is an attractive alternative.

Several studies have compared TPTD to other methods of hemodynamic monitoring. Sakka compared TPTD and PA catheter TD in 12 critically ill surgical patients and found good agreement between the two methods ($r = 0.98$, $P < 0.0001$).[26] Segal likewise found good correlation between TPTD (using an axillary artery as a distal thermistor site) and TD in 22 critically ill patients. ($R^2 = 0.82$).[27] A study by Goepfert found that a goal-directed therapy approach using TPTD in 40 cardiac bypass patients led to reduced pressor use, increased colloid administration, fewer days of mechanical ventilation, and a shorter time to achieve the status "fit for ICU discharge."[28]

Thoracic Electrical Bioimpedance

A known technology for the last 80 years, the thoracic electrical bioimpedance (TEB) has only recently become routinely available in the critical care setting. TEB is founded on the principles of Ohm's law ($V = IR$), where impedance is based on the electrical resistance (R) of a circuit. In the human body, the electrical resistance of an applied current is affected by the relative water content in the descending aorta and will vary with the amount of blood flow through this vessel. Thus, a volume-replete patient will exhibit a low TEB compared with that of a volume-depleted patient. In practice, TEB is calculated using a system of connected electrodes through which a high-frequency, low-amplitude current is passed and is tracked on a recording device (Fig 6). TEB loses accuracy in the setting of increased extravascular lung water.[29]

TEB has been studied in various clinical scenarios and results have been mixed. Resiner compared measuring CO by TEB versus by pulse contour analysis (see below) in healthy patients undergoing lower body negative pressure to simulate central hypovolemia. The two methods correlated well.[30] Gujjar studied 35 postoperative cardiac surgical patients and showed that TEB performed similarly to the PA catheter TD ($r = 0.856$, $P < 0.01$).[31] In contrast, Petter found that TEB correlated poorly with TD in 33 heart failure patients.[32] Moreover, a systematic review by Jensen concluded that TEB as a hemodynamic monitoring device is neither accurate nor precise.[29] Further research and advancements in technology are needed before this method becomes widely adopted in the critical care setting.

Esophageal Doppler

Estimation of aortic blood flow through the use of continuous Doppler ultrasound positioned in the esophagus (ED) is a relatively noninvasive method of measuring CO. This technique is based on the principle that the velocity of blood flow travelling through the aorta is inversely related to the aortic diameter and directly related to flow (CO; Equation 4).

$$v = Q/A \qquad \text{(Equation 4)}$$

where v = velocity, Q = flow, and A = cross-sectional area. In the setting of reduced CO due to hypovolemia, flow velocity and aortic diameter will fall, as measured by the esophageal probe. As with all other tools used to estimate CO, ED has its limitations. Patients must be intubated to position the esophageal probe. Turbulent flow through the aorta caused by an aneurysm or atherosclerosis may confound calculations.[33] Finally, it should be noted that aortic blood blow is only an estimation of CO because a significant portion of blood (upward of 30%) ejected from the left ventricle never reaches the thoracic aorta but flows to the vessels that stem from the aortic arch.

Despite these limitations, evidence supports the use of ED. A systematic review of 2400 paired measurements from 314 patients calculated a mean bias between TD-calculated and ED-calculated CO of only 0.19 L/min. Moreover, agreement for measuring change in CO during a fluid challenge was 86% ($P < 0.03$).[34] A review of 25 studies by Laupland also showed good correlation between TD and ED ($R = 0.89$).[33] Despite this evidence, this technique has not been widely adopted in critical care settings.

Pulse Contour Analysis

Pulse contour analysis (PCA) has recently emerged as an accurate method for measuring cardiac performance and has gained popularity because of its minimally invasive technique. In addition to measuring cardiac performance (SV, CO, CI), PCA provides dynamic markers (specifically SVV) that assist in determining volume responsiveness. PCA can be determined manually by obtaining routine measurements of an arterial line tracing and performing simple mathematics to determine variability throughout the respiratory cycle. Practically speaking, this can be accomplished by standing at the bedside for 30 seconds and observing the undulation on the arterial line monitor. Associated costs aside, the benefit of using a commercially available proprietary bedside computer to do this allows the clinician to calculate several metrics that would otherwise be difficult to accomplish (such as CO, CI, and SVV).Moreover, manufacturers of this technology argue that their proprietary models integrate several variables aimed at decreasing noise (age, sex, height, weight). However, data on this incremental benefit are lacking. There are several different PCA devices available, including the PICCO (Pulsion Medical Systems, Munich, Germany), the PulsCO (LidCO Limited, Cambridge, United Kingdom), and the FloTrac (Edwards Lifescience LLC, Irvine, CA). Of these devices, only the FloTrac does not require calibration before use. PICCO must be precalibrated with TPTD and thus needs a central venous catheter in addition to an arterial line. The PulsCO uses a lithium indicator and must be calibrated every 8 hours (and is contraindicated in patients on lithium or who are pregnant). All of these systems perform similarly in comparative trials.[35]

PCA technology has its limitations. The arterial catheter site or the presence of atherosclerosis may adversely affect the accuracy of the technology.[6] Additionally, chest wall compliance, tidal volumes, and level of positive end-expiratory pressure reduce the accuracy of PCA.[6,7] In patients with open chests, PCA was not found to be helpful in predicting volume status.[36] Likewise, Lahner found that SVV determined by the FloTrac system failed to predict volume responsiveness in patients undergoing major abdominal surgery.[37] PCA has not been validated in unstable patients, spontaneously breathing patients, or in those with cardiac rhythms other than sinus (although research is ongoing).[38-40]

There has been some attention paid recently to pulse oxymetry waveform variation as a means to calculate volume status. The principle behind this technology is similar to the method using an arterial catheter. The pulse oxymetry curve represents the infrared light absorbed by circulating hemoglobin during a cardiac cycle. Variation in the amplitude of this curve can be mathematically related to the amount of blood in the capillary bed, which is in turn related to a patient's volume status. A systematic review of pulse oxymetry waveform variation demonstrated that this method accurately predicted volume responsiveness.[41] The less invasive nature of this method makes it an attractive option for future directions of research.

Summary

In summary, there are several hemodynamic monitoring tools available in the critical care setting to assist in determining CO and volume responsiveness. Fluid status and the potential to improve cardiac performance with volume challenge can be measured by static and dynamic measures, respectively. In general, dynamic metrics appear to be more robust in determining volume responsiveness. Monitoring cardiac performance (SV and CO) can also prove invaluable when caring for the hemodynamically unstable patient, and there are various bedside technologies that provide this information. The PA catheter TD technique remains an accurate means of monitoring CO and remains the gold standard. Other less invasive monitoring systems are now available and are in the process of validation. Ultimately, good clinical judgment, appropriate interpretation of values, and judicious use of devices can, in aggregate, improve hemodynamic management and end organ perfusion. Continued research comparing these tools, increased availability in intensive care unit settings, and advancements in technology will further shape the landscape in hemodynamic monitoring.

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Update in Critical Care for the Nephrologist: Transfusion in Nonhemorrhaging Critically Ill Patients

Majid Afshar and Giora Netzer

A growing number of guidelines and recommendations advocate a restrictive transfusion strategy. Strong evidence exists that a hemoglobin threshold of less than 7 g/dL conserves resources and may improve outcomes in critically ill patients and that platelet counts greater than 10,000/μL are well tolerated. Patients with coronary artery disease can be safely managed with a restrictive transfusion strategy, utilizing a hemoglobin threshold of less than 7 or 8 g/dL; a threshold of less than 8 g/dL can be applied to patients with acute coronary syndromes. In the absence of coagulopathy with bleeding or high risk for bleeding, plasma transfusion should be withheld. Complications from transfusion are significant and previously under-recognized immunologic complications pose a more serious threat than infections. Erythropoietin and iron administration do not reduce transfusion needs in the critically ill. Interventions to reduce blood loss and educate clinicians are successful in reducing transfusion requirements.
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Introduction

Patients with CKD or end-stage kidney disease comprise 0.9-6.8% of all patients admitted to the intensive care unit (ICU).[1-4] Chronic anemia is common in patients with CKD and is noteworthy given that two thirds of patients admitted to the ICU have a baseline hemoglobin (Hgb) level of less than 12 g/dL.[5,6] CKD patients admitted to the ICU on dialysis have lower mean hematocrit (Hct) level than nondialysis patients.[4]

Between one third and one half of the critically ill receive red blood cell (RBC) transfusions during their ICU stay.[7,8] Approximately 90% of RBC transfusions in the ICU occur in the context of stable anemia and, despite transfusion, patients admitted to the ICU with baseline anemia continue to be anemic.[8] Although considerable data exist for the treatment of anemia in patients with CKD in the outpatient setting, a paucity of information addresses transfusion therapy in these patients when critically ill.[9] However, clinicians caring for these patients in the ICU may find guidance from an array of randomized clinical trials and observational data evaluating transfusion across a spectrum of patients.

Pathophysiology of Anemia in Critical Illness

Multiple etiologies, iatrogenic and disease-specific, contribute to anemia in critically ill patients. Phlebotomy results in 40-50 mL of blood loss per patient-day in the ICU and as much as 64 mg of iron loss per day, surpassing normal dietary iron intake (1-2 mg per day).[7,10,11] Increased losses from the gastrointestinal tract commonly occur from weakened mucosal integrity because of stress gastritis from mechanical ventilation, nutritional deficiencies, and acute kidney failure.[12,13] During critical illness, erythropoietin (EPO) concentrations fall quickly and remain low from kidney disease and by various proinflammatory mediators, including interleukin (IL)-1.[14,15] These mediators also inhibit bone marrow RBC production.[16] Iron-deficiency anemia may affect as many as 30-40% of critically ill patients.[17] Other nutritional deficiencies may contribute and account for over 10% of cases in ICU patients.[18]

RBCs and the Storage Lesion

A unit of RBCs in additive solution contains 450-500 mL of total volume and a Hct between 55% and 65%. Each unit increases the Hgb by approximately 1 g/dL (3% Hct) in a 70-kg male. Although leukoreduced blood is now ubiquitous in the United States and has been shown to reduce morbidity,[19] the residual white cell load in leukocyte reduced blood ($<5.0 \times 10^6$) is still immunosuppressive and proinflammatory.[19,20] Storage lesions include rheologic changes, membrane carbohydrate loss, oxidative injury to lipids and proteins, changes in oxygen affinity and delivery, increased adhesion of RBCs to endothelial cells, and reduced RBC lifespan.[21-23] Hyperkalemia can occur.[24] It remains unknown how the storage lesion affects patient outcomes. Although observational studies have associated older blood with increased mortality,[25] three small randomized clinical trials (RCTs) have failed to detect a difference between fresh and old blood.[26-28] Two large RCTs, the Canadian Age of Blood Experiment (ABLE) and the U.S. Red Cell

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Storage Study (RECESS) are underway to evaluate the safety of aged blood.[29,30]

Indications for Packed RBC Transfusion: Transfusion Thresholds and Guidelines

The bulk of data supporting current transfusion strategy in the ICU comes from the landmark Transfusion Requirements in Critical Care (TRICC) trial.[31] TRICC randomized 838 critically ill patients to a strategy of transfusing RBCs at Hgb levels below 7 g/dL to maintain Hgb levels at 7-9 g/dL (restrictive arm) vs a threshold of Hgb 10 g/dL to maintain Hgb 10-12 g/dL (liberal arm). Patients with hemorrhage and acute coronary syndromes (ACS) were excluded from this analysis, as were patients with baseline Hgb less than 9.0 g/dL, which may have under-represented patients with CKD. Patients with cardiovascular disease were included in the trial. Individuals in the restrictive arm, on average, received half of the number of units transfused to the liberal arm. No difference in in-hospital, 30-day, or 60-day mortality was found between the two arms. Restrictively transfused patients experienced fewer cardiac adverse events and had smaller changes in multiorgan dysfunction from baseline. In a post hoc analysis, in patients with APACHE II scores less than 20 and with ages younger than 55 years of age, significant reductions in 30-day mortality were found. A liberal transfusion strategy did not speed extubation in mechanically ventilated patients.[32] In pediatric patients, a similar trial compared a restrictive (Hgb $<$ 7 g/dL) vs liberal (Hgb $<$ 9.5 g/dL) transfusion strategy.[33] Assessing a composite outcome of death and multiple organ dysfunction, the study found the restrictive strategy noninferior.

CLINICAL SUMMARY

- RBC transfusion for trigger Hgb less than 7 g/dL is as good as or better than Hgb less than 10 g/dL. Hgb down to 6 g/dL can be tolerated in asymptomatic patients without cardiac comorbidities.
- Transfusion thresholds of Hgb of 7 or 8 g/dL or less are required in coronary artery disease, whereas 8 g/dL or less should be used in acute coronary syndrome patients.
- Prophylactic platelet transfusion is not necessary until thrombocytopenia reaches 10,000/μL or less.
- Plasma should not be transfused without clinical evidence of coagulopathy and active bleeding or high risk of bleeding.

A recent Cochrane review identified 19 trials with intervention groups assigned to a transfusion trigger.[34] Three trials were conducted in adult and pediatric critical care units, including TRICC, with significant heterogeneity among trials with transfusion triggers ranging from 7 to 9 g/dL. Pooled data analysis showed that a restrictive compared with liberal transfusion strategy did not affect the rate of adverse events (ie, mortality, cardiac events, myocardial infarction, stroke, pneumonia, and thromboembolism). The Cochrane reviewers concluded that giving less blood is safe and transfusion is not necessary until Hgb levels drop below 7-8 g/dL.[34] Recent American Association of Blood Banks (AABB) guidelines recommend transfusion at Hgb levels of 7 g/dL or less in critically ill patients.[35]

Because approximately 80% of ESRD patients have left ventricular dysfunction, and cardiovascular and all-cause mortality increases with decreasing glomerular filtration rate (more pronounced for glomerular filtration rate less than 60 mL/minute/1.73 m^2),[36,37] careful consideration of transfusion thresholds in the background of cardiac disease is important in this group. The Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair (FOCUS) trial addressed the withholding of RBC transfusion in patients with ischemic cardiovascular disease and clinical equivalents undergoing surgery. A strategy of transfusing at Hgb levels less than 8.0 g/dL or when symptomatic in FOCUS was not found to be different from a strategy of transfusing for Hgb levels less than 10 g/dL for a composite outcome of death and the inability to walk independently, with neither component different between groups.[38] These results are consonant with TRICC's findings that among patients with cardiovascular disease (357 of 838), no improvements in outcomes resulted from a liberal transfusion strategy.[39] The AABB follows suit and recommends adhering to a restrictive strategy in hospitalized patients with pre-existing cardiovascular disease, utilizing a transfusion threshold of a Hgb level of 8 g/dL or less.[35]

Remarkably, no randomized trials have evaluated transfusion thresholds in patients suffering from ACS.[31] These patients were excluded from the TRICC trial. Observational data suggest that patients with ACS may require transfusion at higher Hgb thresholds. Although it is clear that anemia is associated with worsened outcomes, with increased mortality at Hgb levels less than 14 g/dL in ST elevation myocardial infarction and Hgb levels less than 11 g/dL in non-ST elevation myocardial infarction, the optimal transfusion trigger is unclear.[40] Two studies have found that transfusion at Hct of 24% or 25% is associated with reduced mortality, but that transfusions at Hct higher than these increases the risk of death.[41,42] Although a large observational trial of older patients with myocardial infarction concluded that RBC transfusion at Hct less than 30% was associated with reduced mortality, it also found that transfusion at higher Hct was associated with increased

mortality.[43] A systematic review of 11 studies found association with reduced mortality with transfusion for Hgb less than 8 g/dL whereas transfusions given for Hgb greater than 11 g/dL increased mortality risk.[44] AABB guidelines do not recommend for or against a liberal or restrictive transfusion threshold in ACS patients, whereas the Society of Critical Care Medicine-Eastern Association for the Study of Trauma (SCCM-EAST) recommends transfusion for Hgb levels of 8.0 g/dL or less.[45] Clinical trials to identify safe transfusion thresholds in patients with ACS are currently underway (ClinicalTrial.gov NCT01167582) but, in the meantime, a transfusion trigger of 8.0 g/dL may be appropriate.

In the treatment of severe sepsis and septic shock, controversy continues. In one study, the use of a protocol including transfusion to achieve a Hct of 30% was found to reduce mortality.[46] Subsequently, this transfusion goal was included in some guidelines for the treatment of early sepsis.[47] Because transfusion was one of several therapies administered in the trial by Rivers and colleagues, it is difficult to parse its discrete effect on outcomes. Moreover, this transfusion goal applied only to patients with a central venous saturation ($SCVO_2$) of less than 70% and only for the first 6 hours of treatment. Whereas small prior studies including transfusion in the treatment of sepsis found benefit,[48,49] these were limited by poor protocol design and the shared measurement error incurred by the use of pulmonary artery catheter measurement of oxygen delivery (DO_2) and oxygen consumption (VO_2).[48,50-53] Significant differences in volume resuscitation and fluid selection between the two groups in the study by Rivers and colleagues may have resulted in the survival imbalance found.[54] Trials using indirect calorimetry to independently determine VO_2 and DO_2 found no dependency of VO_2 on DO_2, and treatment aimed at increasing oxygen delivery did not reduce morbidity and mortality in sepsis and lung injury patients.[55-57] In septic patients, multiple studies have found no improvement in end organ perfusion by gastric tonometry or sublingual microvascular spectrography.[58-61] Given these data, the SCCM-EAST guidelines conclude, "The transfusion needs for each septic patient must be assessed individually because optimal transfusion triggers are not known and there is no clear evidence that blood transfusion increases tissue oxygenation."[62]

The studies above utilized discrete Hgb "triggers" for assessing the effect of transfusion in the critically ill (although the FOCUS study's restrictive arm included the option of symptomatic transfusion). However, the physiologic tolerance for anemia varies among individuals. Patients may tolerate values below the thresholds above. In healthy adults, acute isovolemic anemia as low as Hgb levels of 5 g/dL is well tolerated.[41] Whereas TRICC evaluated a Hgb threshold of 7.0 g/dL, this does not reflect an absolute indication for transfusion in asymptomatic patients. The AABB states that transfusion decisions should be based on symptoms as well as Hgb levels.[35] The American Society of Anesthesiology and the American Red Cross (ARC) recommend that, in critically ill and perioperative patients, transfusion is not mandated until Hgb levels fall below 6 g/dL in asymptomatic, isovolemic anemia.[63,64] Conversely, patients who are symptomatic at Hgb values higher than the thresholds above should be transfused regardless of their laboratory Hgb measures. Clinically significant symptoms in isovolemic patients include cardiac chest pain, congestive heart failure, unexplained tachycardia, or hypotension unresponsive to fluid replacement.[38] This definition of hypotension does not include hypotension ascribable to other causes (eg, sepsis). Recommendations by the Kidney Disease Outcomes Quality Initiative assert than no Hgb concentration justifies or requires transfusion.[9] These recommendations are summarized in Table 1.

Platelet Transfusion

Platelets are administered by units collected either by single-donor apheresis or pooled from six random donors (hence, the term "six pack"). In the clinical setting, a unit of apheresed platelets will increase the patient's platelet count by approximately 28,000/μL whereas a unit of pooled platelets will increase the count by 26,000/μL.[65] Minor ABO incompatibilities dramatically decrease the response to platelet transfusion.[66] In multiply transfused patients, a progressive decrease in platelet increments and days until next transfusion occurs with each transfusion episode, suggesting that physicians should wisely choose appropriate platelet transfusion indications.[67]

The most frequent clinical indication for platelet transfusion in the ICU is prophylaxis for bleeding risk.[68] Four RCTs and three nonrandomized trials in oncology patients have evaluated platelet transfusion thresholds of 10,000/μL vs 20,000/μL and vs 30,000/μL and found no benefit using higher thresholds.[69,70] In a recent large RCT, Dose of Prophylactic Platelet Transfusions and Preventions of Hemorrhage (PlaDo), 1272 patients undergoing stem cell transplant or chemotherapy were transfused at a threshold of 10,000/μL and assigned to three platelet doses to maintain this level.[65] PlaDo validated the safety of this platelet transfusion trigger; although minor bleeding was common, life-threatening hemorrhage at this threshold was rare. Most bleeding events occurred at a platelet count below 7000/μL. More aggressive platelet transfusion at the threshold of 10,000/μL did not decrease the frequency of hemorrhage. Although the ICU setting differs (eg, the presence of bleeding diatheses), the data are robust and compelling to extrapolate that in critically ill patients, a threshold of 10,000/μL is safe.[71]

Table 1. Red Cell Transfusion Guidelines

Critically Ill Patient Type	Organization/Study	Hgb Level
General	TRICC	Hgb < 7 g/dL
	AABB	Hgb ≤ 7 g/dL
	SCCM-EAST	Trigger to be avoided but consider Hgb < 7 g/dL (mechanical ventilation, resuscitated
	ASA, ARC	patients) or based on patient characteristics*
		Hgb < 6 g/dL in asymptomatic patients
CAD	FOCUS	Hgb < 8 g/dL or symptomatic†
	AABB	Hgb ≤ 8 g/dL or symptomatic†
	SCCM-EAST	Hgb < 7 g/dL (Class II/III evidence)
	TRICC	Hgb < 7 g/dL
ACS	Garfinkle et al.[44]	Hgb < 8 g/dL
	SCCM-EAST	Hgb ≤ 8 g/dL on hospital admission
	AABB	No optimal threshold because of very low quality of evidence
Sepsis	SCCM-EAST	No Hgb trigger for tissue oxygenation
	Surviving Sepsis	Hgb ≤ 7 g/dL
		Hct ≥ 30% if central venous O_2 saturation target not achieved during initial resuscitation
CKD‡	KDOQI	No Hgb justifies transfusion and should be based on symptoms

Abbreviations: ASA, American Society of Anesthesiology; CAD, coronary artery disease; FOCUS, Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair; KDOQI, Kidney Disease Outcomes Quality Initiative.
*Intravascular volume status, evidence of shock, duration and extent of anemia, and cardiopulmonary physiologic parameters.
†Cardiac chest pain, congestive heart failure, unexplained tachycardia, or hypotension unresponsive to fluid replacement.
‡For all patient types.

Current guidelines for patients with massive bleeding or need for invasive procedures recommend a platelet transfusion threshold of 50,000/μL, but they are based on expert opinion and they lack sufficient evidence (Table 2).[67,72] Higher thresholds at 100,000/μL are recommended for patients who have a central nervous system injury, have multisystem trauma, and are undergoing neurosurgery.[67] In injured, bleeding patients, coagulopathy is common and associated with high mortality.[73] This coagulopathy reflects not only the trauma itself, but also the interaction of shock, hemodilution, hypothermia, acidemia, and inflammation.[74] In these patients with exsanguinating hemorrhage (commonly defined as necessitating >10 units of RBCs within 24 hours), the use of massive transfusion protocols incorporating a 1:1:1 ratio among RBCs, plasma, and single-donor platelets (equivalent to one-sixth unit of apheresed or pooled platelets) has been associated with decreased mortality.[75]

Plasma Transfusion

Indications for plasma transfusion in the critically ill are primarily based on clinical experience and biological rationale. Plasma is the aqueous part of blood, and important elements include albumin, coagulations factors, fibrinolytic proteins, and immunoglobulin. It can be frozen as fresh frozen plasma (FFP) and later thawed with

Table 2. Platelet and Plasma Transfusion Guidelines

Problem	Organization/Study	Indication
Platelets		
Prophylaxis	PlaDo, ASH	≤10 x 10^9/L
Massive bleeding/invasive procedures	ASH	50-100 x 10^9/L
	ARC, ASA, AFSSaPS	≤50 x 10^9/L
Multisystem trauma/CNS injury/neurosurgery	ASH, ARC	≤100 x 10^9/L
Invasive ICU procedures*	ARC, ASCO[123]	40-50 x 10^9/L
Plasma		
Warfarin anticoagulation and intracranial hemorrhage	AABB	Elevated INR
Invasive or operative procedures excluding paracentesis	ARC	PT > 1.5 times midrange normal
Acute pancreatitis, organoposphate poisoning, acetaminophen overdose with coagulopathy	AABB	Not indicated
Intracranial hemorrhage without coagulopathy	AABB	Not indicated
Surgery in absence of massive transfusion	AABB	Not indicated
Increasing blood volume or albumin concentration	ARC	Not indicated
Asymptomatic patients with coagulopathy and low risk for bleeding	ACP, ARC	Not indicated; correct with vitamin K

Abbreviations: AFSSaPS, French Safety Agency for Health Products; ACP, American College Chest Physicians; ASCO, American Society of Clinical Oncology; ASH, American Society of Hematology; CNS, central nervous system; PT, prothrombin time.
*Central venous pressure placement, paracentesis, thoracentesis, respiratory tract/gastrointestinal biopsies, closed liver biopsy, lumbar puncture.

removal of the insoluble cryoprecipitate by centrifugation.

The most common rationale for plasma administration in the ICU is to normalize an elevated preprocedural international normalized ratio (INR).[76] Observational studies have shown an inability of FFP to correct INR values up to 1.85.[77] The ARC recommends FFP should not be used for coagulopathy that can be corrected with vitamin K, and prolonged coagulation tests up to 1.5 times normal are generally safe for operative or invasive procedures.[63] Plasma transfusion from warfarin-associated coagulopathy for an invasive procedure in asymptomatic patients without bleeding is also not necessary, and withholding warfarin or administering vitamin K is recommended by the American College of Chest Physicians.[78] Furthermore, plasma transfusion is not required in various acute disease states that can lead to coagulopathy, which are listed in Table 2.[79] Transfusing plasma is associated with an increased risk of developing lung injury and a trend toward increased mortality.[80,81] Given these effects, plasma should not be given as a volume expander in lieu of nonbioactive colloid, and the British Committee for Standards in Hematology recommends against using it for this purpose.[82]

Evidence-based indications for plasma administration in nonmassive transfusions include patients taking warfarin anticoagulation who have intracranial hemorrhage.[79] FFP can be transfused for emergent procedures or patients actively bleeding with coagulopathy. Massive transfusion requires all blood products to be in equal ratio of administration as mentioned above. It is unnecessary to use FFP for paracentesis in cirrhotic patients, per the American Association for the Study of Liver Diseases.[83] FFP can be used in patients with selected coagulation factor deficiencies, congenital or acquired, for which no specific coagulation concentrates are available, and with rare specific plasma protein deficiencies, such as C1 inhibitor, when recombinant products are unavailable.[63] As a general rule, FFP should not be given without clinical evidence of bleeding or anticipated bleeding in the background of coagulopathy.

Blood Products and Their Associated Risks

Attention has transitioned from blood-borne infections, which are now rare, to focus on noninfectious complications, which are better recognized and appreciated.[84] Given the presence of antigen-presenting cells in the transfusate, allogeneic blood transfusion can be viewed as organ transplantation without the stringent evaluation typical for solid and liquid organ transplantation. Immunologic complications of blood products include transfusion-related acute lung injury (TRALI) and transfusion-related immunomodulation (TRIM).

TRALI is the new onset of acute lung injury (ALI) within 6 hours of receiving a plasma-containing blood component in the absence of other causes of ALI.[85] Before the current definition, the true incidence of TRALI was underestimated from lack of recognition or underreporting, but it is now the leading cause of transfusion-related morbidity and mortality.[86] The incidence of TRALI has been reported to be as high as 1:20 patients and, in some settings, an incidence at 50 times higher than previous estimates.[80,87] TRALI is 2-3 times more common from plasma-rich products.[80] An active, multicenter surveillance study found that among patients, higher IL-8 levels, high peak airway pressures (>30 cm H_2O), shock, tobacco and alcohol abuse, and positive fluid balance increased TRALI risk whereas transfusion-related risk factors were increased anti-human leukocyte antigen class II antibodies and anti-human neutrophil antibodies, plasma administration, and blood from female donors.[88] The elimination of female donors dramatically reduced the case rate of TRALI, although this reduced rate was still higher than previous estimates derived from passive surveillance.

TRIM is the immunosuppressive effect on transfusion recipients from donor antigens. It was first identified in the 1970s when kidney allograft recipients receiving allogeneic blood transfusions experienced longer allograft survival.[89] Stored RBC supernatant containing transforming growth factor-β1 inhibits neutrophil chemotaxis and red cells release arginase, which may attenuate lymphocyte function.[90-93] Impairment of natural killer cell function occurs alongside tumor necrosis factor-α attenuation and IL-10 augmentation. Ultimately, infusion of donor leukocytes and bioactive factors leads to immunosuppression with an increased risk of recurrence of malignancy and hospital-acquired infection.[94]

The most common adverse event associated with transfusion is transfusion-associated circulatory overload, a nonimmunologic entity in which transfusion results in hydrostatic edema.[95] This occurs in nearly 8% of all transfusions[96] and is seen most frequently in ICU patients, who develop the condition after an average of four units of plasma with a rate of infusion of 650 cc/hour.[97] Patients with acute and CKD may be at particularly high risk for transfusion-associated circulatory overload because positive fluid balance is a risk factor for its development.[98] One small case series suggests that hemodialysis dependency may be a risk factor.[97]

Reducing the Amount of Blood Transfused

The potential complications from blood transfusion in critically ill patients elicit a high priority for effective interventions to reduce the quantity of units transfused and patients receiving transfusion. Various techniques and therapies have surfaced over the years as alternatives for blood transfusion.[99] EPO, iron supplementations, and behavioral changes are among these studied.

The benefits of EPO for the treatment of anemia in patients with CKD are clear within the outpatient setting.[9] For this reason, research has been directed to evaluate its potential benefit in treating anemic patients in the ICU. Three RCTs evaluating EPO in the critically ill have been conducted by the EPO Critical Care Trials Group.[100-102] Although the first two found reductions in transfusion frequency, these studies were conducted without a restrictive transfusion protocol. In a trial using a Hgb trigger compatible with the TRICC trial (Hgb $<$ 7.0 g/dL), no difference in transfusion frequency was found between placebo and EPO.[102] However, EPO was associated with an increased rate of thrombotic events, including cerebrovascular accident and myocardial infarction. This increase in thrombotic events has occurred in multiple EPO trials across various acute clinical settings.[103-105] On the basis of these data, EPO should not be used for the treatment of anemia in the general population of the critically ill.

In assessing the potential benefit of EPO for critically ill patients with CKD, RCT data preclude clear conclusions. Hemodialysis-dependent patients were excluded from all three of the RCTs above. In the first two,[100,101] the proportion of patients enrolled with CKD is not reported. In the third trial, published in 2007,[102] the trial reports that 75 of the 1460 patients enrolled had CKD. However, a subgroup analysis was not performed and it is not clear, on the basis of the relatively small proportion of patients (5.1%), whether this would be illuminating. Although the argument can be advanced that because patients with CKD benefit from EPO in the outpatient setting the medication should be continued in the ICU, the opposite may be true. Because CKD patients suffer from EPO resistance,[106] they may be the least likely to benefit from a therapy that does not benefit a general population, thus shifting the potential further toward harm. At this time, no incontrovertible recommendations can be given.

In addition to its effects on hematopoiesis, EPO also exerts anti-apoptotic effects and may have kidney tissue protective effects and modulate calcium homeostasis. Animal data suggest that EPO may improve recovery after ischemia-reperfusion and contrast-induced kidney injury.[107] Two RCTs evaluating nephroprotective effects have been performed in human subjects. A modestly sized ($n = 71$) study evaluated the effect of preoperative EPO administration on patients undergoing coronary bypass surgery.[108] A smaller proportion of patients receiving EPO developed acute kidney injury (3 of 26 vs 10 of 35, $P = 0.035$). In the ICU, a larger study, the Early Intervention in Acute Renal Failure trial assessed the effect of EPO on patients deemed at high risk for acute kidney injury (elevated urine γ-glutamyl transpeptidase and alkaline phosphatase).[109] This study ($n = 162$) found no difference in the primary outcome of relative average creatinine values or its secondary outcomes of ICU and hospital lengths of stay. Whereas EPO remains a therapy of interest in acute kidney injury and additional RCTs are ongoing, at this point insufficient evidence exists for its clinical use for nephroprotection.

Critically ill patients may downregulate iron metabolism and EPO synthesis as a part of nonspecific immunity.[110] Bacteria require iron for growth, and it is biologically plausible that low serum iron level in critically ill patients evolved as a protective mechanism to hinder survival of invading pathogens.[111] Surgical critical care patients receiving enteral ferrous sulfate vs placebo did not have differences in Hct, iron markers, infection rates, hospital length of stay, or mortality.[112] In a small, unblinded trial investigating intravenous iron, its use had no effect on erythropoiesis as measured by serum transferrin receptor, or Hgb concentration, by itself or in conjunction with EPO.[113] At this time, evidence does not support routine iron supplementation.

The easiest way to reduce transfusion in the ICU is by reducing blood loss. Phlebotomy is the most common cause in the ICU.[114] Strategies to minimize blood loss can be incorporated into educational initiatives and behavioral interventions to minimize phlebotomy.[115] Indwelling arterial catheters increase blood losses by 44% and lead to more daily blood draws.[116,117] The use of pediatric tubes reduces blood loss by more than 33%.[114,116] Point-of-care analysis can provide quick, reliable laboratory data.[118,119] Reducing the number of laboratory studies in the ICU does not compromise care; automatic daily laboratory orders should not be routine.[99]

After TRICC publication, changes in transfusion practice suggested a gradual adoption of restrictive transfusion strategy among clinicians.[120] Although physician behavior may be gradually changing over time, additional efforts are necessary to implement evidence-based practice. Various behavioral interventions have been evaluated to reduce physician blood use.[99] The use of computer order entry algorithms emphasizing best evidence, when combined with educational programs, seems to be particularly effective.[121] Although it is difficult to parse the economic benefits of complete adoption of a restrictive transfusion strategy, one study estimates a savings of nearly $1 billion in costs from reductions in blood use and transfusion-attributable complications.[122]

Conclusions

Anemia is common among patients with CKD and the critically ill. In the ICU, a restrictive RBC transfusion strategy is safe and may improve outcomes. Multiple studies have validated a restrictive platelet threshold of 10,000/μL in nonbleeding patients. FFP transfusion benefits patients with bleeding or anticipated blood loss but it should be held in others. Clinicians should work to

reduce blood loss in the ICU and guide physician behaviors to conserve transfusion resources and improve adherence to best evidence.

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An Update on Neurocritical Care for the Patient With Kidney Disease

Karen G. Hirsch and S. Andrew Josephson

Patients with kidney disease have increased rates of neurologic illness such as intracerebral hemorrhage and ischemic stroke. The acute care of patients with critical neurologic illness and concomitant kidney disease requires unique management considerations including attention to hyponatremia, renal replacement modalities in the setting of high intracranial pressure, reversal of coagulopathy, and seizure management to achieve good neurologic outcomes.

Key Words: Neurocritical care, Hyponatremia, Seizures, End-stage renal disease

Introduction

Critical care neurology encompasses a broad range of neurologic conditions and patient populations, including patients with primary neurologic illness as well as those with neurologic complications of medical or surgical illness. Patients with kidney disease have various neurologic complications, including uremic encephalopathy, polyneuropathy, and cognitive impairment as well as higher rates of ischemic and hemorrhagic stroke and frequent seizures.[1,2] Given these common acute neurologic conditions, physicians who care for patients with kidney disease must be aware of the evaluation and treatment of neurologic disease to achieve good neurologic outcomes.

Neurologic Conditions in the Neurocritical Care Unit

Stroke, seizures, and traumatic brain injury (TBI) are common primary neurologic diagnoses encountered in neurocritical care. Ischemic and hemorrhagic stroke occur with higher frequency in patients with kidney failure with an adjusted relative risk in patients undergoing dialysis of 4.4-9.7, depending on race and gender, compared with the general population.[1] Intracerebral hemorrhage (ICH) accounts for approximately 10-15% of all strokes, yet it causes high morbidity and mortality, especially in the setting of acute hematoma expansion, a complication particularly relevant to kidney failure patients because of platelet dysfunction and possibly thrombocytopenia.[3] Chronic hypertension in patients with kidney disease is a major risk factor for ICH. Blood pressure targets in the acute setting of ICH remain controversial because one must balance the risk of perihematoma ischemia due to relative hypotension with the risk for hematoma expansion associated with higher blood pressures. In general, a modest reduction in blood pressure (15-20%) in hypertensive patients with ICH should be achieved acutely, and intravenous (IV) agents should be used. The choice of blood pressure agent must be based on the patient's other medical comorbidities, although generally beta-blockers or calcium channel blockers are the agents of choice, and venodilators are to be avoided.[4] Other important considerations in the management of patients with ICH include reversal of coagulopathy and management of elevated intracranial pressure (ICP) as discussed below. There are multiple ongoing trials in ICH that will be released in the coming years, including those investigating optimal blood pressure targets, treatment of intraventricular hemorrhage, and the relatively rare indications for surgical intervention.

Although hemorrhagic stroke is a significant cause of morbidity and mortality, ischemic stroke is also frequently encountered in the neurocritical care setting. Patients with large strokes at risk for significant cerebral edema and patients who have received IV thrombolysis or endovascular therapy for acute ischemic stroke are generally admitted to the intensive care unit. Patients with end-stage renal disease have more severe atherosclerotic disease, both of the carotid arteries as well as the cerebral vasculature,[1] and patients with chronic kidney disease and end-stage kidney failure also have higher rates of atrial fibrillation.[5] All of these risk factors contribute to a higher incidence of ischemic stroke in patients with kidney disease.

The indications for acute stroke treatment with IV thrombolysis have traditionally been within 3 hours of stroke onset. However, a recent study showed safety and efficacy of IV alteplase when given up to 4.5 hours after stroke onset in certain patient populations, and the U.S. Food and Drug Administration (FDA) is currently considering expanding this time window.[6] Endovascular techniques including mechanical clot extraction are currently used up to 8 hours from stroke onset.[7,8] Future directions include imaging-based criteria that expand

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these time windows, although often these imaging studies require iodinated contrast dye and therefore may limit availability for some patients with chronic kidney disease.

Seizures are also common in patients with kidney disease, and prolonged seizures or status epilepticus merit admission to an intensive care unit. Patients with kidney disease require an extensive work-up for first-time seizures, including central nervous system imaging, a full laboratory panel including calcium and magnesium, and consideration of lumbar puncture to exclude central nervous system infection given a relatively immunocompromised state. A recent study demonstrated that patients in status epilepticus who were treated in the prehospital setting with intramuscular midazolam had better outcomes compared with those treated with IV lorazepam.[9] Although both of these agents are hepatically metabolized, other antiepileptic medications such as levetiracetam are metabolized by the kidneys and require dosing adjustment that is based on kidney function.

In addition to stroke and seizures, TBI is a common diagnosis in the neurocritical care setting. TBI affects over 1.7 million Americans each year, and the elderly population encompasses a large portion of TBI patients, usually because of falls. There are more than 320,000 TBIs annually in adults over the age 55.[10] Given that older Americans are suffering an increasing proportion of TBIs, many of these patients likely have concomitant kidney disease. There are several important considerations in management, including the use of hyperosmolar agents to treat elevated ICP, the timing and modality of dialysis, and the use of medications to facilitate cognitive rehabilitation. A recent trial in TBI patients in vegetative or minimally conscious states showed that amantadine, an *N*-methyl-D-aspartate antagonist and indirect dopamine agonist, improved the rate of functional recovery during administration.[11] Unfortunately, patients with serious kidney disease (creatinine clearance less than 60 mL per minute) were excluded from the study, highlighting the importance of considering the applicability of therapies for TBI patients with kidney failure.

CLINICAL SUMMARY

- Patients with kidney failure have high rates of ischemic and hemorrhagic stroke.
- The management of acute neurologic conditions such as seizures and elevated intracranial pressure requires special considerations in patients with kidney disease.
- Acute neurologic hyponatremia occurs commonly in various neurologic conditions.
- Some central nervous system imaging modalities are contraindicated in patients with kidney disease.

Specific Management Issues

The acute care of brain injury patients involves a complex set of medical issues, regardless of the cause of the initial insult. After neurologic injury, the goal of neurocritical care is to prevent secondary injury to the brain and to preserve at-risk brain regions. Complications such as elevated ICP, hyponatremia, anticoagulant-associated coagulopathy, and seizures are common and must be treated in a timely and effective manner to minimize this secondary injury.

Elevated ICP

Elevated ICP may occur because of various etiologies including space-occupying lesions such as stroke or hemorrhage, metabolic disturbances such as fulminant hepatic failure, or diffuse cerebral edema from hypoxic-ischemic injury. Elevations in ICP occur based on the theory of the Monroe-Kelley hypothesis that the brain, cerebrospinal fluid, and intracranial circulation exist within the closed vault of the skull. Any process or lesion that causes an increase in these contents, including the presence of a foreign body, will cause displacement of the normal structures within a closed system and therefore lead to an increase in pressure. Medical management of elevated ICP focuses on several interventions, including patient positioning, hyperventilation, reducing the brain's metabolism, and the use of hyperosmolar agents. Mannitol is historically the most widely used hyperosmolar agent and is recommended in brain injury guidelines; however, emerging evidence suggests that hypertonic saline has comparable or even better efficacy compared with mannitol with fewer side effects.[12,13] Hyperosmolar therapy is likely effective via multiple mechanisms, including a diuretic effect, osmotic fluid shifts, vasoconstriction, and improvements in cerebral blood flow.[14-17]

There has historically been hesitancy to use mannitol and other hyperosmolar agents in patients with kidney disease. A recent small study showed that hyperosmolar agents could be used safely and effectively in anuric patients on dialysis, but additional trials are needed to confirm the finding.[18] In general, in the brain-injured patient with kidney failure, hyperosmolar therapy with mannitol, or hypertonic saline can be used to treat elevated ICP with careful attention to volume status and electrolyte levels. It is also important to note that the hypernatremia that occurs after administration of hypertonic saline is desired in the setting of elevated ICP and should not necessarily be corrected with dialysis.

In the patient with brain injury and elevated ICP, the timing and modality of dialysis must be carefully chosen. Changes in systemic hemodynamics affect cerebral perfusion, where cerebral perfusion pressure

(CPP) = mean arterial pressure – ICP. It is important that dialysis not cause elevations in ICP or reductions in cerebral perfusion. Intermittent modes of renal replacement therapy have been shown to increase ICP, reduce CPP, and induce rapid changes in serum osmolality.[19] In one study comparing intermittent to continuous modalities in patient with neurologic dysfunction due to fulminant hepatic failure, intermittent hemodialysis caused an increase in ICP 60% from baseline and a decrease in CPP, whereas continuous therapies did not affect these parameters.[20] One small study of dialysis modes in neurosurgical patients showed that those undergoing continuous dialysis had lower mortality compared with patients who underwent intermittent hemodialysis.[21] As such, continuous renal replacement therapies are the modality of choice in brain injury, and if they are not available, then intermittent therapies should be provided with slow flow rates. If feasible, high dialysate sodium concentrations should also be used to avoid hyponatremia and maintain relative hypernatremia when indicated, recognizing that this may affect the concentration of other dialysate components, including bicarbonate.[22] For patients on continuous renal replacement modalities, the concentration of sodium in the replacement fluid may be increased or a hypertonic saline infusion may be used to increase the serum sodium concentration. In addition to concerns about sodium levels in the setting of elevated ICP, focus must also be directed toward bicarbonate and carbon dioxide balance. Increases in carbon dioxide, such as may occur during intermittent hemodialysis, may cause cerebral vasodilation and subsequent increases in ICP. As such, caution is prudent when initiating or changing dialysis, and abrupt changes in serum bicarbonate should be avoided.

Hyponatremia

Hyponatremia occurs frequently in patients with brain injury, and it can cause secondary injury including seizures or worsening brain edema. The exact mechanism underlying acute hyponatremia caused by neurologic injury is unclear, with some proposing it is on the spectrum of the syndrome of inappropriate secretion of antidiuretic hormone and others supporting an underlying mechanism of cerebral salt wasting.[23] In practice, the two are differentiated only by clinical assessment and volume status; as such, some authors proposed the term "acute neurologic hyponatremia" (ANH) to describe the finding.[24] ANH can occur in various neurologic disease states, including subarachnoid hemorrhage, TBI, ICH, ischemic stroke, Guillain-Barre, and meningitis.[25] (Table 1) Regardless of the underlying mechanism of ANH, treatment with fluid restriction, as is used for the syndrome of inappropriate secretion of antidiuretic hormone in medical illness, is not recommended in the setting of neurologic injury given the importance of maintaining euvolemia and cerebral perfusion. The standard treatment for ANH involves administration of oral salt tabs and normal saline or hypertonic saline IV fluids to maintain euvolemia. There are published standardized protocols for hypertonic saline titrations, although institutional protocols vary widely (Fig 1).[24]

Table 1. Neurologic Diseases that May Cause Hyponatremia

Central nervous system conditions	Aneurysmal subarachnoid hemorrhage
	TBI
	Pituitary surgery
	ICH
	Subdural hemorrhage
	Obstructive hydrocephalus
	Fulminant multiple sclerosis
Meningitis	Bacterial
	Tuberculous
	Aseptic
Neuromuscular disease	Guillain-Barre syndrome

In addition to supplementing with oral or IV sodium therapy, pharmacologic agents are increasingly being used to maintain normal sodium levels. Fludrocortisone is a mineralocorticoid that impairs natriuresis and enhances kidney sodium reabsorption. It is used in subarachnoid hemorrhage to treat volume loss and hyponatremia.[26] Careful attention must be paid to other electrolyte levels, especially potassium, and signs of clinical volume overload in patients treated with this drug. In addition to fludrocortisones, the vaptans are a relatively new class of vasopressin antagonist medications being used to treat hyponatremia.[27] Although their effect on serum sodium is potent, their use in neurologic syndromes may be limited by the volume loss they cause, although additional studies are needed to investigate their role in neurologic hyponatremia.

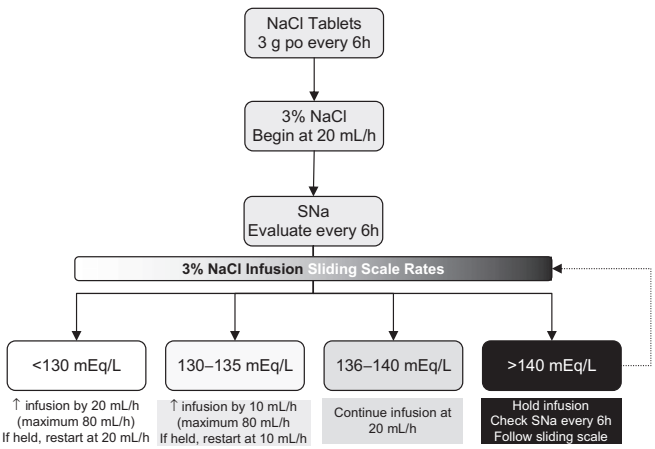

Figure 1. Example of a standardized protocol of hypertonic saline (3% NaCl) administration.[24] Abbreviations: PO, administered orally; NGT, administered via nasogastric tube; SNa, serum sodium concentration.

Coagulopathy

Given the increased prevalence of stroke and atrial fibrillation in patients with kidney disease, a substantial number of these patients may be taking oral anticoagulants. For patients on warfarin, various reversal agents consisting of various coagulation factors exist. Prothrombin complex concentrate (PCC) contains factors II, VII, IX, and X,[28] and fresh frozen plasma is pooled plasma from human donors containing all plasma proteins, including procoagulant and inhibitory components of the coagulation system, immunoglobulins, and albumin.[29] Several studies have shown rapid reversal of warfarin-associated coagulopathy with relatively low volumes of total infusate when using PCC compared with traditional fresh frozen plasma infusions, although no studies have shown significant differences in clinical outcomes.[30-35] Other agents such as factor VIIa have been studied in acute ICH to limit hematoma expansion and reverse anticoagulation. However, randomized trials suggest that although factor VIIa limits hematoma growth, it does not change outcome, and therapy is complicated by increased rates of thromboembolism.[36] As such, its use is not currently recommended in acute ICH. In patients with kidney failure and warfarin-associated bleeding, PCC is the agent of choice to reverse coagulopathy in the setting of neurologic hemorrhage given the lower infusion volumes and rapid effective reversal of coagulopathy. Many of the newer classes of oral anticoagulants such as the direct thrombin inhibitors and factor Xa inhibitors do not have known reversal agents, posing a unique problem in anticoagulant-related ICH.[28] Dabigatran is one commonly used FDA-approved novel oral anticoagulant for stroke prevention in the setting of atrial fibrillation, and its use is limited in patients with kidney compromise.[37] For catastrophic bleeding associated with these agents, recent guidelines recommend supportive care, activated charcoal, and consideration for hemodialysis for dabigatran-associated hemorrhage.[38]

Seizures

Seizures are common in patients with kidney dysfunction and may occur during dialysis, they may be provoked by an underlying brain lesion such as a hemorrhage, or they may be due to epilepsy. Some antiepileptic drugs (AEDs) are at least partially renally metabolized and therefore require dose adjustments and/or additional dosing after dialysis. Newer AEDs have fewer drug-drug interactions, making them good options for use in patients with kidney dysfunction.[39] In the outpatient setting, medications may be titrated following guidelines for dose adjustment as addressed in recent reviews.[39,40] However, in the acute critical care setting, the choice of medication and initial dosing is even more crucial. Status epilepticus has historically been defined as seizures lasting longer than 30 minutes without a return to baseline, although newer definitions refer to more than 5 minutes of continuous seizures or consecutive seizures between which there is not recovery of consciousness.[41] Status epilepticus is a neurologic emergency and requires prompt intervention. Classic algorithms for the treatment of status epilepticus involve administration of benzodiazepines followed by treatment with IV fosphenytoin or IV valproic acid.[42] IV levetiracetam is not approved by the FDA for the treatment of status epilepticus, but in practice it is frequently used as an adjunct to other AEDs in the acute setting. Although initial loading doses of AEDs in status epilepticus patients with kidney failure do not need dose adjustment, maintenance dosing must be adjusted appropriately.

Central Nervous System Imaging

The choice of central nervous system imaging modality depends on the clinical question, patient characteristics, and availability of specific imaging modalities. In general, computed tomography (CT) scanning is useful for identification of acute hemorrhage, hydrocephalus, fractures, and relatively large areas of edema or infarct.[43] Lesions due to ischemia may not be apparent by CT scan for at least 24 hours, and imaging of the posterior fossa is limited. Magnetic resonance imaging (MRI) provides more detailed imaging quality and is important for identifying tumors, infectious lesions, areas of demyelination, and smaller strokes that may not be visualized with CT. CT and MRI may be performed with contrast, with CT utilizing iodinated contrast dye and MRI using gadolinium contrast. The use of contrast in either setting provides additional information regarding breakdown of the blood-brain barrier and is useful in the evaluation of malignancy, infection, inflammation, and demyelination. Contrast is also used to image the cerebral vasculature in the evaluation of vascular occlusion, stenosis, spasm, or malformation. In patients with kidney failure, gadolinium and iodinated contrast are relatively contraindicated. Gadolinium may cause nephrogenic systemic fibrosis, a systemic fibrosing disease that affects the skin and multiple other organs, when administered to patients with acute or chronic kidney failure.[44] As a result, gadolinium use is not recommended in patients with compromised kidney function and is contraindicated in any patient with creatinine clearance less than 30 mL/min/1.73 m^2.[44] Iodinated contrast dye is also contraindicated in patients with creatinine clearance less than 45 mL/min/1.73 m^2 because it may cause worsening kidney function due to contrast-induced nephropathy.[45] CT angiography requires iodinated contrast. In contrast, magnetic resonance angiography (MRA) may be performed with or without gadolinium. Time-of-flight MRA is a flow-based study that provides images of the cerebral vasculature without the use of gadolinium and provides

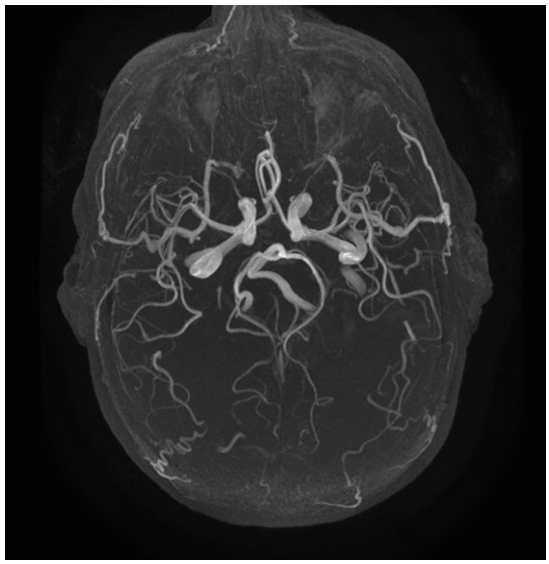

Figure 2. Nonenhanced, time-of-flight MRA of the intracranial vasculature.

an important option to image the vasculature in patients with compromised kidney function (Fig 2).

Immunotherapy

In addition to stroke, seizures, and TBI, immune-mediated neurologic diseases account for a significant portion of neurologic disorders encountered in the neurocritical care setting. Recognition of these disorders and therapeutic options for their treatment are rapidly expanding. Autoimmunity plays a role in many forms of kidney disease, and as such there is significant overlap with autoimmune neurologic diseases, including encephalitis, myelitis, neuropathy, myopathy, and demyelinating diseases. Immunomodulators are used extensively in neurology, and patients with autoimmune neurologic diseases are often cared for in a neurocritical care setting given the potential for neuromuscular respiratory failure, seizures, or other complications of severe disease. IV immunoglobulin (IVIg) and plasmapharesis are the two therapies most commonly used for autoimmune neurologic disorders. There are several important considerations in the use of these therapies.[46,47] Plasmapharesis or plasma exchange requires central venous access and uses albumin exchange or replacement. The need for central vascular access is concerning in patients with kidney compromise in whom present or future vascular access may be an issue. There is also the theoretical risk of transient hypercoaguability after plasmapharesis. In contrast, IVIg may be given through a peripheral IV, although risks include hypercoaguability and a small risk of infection given that it is derived from pooled plasma. IVIg may also cause kidney failure in patients who are not adequately hydrated, likely because of an osmotic effect, and may interfere with bedside glucometry tests causing falsely elevated glucose readings.[48,49] Few studies exist directly comparing plasmapharesis with IVIg for acute inflammatory neurologic disorders, although disease-specific guidelines are available to help guide choice of treatment.[50-52]

Conclusion

The care of critically ill patients with neurologic disease encompasses a broad range of pathophysiology. Given the significant overlap between neurologic and kidney disease, caring for neurologically ill patients with concomitant kidney dysfunction occurs commonly and poses a unique set of challenges. The management of common complications such as elevated ICP, neurologic hyponatremia, and seizures must be done in the context of a delicate balance between the brain and kidney. With careful attention to these issues, favorable outcomes for patients with neurologic injury and kidney dysfunction can be achieved.

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Fluid Management and Use of Diuretics in Acute Kidney Injury

Annie-Claire Nadeau-Fredette and Josée Bouchard

Critically ill adult patients at risk for or with acute kidney injury (AKI) require careful attention to their hemodynamic status because hypotension and hypovolemia may contribute to or worsen kidney injury. Increasing evidence suggests that isotonic crystalloids should be used instead of colloids for initial expansion of intravascular volume in patients at risk for AKI or with AKI, such as those with sepsis, septic shock, or trauma. The timing and amount of volume to be administered to prevent AKI and other organ damage is still debated, but an aggressive fluid repletion in the early setting is probably beneficial. However, fluid overload has also been associated with increased mortality and reduced rate of kidney recovery in observational studies in critically ill patients with AKI. Diuretics may prevent or treat fluid overload and may also affect kidney function. The efficacy of these procedures in critically ill AKI patients need to be confirmed with randomized controlled trials. This review focuses on early volume resuscitation, overall fluid management, and use of diuretics in critically ill adult patients at risk for or with AKI and their effect on mortality and kidney function in this setting.

Key Words: Acute kidney injury, Diuretics, Fluid, Mortality, Outcomes

Introduction

Acute kidney injury (AKI) is a frequent condition encountered in hospitalized patients, especially in critically ill adult patients in which its incidence can reach 65%.[1-4] Several studies have shown that AKI is associated with an increase in morbidity and mortality in critically ill and hospitalized patients.[1,5,6] However, few therapeutic interventions have been successful in treating or preventing AKI, often because of delayed diagnosis and interventions. Patients at risk for or with AKI require careful attention to their hemodynamic status because hypovolemia can decrease kidney perfusion and contribute to kidney injury. Early fluid administration aims to prevent and/or minimize the effects of AKI. However, recent observational studies in critically ill patients have suggested that fluid overload may have a negative influence on kidney function and mortality.[7-9] In this setting, volume resuscitation, fluid management, and diuretics can influence overall prognosis. In this review, "volume resuscitation" refers to the amount and types of fluids used during the initial period (ie, hours) after an acute event such as sepsis, and "fluid management" to the regulation of input and output over the intensive care unit (ICU) and subsequent hospital stay (ie, days after an acute event). We will successively review recent literature on volume resuscitation, fluid management, and use of diuretics in critically ill adult patients with AKI.

Volume Resuscitation

Intravenous fluid administration is frequently used in hospitalized patients. For example, this intervention is believed to prevent AKI or treat AKI in sepsis, trauma, or burns, although few studies have evaluated its effect on kidney function or mortality, except for the prevention of contrast-induced nephropathy.[10] In severe sepsis and septic shock, since the landmark study by Rivers and colleagues, the administration of intravenous fluids and vasopressors in the first hours of an acute critical illness has been considered one of the most important interventions toward better outcomes.[11] This trial on early goal-directed therapy (EGDT) performed at one emergency department randomized 130 patients for 6 hours to EGDT and 133 patients to standard therapy. EGDT included the administration of crystalloids, vasopressors, and red blood cells according to predefined parameters. The mortality was significantly lower in the EGDT group (30.5% vs 46.5%, $P = 0.009$). The incidence of AKI was not reported; therefore, there are no definitive data on the influence of EGDT on AKI prevention or treatment. Patients in the EGDT group had a significantly higher volume of fluid administered during the first 6 hours (4981 mL vs 3499 mL), and both groups received more than 13 L over 72 hours. Limitations of this study include its single-center design and the specific population. Three large RCTs are currently performed to reassess this therapy in the United States (Protocolized Care for Early Septic Shock [ProCESS]), United Kingdom, and Australia (Australasian Resuscitation In Sepsis Evaluation Randomised Controlled Trial [ARISE]). The ARISE study will analyze the need for renal replacement therapy (RRT) at 28 and 90 days as a secondary endpoint.

In volume resuscitation, the optimal repletion fluid—namely isotonic crystalloids, synthetic colloids (hydroxyethylstarch [HES], gelatin, and dextran), or

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albumin—remains a controversial subject. Crystalloids are thought to exacerbate pulmonary and peripheral edema by increasing fluid extravasation whereas colloids tend to remain in a larger proportion in the intravascular space, reducing the amount of replacement fluid required,[12] the degree of hypoalbuminemia, and perhaps pulmonary leakiness.[13] However, colloids have been associated with an increased risk of complications and adverse effects on kidney function.[14]

Recently, the Kidney Disease Improving Global Outcome (KDIGO) Clinical Practice Guidelines for AKI have suggested that isotonic crystalloids should be used ahead of synthetic and nonsynthetic colloids for intracellular volume expansion in patients at risk or presenting with AKI, in the absence of hemorrhagic shock.[15] This recommendation was based on the adverse effects of synthetic colloids, most commonly HES, over isotonic crystalloids on mortality and other outcomes, including AKI and need for RRT. In 2011, the Cochrane Collaboration group systematically reviewed 56 randomized controlled trials (RCTs) and concluded that colloids are not superior to isotonic crystalloids in terms of mortality when used for intravascular volume repletion in patients with trauma, burns, or after surgery.[14] We will review the recent studies that led to these recommendations (Table 1).

CLINICAL SUMMARY

- There is increasing evidence suggesting that isotonic crystalloids should be used instead of colloids as initial management for expansion of intravascular volume in critically ill adult patients at risk for AKI or with AKI, such as those with sepsis, septic shock, or trauma.
- The optimal timing and amount of initial volume resuscitation to prevent AKI, to reduce its severity, and to improve mortality in these clinical settings still needs to be defined, although a more aggressive early fluid repletion is probably beneficial.
- Once AKI occurs and that hemodynamic status is stabilized, the relevance of restrictive fluid management and the use of diuretics or renal replacement therapy to prevent or treat fluid overload and improve outcomes in this population, without worsening kidney function, needs to be confirmed with randomized controlled trials.

Synthetic Colloids

Different HES preparations exist, and they vary according to their concentration, mean molecular weight, molar substitution, and substitution of hydroxyethyl for hydroxyl groups. The colloid osmotic pressure effect mainly depends on the concentration of colloid in the solution. For example, 6% HES is iso-oncotic and 10% HES is hyperoncotic. The side effects may also vary according to the type of HES.

Studies on HES have looked at their adverse effects on kidney function, need for RRT, and/or mortality in critically ill patients (Table 1). Only one large study concluded that HES seemed safe with regards to kidney function based on kidney SOFA score and RRT requirement.[16] In this retrospective study, 34% of patients received HES (type unspecified), 41% received crystalloids, and 25% received a combination of crystalloids and non-HES colloids (gelatin, dextran, or 5% and 20% albumin). The retrospective nature of the study, the low volume of HES used (total amount 1000 mL in an average of 2 day period), and the absence of data on the specific type of HES used represent major limitations to support the conclusion of the study.

Three large studies have concluded that hyperoncotic colloids increase AKI risk.[17-19] The VISEP RCT, a factorialized study of starch and insulin, compared 10% pentastarch (HES 200 kDa/0.5) and Ringer's lactate in severe sepsis.[17] This trial was stopped for safety reasons in the insulin treatment arm. The interim analysis showed a significant higher incidence of AKI (34.9% vs 22.8%, $P = 0.002$) and RRT (31.0% vs 18.8%, $P = 0.001$) and a trend toward increased mortality at 90 days in the HES group. It is interesting to note that this study suggested a dose-response relationship between colloid administration and mortality. The 90-day mortality was 57.6% with a pentastarch dose greater than 22 mL/kg and 30.9% in the lower dose group ($P < 0.001$). This relationship was not present in patients in the Ringer's lactate group, who received a higher amount of fluids. Unfortunately, the results of this study are confounded by the high doses of HES administered (median cumulative dose of 70 mL/kg), which were higher than the maximal recommended doses in more than 30% of patients. In a prospective cohort study, Schortgen and colleagues looked at the effect of synthetic colloids, albumin, and crystalloids on kidney function in patients with shock.[18] After multivariate adjustment, hyperoncotic colloids (odds ratio [OR] 2.13; 95% confidence interval [CI] 1.08-4.20) and hyperoncotic albumin (OR 5.27; 95% CI 2.44-11.37) were associated with an increased risk of AKI. Hyperoncotic albumin was also associated with an increased risk of death. The median cumulative HES dose was 31 mL/kg, but the amount of fluid volume administered and the fluid balance were not reported, which are potential confounders. Finally, a retrospective study evaluated the risk of AKI using lower doses of pentastarch 10% in patients undergoing cardiac surgery.[19] The risk was dependent on dose (OR per mL/kg 1.08; 95% CI 1.04-1.12), and the optimal cutoff volume predicting AKI was only 14 mL/kg.

Low-molecular-weight HES have also been recently associated with adverse outcomes in critically ill patients.[20] A large RCT in patients with severe sepsis showed that 6% HES 130/0.42 increased mortality and

Table 1. Early Volume Resuscitation: Colloids vs Crystalloids Solutions

Authors, Year	Study Type	Number (*n*) and Characteristics of Patients	Number and Characteristics of Patients in Subgroups	AKI Definition	Outcome	Comments
Sark, 2007[16]	Retrospective (data collected prospectively)	$n = 3147$, ICU	$n = 1075$, HES (type not specified) $n = 2072$, non-HES*	RRT requirement	**Kidney function:** No increased risk for RRT with HES	HES group with more comorbidities and increased mortality
Schorten, 2008[18]	Prospective cohort	$n = 822$, shock	$n = 127$, crystalloids only $n = 189$, hypooncotic colloids† $n = 401$, artificial hyperoncotic colloids‡ $n = 105$, hyperoncotic albumin (20-25%)	Doubling of creatinine or RRT requirement	**Kidney function**: Increased risk for AKI with artificial hyperoncotic colloids OR 2.13 (1.08-4.20) and hyperoncotic albumin OR 5.27 (2.44-11.37)	Volumes of solutions not reported
Brunkhorst, 2008[17]	RCT	$n = 537$, severe sepsis	$n = 262$, pentastarch, $n = 275$, Ringer's lactate	Doubling of creatinine or RRT requirement	**Kidney function**: Increased risk for AKI with pentastarch (34.9% vs 22.8%, $P = 0.002$) **Mortality**: Increased 90-d mortality with pentastarch dose >22 mL/kg	Dose-effect relation with mortality and RRT
Ertmer, 2008[21]	Retrospective	$n = 8408$, ICU	$n = 595$, 10% HES 200/0.5 $n = 7813$, 6% HES 130/0.4,	RRT requirement	**Kidney function:** Higher risk of RRT with 10% HES 200/0.5 compared with 6% HES 130/0.4 (35.5% vs 6.1%; OR 11.5; [9.5-14.1])	Abstract only†
Rioux, 2009[19]	Retrospective	$n = 563$, cardiac surgery	$n = 54$, with AKI, mean dose of pentastarch 16 ± 9 mL/kg $n = 509$, no AKI, mean dose of pentastarch 10 ± 7 mL/kg	50% rise in serum creatinine within 4 d after surgery	**Kidney function:** Pentastarch associated with an increased risk of AKI, adjusted OR per mL/kg of 1.08 (1.04 -1.12)	Optimal cutoff volume to predict AKI = 14 mL/kg
Boussekey, 2010[54]	Retrospective	$n = 363$, ICU > 72 h	$n = 168$, HES (130 kDa/0.4), $n = 195$, non-HES	RIFLE injury or failure	**Kidney function:** No increased risk for AKI with HES	Low-dose HES, 763 ± 593 mL during first 48 h
Perner, 2012[20]	Blinded RCT	$n = 804$, critically ill patients with severe sepsis (798 included in the modified intention-to-treat analysis)	$n = 398$, HES (130 kDa/0.4), $n = 400$, Ringer's acetate up to 33 mL/kg ideal body weight/d	Use of RRT or kidney SOFA score of ≥3 after the patient had a score of ≤2, doubling of serum creatinine in the ICU	**Kidney function**: Higher need for RRT in the 90-d period in patients treated with HES (22% vs 16%; RR 1.35 [1.01-1.80] but no increased risk for RRT at day 90, no difference in AKI **Mortality**: higher mortality at day 90 in patients treated with HES (51% vs 43%; RR 1.17 [1.01-1.36]	Similar results were found in the 282 patients with AKI at baseline, defined by a kidney SOFA score of ≥2 (>1.9 mg/dL or urinary output <500 mL/d)

(*Continued*)

Table 1. Early Volume Resuscitation: Colloids vs Crystalloids Solutions (*Continued*)

Authors, Year	Study Type	Number (n) and Characteristics of Patients	Number and Characteristics of Patients in Subgroups	AKI Definition	Outcome	Comments
SAFE study, 2004[22]	RCT	$n = 6997$, ICU	$n = 3497$, albumin 4%, $n = 3500$, normal saline	Duration of RRT	**Kidney function**: no difference in duration of RRT **Mortality**: No difference in 28-d mortality	
SAFE substudy traumatic brain injury, 2007[23]	Post hoc analysis from SAFE study	$n = 406$, ICU with traumatic brain injury	$n = 255$, albumin 4% $n = 260$, saline	Not defined	**Mortality**: Higher mortality at 24 mo in patients treated with albumin (OR 1.63 [1.17-2.26])	Majority of deaths during the first 28 d in both groups
SAFE substudy, severe sepsis, 2011[24]	Post hoc analysis from SAFE study	$n = 1218$, ICU with severe sepsis	$n = 603$, albumin 4% $n = 615$, saline	SOFA score and RRT requirement	**Kidney function**: no difference **Mortality**: lower risk of death with albumin OR = 0.7 (0.52-0.97)	

Abbreviation: RIFLE, Risk, Injury, Failure, Loss, End-Stage Renal Disease.
*Non-HES group including crystalloids, albumin, and gelatins.
†Hypooncotic colloids: 4% albumin (8% of patients) or gelatins (97% of patients).
‡Artificial hyperoncotic colloids: HES (98% of patients, both modern—130 kDa/0.4—and older starch) or dextran (3% of patients).

the RRT requirement compared with Ringer's acetate (relative risk [RR] 1.17; 95% CI 1.01-1.36 and RR 1.35; 95% CI 1.01-1.80, respectively). There were no differences in terms of dialysis dependence or AKI incidence at 90 days. This study was the only one to predefine an AKI subgroup, and this subgroup also presented an increased mortality and RRT requirement with 6% HES. A retrospective study comparing the effect of 6% HES 130/0.4 and 10% HES 200/0.5 on the RRT requirement in 8408 critically ill patients showed that the need for RRT was lower in patients treated with 6% than with 10% HES (6.1% vs 35.5%; OR 11.5; 95% CI 9.5-14.1).[21] In addition, mean creatinine levels were lower in the 6% compared with the 10% HES group. However, with respect to the results from the recent large RCT completed by Perner and colleagues,[20] low-molecular-weight synthetic colloids seem to have an harmful effect on mortality and kidney function and should be avoided.

Albumin

The SAFE study randomized 7000 ICU patients to either 4% albumin or normal saline for intravascular fluid resuscitation and found no differences in 28-day mortality or in new organ dysfunction, duration of RRT, and other secondary endpoints (Table 1).[22] Kidney function was not independently reported. As expected, patients in the saline group had a higher positive fluid balance during the first 3 days. However a low proportion of patients received large volume fluid resuscitation (>5 L) and thus the results may not be applicable to all patients. Two subgroup analyses were subsequently published. In the traumatic brain injury subgroup, which included 460 patients, patients who received albumin had an increased mortality at 24 months (33.2% vs 20.4%, $P = 0.003$).[23] In contrast, the substudy with severe sepsis showed a lower risk of death in patients treated with albumin (OR = 0.71; 95% CI 0.52-0.97).[24] The kidney Sequential Organ Failure Assessment (SOFA) scores and the incidence of RRT were not different between groups. On the basis of these three studies, 4% albumin should be avoided in patients with traumatic brain injury but could be considered in other patients, especially those with severe sepsis, without major concerns about kidney function. Other risks associated with albumin administration, such as transmission of virus and theoretically, the Creutzfeldt-Jakob disease agent, need to be taken into account in this decision process.

Hyperoncotic albumin was evaluated in a meta-analysis that included 7 RCTs in critically ill and noncritically patients.[25] Albumin at 20-25% was shown to have a protective effect on kidney function (OR 0.24; 95% CI 0.12-0.48) and mortality (OR 0.52; 95% CI 0.28-0.95), as opposed to the results by Schortgen and colleagues previously reported. A major limitation of this meta-analysis is the inclusion of a significant proportion of patients with

cirrhosis (6 of 7 studies). This specific population might benefit more from albumin repletion.

In summary, we do agree with the KDIGO and Cochrane group recommendations and favor the use of isotonic crystalloids over colloids in patients at risk or with AKI. Synthetic colloid solutions should be avoided because of their negative effect on kidney function and survival. Hypooncotic albumin could be used in patients with sepsis bearing in mind their infectious risk and should be avoided in traumatic brain injury. Hypooncotic albumin may also have a role in patients requiring large amounts of fluid, and hyperoncotic albumin should probably be avoided except for cirrhotic patients. Recent studies suggested that the type of crystalloid solution used may also influence outcomes. An observational study showed that a calcium-free balanced crystalloid solution on the day of major surgery was associated with fewer complications than 0.9% saline, including infections and AKI requiring RRT.[26] Future studies on volume resuscitation should assess the role of balanced crystalloid solutions compared with isotonic saline.

Late Fluid Management

Over the last years, a few RCTs and several observational studies have shown that excessive fluid repletion leading to fluid overload may have a negative influence on survival, cardiopulmonary complications, kidney function, and wound healing in critically ill adult patients (Table 2).[7–9,27–32] These studies have not looked at the specific type of fluid administered (namely crystalloids or colloids), which represents a significant limitation. In AKI, once hemodynamic status is stabilized, we usually aim for a neutral or restrictive fluid balance depending on the clinical context to prevent or treat significant fluid overload despite the lack of randomized data. However, the safety and efficacy of this procedure need to be confirmed with RCTs. We will first review recent data on fluid management in critical care patients to provide a broader overview of the results in the literature and then in critical care patients with AKI. We will also briefly discuss the effect of fluid management on AKI diagnosis.

Fluid Management in Critically Ill Adult Patients

The largest RCT performed on late fluid management (LFM), the Fluids and Catheters Treatment Trial (FACTT), showed a negative effect of fluid accumulation on pulmonary function but failed to show an improved survival with a conservative fluid strategy.[27] The trial was powered to assess mortality in patients with acute lung injury and compared a conservative versus a liberal strategy of fluid management over 1 week. Patients in the conservative strategy had a cumulative fluid balance of −136 mL vs +6992 mL in the liberal group. The conservative group had an increased number of ventilator-free days and a shorter length of ICU stay. There was a trend toward lower RRT requirement during the first 60 days in the conservative group (10% vs 14%, $P = 0.06$). A small prospective cohort of ventilated patients also showed that negative fluid balance 24 hours before breathing trial and negative cumulative fluid balance were independently associated with first-day weaning success.[30] Diuretics were not associated with a higher weaning success, and no data were available on kidney function.

Observational studies have shown an association between fluid balance and mortality.[28,29] The Sepsis Occurrence in Acutely Ill Patients (SOAP) study included 3147 ICU patients, among them 1177 with sepsis.[28] Positive cumulative balance within the first 72 hours was associated with an increased risk of mortality in sepsis (OR per liter increase 1.1; 95% CI 1.0-1.1). A smaller retrospective study looked at the combination of adequate initial volume resuscitation and conservative LFM in 212 patients with septic shock and acute lung injury. The study categorized patients according to the initial volume resuscitation strategy used during the first 6 hours of septic shock (initial fluid resuscitation [IFR]) and the fluid strategy used from 6 hours to 7 days after shock onset (LFM).[29] IFR was "adequate" if a fluid bolus greater than 20 mL/kg was administered before vasopressor treatment initiation and if patients had a central venous pressure greater than 8 mmHg during the 6 first hours. For LFM, "conservative" strategy was defined as even-to negative fluid balance for 2 or more consecutive days during the first week. Hospital mortality was lowest for those achieving an adequate IFR and a conservative LFM (18%), and mortality rates increased when patients did not meet late conservative goals (42%), early adequate goals (57%), or both early adequate and late conservative (77%) goals. The incidence and evolution of AKI were not mentioned. This observational study suggests taking into consideration the timing of the critical illness when making decisions on fluid administration and supports the importance of a rapid and adequate fluid repletion in the first hours of septic shock, and, if feasible, a subsequent neutral fluid balance.[11] The effect of such a strategy on kidney function is unknown.

Fluid Management in Critically Ill Adult Patients with AKI

A few observational studies and subsequent analyses of the FACTT and Randomized Evaluation of Normal vs Augmented Level (RENAL) trials have shown an association between fluid balance and mortality in adults with AKI. The effect of fluid overload on kidney function was less consistent. The first study was a subsequent analysis of the SOAP study cited above.[28] Among the initial 3127 patients, 36% had AKI.[8] Mean fluid balance was an independent risk factor for 60-day mortality (HR 1.21 [per

Table 2. Effect of Fluid Balance in LFM

Author, Year	Study Type	Population Number (*n*) and Characteristics	Subgroups Number (*n*) and Characteristics	Assessment of Kidney Function	Outcomes
Upadya, 2005[30]	Prospective observational	$n = 87$, ICU on mechanical ventilation	$n = 38$ with first-day weaning success, $n = 49$ patients with first-day weaning failure	Not reported	**Pulmonary outcome:** Increased first-day weaning success with negative cumulative fluid balance OR 3.4, (1.3-8.4) and 24 h before breathing trial OR 2.9, (1.1-7.6)
ARDS Clinical Trial Network, 2006[27]	RCT	$n = 1000$, ALI	$n = 503$, conservative fluid management (−136 mL) $n = 497$ liberal fluid management (+6992 mL) over 7 d	RRT requirement	**Mortality**: no difference **Pulmonary outcome:** increased number of ventilator-free days (14.6 vs 12.1, $P < 0.001$); **Kidney function**: trend toward lower RRT within 60 d 10% vs 14%, $P = 0.06$)
Vincent, 2006[28]	Retrospective (data collected prospectively)	$n = 3147$, ICU	$n = 1177$, with sepsis (total fluid balance 0.1 ± 5.3 L), $n = 1970$, no sepsis (total fluid balance 0.4 ± 17.8 L)	Kidney SOFA score*	**Mortality**: Increased risk of death OR 1.1 (1.0-1.1) per liter increase of cumulative balance within first 72 h in patients with sepsis
Murphy, 2009[29]	Retrospective	$n = 212$ septic shock and ALI	$n = 93$, adequate IFR + conservative LFM, $n = 31$ inadequate IFR + conservative LFM, $n = 53$ adequate IFR + liberal LFM, $n = 35$ inadequate IFR + liberal LFM	Not reported	**Mortality**: lower mortality with adequate IFR + conservative LFM (18.3%) than other strategies (inadequate IFR + conservative LFM (56.6%), adequate IFR + liberal LFM (41.9%), inadequate IFR + liberal LFM (77.1%), $P < 0.001$)
Payen, 2008[8]	Retrospective	$n = 3147$, ICU	$n = 1120$ with AKI, $n = 2027$ without AKI	Kidney SOFA score*	**Mortality**: with AKI, mean fluid-balance associated with increased 60-d mortality, HR 1.21 (1.13-1.28) per liter per 24 h
Bouchard, 2009[7]	Retrospective (data collected prospectively)	$n = 542$, AKI in ICU	$n = 243$, with FO† $n = 299$, without FO	RRT independence	**Mortality:** increased 60-d death with FO (46% vs 32%, $P = 0.006$), Multivariate analysis: FO at initiation of RRT: OR 2.07 (1.27-3.37), FO at peak creatinine (nondialyzed) OR 3.14 (1.18-8.33) **Kidney function**: no effect of FO at diagnosis on kidney recovery FO at peak creatinine associated with reduced kidney recovery (35% vs 52%, $P < 0.001$)

Heung, 2012[9]	Retrospective	$n = 170$, on RRT with presumed acute tubular necrosis	$n = 61$, kidney recovery $n = 109$, nonrecovery of kidney function	RRT independence RRT independence	**Kidney function:** FO at RRT initiation was a significant negative predictor of recovery of kidney function HR 0.97, (0.95-1.0) for each rise in percent
RENAL Replacement Therapy Study Investigators, 2012[32]	Retrospective (data collected prospectively)	$n = 1453$, on RRT in ICU for AKI	$n = 705$, positive mean daily fluid balance $n = 748$, negative mean daily fluid balance		**Mortality:** negative mean daily fluid balance associated with decreased mortality at 90 d OR 0.318 (0.24-0.43) **Kidney function:** negative mean daily fluid balance was associated with increased RRT-free days ($P = 0.0017$)

Abbreviations: ALI, acute lung injury; FO, fluid overload.
*Kidney SOFA score: creatinine >3.5 mg/dL or urine output 500 mL/d.
†FO defined by percentage of fluid accumulation >10% over baseline weight at hospital admission.

liter per 24 hours], $P < 0.001$). When patients with AKI within or after 2 days after ICU admission were analyzed separately, mean fluid balance remained an independent predictor of mortality only in early AKI. There were no data available on the effect of fluid balance on kidney function. A subsequent analysis of the FACTT trial also recently showed that a positive fluid balance after AKI was strongly associated with mortality.[27] The RENAL trial randomized 1508 AKI patients on RRT to higher versus lower intensity therapy and showed that a negative mean daily fluid balance during RRT was associated with a decreased risk of death and increased RRT-free days.[32] No data on fluid balance were available before RRT initiation.

The PICARD study showed that fluid overload, defined as a percentage of fluid accumulation more than 10% over baseline weight at hospital admission, was also associated with a significantly higher mortality at 60 days and at hospital discharge.[7] After multivariate adjustment, the OR for death associated with fluid overload at dialysis initiation was 2.07 (95% CI 1.27-3.37) and was 3.14 (95% CI 1.18-8.33) for nondialyzed patients at AKI diagnosis. The study also showed an increase in the risk of death proportional to the magnitude and duration of fluid accumulation. The effect of fluid overload on kidney recovery was inconsistent. Fluid overload at the time of AKI diagnosis was not associated with recovery of kidney function; however, patients with fluid overload at their peak serum creatinine were significantly less likely to recover kidney function. There was no relationship between the degree of fluid overload at dialysis initiation and subsequent dialysis independence.

A retrospective smaller study showed that dialyzed patients who subsequently became dialysis-independent had significantly less fluid overload at the time of RRT initiation (3.5% vs 9.3%, $P = 0.004$).[9] Each rise in percent of fluid overload at dialysis initiation was a significant negative predictor of kidney recovery (hazard ratio 0.97, [0.95-1.0]). Similar results were obtained for 1-year survival (OR 0.96; 95% CI 0.92- 0.99).

Fluid Management and AKI Diagnosis

A subsequent analysis of the FACTT trial suggested that adjusting serum creatinine for fluid balance may influence AKI diagnosis and prognosis.[33] Patients with AKI identified after but not before adjusting for positive fluid balance had higher mortality rates (31% vs 12%, $P < 0.001$), and patients who had AKI before but not after adjusting for fluid balance had lower mortality rates after adjustment (31% vs 11%, $P = 0.005$). Another study showed that correcting serum creatinine for fluid balance improved AKI staging.[34] Future studies should consider adjusting serum creatinine for fluid balance and

assessing the effect of these adjustments on AKI diagnosis and prognosis.

In summary, results from observational studies suggest that a conservative fluid approach may be beneficial in terms of mortality and kidney recovery in patients with severe AKI; however, RCTs are required to confirm these findings before any clear recommendation can be made. The type of fluids used should also be included in these studies. Regarding fluid overload as a threshold for RRT initiation in AKI, physicians from a multicenter pediatric study recently agreed that initiating RRT within 24-48 hours of reaching more than 10% fluid overload is clinically acceptable (NCT01416298). To our knowledge, there are no ongoing adult studies on fluid overload in AKI requiring RRT, and this threshold has not been formally adopted for adult patients. Finally, the influence of fluid balance on serum creatinine should also be taken into account to diagnose AKI and assess its prognosis.

Diuretics

Patients with AKI can develop oliguria and fluid retention, which are associated with further complications such as respiratory failure. In many studies, oliguric AKI has been associated with worse outcomes than nonoliguric AKI.[35-37] The use of diuretics in oliguric AKI is frequent; however, the benefit associated with this intervention remains unproven.[36-38] Experimental studies have shown that furosemide could reduce AKI risk by inhibiting the Na-K-2Cl cotransporter to reduce tubular medullar oxygen demand.[39] Increased production of prostaglandins could also have a role.[40] Although interesting, the results of these experimental animal studies might not translate in humans.[41-43] We will review the use of diuretics for the prevention and treatment of AKI.

Diuretics in Prevention of AKI

Several years ago, RCTs reported that loop diuretics do not prevent AKI.[44,45] More recently, Mahesh and colleagues evaluated the renoprotective effect of low-dose furosemide or saline infusion for 12 hours in 42 cardiac surgical patients (Table 3).[46] There were no differences in kidney function between groups, and urine output was higher in the furosemide group. The small number of patients and the short period of furosemide infusion limit the generalization of these results. A recent meta-analysis by Ho and Power also concluded that preventive furosemide administration does not improve the risk of RRT or mortality.[47] On the basis of these results, the recent KDIGO guidelines recommended not using furosemide to prevent AKI (grade 1B).[15]

Diuretics in Treatment of AKI

Numerous studies have been conducted to evaluate the effect of furosemide in treating AKI with conflicting results. We agree with the KDIGO guidelines that diuretics should not be used to treat AKI, except for the management of volume overload (grade 2C).[15] In the meta-analysis by Ho and Power, the use of diuretics in the treatment of AKI was not associated with a significant modification of the risk of mortality or RRT requirement.[47] Six RCTs reported data on mortality and 5 studies reported data on RRT requirement. A significant proportion of these studies were conducted more than 15 years ago, and fluid balance was not reported, which could have influenced the results.

More recent observational studies have confirmed that diuretics seem to have a neutral effect on outcomes after multivariable adjustments. The BEST kidney study, the largest prospective observational study in severe AKI, reported data on 1743 ICU patients.[48] After adjustments, diuretic use was not associated with a significantly increased risk of mortality. Fluid balance was not reported in this study. More recently, data from the FACTT trial were used to assess the association between fluid balance and diuretic use in mortality.[27] Among the 1000 patients from the original study, 306 developed AKI within the first 2 days of the study.[49] Higher furosemide doses were associated with decreased mortality at 60 days (OR 0.38; 95% CI 0.23-0.63); however, this association became nonsignificant after adjustment for post-AKI fluid balance (OR 0.73; 95% CI 0.42-1.26). These results could be explained by the effect of fluid overload, and not diuretics per se, on mortality. In contrast, an older retrospective study found that diuretic use was associated with an increased risk of death (OR 1.68; 95% CI 1.06-2.64), and these results were driven by patients receiving high doses of diuretics, perhaps representing a relative unresponsiveness.[50] This study was criticized for collinearity in the covariable analysis and nonoptimal statistical methods. In addition, fluid balance was not reported.

Diuretics in Treatment of AKI with RRT

Two RCTs recently showed that loop diuretics do not improve recovery of kidney function in AKI requiring RRT. In the largest RCT on furosemide in AKI, patients were randomized to furosemide at 25 mg/kg/day intravenously, or furosemide at 35 mg/kg/day orally, or matched placebo.[51] Patients were randomized before RRT initiation, and furosemide was administered after RRT initiation. There were no differences in survival or kidney recovery rates between the groups. Patients with high-dose furosemide had a higher urine output, but this did not translate into differences in the number of dialysis sessions or time on dialysis. In a smaller RCT, furosemide infusion (0.5 mg/kg/hour) started at the end of the continuous venovenous hemofiltration compared with placebo did not significantly improve kidney recovery.[52] Once again, urinary output (median

Table 3. Diuretics in Prevention and Treatment of AKI

Author, Year	Study Type	Patients Number (n) and Characteristics	Patients Number (*n*) on Diuretics; Specific Types (%) and Doses	Patients Without Diuretics (or on Low Dose)	AKI Definition or Evaluation of Kidney Function	Outcomes	Comments
Prevention of AKI							
Mahesh, 2008[46]	RCT	$n = 50$, cardiac surgical patients at risk for AKI*	$n = 21$ furosemide 4 mg/h for 12 h after surgery	$n = 21$, saline 2 mL/h for 12 h after surgery	Creatinine >1.47 mg/dL or increase of 50% if already over 1.47 mg/dL†	**Kidney function:** no difference	Higher diuresis in the furosemide group
Treatment of AKI							
Mehta, 2002[50]	Retrospective cohort	$n = 552$, AKI in ICU	$n = 326$, furosemide (62%) 80 mg, bumetanide (59%) 10 mg, metolazone (33%) 10 mg	$n = 226$, no diuretics	BUN >40 mg/dL, creatinine >2.0 mg/dL, or sustained rise creatinine of 1 mg/dL for CKD patients	**Mortality:** OR 1.68 (1.06-2.64) **Nonrecovery of kidney function:** OR 1.79 (1.19-2.68)	Higher risk of death or nonrecovery with a ratio of daily furosemide dose on total 24 h diuresis >1.0, OR 2.94 (1.61-5.36)
Uchino, 2004[48]	Prospective cohort	$n = 1743$, AKI in ICU	$n = 1117$, furosemide (98.3%) 240 mg daily	$n = 626$, no diuretics	RRT requirement, and/or urine output <200 mL in 12 h, and/or BUN >86 mg/dL, and/or serum potassium >6.5 mEq/L	**Mortality:** no difference	Three different statistic models reproduced the same results
Cantarovich, 2004[51]	RCT	$n = 338$, AKI and RRT (ICU or nephrology units)	$n = 166$, furosemide 25 mg/kg/d IV (max 2 g) or 35 mg/kg/d orally	$n = 164$, placebo	RRT independence	**Mortality:** no difference **Kidney function:** no difference	High-dose furosemide decreased time to achieve 2-L/d diuresis but no difference in number and duration of dialysis sessions
Van der Voort, 2009[52]	RCT	$n = 71$, CVVH in ICU	$n = 36$, furosemide 0.5 mg/kg/h started at CVVH discontinuation	$n = 35$, placebo infusion	RRT independence	**Kidney function:** no difference	Diuretics increased urine output and sodium excretion
Grams, 2011[49]	Retrospective (data collected prospectively)	$n = 306$, AKI	$n = 169$ conservative fluid therapy; furosemide, mean dose 80 mg/d	$n = 137$ liberal fluid therapy; furosemide 23 mg/d	50% or 0.3-mg/dL increase in creatinine from baseline, occurring over ≤48 h	**Mortality:** no effect of furosemide dose after adjustment for fluid balance	Mortality OR 0.38 (0.23-0.63) for furosemide dose before fluid balance adjustment

Abbreviations: BUN, blood urea nitrogen; CVVH, continuous venovenous hemofiltration.
*Risk of AKI defined by one or more of the following criteria: creatinine >1.5 mg/dL, left ventricular ejection fraction <50%, diabetes, combined coronary-aortic bypass and valve surgery, redo cardiac surgery.
†To convert serum creatinine in mg/dL to mol/L, multiply by 88.4; to convert urea nitrogen in mg/dL to mmol/L, multiply by 0.357.

247 mL/hour vs 117 mL/hour, $P = 0.003$) and sodium excretion were higher in the group treated with furosemide.

In summary, the use of diuretics in AKI has no clear benefit on the recovery of kidney function and mortality, and their role in preventing or treating fluid overload needs to be evaluated. Therefore, we agree with the KDIGO guidelines that diuretics should not be used to treat AKI, except for treating volume overload.[15] Two ongoing studies might bring new insights to these clinically relevant questions. The SPARK study is a phase II randomized, blinded, placebo-controlled trial of a low-dose infusion of furosemide titrated to urine output in critically ill patients with early AKI.[53] The study is expected to enroll 216 critically ill patients and its primary outcome is progression in AKI severity. Secondary outcomes include fluid balance, need for RRT, duration of AKI, rate of kidney recovery, and mortality. The study should soon be completed. Another study, "The Effect of Loop Diuretics on Severity and Outcome of Acute Kidney Injury", will evaluate the effect of 1.0 or 1.5 mg/kg/hour of intravenous furosemide on kidney recovery. This prospective, nonrandomized trial is expected to enroll 150 patients and should be completed by 2015.

Conclusion

There is increasing evidence suggesting that isotonic crystalloids should be used instead of colloids as initial management for expansion of intravascular volume in patients at risk for AKI or with AKI, such as those with sepsis, septic shock, or trauma. The optimal timing and amount of initial volume resuscitation to prevent AKI, to reduce its severity, and to improve mortality still needs to be defined. A more aggressive fluid repletion in the early setting is probably beneficial. Once AKI occurs and that hemodynamic status is stabilized, the relevance of a restrictive fluid balance and the use of diuretics or RRT to prevent or treat fluid overload and improve outcomes in this population, without worsening kidney function, needs to be confirmed with RCTs. Ongoing studies, such as SPARK[53] and "The Effect of Loop Diuretics on Severity and Outcome of Acute Kidney Injury" might bring new insights on these questions.

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Cardiorenal Syndrome in Critical Care: The Acute Cardiorenal and Renocardiac Syndromes

Dinna N. Cruz

Heart and kidney disease often coexist in the same patient, and observational studies have shown that cardiac disease can directly contribute to worsening kidney function and vice versa. Cardiorenal syndrome (CRS) is defined as a complex pathophysiological disorder of the heart and the kidneys in which acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ. This has been recently classified into five subtypes on the basis of the primary organ dysfunction (heart or kidney) and on whether the organ dysfunction is acute or chronic. Of particular interest to the critical care specialist are CRS type 1 (acute cardiorenal syndrome) and type 3 (acute renocardiac syndrome). CRS type 1 is characterized by an acute deterioration in cardiac function that leads to acute kidney injury (AKI); in CRS type 3, AKI leads to acute cardiac injury and/or dysfunction, such as cardiac ischemic syndromes, congestive heart failure, or arrhythmia. Both subtypes are encountered in high-acuity medical units; in particular, CRS type 1 is commonly seen in the coronary care unit and cardiothoracic intensive care unit. This paper will provide a concise review of the epidemiology, pathophysiology, prevention strategies, and selected kidney management aspects for these two acute CRS subtypes.

Key Words: Acute coronary syndrome, Acute kidney injury, Cardiac surgery, Cardiorenal syndrome, Heart failure

Consensus Definition and Classification of the Cardiorenal Syndromes

Various organ systems within the human body are intimately connected to each other. This so-called "organ crosstalk" refers to the complex biological communication and feedback between organ systems mediated via various soluble and cellular mediators. In the normal state, this crosstalk helps to maintain homeostasis and optimal functioning of the human body. However, during disease states this very crosstalk can carry over the influence of the diseased organ to initiate and perpetuate structural and functional dysfunction in other organs.[1,2]

Heart and kidney disease often coexist in the same patient in acute and chronic states. Observational and clinical trial data have accrued to show that acute/chronic cardiac disease can directly contribute to acute/chronic worsening kidney function and vice versa. Considering the complex and bidirectional relationship between these two organs, the Acute Dialysis Quality Initiative recently proposed a consensus definition and classification of cardiorenal syndromes (CRS).[3] CRS is defined as "a complex pathophysiological disorder of the heart and the kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ." The classification into five subtypes is based on the primary organ dysfunction, whether heart (called "cardiorenal" syndromes) or kidney (called "renocardiac" syndromes), and on whether the organ dysfunction is acute or chronic (Table 1).[3] The classification is not intended to be static; it is acknowledged that many patients may transition between different CRS subtypes during the course of their disease.[4] An example of such a situation is that of a patient with chronic heart failure (CHF) and CKD; that patient is considered to have CRS type 2. Many such patients may have an episode of acute decompensation requiring hospitalization that may be complicated by acute kidney injury (AKI) in 24-45% of cases; the patient will then slip into CRS type 1. Treatment of the acute decompensation will restore the patient to their baseline state. The AKI in such situation is often transient, and the kidney function recovers to its preexisting level; the patient then moves back into CRS type 2. Further subclassifications into transient or reversible dysfunction and slowly or acutely progressive vs stable disease are avoided to keep the classification parsimonious.

Acute Cardiorenal and Renocardiac Syndromes

Epidemiology

Of particular interest to the critical care specialist are CRS type 1 (acute cardiorenal syndrome) and type 3 (acute renocardiac syndrome). Both subtypes are encountered in high-acuity medical units; in particular, CRS type 1 is commonly seen in the coronary care unit and cardiothoracic intensive care unit (ICU).

CRS Type 1

CRS type 1 is characterized by an acute deterioration in cardiac function that then leads to AKI (Table 1). The spectrum of acute cardiac dysfunction that could result in AKI includes acute decompensated heart failure (AHF), acute coronary syndrome (ACS), and postcardiotomy low cardiac output syndrome, among others. There

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are several studies describing the epidemiology of CRS type 1, most commonly referred to in the literature as "worsening renal function" in AHF and ACS. An extensive review on this topic can be found elsewhere.[4,5] Increases in serum creatinine (sCr) ranging from 0.1 to 0.5 mg/dL and 25-50% from baseline have been used to define CRS type 1. Other definitions used in the literature include change (Δ) in estimated glomerular filtration rate (eGFR; eg, decrease in eGFR by 25%), by either ΔsCr and/or urine output (eg, <20 mL/hour), or by Δblood urea nitrogen (eg, increase by 50%). Different studies also considered variable timeframes for ascertainment of this end point, which would also influence epidemiologic estimates. Most commonly, the period of observation is within the hospital admission, but other studies have also looked at 2 weeks[6] or at a longer term such as 6 months.[7] It has been recommended that established AKI consensus definitions/classifications (RIFLE, AKIN, KDIGO)[8-10] and a defined relevant time frame (eg, first 7 days of hospitalization) be used in future studies enrolling AHF/ACS patients.[4] This would enable integration of type 1 CRS into the broader context of AKI and permit greater standardization of data across future epidemiologic investigations.

Recognizing the limitations of having varied definitions, CRS type 1 has been described in 27-45% of hospitalized AHF patients[11-17] and in 9-54% of ACS patients[6,18–23] (Fig 1). A significant proportion of cases occurs in the first 3-5 days after admission in AHF and ACS.[13,18,24] It is likely that the pathophysiology of CRS type 1 (discussed further below) may vary at different time points. For example, early AKI may be related to a low cardiac output state and/or marked increase in venous pressure. On the other hand, investigations (ie, cardiac catheterization and contrast media exposure) or interventions (ie, furosemide, angiotensin-converting enzyme [ACE] inhibitors) may be the factors responsible for CRS type 1 occurring later in the hospital course.

Several risk factors have been identified in the literature. Nonmodifiable risk factors include a history of diabetes or prior admissions for AHF or myocardial infarction and evidence of more severe cardiac dysfunction at the time of presentation (eg, presence of pulmonary edema or tachyarrhythmias, worse Killip class,[25] or lower ejection fraction[6,15,18]). Worse kidney function on admission, whether defined by sCr or eGFR, has consistently been associated with higher risk for CRS type 1 in almost all studies. In terms of the so-called modifiable risk factors, high-dose diuretic (eg, daily furosemide dose >100 mg/day or in-hospital use of thiazides) and/or vasodilator therapy as well as higher radiocontrast volumes (eg, contrast media volume-to-creatinine clearance ratio [V/CrCl] >3.7) during cardiac catheterization and intervention have been frequently cited in epidemiologic studies.[11,12,15,17,24,26,27] However, it is likely that these are merely surrogate markers for more severe acute cardiac dysfunction or ischemia.

In AHF and ACS, the development of CRS type 1 has been associated with worse clinical outcomes, rehospitalization, and increased health care expenditures.[16,17,19,28] The mortality risk associated with CRS type 1 is most pronounced early on, but it persists beyond the short term.[28] Indeed, an increased risk for death can be seen as far as 10 years out from the index hospitalization for acute myocardial infarction (AMI).[21] Furthermore, a biological gradient has been observed between severity of CRS type 1 and mortality risk.[21,28] More recently, CRS type 1 has also been associated with an independent higher risk for ESRD; likewise, the more severe the AKI episode, the higher the risk of ESRD.[20]

CLINICAL SUMMARY

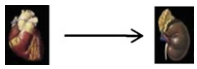
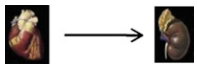
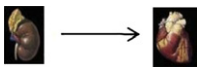
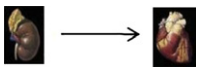
- Cardiorenal Syndrome (CRS) is a complex pathophysiological disorder of the heart and the kidneys wherein acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ.
- CRS Type 1 (acute cardiorenal syndrome) is characterized by an acute deterioration in cardiac function, which leads to acute kidney injury (AKI).
- In CRS Type 3 (acute renocardiac syndrome), AKI leads to acute cardiac injury and/or dysfunction, such as cardiac ischemic syndromes, congestive heart failure, or arrhythmia.
- The management of these acute CRS subtypes is challenging due to the multitude and complexity of pathophysiological interactions between heart and kidney.

CRS Type 3

CRS type 3 is characterized by AKI that then leads to an acute cardiac injury and/or dysfunction, such as AMI, congestive heart failure (HF), or arrhythmia (Table 1). Acute kidney conditions that are typical for this syndrome include cardiac surgery-associated AKI, AKI after major noncardiac surgery, contrast-induced AKI (CI-AKI), other drug-induced nephropathies, acute glomerulonephritis, and rhabdomyolysis.

In contrast to CRS type 1, there is a relative paucity of data regarding the epidemiology of CRS type 3. Perhaps the earliest clinical reports of CRS type 3 were that of electrocardiographic (ECG) changes in patients with AKI and electrolyte disorders dating back to 1961.[29,30] In 60 patients with kidney failure, increased PQ interval was noted among the patients with K greater than 7 meq/L, and a prolonged QT wave was associated with the presence of hypocalemia.[29] The authors noted that ECG changes were more frequently observed among AKI patients as compared with those with CKD, even at similar levels of potassium. In another early series of 69 AKI patients, ECG was performed before and after

Table 1. Classification of CRS

Class	Type	Description	Clinical Scenarios (Examples)
1	Acute CRS 	Abrupt worsening of cardiac function leading to AKI	- AHF - Cardiac surgery - ACS - CIN after coronary angiogram
2	Chronic CRS 	Chronic abnormalities of cardiac function leading to CKD	- IHD/hypertension - CHD - CHF
3	Acute renocardiac syndrome 	Abrupt worsening of renal function leading to acute cardiac dysfunction	- Acute pulmonary edema in AKI - Arrhythmia - CIN with adverse cardiac outcomes
4	Chronic renocardiac syndrome 	CKD leading to chronic cardiac dysfunction	- Cardiac hypertrophy in CKD - Adverse cardiovascular events in CKD - ADPKD with cardiac manifestations
5	Secondary CRS 	Systemic disorders causing cardiac and renal dysfunction	- Sepsis - SLE - DM

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; CHD, congenital heart disease; CIN, contrast-induced nephropathy; DM, diabetes mellitus; IHD, ischemic heart disease; SLE, systemic lupus erythematosis.

hemodialysis.[30] They were divided into 4 groups based on predialysis potassium level (<3.8, 3.8-5.1, 5.1-6.5, and >6.5 meq/L). All patients exhibited tachycardia with shortening of PQ and QRS intervals after hemodialysis. This shortening was most marked among the patients with significant hyperkalemia (>6.5 meq/L) before dialysis. In contrast, U wave was observed in all hypokalemic AKI patients before dialysis and disappeared only in some patients afterward.

Very few clinical studies that focused on AKI have reported on the event rates of acute cardiac dysfunction. Therefore, estimates of incidence and associated

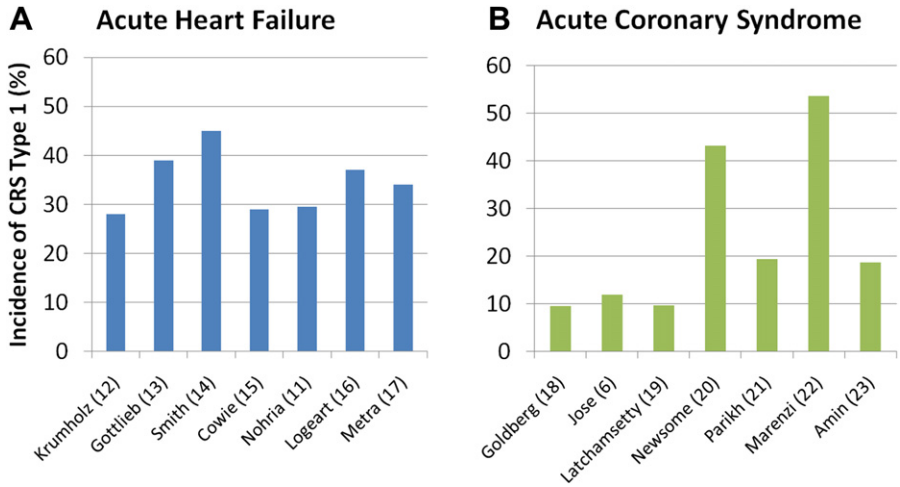


Figure 1. Incidence of CRS type 1 in selected studies on (A) AHF and (B) ACS.

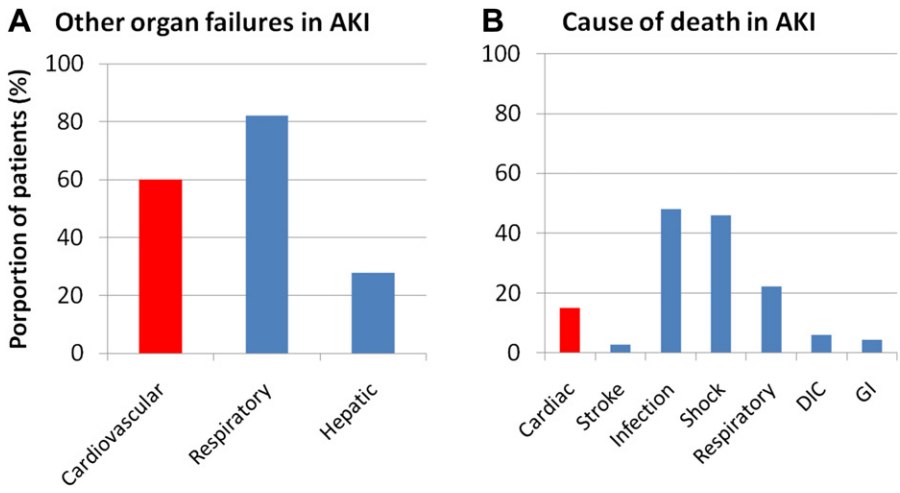


Figure 2. Other organ failures seen in AKI patients (A); adapted with permission from Liano et al.[31] Reported causes of death in AKI patients (B).[31–32]

outcomes of CRS type 3 are challenging. In a multicenter AKI cohort, the organ failures most commonly seen were respiratory, cardiovascular, and hepatic failure[31] (Fig 2A). The mortality of AKI patients in the ICU increased concomitantly with the number of other organ failures. These same authors reported the cause of death in 748 cases of AKI in 13 hospitals in Madrid over a 9-month period.[32] Heart disease was the reported cause of death in 15% of AKI patients; the top causes were infection, shock, and respiratory disease (Fig 2B). With the lack of good quality data on this syndrome, it has been recommended to include cardiovascular events as outcomes in studies focused on AKI, to conduct primary investigations to characterize factors associated with susceptibility for acute cardiac dysfunction in AKI, and to determine whether these factors may be preventable and/or modifiable.[4]

Pathophysiology

CRS Type 1

The presence of AHF may affect kidney function by several mechanisms including disturbed hemodynamics, presence of external factors, and immune-mediated processes.[33,34]

At the onset of AHF, particularly with the presence of systolic dysfunction and decreased cardiac output, kidney arterial underfilling and increased venous congestion are expected complications leading to decreased glomerular filtration rate.[35]

A lower kidney perfusion in the setting of AHF overactivates the renin-angiotensin-aldosterone system (RAAS), promoting water and sodium retention, which will contribute to systemic and kidney hypertension and consequently endothelial and glomerular injury. Additionally, angiotensin II and aldosterone have profibrotic and proinflammatory properties that further contribute to kidney damage.

Some drugs commonly prescribed for the treatment of AHF can also contribute to development of AKI by disturbing systemic and kidney hemodynamics. Diuretics are recommended in AHF to control dyspnea and edema, but their use may be complicated by excessive intravascular volume depletion and further compromise kidney perfusion.[36,37] Diuretic resistance may also complicate the clinical picture of CRS type 1 by acutely or chronically increasing sodium retention.[38] ACE inhibitors, angiotensin receptor blockers (ARBs), and aldosterone receptor antagonists are included in the protocols for the management of HF[39] because these drugs have been shown to significantly improve the survival of these patients in many randomized control trials.[40-46] However, they affect kidney hemodynamics, and their use must be carefully monitored to avoid AKI in decompensated patients.

Another important iatrogenic nephrotoxin in AHF and ACS is radiocontrast media for imaging procedures. Iodinated contrast agents induce intense and prolonged vasoconstriction at the corticomedullary junction of the kidney and directly impair the autoregulatory capacity of the kidney through a reduction in nitric oxide synthesis.[47,48] These effects, coupled with direct tubular toxicity of iodinated radiocontrast, lead to overt acute tubular necrosis and CI-AKI.

Immune-mediated mechanisms have also been implicated in the development of CRS type 1.[49,50] Evidence has suggested that an increased number of proinflammatory cytokines, a higher rate of apoptosis, and monocyte reprogramming have a pathogenic role in AKI.[51-53] It has been recently demonstrated that plasma-induced apoptosis, capsase-3 and 8 activities, and interleukin-6 levels were significantly higher in CRS type 1 patients when

compared with healthy controls and with patients with AHF but without kidney impairment.[54,55] However, the specific role of these cytokines in the causation of AKI in the setting of AHF remains to be elucidated.

CRS Type 3

The mechanisms underlying CRS type 3 are not clearly understood, but two general categories of effects have been proposed: direct effects of AKI on the heart and effects of AKI on remote organ function with indirect effects on the heart.[56] AKI triggers activation of the innate and adaptive immune systems, and in animal models of bilateral kidney ischemia increased levels of tumor necrosis factor α (TNF-α), interleukin-1, and intracellular adhesion molecule-1 (ICAM-1) mRNA were found in the heart after 48 hours of AKI and were accompanied by evidence of cardiac cell apoptosis and functional changes on echocardiography.[57,58]

Physiologic functions of the kidney are compromised during AKI, leading to dangerous complications that indirectly affect the heart, including fluid overload contributing to the development of edema, cardiac overload, hypertension, pulmonary edema, and myocardial dysfunction; hyperkalemia and other electrolyte imbalances that can be implicated in the development of arrhythmias; acidemia that disturbs myocyte metabolism and contributes to pulmonary vasoconstriction, increased afterload for the right ventricle, and has a negative inotropic effect; and accumulation of uremic toxins that depress myocardial contraction.[56] In addition, uremia is characterized by increased oxidative stress and inflammation that aggravates HF.[35]

Furthermore, kidney and heart can activate RAAS and the sympathetic nervous system. These two systems interact and potentiate each other, contributing to perpetuate volume overload, increased sympathetic tonus, and angiotensin II release with the final deleterious effects on heart including myocyte apoptosis, hypertrophy, and focal necrosis.[59]

Prevention and Management

CRS is an end result of the interaction between complex pathogenic factors, and once the syndromes set in, they are difficult to abort and are often not reversible in many cases. Most importantly, they are associated with adverse outcomes, even if the AKI episode is transient.[16,19] The pathophysiology of CRS also highlights the importance of limited organ reserve to recover from insults/injury due to the chronically damaged nature of the organs in the disease process. Thus, prevention of CRS is paramount in clinical practice with an aim to identify and avoid precipitating factors as well as to use measures to maintain optimal functioning of the diseased heart and kidney. This may involve multimodality and multidisciplinary preventive strategies, working via diverse therapeutic targets. Apart from pharmacological measures, some nonpharmacological and general preventive measures have to be reinforced across the whole spectrum of CRS. These include weight monitoring and management, smoking cessation, exercise, diet and nutrition, and improving compliance to pharmacological treatment.

Although standard evidence-based guidelines currently exist for management of AHF[60,61] and ACS,[62-64] and more recently for AKI,[10] there are no clear recommendations for the management of CRS types 1 and 3.[65] The multitude of pathophysiological interactions and their complexity render the management of CRS challenging. Only selected key aspects of kidney-related management will be reviewed here.

CRS Type 1

Improving the natural history of CHF and avoiding acute decompensation are the cornerstones of prevention in CRS type 1.[66] Strategies for prevention in these patients should follow those recommended by the ACC/AHA for stage A and B HF.[67] These include coronary artery disease risk factor modification and avoidance of medications that may precipitate salt and water retention, including nonsteroidal anti-inflammatory agents and thiozolidinediones. More importantly, use of RAAS antagonists and β-blockers (BBs) should be optimized appropriately. In patients with CKD, "therapeutic nihilism" should be avoided, and efforts must be made to cautiously introduce these cardioprotective agents, with the knowledge that close monitoring of kidney function will be needed.

Outpatient pharmacologic therapy of CHF needs to be individualized, reviewed frequently, and titrated against the patient's status regularly to avoid episodes of acute decompensation. In a recent meta-analysis of 14 trials involving 4264 patients, the use of remote telephone monitoring to ensure compliance and monitoring has shown to decrease hospitalization by 21% and all-cause mortality by 20%.[68] The use of biomarkers may further enhance telemedicine.[69] In a proposed telemedicine algorithm, patients are monitored on an outpatient basis with regular weight monitoring. When patients report a weight gain of 3-5 lb with HF symptoms, diuretic dose is to be adjusted and optimized via telephone advice. In patients who report a weight gain of 3-5 lb but without any overt signs of HF, brain natriuretic peptide (NP) is measured. The diuretic dose is then titrated based on changes in NP levels from baseline to achieve avert further volume overload.

Another mainstay of prevention is to recognize patients at risk for CRS. Patients who develop CRS type 1 are generally older, have a history of previous hospitalizations for HF or myocardial infarction, and often have baseline kidney dysfunction and hypertension. Risk

Table 2. Renoprotective Strategies in Patients at High-Risk for AKI or With AKI

General	Higher acuity monitoring (fluid balance, urine output, creatinine, blood pressure, cardiac function)
	Accurate evaluation of volume status (clinical and biomarker evaluation, bioimpedance analysis)
	Hold ACE inhibitors/ARB as appropriate
	Optimize volume status and perfusion pressure
	Adjust diuretic doses
	Pharmacovigilance (drug monitoring/dosing, avoiding nephrotoxins, attention to drug interaction)
AHF	Initial use of vasodilators, including nitrates, hydralazine, and nesiritide (in AHF)
CI-AKI	Consider alternative imaging methods to radiocontrast procedures
	Volume optimization with intravenous isotonic sodium chloride or sodium bicarbonate solutions prior to contrast procedure
	Minimize volume of radiocontrast media
	Iso- or low osmolar contrast media
	Consider oral *N*-acetylcysteine
ICU	Use isotonic crystalloids rather than colloids as initial management for intravascular volume expansion in the absence of hemorrhagic shock
	Use of vasopressors in conjunction with fluids
	Protocol-based management of hemodynamic and oxygenation parameters

Adapted from References.[10,102]

prediction scores for AKI have been published for AHF,[24] for CI-AKI after percutaneous coronary intervention[70] and after cardiac surgery,[71] and in hospitalized patients,[72] among others. Such scoring systems can be used to recognize preemptively the patients at a high intrinsic risk of developing acute kidney or cardiac complications. The use of biomarkers, such as the NPs, troponins, and novel kidney biomarkers may further enhance risk prediction, in addition to the clinical risk scores. These CRS biomarkers are extensively reviewed elsewhere.[73] Renoprotective measures can then be selectively instituted in high-risk patients with the aim of reducing the risk of acute CRS (Table 2).

In terms of management, diuretics have remained the cornerstone of treatment for AHF over the years and are used to treat signs and symptoms due to sodium and water retention.[36,37] However, loop diuretics predispose patients to electrolyte imbalance and hypovolemia, which in turn lead to neurohormonal activation and AKI. Furthermore, it is well-known that diuretic braking phenomena exist and postdiuretic sodium retention may further decrease responsiveness to diuretics, especially among patients with CKD. Therefore, aggressive diuresis may be needed to achieve clinical goals but may lead to undesirable consequences.

The optimal regimen for diuretics remains unclear. Continuous intravenous infusion of diuretics has traditionally been considered more effective than bolus in severe AHF.[74,75] However, in the recent DOSE-AHF randomized trial, there were no significant differences in patients' symptoms or in the change in kidney function when diuretic therapy was administered by bolus as compared with continuous infusion, or at a high dose (2.5 times the previous outpatient oral dose) as compared with a low dose (equivalent to the previous oral dose).[76] The high-dose strategy was associated with greater diuresis and more favorable outcomes in some secondary measures but also with transient worsening of kidney function (23% vs 14% in low-dose, $p = 0.04$). This is an important caveat. At least two studies, one in AHF[16] and another in the ACS,[19] have shown that the risk of poor outcome (death and rehospitalization) persisted regardless of whether CRS type 1 was transient or sustained. It is likewise important to note that patients with sCr greater than 3 mg/dL were excluded from this study. Such patients are more likely to need higher doses of furosemide and are more susceptible to develop CRS type 1 during hospitalization for AHF.

In addition to risk prediction, biomarkers can be used to monitor therapy and avoid overdiuresis. NP-guided therapy has been shown to be superior to symptom-guided therapy alone during hospitalization for AHF.[69,77,78] It has also been suggested that novel kidney biomarkers, such as neutrophil gelatinase- associated lipocalin and others, could potentially provide a biomarker "warning" that will trigger the physician to modify or suspend diuretic therapy and potentially avoid full-blown AKI, although this approach has not yet been studied in trials.[79] Furthermore, bioelectrical impedance analysis is a reliable and simple method to assess fluid status and fluid distribution in HF patients.[80] These methods provide more objective estimates of volume status in such patients. Used in conjunction with standard clinical assessment and biomarkers such as the NPs, bioimpedance analysis may be useful in guiding pharmacologic and ultrafiltration (UF) therapies and subsequently restoring such patients to a euvolemic or optivolemic state.[37,80]

UF is a potentially attractive alternative to loop diuretics for the management of fluid overload in patients with AHF and worsening kidney function. The UNLOAD trial, in which 200 patients were randomized to UF or intravenous diuretics, demonstrated that in AHF, UF safely produced greater weight and fluid removal

than intravenous diuretics, reduced 90-day resource utilization for HF, and was an effective alternative therapy.[81] The role of UF as a rescue therapy in patients with AHF and CRS will be compared with stepped pharmacologic care in the ongoing CARRESS-HF trial (see addendum below).[82]

The beneficial effects of ACE inhibitors, ARBs, aldosterone antagonists, and BBs in HF and ACS are well recognized.[40,41,43,45,83–87] However, the administration of BBs in patients with CRS type 1 merits great caution and generally should be avoided until the patients have been stabilized. This is because in such situations, maintenance of cardiac output is achieved via activation of the sympathetic nervous system and reflex tachycardia. Blunting of this compensatory response can thus precipitate cardiogenic shock.[88] Furthermore, aldosterone antagonist therapy is associated with a small but significant risk of severe hyperkalemia. Careful monitoring is therefore essential, particularly in patients with CKD. Vasodilators including nitroglycerin, isosorbide dinitarte, nitroprusside, and hydralazine have been used in the management of CRS especially in situations in which ACE inhibitors/ARBs may be contraindicated.[89] Evidence regarding the potential kidney-preserving effects of nesiritide is mixed, and it is not currently recommended for the prevention of AKI.[10]

CRS Type 3

In an analogous manner, optimized management of CKD as per established guidelines[90] and attention to potential AKI triggers are important in the prevention on CRS type 3. As noted above, appropriate renoprotective strategies specific for the clinical situation can be implemented in high-risk patients (Table 2). For example, an important factor contributing to kidney dysfunction in AHF and ACS is the administration of radiocontrast for imaging and procedures. Appropriate prophylaxis should be done to avoid CI-AKI.[10,91] In critically ill patients and in patients who undergo high-risk surgery, protocol-based management of hemodynamic and oxygenation parameters are recommended for the prevention of AKI.[92,93] These include the use of isotonic crystalloids rather than colloids as initial management for intravascular volume expansion in the absence of hemorrhagic shock and the appropriate use of vasopressors in conjunction with fluids.[10] Several pharmacologic strategies have shown promise in animal and/or early clinical studies, including loop diuretics, mannitol, low-dose dopamine, fenoldopam, atrial NP, and recombinant human insulin-like growth factor-1. To date none have been shown to provide consistent benefit for the prevention or attenuation of AKI, and are currently not recommended by consensus AKI guidelines.[10,94] Likewise, it is not recommended to select off-pump coronary artery bypass graft surgery for the sole purpose of reducing postoperative AKI.[10]

Although clinical models are in use for prediction of adverse cardiovascular outcomes after acute cardiac events (eg, after ACS[95-97]), there are currently no validated models for predicting the acute cardiac events themselves. In view of this knowledge gap, an important

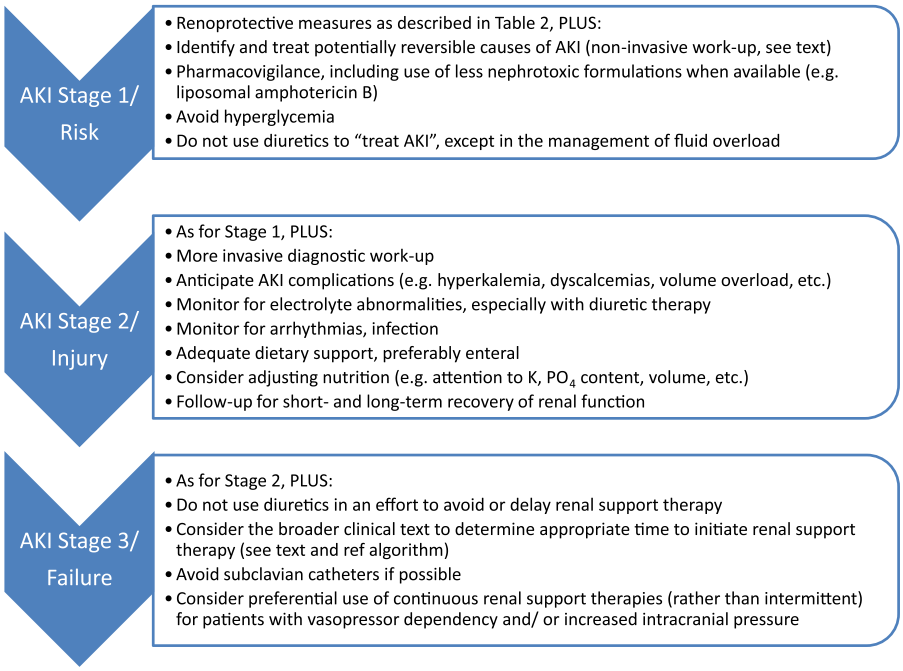


Figure 3. Supportive management in patients with established AKI. Modified with permission from Chuasuwan and Kellum [56] and the KDIGO group.[10]

research agenda would be to include acute and chronic cardiovascular events as outcomes in studies focused on AKI and to develop such models for external validation.

In the patient who already has established AKI, stage-based management of CRS type 3 has been proposed.[56] These are summarized in Figure 3. It is important to establish a diagnosis as soon as possible. Context-specific biomarkers (for example, brain NP and NT-pro-brain NP for HF; bilirubin and hepatic enzymes for hepatic failure; procalcitonin, endotoxin activity assay, and cultures for sepsis; and imaging and other studies [eg, urine sediment]) should be used to accurately establish the etiology of AKI. Moreover, it is important to search for reversible hemodynamic components and potential direct nephrotoxins. In milder stages of AKI (eg, AKIN Stage 1, RIFLE Risk), a noninvasive workup may be adequate. However, in more severe AKI, more invasive evaluation, including kidney biopsy, may be indicated. The previously described renoprotective measures (Table 2) should continue to be implemented in the AKI patient. In a prospective controlled nonrandomized intervention study, these relatively simple measures, recommended during the course of a prompt one-time nephrology consult within 18 hours of fulfilling AKI criteria, was associated with a lower peak sCr.[98] However, there were no cardiac endpoints described in this study. Electrolyte abnormalities, such as hypokalemia, hyopmagnesemia, and dysnatremias, are frequently encountered during diuretic therapy[36] and should be closely monitored.

The most common pathophysiology of acute cardiac decompensation in AKI is sodium and water retention. Hence, in AKI, a prompt aggressive avoidance of hypervolemia may avoid cardiac decompensation.[99,100] Moreover, uremic changes and acid-base and electrolyte abnormalities (such as metabolic acidosis) exhibit adverse consequences on cardiac contractility and its responsiveness to catecholamines. Electrolyte disturbances, such as hyperkalemia and hypokalemia, should be corrected to prevent arrhythmias with undesirable hemodynamic effects. Correction of the abnormal milieu in AKI with timely and appropriate interventions, including renal support therapy, may avert these complications.[101]

Conclusions

In summary, CRS is a complex and multidimensional entity that is commonly encountered in clinical practice but has a significant effect on morbidity and mortality. It is classified into five subtypes based on the primary organ dysfunction, whether heart ("cardiorenal" syndromes) or kidney ("renocardiac" syndromes) and on whether the organ dysfunction is acute or chronic. Of particular interest to the critical care specialist are CRS type 1 (acute CRS) and type 3 (acute renocardiac syndrome). Both subtypes are encountered in high-acuity medical units; in particular, CRS type 1 is commonly seen in the coronary care unit and cardiothoracic ICU. Preventive strategies in general for all patients with CKD and cardiac diseases, including HF and especially those in high-risk patients, will help decrease the incidence of acute deterioration of organ function. The management of these acute CRS subtypes is challenging because of the multitude and complexity of pathophysiological interactions between heart and kidney. Although standard evidence-based guidelines currently exist for management of AHF, ACS, and AKI, at present there are no clear recommendations for the management of CRS types 1 and 3.

Addendum: The CARRESS-HF study has been published.[103] The use of a stepped pharmacologic-therapy algorithm was superior to a strategy of ultrafiltration for the preservation of renal function at 96 hours, with a similar amount of weight loss with the two approaches. Ultrafiltration was associated with a higher rate of adverse events.

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Perioperative Acute Kidney Injury

Charuhas V. Thakar

The incidence of acute kidney injury (AKI) is generally 5-7.5% in all acute care hospitalizations and accounts for up to 20% of admissions to intensive care units (ICUs). Of all of the cases of AKI during hospitalization, approximately 30-40% are observed in operative settings. AKI is a serious morbidity that is associated with greater length of hospital stay, high risk of hospital mortality, and increased risk of incident and progressive chronic kidney disease. The incidence of AKI is variable depending on the specific surgical setting under consideration. Much of our knowledge regarding the epidemiology of AKI is derived from studies related to cardiac or vascular surgery. With limited treatment options, prevention of AKI and amelioration of its severity remain important cornerstones of improving patient outcomes. The magnitude of the problem and the unique set of patient characteristics calls for a multidisciplinary approach for the perioperative management of renal complications. The purpose of the review presented here is to discuss the current knowledge regarding the epidemiology and risk factors, outcomes, diagnoses, and prevention and treatment of AKI during the perioperative period in cardiovascular and noncardiovascular surgical settings.

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Key Words: Acute kidney injury, Major surgery

Introduction

Acute kidney injury (AKI) is a serious morbidity occurring during acute care hospitalizations that is associated with greater length of hospital stay and a high risk of death during hospitalization.[1-3] AKI during hospitalization also increases the risk of incident and progressive CKD and is associated with poor long-term survival.[4] The recent Kidney Disease: Improving Global Outcomes (KDIGO; www.kdigo.org) clinical practice guidelines for AKI have adopted the Acute Kidney Injury Network criteria to define AKI and classify it based on severity of injury.[5,6] According to these criteria, AKI is present when an abrupt (over 48 hours) reduction in kidney function results in an absolute increase in serum creatinine of more than or equal to 0.3 mg/dL, a percentage increase in serum creatinine of more than or equal to 50% (1.5-fold increase from baseline), or a reduction in urine output (oliguria of $<$0.5 mL/kg per hour for $>$6 hours). AKI is further classified into three stages (arbitrarily) based on the severity of kidney injury (Table 1), as indicated by either the degree of rise of serum creatinine or loss of urine output.

The incidence of AKI is generally 5-7.5% in all acute care hospitalizations, but it accounts for up to 20% of admissions to intensive care units (ICUs). Of all of the cases of AKI during hospitalization, approximately 30-40% are observed in operative settings.[2,3] The incidence of AKI is variable depending on the specific surgical setting under consideration (Fig 1). Much of our knowledge regarding the epidemiology of AKI is derived from studies related to cardiac or vascular surgery.

With limited treatment options, prevention of AKI and amelioration of its severity remain important cornerstones of improving patient outcomes. The purpose of the present review is to discuss the current knowledge regarding the epidemiology and risk factors, outcomes, diagnoses, and prevention and treatment of AKI during the perioperative period in cardiovascular and noncardiovascular surgical settings.

Cardiovascular Surgery

Incidence

When defined as a requirement of dialysis during the postoperative period (Stage III AKI), the incidence of AKI after cardiac surgery is less than 5%.[7-9] As expected, the incidence of milder degrees of kidney injury (Stage I or II AKI) is higher (10-20%).[10-12] In the setting of cardiac transplantation, the incidence of severe AKI requiring dialysis can be 3-fold higher than nontransplant cardiac surgery.[13-15] The incidence of AKI after abdominal aortic aneurysm (AAA) repair depends on the surgical technique and the anatomical location of the aneurysm. When defined as moderate-to-severe AKI, which occurs in 10-15% of patients undergoing open AAA repair, the incidence is slightly lower in those undergoing endovascular repair.[16] In contrast, the overall incidence of AKI in thoracic aortic aneurysm surgery is as high as 25%, with up to 8% of the incidences of AKI requiring dialysis.[17,18]

Risk Factors

Preoperative Risk Factors

Several studies have identified risk factors of AKI after cardiac surgery.[10,19-22] The risk is influenced by demographic factors, comorbid conditions, and type of surgical procedure. As shown in Table 2, demographic characteristics such as female gender and older age are

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independent risk factors of AKI. Insulin-requiring diabetes, peripheral vascular disease, congestive heart failure, and chronic obstructive pulmonary disease (COPD) are some of the comorbid diseases that are consistently associated with postoperative AKI. A preoperative level of kidney function is one of the most important determinants of postoperative AKI after cardiac surgery. The method of assessment of preoperative kidney function may influence the magnitude of the association; nevertheless, the qualitative relationship between preoperative kidney function and postoperative AKI remains the same. Presence of proteinuria during preoperative assessment can further stratify the risk of postoperative AKI at different levels of baseline kidney function.[23] Additionally, a recent post hoc analysis of the Atrial Fibrillation and Renin Angiotensin Aldosterone System study, demonstrated an association between body mass index (BMI) and postoperative AKI. The authors hypothesize that this risk is, in part, mediated by F(2)-isoprostane levels.[24] Certain risk factors of AKI are unique to the cardiac surgical setting and are outlined in Table 2.

Preoperative risk factors for AKI after cardiac transplantation are subtly different than nontransplant settings. A large cohort of over 750 cardiac transplants indicated that insulin-requiring diabetes, preoperative kidney dysfunction, and a longer cold-ischemia time of the solid organ were associated with an increased risk of AKI whereas a higher level of preoperative albumin was associated with a lower risk of postoperative AKI requiring dialysis.[13,15,25]

CLINICAL SUMMARY

- One in three cases of AKI occur in perioperative settings.
- Incidence and risk factors, some modifiable, are unique to each surgical setting.
- A multidisciplinary care approach holds promise to improve patient outcomes.

Intraoperative Risk Factors

Intraoperative factors are difficult to quantify in observational studies and may serve as a surrogate for other immeasurable events during the surgical procedure. In cardiac surgery, intraoperative risk factors for postoperative AKI include use of an intra-aortic balloon pump, hypothermic circulatory arrest, low-output syndrome, vasopressor requirement during cardiopulmonary bypass, and the number of blood transfusions during surgery.[26] One candidate risk factor that is consistently linked with AKI is the exposure to a cardiopulmonary bypass (CPB) circuit along with its duration. In patients undergoing on-pump surgery, the risk of AKI increases with duration on a bypass machine. Although the causal association is not entirely clear, exposure to a CPB circuit promotes a proinflammatory state that may lead to ischemic tissue injury.[27] Additionally, evidence also suggests that lack of pulsatile blood flow can impair kidney perfusion despite relative preservation of mean arterial pressure.[27,28] Thus, reducing the duration of exposure, or performing off-pump bypass surgery, can be viewed as a potentially modifiable risk factor for AKI.

Several observational and randomized studies have compared kidney outcomes in patients undergoing on-pump versus off-pump procedures. A systematic review and meta-analysis by Nigewkar and colleagues included 22 studies (27,806 patients) that have reported kidney outcomes comparing exposure to CPB.[29] Overall, off-pump surgery was associated with a 43% reduction in the risk of postoperative AKI compared with on-pump surgery (odds ratio: 0.57, 95% confidence interval [CI], 0.43-0.76). The authors caution that the definitions of AKI were variable and that the randomized controlled studies were relatively smaller with low event rates. In a more recent cohort from the Society of Thoracic Surgeons' registry, Chawla and colleagues demonstrated that off-pump surgery was associated with a lower risk of in-hospital death or renal replacement therapy in a propensity-matched comparison stratified by preoperative kidney function.[30] The authors indicate that patients with lower preoperative kidney function may stand to benefit more. Although prospective studies are warranted to reach a conclusive recommendation, it is reasonable to propose that given a high-risk preoperative profile for AKI, if feasible, off-pump surgery could be considered as a potentially modifiable risk factor of AKI.

The use of aprotinin during cardiopulmonary bypass and the associated risk of AKI remains a topic of controversy. It is a potent and effective antifibrinolytic that was used primarily in complex cardiac surgery as an adjunct to decrease postoperative bleeding and complications. After a large retrospective and a randomized controlled trial indicating an increased risk of AKI and mortality, the use of aprotinin was banned in 2008.[31,32] More recently, a re-evaluation of the literature has resulted in the lifting of this ban by Health Canada (as of February 2012) and the European Medicines Agency. It was determined that the risk profile of the drug was favorable when used appropriately ("on label" indication of coronary artery bypass graft surgery) and with necessary warnings. Whether the drug will ever be marketed in the United States remains unclear at this point.

Intraoperative factors during vascular surgery, including repair of AAA, indicate that duration of renal ischemia (clamp time) and intraoperative hypotension are two primary determinants of postoperative AKI in this setting. Additionally, newer techniques, such as endovascular aneurysm repair, may be associated with a lower risk of AKI than an open surgical approach.[16]

Table 1. Stages of Severity of AKI According to Acute Kidney Injury Network Criteria[5]

Stage	Change in Serum Cr	UOP
I	Increased Cr 0.3 mg/dL or 1.5- to 2.0-fold of baseline.	UOP < 0.5 mL/kg/h for >6 h
II	Cr increase of >2- to 3-fold of baseline.	UOP < 0.5 mL/kg/h for > 12 h
III	Cr increase >3-fold of baseline (or Cr > 4 mg/dL with 0.5 mg/dL acute increase). AKI requiring dialysis.	UOP < 0.3 mL/kg/h for 24 h or anuria for 12 h

Abbreviations: Cr, creatinine; UOP, urine output.

Models of Risk Stratification

Accurate assessment of the risk of AKI allows for an informed decision-making process for the healthcare provider and the patient. The predictive tools can also be used to compare outcomes across healthcare systems. Most importantly, identification of high-risk patients provides an opportunity to optimize preoperative care and potentially modify outcomes. Furthermore, predicting AKI in this setting offers the promise to discover and validate novel strategies for diagnosis and therapeutic interventions early in the course of kidney injury.

Chertow and colleagues were among the first to develop a preoperative kidney risk stratification algorithm to predict postoperative dialysis requirement in a Veterans Affairs coronary artery surgery study cohort.[19] Subsequently, improved methodology and refinements in characterizing preoperative risk factors have led to the development of several scoring systems used to predict postoperative AKI.[20,33-39] Three such scoring systems (Cleveland Clinic Foundation, Society of Thoracic Surgeons, and Simplified Renal Index)[33,34,36] have been externally validated in other cohorts. Engelberger and colleagues[38] reported that the accuracy of prediction (as measured by the area under the receiver operator characteristics curve) of these scoring systems in an independent cohort to predict Stage II or III AKI was 0.81, 0.76, and 0.75 for the Cleveland Clinic Foundation, Society of Thoracic Surgeons, and Simplified Renal Index scores, respectively (Fig 2). Such tools have improved the clinicians' ability to provide rapid bedside assessment of postoperative risk of developing AKI.

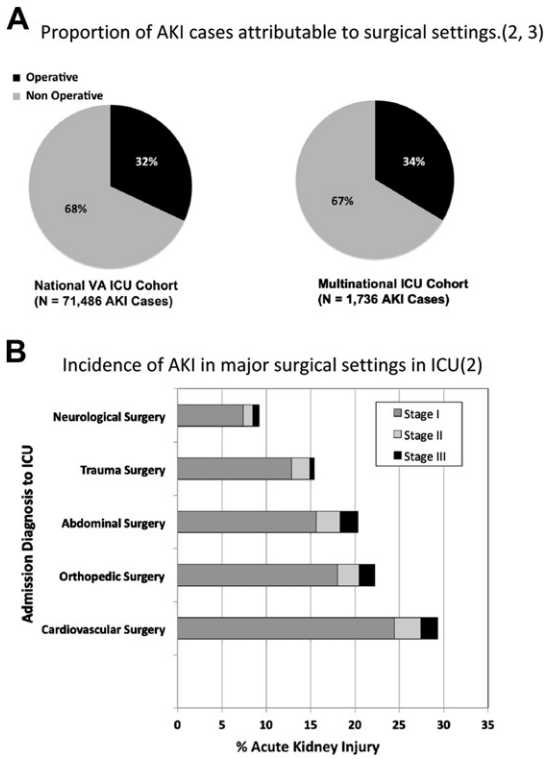

Figure 1. Incidence and severity of AKI in critically ill patients in surgical settings: (A) proportion of AKI cases attributable to surgical settings,[2,3] and (B) incidence of AKI in major surgical settings in ICU.[2]

Noncardiovascular Surgery

Incidence

Noncardiovascular surgical settings have been less extensively studied compared with cardiovascular surgery. When studied in patients undergoing noncardiac surgery with normal preoperative kidney function, the incidence of postoperative AKI was less than 1%,[39] with AKI defined as an absolute level of estimated glomerular filtration rate (GFR) less than 50 mL/min during the postoperative period (representing a 40% reduction from preoperative levels). Gastric bypass surgery for morbid obesity, an increasingly common procedure in the United States, is associated with an 8.5% incidence of postoperative AKI, defined as either a 50% increase in serum creatinine or dialysis requirement.[40] Similar to cardiac transplantation, the incidence of AKI is also high in other nonrenal solid organ transplant settings. For example, 1 in 3 patients undergoing liver transplantation can experience postoperative AKI, and frequency of severe AKI requiring dialysis can be as high as 17%.[41-44] The cause of AKI after liver transplantation differs with timing of onset: prerenal azotemia and acute tubular necrosis were the leading causes in the first postoperative week, whereas sepsis and calcineurin inhibitor toxicity were the leading causes in postoperative weeks 2-4 after liver transplantation.[41]

Risk Factors

Preoperative Risk Factors

In noncardiovascular surgery, a different set of risk factors for AKI have been identified. For example, patients

Table 2. Preoperative and Intraoperative Risk Factors of AKI After Cardiac Surgery

Preoperative Risk Factors	Intraoperative Risk Factors
Demographic: Age, gender Comorbid conditions: Diabetes, COPD, PVD, obesity Cardiac specific: CHF, IABP use, LV function < 40%, prior cardiac surgery, emergency surgery, left main disease > 70%. Biochemical assessment: Renal function, glucose levels, proteinuria	Type of procedure: Valve surgery, CABG + valve, on-pump vs. off-pump Intraoperative events: Bypass time, crossclamp time, hypotension, vasopressor use, blood transfusion requirements, aprotinin

Abbreviations: CABG, coronary artery bypass grafting; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; IABP, intra-aortic balloon pump; LV, left ventricular; PVD, peripheral vascular disease.

undergoing gastric bypass surgery present a unique comorbidity profile, including high BMI and high prevalence of diabetes, hypertension, hyperlipidemia, and osteoarthritis, and they are commonly exposed to drugs such as angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), diuretics, and nonsteroidal anti-inflammatory agents. In a single-center study that examined over 300 gastric bypass surgeries, risk factors associated with postoperative AKI included higher BMI, hyperlipidemia, and preoperative use of ACEI/ARB agents.[40]

Similar to cardiac surgical settings, Kheterpal and colleagues have developed a preoperative renal-risk index in noncardiovascular surgeries. The following were identified as independent risk factors for postoperative AKI: older age, emergency surgery, liver disease, high BMI, high-risk surgery, peripheral vascular disease, and COPD.[39] Higher risk scores were associated with a greater frequency of AKI, which ranged between 0.3 and 4.5% depending on the risk category (Table 3).

In liver transplantation, risk factors of AKI can be different depending on the timing of onset of AKI during the postoperative period: serum albumin less than 3.2 g/dL, preoperative renal dysfunction, dopamine use, and graft dysfunction are associated with early AKI (within 1 week of surgery) whereas bacterial infection/sepsis are associated with late-onset AKI (2-4 weeks after surgery).[41,42]

Risk Factor	Score
Female	1
CHF	1
LVEF < 35%	1
Pre-op IABP	2
COPD	1
IDDM	1
Prior Surgery	1
Emergency surgery	2
Surgery Type:	
Valve only	1
CABG + Valve	2
Other	2
Pre-op Creatinine:	
1.2 to < 2.1 mg/dl	2
2.1 mg/dl or greater	5

Score Group	AKI Dialysis
0 - 2	0.4%
3 - 5	2%
6 - 8	8%
9 - 13	21%

Outcome	ROC value
CCF Score	
AKI – Dialysis	0.82
External Validation of CCF Score	
AKI Dialysis	0.86
Stage II or III AKI	0.81

ROC – receiver operating characteristics
CCF – Cleveland Clinic Foundation score

Figure 2. Clinical Score to Predict AKI requiring Dialysis (AKI-D) after Cardiac Surgery.[36,38]

Intraoperative Risk Factors

Incorporating the effect of intraoperative risk factors contributes to improving the accuracy of predictive models. For example, the area under the curve of a risk index improved from 0.77 to 0.79 after incorporating the effect of intraoperative risk factors such as use of a vasopressor infusion, number of vasopressor bolus doses administered, and the administration of furosemide or mannitol.[39]

Postoperative Assessment and Outcomes

Postoperative AKI and Other Organ Dysfunction

Events during the immediate postoperative period also influence kidney function. The literature in this regard is more difficult to interpret because of a lack of clear temporality between nonrenal events and AKI. In cardiac surgery, Slogoff and colleagues reported that postoperative myocardial infarction, postoperative blood loss or transfusions, and the need for emergent re-operation were associated with new kidney dysfunction.[26] In the setting of cardiac transplant, Boyle and colleagues found that most cases (60%) of AKI requiring dialysis were preceded by other nonrenal serious complications such as sepsis or cardiac failure.[15] In liver transplant settings, liver graft dysfunction, surgical re-operation, and postoperative infection were significantly associated with AKI.[41] Regardless of the unclear cause-and-effect

Table 3. Incidence and Risk Factors of AKI After Noncardiovascular Surgery[39]

Risk Factors	Risk Category	AKI Frequency
Age > 59 y	Class I (0 risk factors)	0.3%
BMI > 32	Class II (1 risk factor)	0.5%
Emergency surgery	Class III (2 risk factors)	1.3%
High-risk surgery	Class IV (≥3 risk factors)	4.3%
Peripheral vascular disease		
COPD		
Liver disease		

relationship between AKI and other nonrenal complications during the postoperative period, it is well recognized that the number of organ system failures directly correlates with increased risk of mortality. Hence, patients who suffer from AKI and other nonrenal complications may need more intensive perioperative monitoring.

Short- and Long-Term Outcomes

Although the overall mortality rates after major surgery are low (2-5%), the crude mortality rates among patients who develop AKI can be as high as 50-60%, accounting for half of the overall deaths during hospitalization. In the long term, AKI remains a "triple threat" and is associated with increased risk of re-admissions,[45] a greater risk of incident and progressive CKD,[44,46] and poor long-term survival.[47,48] Thus, AKI can be viewed as a distinct therapeutic target in which its prevention and/or treatment is expected to offer a survival benefit. Table 4 summarizes key elements in the natural history of AKI's various surgical settings and its prognostic significance.

There have been improvements in hospital mortality associated with postoperative AKI over time. In a large cardiac surgery cohort, although the incidence of postoperative AKI increased, mortality in AKI showed a 20-40% reduction over a 10-year period.[49] It can be speculated that changes in the practice and technology of dialysis over the past decade may have contributed to these trends, along with improvements in the delivery of postoperative care in surgical ICUs. However, such factors are very difficult to quantify in a retrospective study design.[39]

The magnitude of the problem and the unique set of patient characteristics call for a multidisciplinary approach for the perioperative management of kidney complications. A coordinated care model (Fig 3) with participation from nephrologists, anesthesiologists/critical care specialists, surgeons, and internists/hospitalists is necessary to achieve the desired change in improving patient outcomes. Such interdisciplinary teams are also necessary to conduct clinical trials that can translate novel strategies of AKI diagnosis and treatment into clinical practice.

Early Diagnosis of Postoperative AKI—Role of Novel Biomarkers

Lack of reliable methods of early diagnosis of AKI and the ensuing treatment are the major impediments in translating successful therapies from bench to bedside. Although serum creatinine remains the gold standard to diagnose AKI, there is increasing interest in the discovery and validation of sensitive and tissue-specific biomarkers of early phases of AKI.[50,51] Interleukin-18 and neutrophil gelatinase-associated lipocalin are two such biomarkers that have been tested in clinical settings, including cardiac surgery. Evidence suggests that these are promising biomarkers (measurable in urine and serum) for rapid and early detection of kidney injury among cardiac surgery patients.[52-54] Neutrophil gelatinase-associated lipocalin and interleukin-18 levels in urine increase between 2 and 10 hours after cardiopulmonary bypass in those patients who go on to develop AKI at 48 hours; recent multicenter studies in adult and pediatric cardiac surgery patients indicate modest accuracy of these markers to predict postoperative AKI (area under the receiver operator characteristic curve values ranging between 0.70 and 0.79).[55,56] Cystatin C is another marker that has been studied in acute care settings, including cardiac surgery.[57-60] This substance, measured in serum, provides a more precise measurement of GFR than serum creatinine. Elevation of cystatin C in response to a sudden decline in GFR is more rapid than the kinetics of serum creatinine, and this may allow for earlier determination of AKI. As of 2012, there are several ongoing studies to validate biomarkers of AKI to enable their assessment in a rapid, reproducible, and cost-effective manner. It is envisioned that along with clinical risk assessment, reliable and valid biomarkers could facilitate interventions earlier in the course of kidney injury, which may improve patient outcomes in perioperative AKI.

Prevention and Treatment of AKI

Several agents have been tested in clinical trials to examine their effect on AKI after cardiovascular and other major surgeries. This section will focus on the major classes of therapeutic agents and highlight the commonly tested/promising agents in major surgical settings.

Table 4. Key Elements in the Natural History of AKI: Prognostic Significance

AKI Natural History	Setting	Short-Term Outcome	Long-Term Outcome
Timing of onset	Surgical ICU, sepsis	Hospital mortality	Not studied
Severity of injury	Cardiac surgery, bariatric surgery, vascular surgery, nonrenal solid organ transplant	Hospital mortality, 30-d re-admissions	Incident and progressive CKD, end-stage renal disease, survival
Duration of injury	Major surgery	Not studied	Survival
Transient injury	Vascular surgery	Hospital mortality	Survival

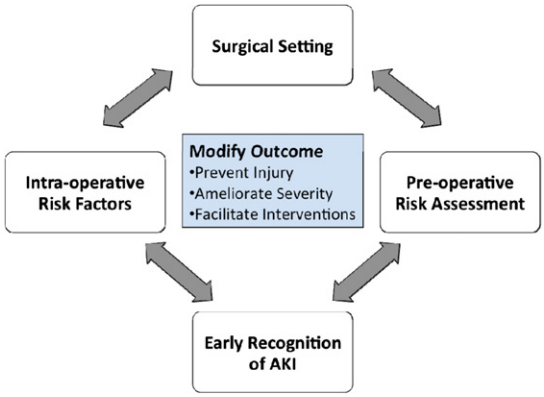

Figure 3. Perioperative AKI: A conceptual model of care.

Vasoactive Agents and Diuretics

Multiple vasoactive agents such as dopamine,[61,62] fenoldopam,[63] or theophylline[64] have been studied in the treatment of postoperative AKI, but they have failed to demonstrate any conclusive benefits in ameliorating kidney injury. In contrast, infusion of recombinant human atrial natriuretic peptide (ANP) was associated with reduced probability for dialysis and improved dialysis-free survival in patients who underwent cardiac surgery and experienced postoperative cardiogenic shock.[65] Natriuretic peptides have also been used in treatment of AKI in the setting of solid organ transplants. Nigwekar and colleagues (American Society of Nephrology, 2009, Abstract) performed a systematic review and meta-analysis of 7 such randomized controlled trials (3 liver transplantation trials, 3 kidney transplantation trials, and 1 heart transplantation trial) involving 238 participants. Pooled analysis showed a reduction in AKI requiring dialysis in the natriuretic peptide group (risk ratio: 0.60, 95% CI 0.37-0.98) as well as a reduction in the duration of dialysis requirement (–44.0 hours, 95% CI –60.5 to –27.5 hours). Studies thus far suggest that ANP may have a role in modifying the risk of AKI given the right set of perioperative risk factors and timing and dose of administration. However, individual clinical trials in cardiac and nonrenal organ transplant settings have been small and underpowered. The recent clinical practice guidelines for AKI (www.KDIGO.org) concluded (2B/2C recommendation) that given the potential harm of hypotension and the quality of the positive studies, the overall recommendation is not to routinely use ANP in the prevention or treatment of AKI.

ACEI/ARB agents are commonly prescribed for comorbid conditions such as hypertension, cardiac failure, or diabetic nephropathy and may have adverse effects on kidney function during the perioperative period. Thakar and colleagues showed that in patients undergoing gastric bypass surgery, preoperative use of ACEIs/ARBs was associated with a 2-fold increase in the risk of postoperative AKI.[40] The association between preoperative use of ACEIs/ARBs and postoperative AKI in cardiac surgery is less clear. Arora and colleagues showed that preoperative ACEI/ARB use was associated with a 27% greater risk of postoperative AKI[66]; in contrast, Benedetto and colleagues showed that the incidence of AKI was lower in those receiving preoperative ACEI/ARB agents (6.4% vs. 12.2%, $P < 0.001$).[67] Clearly, these retrospective studies do not conclusively provide any specific therapeutic recommendations. However, after studying the patient characteristics in each of these studies, it can be speculated that except in patients with reduced ejection fraction in which ACEI/ARB use is indicated during acute care, temporarily withholding these agents in the short term may offer renoprotection.

Diuretic use, with a rationale that it may reduce oxygen consumption and prevent intratubular obstruction, has also been a matter of controversy in AKI treatment. In the setting of cardiac surgery, a double-blind randomized controlled trial ($n = 126$) demonstrated that use of furosemide was associated with a higher rate AKI.[68] Similar results have been confirmed by other studies, suggesting that diuretic use, as an intervention to treat postoperative AKI, should be avoided.[69]

Cytoprotective Therapy

Proinflammatory cytokines have been extensively studied as mediators of ischemia-reperfusion injury in experimental models of AKI. Their role in the cardiac surgery setting is of particular interest because of the stimulation of inflammatory mediators upon exposure to an extracorporeal circuit. However, clinical trials of cytoprotective therapy have been less than promising in reducing the risk of AKI after cardiac surgery.

Steroids and *N*-acetylcysteine (NAC) have been examined in cardiac surgery patients without any conclusive benefits. With over 10 randomized trials examining NAC use in cardiac surgery, neither the individual trials nor a recent meta-analysis showed any benefits for using NAC to reduce the risk of postoperative AKI.[70-74]

Intensive glucose control achieved by insulin infusion has been extensively studied in surgical settings. A post hoc analysis of randomized studies indicated that the risk of AKI was lower in patients who had tighter blood sugar control in perioperative settings, including cardiothoracic surgery.[75,76] Whether glucose control modifies outcome in AKI remains to be examined.

Few retrospective studies have examined the role of HMG-CoA reductase inhibitors (statins) as a treatment of postoperative AKI. In one cardiac surgery study ($N = 3000$) preoperative use of statins was associated with a 40% reduction in the risk of postoperative AKI requiring dialysis in patients undergoing coronary artery bypass, but this benefit was not found in higher risk surgical procedures such as valve surgery.[77] In contrast, in another cardiac surgical cohort ($N = 10,000$) statin use

did not significantly alter the risk of postcardiac surgery AKI.[78] In a vascular surgery setting, statin use did not show any difference in risk of AKI, but it was associated with a greater likelihood of renal recovery once AKI ensued.[79] A more recent population-based study examining over 200,000 major surgical procedures in Canada reported a 16% lower risk of postoperative AKI associated with statin use.[80] Similar to the experience in ACEI/ARB use, a therapeutic recommendation regarding statin therapy for AKI cannot be made because of a lack of prospective studies.

Studies have also evaluated the role of intravenous bicarbonate infusion, along with ascorbic acid treatment, on the risk of postoperative AKI after cardiac surgery. The results remain inconclusive regarding the clear benefits of these therapies in reducing the risk of AKI.[81]

Extracorporeal Therapies

Dialysis support is indicated for the treatment of metabolic complications such as acidosis, hyperkalemia, and hypervolemia, which may otherwise be associated with poor outcomes. Optimal timing of initiation is unclear, and for now this remains a subjective clinical decision. Liu and colleagues indicated that in the PICARD registry, patients who were started on dialysis in the ICU at lower predialysis urea levels (used as a surrogate for early initiation) had better survival.[82]

Continuous renal replacement therapy (CRRT) is used intraoperatively during liver transplantation. Townsend and colleagues recently reported their experience with intraoperative CRRT in orthotopic liver transplantation.[83] CRRT was used in 6.4% of liver transplant recipients and was initiated for standard indications such as azotemia, hyperkalemia, acidosis, and hypervolemia in addition to indications unique to liver transplantation such as need for significant transfusion, lactic acidosis, hypernatremia, and hyponatremia. Most cases were on CRRT for more than 50% of the operative time. Given the fluid, electrolyte, and acid/base abnormalities associated with liver transplantation, CRRT can be a potentially useful tool in effective intraoperative management in these patients, but prospective studies are lacking.

Conclusion

In summary, 1 in 3 cases of AKI in the hospital occur in perioperative settings. Sufficient information exists to indicate that incidence and risk factors (some modifiable) of AKI are unique to specific surgical settings. Several key elements in the natural history of AKI offer important prognostic information to the patients and providers alike and may be viewed as viable therapeutic targets. Rapid advances in the field of biomarkers and novel therapies offer hope that timely intervention may modify patient outcomes. Although there are no "silver bullets" that can prevent or treat AKI, a concerted multidisciplinary effort is needed to optimize perioperative management to improve patient outcomes.

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Renal Replacement Therapy in Acute Kidney Injury

Paul M. Palevsky

Although the use of renal replacement therapy (RRT) to support critically ill patients with acute kidney injury (AKI) has become routine, many of the fundamental questions regarding optimal management of RRT remain. This review summarizes current evidence regarding the timing of initiation of RRT, the selection of the specific modality of RRT, and prescription of the intensity of therapy. Although absolute indications for initiating RRT—such as hyperkalemia and overt uremic symptoms—are well recognized, the optimal timing of therapy in patients without these indications continues to be a subject of debate. There does not appear to be a difference in either mortality or recovery of kidney function associated with the various modalities of RRT. Finally, providing higher doses of RRT is not associated with improved clinical outcomes.

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Key Words: Acute kidney injury, Hemodialysis, Hemofiltration, Continuous renal replacement therapy, Critical illness

Acute kidney injury (AKI) is 1 of the most common serious complications in critically ill patients. Severe AKI occurs in more than 1 of every 20 patients requiring intensive care unit (ICU) care[1] and has been associated with mortality rates ranging from 50% to more than 70%.[1-4] In the absence of any effective pharmacologic therapies for AKI, its management remains supportive, focused on optimizing fluid balance, maintaining nutrition, preventing or treating electrolyte and acid-base disturbances, adjusting the dosing of medications that are excreted by the kidney, and avoiding secondary hemodynamic and nephrotoxic renal injury. Although these conservative therapies provide the initial underpinning of AKI management, renal replacement therapy (RRT) using 1 or more of the multiple modalities of dialysis and hemofiltration is often required. This review summarizes current evidence regarding the timing of the initiation of RRT, the selection of the specific modality of RRT, and the prescription of intensity of therapy.

Timing of the Initiation of Renal Replacement Therapy

The issue of when to initiate RRT in patients with AKI has been debated nearly as long as hemodialysis has been part of the armamentarium of clinical medicine. In 1960, in their seminal article on prophylactic dialysis in acute kidney injury, Paul Teschan and colleagues wrote:

> "While there is increasing recognition of the value of earlier dialysis, the *published* consensus, and the practice in many centers at present, is still to apply dialysis to relatively ill rather than to relatively healthy patients. This is implied by the usually quoted indications for dialysis, namely, definite or progressive clinical uremic illness and/or progressive potassium intoxication, occurring despite careful suppressive therapy."[5]

Emergent initiation of RRT in AKI in response to these standard indications—volume overload unresponsive to diuretic therapy; electrolyte and acid-base disturbances refractory to medical management, particularly severe hyperkalemia and metabolic acidosis; and overt uremic manifestations, such as pericarditis and encephalopathy—can be characterized as "rescue" therapy, in which initiation of treatment forestalls imminent death. More commonly, however, current practice is to initiate RRT pre-emptively, well before the development of these advanced complications, in patients with severe AKI in whom imminent recovery of kidney function is unlikely. The conundrum regarding the optimal timing for initiation of renal support in AKI derives in large part from uncertainty in predicting if and when kidney function will recover. In the absence of robust predictive markers, initiating therapy earlier increases the probability of exposing patients who might uneventfully recover kidney function if managed conservatively to the potential risks of RRT.

This tension between benefits of earlier treatment and risks of unnecessary treatment has been central to the long-standing debate over the timing of therapy. In 1960, Teschan and colleagues opined:

> "We would urge that dialyses applied to patients who might otherwise survive should not under any circumstances be considered to be superfluous. Rather, the judgment of whether to undertake dialysis should also be made in view of the possible risks of *not* employing this procedure. We would question both the wisdom and the safety of subjecting patients to several days of avoidable nausea, vomiting, drowsiness and thirst, which not only implies significant discomfort to the patient but may also impose considerable risk of aspiration, pneumonia and other unexpected 'complications.'"[5]

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One of the primary factors that has changed over the ensuing half-century is our concept of what constitutes "early" as opposed to "late" therapy. At the time that Teschan and colleagues were pioneering the use of prophylactic dialysis, conventional management was to wait until severe uremic symptoms were present.[5,6] In contrast, as the technology for RRT has become safer and treatment has become more routine, practices that in previous decades would have been considered "early" therapy are now considered to represent the "late" initiation of RRT. Despite increased safety, RRT remains associated with numerous risks—including catheter-related complications from insertion and infection; mechanical complications associated with the extracorporeal circuit, including the risk of severe blood loss; electrolyte disturbances and hemodynamic compromise associated with fluid and electrolyte shifts during treatment; and activation of humoral and cellular mediators from exposure to the extracorporeal circuit.[7-9] Exposure of blood to bioincompatible surfaces in the extracorporeal circuit and recurrent episodes of dialysis-associated hypotension have been postulated to delay recovery of kidney function.[7,9–12] In addition, consideration must also be given to the financial implications of the earlier initiation of treatment.

CLINICAL SUMMARY

- The optimal indications and timing of initiation of renal replacement therapy in critically ill patients with acute kidney injury is not known.
- There is no evidence that any single modality of renal replacement therapy is associated with improved survival or recovery of kidney function, although slower modalities (e.g., CRRT, PIRRT) may be better tolerated in hemodynamically unstable patients and may permit achievement of more negative fluid balance.
- Augmented doses of renal replacement therapy in critically ill patients with acute kidney injury are not associated with improved outcomes.

Although numerous studies over more than a half century have attempted to resolve the issue of optimal timing, the level of evidence guiding current practice remains weak, derived primarily from retrospective and observational cohort studies and small underpowered prospective trials. A series of observational studies published in the 1960s and early 1970s compared outcomes of patients with AKI who were treated in the years immediately before and after adoption of strategies using prophylactic initiation of dialysis.[13-15] In each series, during the earlier periods when dialysis was initiated "late" (blood urea nitrogen [BUN] levels >163-200 mg/dL), mortality rates were higher than subsequently when dialysis was started earlier (BUN levels <93-150 mg/dL).[13-15] Subsequently, 2 small prospective studies compared more intensive strategies of dialysis management, with earlier initiation of therapy, to more "conventional" management.[16,17] In the first study, 18 patients with post-traumatic AKI were assigned to either a more intensive regimen that maintained the predialysis BUN level at <70 mg/dL and the serum creatinine at <5 mg/dL or to a less intensive strategy in which dialysis was not performed until the BUN level approached 150 mg/dL, the serum creatinine level reached 10 mg/dL, or other indications for dialysis were present.[16] Five of 8 patients (64%) assigned to the more intensive regimen survived compared with 2 of 10 patients (20%) assigned to the less intensive strategy ($P = .14$). Major complications, including hemorrhage and sepsis, were also less frequent with earlier and more intensive dialysis. In the subsequent study, 34 patients with severe AKI were randomized in a paired fashion when their serum creatinine reached 8 mg/dL to either an intensive regimen, designed to maintain the predialysis BUN level at <60 mg/dL and the serum creatinine at <5 mg/dL, or to a delayed and less intensive regimen, in which the BUN value was allowed to reach 100 mg/dL and the serum creatinine reached 9 mg/dL.[17] The mean time from onset of AKI to initiation of dialysis was 2 days shorter (5 ± 2 days vs 7 ± 3 days) in the more intensive regimen. Mortality was slightly higher with the earlier and more intensive therapy (58.8% vs 47.1%); however this difference did not reach statistical significance ($P = .73$). On the basis of these data, conventional teaching was that in the absence of specific metabolic indications or symptoms, dialysis should be initiated when the BUN value approached a level of approximately 100 mg/dL but that no benefit was associated with earlier initiation of therapy.

The topic of timing of therapy then remained quiescent until the late 1990s, when Gettings and colleagues published a retrospective analysis of the timing for the initiation of continuous renal replacement therapy (CRRT) in 100 consecutive patients with post-traumatic AKI.[18] They observed that 39.0% of patients who were started on CRRT when their BUN level was <60 mg/dL (mean BUN level, 42.6 ± 12.9 mg/dL) survived compared with 20.3% of patients in whom CRRT was not begun until their BUN level was >60 mg/dL (mean BUN level, 94.5 ± 28.3 mg/dL; $P = .041$). Although this was not a randomized study, demographic factors and severity of illness at admission were comparable in the 2 groups, although rhabdomyolysis was more common in the early-initiation group and multisystem organ failure was seen more often in the late-initiation group.

In the past decade, there have been multiple additional studies comparing early and late initiation of dialysis.[19-32] The majority have been retrospective cohort studies or prospective observational studies and have used a wide variety of definitions for "early" and "late"

dialysis, with only 2 small randomized controlled trials. In the first of these trials, Bouman and colleagues randomized 106 critically ill patients with AKI to early high-volume continuous venovenous hemodiafiltration (CVVHDF) (n = 35), early low-volume CVVHDF (n = 35), and late low-volume CVVHDF (n = 36).[19] Hemodiafiltration was initiated in the 2 early-therapy groups within 12 hours of meeting study inclusion criteria, whereas it was withheld in the late group until metabolic or clinical criteria were met. There were no significant differences in survival among the 3 groups. Of note, of the 36 patients randomized to late therapy, 6 were never treated with RRT; 4 recovered kidney function and 2 died before meeting the criteria for late initiation of therapy. In the other randomized trial, 36 patients with AKI after coronary artery bypass surgery were randomized when their urine output was ≤30 mL/h and their serum creatinine had increased by ≥0.5 mg/dL per day.[20] In the early group, dialysis was started when the urine output remained <30 mL/h for 3 consecutive hours, whereas in the late group it was not started until the urine output fell to <20 mL/h for at least 2 hours. Only 28 patients (14 in each group) actually received protocol treatment; the remaining 8 patients did not fulfill the criteria for initiation of therapy. Of the patients treated per protocol, 12 patients in the early group (86%) were alive at 2 weeks compared with only 2 patients (14%) in the late group ($P < .01$).

A recent systematic review and meta-analysis of studies comparing early and late initiation of renal support published between 1985 and July 2010 by Karvellas and colleagues included 15 unique studies, including the 2 randomized controlled trials just described[33] (Fig 1). They calculated an odds ratio for 28-day mortality of 0.45 (95% confidence interval [CI], 0.28-0.72) associated with early initiation of renal support but noted that the methodologic quality of the included studies was low. In evaluating both the primary studies and the pooled conclusions of this meta-analysis, it is important to recognize a critical methodologic flaw affecting the majority of studies evaluating the timing of RRT. The vast majority of these studies restricted their analyses to patients who received RRT. However patients who do not receive early RRT can follow several paths: in addition to the late initiation of RRT, patients may die before initiation of dialysis or may survive and recover kidney function without ever requiring renal support. Limiting the comparison to patients treated early or late neglects the large number of patients who meet criteria for early treatment but never undergo dialysis. Thus rather than "early" vs "late," the issue would be more appropriately framed as "early" vs "not early" initiation of therapy.

The issue of the severity of volume overload as an indication for initiation of renal support has garnered considerable attention and deserves special mention. Multiple studies have demonstrated that the severity of volume overload at initiation of RRT is a strong predictor of mortality.[34-37] For example, in a pediatric cohort of patients undergoing CRRT, Sutherland and colleagues observed an increase in mortality from 29.4% in patients whose fluid gain was <10% of premorbid body weight as opposed to 65.6% in patients with ≥20% fluid overload at initiation of therapy.[37] After adjusting for comorbidities, the presence of ≥20% fluid overload was associated with an odds ratio for death of 8.5 (95% CI, 2.8-25.7). Similarly, Bouchard and colleagues observed an adjusted odds ratio for death of 2.1 (95% CI, 1.3-3.4) associated with the presence of >10% fluid overload at initiation of RRT in a cohort of 396 critically ill adult patients.[36] These data need to be interpreted with caution, as association does not imply causality. It is likely that many patients with more severe fluid overload required

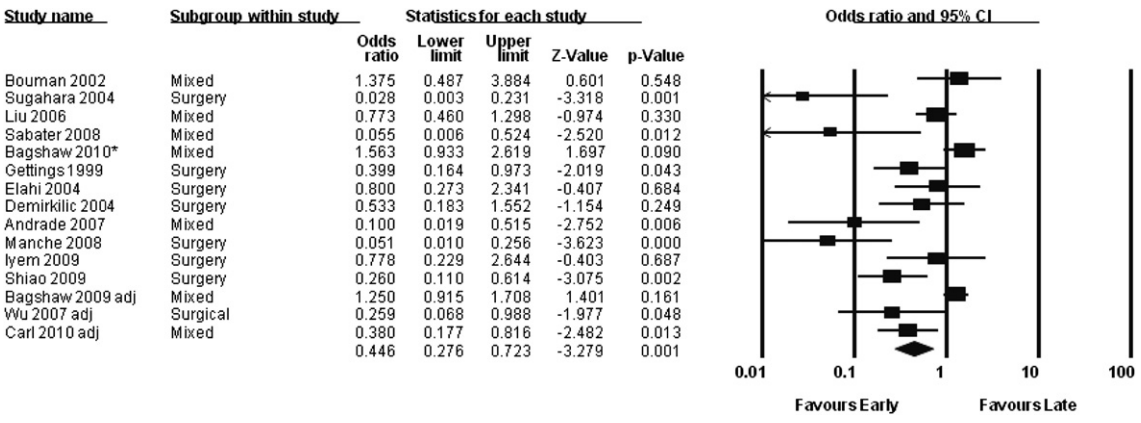

Figure 1. Forrest plot of pooled odds ratios for mortality of studies comparing early to late initiation of renal replacement therapy published between 1985 and July 2010. Using a random effects model, the calculated pooled odds ratio is 0.45 (95% confidence interval [CI], 0.28-0.72). Reprinted with permission from Karvellas CJ, Farhat MR, Sajjad I, et al. A comparison of early versus late initiation of renal replacement therapy in critically ill patients with acute kidney injury: a systematic review and meta-analysis. Crit Care 2011;15:R72.

more aggressive volume resuscitation, potentially suggesting a greater severity of their underlying critical illness. Although these analyses adjusted for severity of illness, residual confounding is a concern. Although these data provide a strong caution regarding overly aggressive volume administration, the hypothesis that earlier initiation of renal support to prevent or reverse volume overload still needs to be tested in prospective clinical trials.

Modality of Renal Replacement Therapy

Over the past 3 decades, the use of various forms of continuous and prolonged intermittent RRT (PIRRT) in the management of critically ill patients with AKI has increased dramatically. These modalities are characterized by a "go slow" approach, prolonging the daily duration of therapy while reducing the rate of solute clearance and net ultrafiltration, based on the rationale that slower, gentler treatment will be better tolerated in hemodynamically compromised patients. Whether this approach is associated with better clinical outcomes, including improved survival and recovery of kidney function, remains a subject of debate.

Comparing outcomes between modalities is complicated. Patients treated with continuous or extended-duration therapy are more likely to have greater severity of illness and be hemodynamically unstable. Comparing outcomes between CRRT or PIRRT and conventional intermittent hemodialysis (IHD) in observational cohorts is therefore subject to selection bias. Not unexpectedly, observational studies have generally found higher unadjusted mortality when comparing CRRT to conventional IHD.[38-44] Although statistical compensation for the inherent differences in patient characteristics can be provided by adjusting for differences in demographics, chronic comorbidities, and severity of illness using multivariate and propensity score–adjusted analyses, such analyses have yielded varying conclusions ranging from improved survival[42] to no difference in outcome[39] to increased mortality[44] associated with CRRT.

Several randomized controlled trials comparing intermittent to continuous RRT have been performed,[45-50] although many of these trials have been hampered by issues of patient selection and protocol adherence, excluding patients or having them cross between treatment arms because of hemodynamic instability. The largest of these trials, the Hemodiafe study, enrolled 360 patients across 21 ICUs in France.[49] Patients were well matched with regard to severity of illness, with more than 85% of patients requiring vasopressor support and more than 95% being ventilator dependent. Only 6 of the 184 patients (3%) randomized to intermittent therapy needed to cross over to continuous therapy, although 31 of the 175 patients (18%) randomized to CRRT crossed over; 14 (8%) per protocol to allow transfer out of the ICU and 17 (10%) predominantly because of bleeding complications associated with anticoagulation or difficulty maintaining circuit patency. No difference in survival at 2, 60, or 90 days (60-day survival, 31.5% with IHD vs 32.6% with CRRT; $P = .98$) or recovery of kidney function was observed between groups. It should be noted, however, that the median

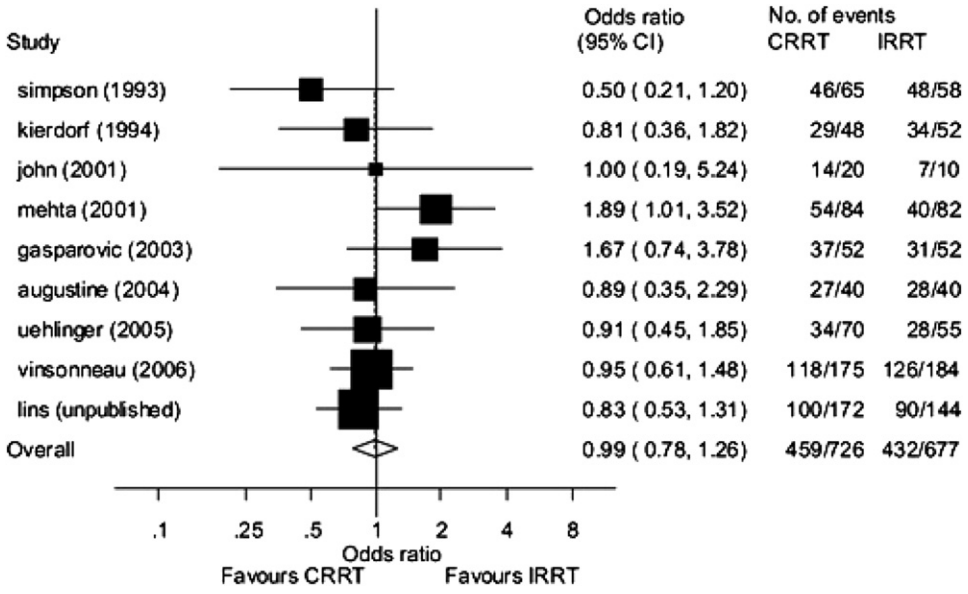

Figure 2. Forrest plot of pooled odds ratios for mortality from 9 randomized trials comparing intermittent renal replacement therapy (IRRT) to continuous renal replacement therapy (CRRT). Using a random effects model, the calculated pooled odds ratio is 0.99 (95% confidence interval [CI], 0.78-1.26). Reprinted with permission from Bagshaw SM, Berthiaume LR, Delaney A, Bellomo R. Continuous versus intermittent renal replacement therapy for critically ill patients with acute kidney injury: a meta-analysis. Crit Care Med 2008;36:610-617.

treatment duration for each IHD session was 5.2 hours, significantly longer than is typical in clinical practice.

Three systematic reviews and meta-analyses of modality for renal support in AKI have been published in the past 5years, all of which found no differences in mortality or recovery of kidney function across modalities[51-53] (Fig 2). Analyses have suggested, however, that the cost of CRRT is higher than that of intermittent therapy[52] and that continuous therapy is more effective at attaining negative fluid balance.[36]

Based on these data, the recent Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for Acute Kidney Injury recommended that continuous and intermittent modalities of RRT be used as complementary therapies, with the suggestion that CRRT be used preferentially for hemodynamically unstable patients.[54] In patients with acute brain injury or increased intracranial pressure resulting from intracranial hemorrhage, fulminant liver failure, or other causes, IHD has been associated with greater decreases in cerebral perfusion than has CRRT.[55-59]

Only limited comparisons between PIRRT and either intermittent or continuous therapy are available. These comparisons have demonstrated similar hemodynamic stability and metabolic control[60-62] and comparable clinical outcomes[63] with prolonged IHD compared with CRRT. Peritoneal dialysis (PD) has long been used as a dialytic therapy in AKI; however only few studies have directly compared PD to other modalities of renal support. Although Phu and colleagues found substantially higher mortality associated with PD compared with continuous venovenous hemofiltration (CVVH) (47% vs 15%; $P = .005$) in a 70-patient single-center study, the interpretation of this study must be tempered by issues related to PD technique (use of rigid catheters, locally prepared acetate-buffered dialysate, manual exchanges, and an open drainage system)[64]. In addition, it is possible that the low-dose anticoagulation used during CVVH had an independent beneficial effect in the large proportion of patients (69%) with falciparum malaria–associated AKI.[65] In contrast, Gabriel and colleagues have demonstrated biochemical and patient outcomes with high-volume PD comparable to those seen with IHD.[66-68]

A final issue related to modality of therapy is the relative benefits of convective (hemofiltration) vs diffusive (hemodialysis) therapies. Convective therapies are generally thought to provide better clearance of solutes with molecular weights >1000 Da.[69,70] It has therefore been suggested that convective therapies might provide an added benefit in patients with sepsis-associated AKI through enhanced removal of proinflammatory mediators.[71] However the cytokine clearances attainable with even high-volume CVVH are trivial in comparison to endogenous production, and cytokine removal by hemofiltration is nonselective and results in removal of both proinflammatory and anti-inflammatory mediators.[72] In addition, the effects of convective solute flux as the result of internal filtration/backfiltration and protein concentration polarization along the membrane surface when high-flux membranes are used may minimize the differences in solute clearance between convective and diffusive therapies [73]. More importantly, no clinical trials have demonstrated better outcomes with hemofiltration compared with hemodialysis.

Intensity of Renal Support in Acute Kidney Injury

Just as it has been hypothesized that prevention of severe metabolic derangements by earlier initiation of RRT in AKI might be beneficial, prevention or correction of severe metabolic derangements by providing more intensive RRT has also been proposed. Most studies evaluating the effect of more intensive RRT have quantified the dose of therapy in terms of the clearance of low-molecular-weight solutes, such as urea. It should be recognized, however, that modeling intensity of RRT based solely on urea clearance provides an incomplete assessment of the adequacy of therapy, ignoring the clearance of higher-molecular-weight solutes and, even more importantly, the management of extracellular volume.

The dose of IHD is dependent on both the intensity of therapy delivered with each individual treatment, usually quantified in terms of the urea reduction ratio or the fractional clearance of urea (Kt/V_{urea}), and the frequency with which the treatments are provided. No prospective studies have evaluated the effect of dose per treatment on outcomes; the single prospective study of intensity of conventional IHD assessed the effect of increasing the frequency of treatment from every other day to daily while maintaining a constant dose per treatment[74] (Table 1). Although this study reported a marked improvement in mortality with daily hemodialysis sessions (46% with alternate-day therapy vs 28% with daily dialysis; $P = .01$), the delivered Kt/V_{urea} was substantially lower in both treatment arms (0.94 ± 0.11 in the alternate-day group and 0.92 ± 0.16 in the daily dialysis group) than the target of 1.2 per treatment, potentially accounting for high rates of altered mental status, gastrointestinal bleeding, and sepsis in the alternate-day arm. Thus rather than demonstrating a benefit to augmenting an adequate dose of therapy, this study demonstrated that a dose of therapy that is inadequate when delivered every other day becomes sufficient when delivered on a daily schedule.[75] In contradistinction, the Hanover Dialysis Outcome Study, which compared standard (daily) to intensified (more frequent) PIRRT found no differences in survival at either day 14 or day 28.[76]

During continuous therapy, there is equilibration of low-molecular-weight solutes between the blood and dialysate and/or ultrafiltrate,[77] although the degree of equilibration may be reduced by administration of replacement fluids before filtering or by fouling of the membrane

Table 1. Studies of Intensity of Renal Replacement Therapy in Acute Kidney Injury

Study	N	Dose of RRT		Mortality		p Value
		Less-Intensive Arm	More-Intensive Arm	Less-Intensive Arm	More-Intensive Arm	
Conventional Intermittent Hemodialysis						
Schiffl et al[74]	160	Every other day Delivered Kt/V 0.94 ± 0.11	Daily Delivered Kt/V 0.92 ± 0.16	46%*	28%*	.001
Prolonged Intermittent Hemodialysis						
Faulhaber-Walter et al[76]	156	Daily Target BUN: 56-70 mg/dL	1-2× per day Target BUN <42 mg/dL	44.4%†	38.7%†	.47
Continuous Renal Replacement Therapy						
Ronco et al[79]	425	CVVH: 20 ml/kg/h	CVVH: 35 ml/kg/h CVVH: 45 ml/kg/h	59%*	57%* (35 ml/kg/h) 58%* (45 ml/kg/h)	<.001
Bouman et al[19]	106	CVVH: 24-36 L/d	CVVH: 72-96 L/d	25.7%†	28.2%†	.80
Saudan et al[80]	206	CVVH Q_{UF}: 25 ± 5 ml/kg/h	CVVHDF Q_{UF}: 24 ± 6 ml/kg/h Q_D: 18 ± 5 ml/kg/h	39%†	59%†	.03
Tolwani et al[81]	200	CVVHDF: 20 ml/kg/h	CVVHDF: 35 ml/kg/h	56%‡	49%‡	.23
Bellomo et al[82]	1508	CVVHDF: 25 ml/kg/h	CVVHDF: 40 ml/kg/h	44.7%¶	44.7%¶	.99
Combined Modalities						
Palevsky et al[8]	1124	IHD: 3× per wk Delivered Kt/V 1.32 ± 0.37 PIRRT: 3× per wk CVVHDF: 20 ml/kg/h	IHD: 6× per wk Delivered Kt/V 1.31 ± 0.33 PIRRT: 6× per wk CVVHDF: 35 ml/kg/h	51.5%§	53.6%§	0.47

Abbreviations: CVVH, continuous venovenous hemofiltration; CVVHDF, continuous venovenous hemodiafiltration; IHD, intermittent hemodialysis; PIRRT, prolonged intermittent renal replacement therapy; Q_D, dialysate flow rate; Q_{UF}, ultrafiltration rate; RRT, renal replacement therapy.
*Mortality 15 days after discontinuation of study therapy.
†Twenty-eight–day mortality.
‡Thirty-day mortality.
§Sixty-day mortality.
¶Ninety-day mortality.

caused by clotting and by protein concentration polarization.[78] The dose of CRRT has therefore been quantified based on effluent flow rates (the sum of the ultrafiltrate and dialysate) normalized to body weight. In a seminal study of 425 critically ill patients randomized to effluent flow rates of 20, 35, or 45 mL/kg per hour, Ronco and colleagues observed an increase in survival 15 days after discontinuation of CRRT from 41% in the lowest-dose group to 57% and 58%, respectively, in the 2 higher-dose groups ($P < .001$).[79] However subsequent small studies yielded conflicting results,[19,80,81] and a definitive multicenter randomized controlled trial found no benefit to higher doses of CVVHDF.[82] In this study, the Randomized Evaluation of Normal Versus Augmented Level (RENAL) Replacement Therapy study, 1508 patients in 35 ICUs in Australia and New Zealand were randomly assigned to 2 doses (25 or 40 mL/kg per hour) of CVVHDF during ICU care. The mean duration of study therapy and overall duration of RRT were 6.3 ± 8.7 days and 13.0 ± 20.8 days, respectively, in the higher-intensity arm and 5.9 ± 7.7 days and 11.5 ± 18.0 days, respectively, in the less-intensive arm, reflecting the use of nonprotocol hemodialysis after ICU discharge. Survival to 90 days was 55.3% in both treatment arms ($P = .99$).

In contrast to the studies that compared lower and higher doses of individual modalities of RRT, the Veterans Administration/National Institutes of health Acute Renal Failure Trial Network study randomized 1124 critically ill patients to lower- or higher-intensity RRT using a strategy that allowed patients to shift between modalities as hemodynamic status changed over time.[8] In the intensive arm, CVVHDF was provided with a total effluent flow of 35 mL/kg per hour, and conventional and prolonged IHD were provided 6 times per week (daily, except Sunday) with a target Kt/V_{urea} of 1.2 to 1.4 per treatment; in the less-intensive arm, the dose of CVVHDF was 20 mL/kg per hour, and conventional and prolonged IHD was provided 3 times per week (every other day, except Sunday), with the same target Kt/V_{urea}. Sixty-day all-cause mortality was 53.6% in the more-intensive arm compared with 51.5% in the less-intensive arm ($P = .47$).

Two systematic reviews reported meta-analyses of the pooled results from these trials.[83,84] Both found no significant benefit associated with more intensive RRT, although both observed significant statistical heterogeneity across the studies associated, in 1 analysis,[83] with year of publication and study quality as assessed by Jadad score.

Although the published literature does not support the concept that more RRT is better, the data also suggest that there must be some floor below which mortality will increase, the precise level of which is not known. Based on these data, the KDIGO AKI guidelines recommend delivering an effluent volume of 20 to 25 mL/kg per hour for CRRT and a Kt/V_{urea} of 3.9 per week (the equivalent of 1.2-1.4 3 times per week) when using conventional or

prolonged IHD.[54] Given the well-known discrepancies between prescribed and delivered doses of RRT in the acute setting, prescribing a modestly higher dose of therapy may be necessary to actually deliver the desired target doses. In addition, the delivered dose of therapy should be closely monitored to ensure that the targeted dose is actually achieved. Finally, it is important to recognize that the delivery of treatment must be individualized and that higher doses of therapy may be required for extremely hypercatabolic patients or for control of severe hyperkalemia. However when higher doses of therapy are used, careful attention must be given to the effects on drug clearance and the potential need for enhanced monitoring of drug levels and modification of drug dosing. In addition, in patients receiving intermittent therapy, increased treatment frequency may be required to optimize volume management, even if additional solute clearance is not required.

Summary

Although the use of RRT to support critically ill patients with AKI has become routine, many of the fundamental questions regarding optimal management of RRT remain. Although absolute indications for initiating RRT, such as hyperkalemia and overt uremic symptoms, are well recognized, the optimal timing of therapy in patients without these indications continues to be a subject of debate. The selection of modality does not appear to have a major impact on mortality or recovery of kidney function. Selection of modality for renal support should therefore be based on local expertise and logistic factors, with the emphasis on ensuring that the treatment provided is the safest and most cost-efficient for the particular health setting. Finally, reasonable minimal standards for the delivered dose of therapy appear to have been identified; a process for local quality assurance and performance improvement should be implemented to ensure that these are achieved. The mortality associated with severe AKI remains unacceptably high; however there is little evidence to suggest that this mortality will be substantially altered by improvements in the delivery of renal support. Rather, we must be realistic in our expectations of what dialysis and hemofiltration can accomplish and vigorously pursue other strategies to improve the care of these patients.

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Antimicrobial Dosing in Acute Renal Replacement

William H. Fissell

Acute kidney injury (AKI) is a common problem in hospitalized patients and is associated with significant morbidity and mortality. Two large trials showed no benefit from increased doses of renal replacement therapy (RRT) despite previous clinical data suggesting that increased clearance from RRT has beneficial effects. Since infection is the leading cause of death in AKI, my group and others hypothesized that increased RRT antibiotic clearance might create a competing morbidity. The data from my group, as well as those of other groups, show that many patients are underdosed when routine "1 size fits all" antibiotic dosing is used in patients with AKI receiving continuous RRT (CRRT). Here, concepts of drug distribution and clearance in AKI are briefly discussed and then 1 antibiotic (piperacillin) is discussed in depth to illustrate the challenges in applying the medical literature to clinical practice. The fact that published data on drug dosing in AKI and dialysis reflect the evolution of practice patterns and often do not apply to present prescribing habits is also discussed. A more general approach to drug dosing facilitates situation-specific prescribing by the nephrologist and critical care specialist.

Key Words: Acute kidney injury, Continuous renal replacement therapy, Hemodialysis, Sustained low-efficiency dialysis, Antimicrobial agents

Background and Scope of Problem

Acute kidney injury (AKI) is a common problem in hospitalized patients and is associated with significant morbidity and mortality.[1] Despite numerous clinical trials that have aimed to improve the outcomes of patients with AKI or prevent AKI, at present the only intervention for severe AKI is renal replacement therapy (RRT, also known as dialysis), and AKI requiring RRT is associated with mortality rates of at least 40% to 50% in critically ill patients.[2,3] It has been estimated that the cost associated with AKI in the United States is upward of $10 billion per year. The public health and clinical importance of AKI has been further underscored recently by studies demonstrating that the incidence of AKI is rising rapidly (~7% per year), independent of potential changes in diagnostic coding.[1] Two large trials showed no benefit from increased doses despite previous clinical and preclinical data suggesting that increased clearance from RRT has beneficial effects.[2-6]

Since infection is the leading cause of death in AKI, many have hypothesized that the effects of an increased RRT dose on antibiotic clearance may create a competing morbidity. My group's data, as well as those of other groups, show that many patients are underdosed when routine "1 size fits all" antibiotic dosing is used in patients with AKI receiving continuous RRT (CRRT).[7,8] Underdosing jeopardizes recovery from infection and drives the evolution of resistant bacterial strains.[9] Thus dialysis, the very therapy that we consider life-saving, may also increase mortality because it results in antibiotic underdosing. Design of better antibiotic dosing regimens requires insight into not only pharmacokinetic but also pharmacodynamic targets and identification of a high-risk patient population that is most likely to benefit.

There is a lack of knowledge about how to dose antibiotics in critically ill patients receiving RRT. Although it is clear that dialysis is life-saving because it clears the blood of toxins—including potassium, organic acids, and nitrogenous waste products—dialysis may also have deleterious effects through clearance of medications, including antibiotics. Medication dosing for RRT, and in particular CRRT, is frequently extrapolated from small case series of patients. Indeed, my group's studies suggest that 25% to 60% of patients receiving CRRT have subtherapeutic antibiotic levels, despite dosing of antibiotics consistent with standard of care.[8,10] Although a handful of antibiotics (vancomycin, aminoglycosides) can be dosed according to measured drug concentrations in blood (therapeutic drug monitoring) because levels are routinely measured by hospital clinical laboratories, it is not feasible to measure drug levels for the vast majority of antibiotics.

Brief Review of Pharmacokinetic and Pharmacodynamic Principles

The study of drug effects in animals and humans includes pharmacokinetics—or the processes by which the body takes in, distributes, and disposes of a drug—and pharmacodynamics, which refers to the processes by which the drug has its desired effect. For critically ill patients with kidney failure, drug disposition is likely to be altered from that observed in healthy volunteers, and consequently the ability of a particular dosing

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regimen to achieve therapeutic goals in an individual patient may vary considerably from what the clinician expects.

Absorption

Enteric drug absorption in the critically ill patient may be quite unpredictable for several reasons: proton-pump inhibitors administered for ulcer prophylaxis may raise gastric pH enough to dissolve pH-dependent coatings on tablets; fluid overload and gut edema, as well as loss of enteric microarchitecture, may impair absorption across the enteric mucosa; cholestasis in the setting of shock or sepsis may alter enterohepatic recirculation; disruption of epithelial tight junctions, loss of enteric mucosa, or partial denudation of the enteric lumen may lead to increased absorption[11]; and first-pass effects may be altered by portosystemic shunts. For these reasons, oral administration of pharmacologic agents frequently is not even discussed in reviews of drug dosing in critical illness.[12,13] Parenteral administration generally means intravenous infusion, although intraperitoneal and intrathecal administration may be preferred in certain settings.[14,15]

CLINICAL SUMMARY

- Adult patients treated with continuous RRT in the intensive care unit are probably at risk for antibiotic underdosing and therapeutic failures.
- One-size-fits-all dosing is likely inappropriate.
- Estimation of kidney function in acute injury is very challenging, but recently short-interval creatinine clearance measurements have been demonstrated.
- Widely available drug databases support individualized decision making.
- There is little literature to support adjusting the loading dose of antibiotic in AKI.
- The sum of kidney creatinine clearance and CRRT effluent rate normalized for drug protein binding provides a starting point for kidney-based dose adjustment for subsequent doses of antibiotic.
- When available, therapeutic drug monitoring should be used, especially for drugs with a low therapeutic index.

Distribution

After an agent is administered—either orally or parenterally—it will be transported to a greater or lesser extent from its original location (blood, cerebrospinal fluid, ascites) throughout the rest of the body. For this discussion, we will assume intravenous administration. As a result of this active and passive transport, the measured concentration of drug in the plasma will be less than just the administered dose divided by the estimated plasma volume. The dose administered divided by the final concentration yields a number with units of volume, called the "volume of distribution." It can be helpful in dose calculation to frame drug distribution in this way, even though the volume of distribution does not correspond to any particular anatomic space in the body.

Once the drug has been distributed throughout the body, it will have some final concentration that then gradually decreases as the body eliminates the drug. It may be challenging to distinguish drug excretion or metabolism from delayed distribution.

Unfortunately, the nomenclature is not entirely consistent in describing volume of distribution, so it is worth some discussion here. Almost all drugs will exist in equilibrium between free drug—the active form of the drug—and drug that is specifically and nonspecifically bound to plasma and tissue proteins. Some drugs also partition into lipids. Often, it is not clear whether descriptions of drug concentration and volume of distribution refer to both free and bound forms ("total drug") or the active free form alone. An example familiar to most practicing nephrologists illustrates the point. Phenytoin, a commonly used antiepileptic agent, is highly protein bound to albumin (>90%), and the total drug has a relatively small volume of distribution—about 0.7 L/kg in adults. The free, pharmacologically active form of the drug is thus only about 10% of the total drug and circulates at a therapeutic concentration of 1 to 2 μg/mL. The volume of distribution for the free, active form of the drug is quite different (7 L/kg vs 0.7 L/kg) from the volume of distribution for the total drug, and the exact concentration of free drug is exquisitely sensitive to plasma protein concentrations and also uremic toxins, which is relevant for CKD and AKI.[16] For this discussion, volume of distribution will refer to the free drug and not the protein- or tissue-bound forms. A few other examples of drug distribution familiar to the practitioner from everyday experience may be helpful in anchoring the discussion. At 1 end of the spectrum, monoclonal antibodies, such as infliximab, are large molecules that are almost entirely retained in plasma and have very low volumes of distribution.[17] In contrast, antimetabolites used in cancer chemotherapy are small molecules that bind extensively and nearly instantly to tissues and have volumes of distribution in the hundreds of liters.[18-28]

The time course for transport of a drug depends on its chemical characteristics, especially size and protein binding, as well as the nature of the tissues into which it distributes. This matters in optimizing dosing strategies for the site of infection; in addition, half-lives are affected by distribution because reservoirs of drug in tissues may refill the plasma compartment as the kidney or liver removes the drug. Blood flow distribution to splanchnic circulation, skeletal muscle, and fat is altered in AKI and critical

illness, so the apparent volume of distribution may change over the dosing cycle as well over the course of the illness. This effect may be modeled as early, nearly instant drug distribution into a "central" compartment and then slower distribution into 1 or more peripheral compartments. It is tempting but inaccurate to assign the identities of the modeled peripheral compartments to a particular organ or fluid. Drugs do not distribute into the entire body, and there are certainly anatomic compartments in the body to which some antibiotics have poor access, such as abscesses, bone, and cerebrospinal fluid. Many antibiotics administered intravenously (IV) penetrate the blood-brain barrier slowly or not at all.[14] This is a major challenge in therapeutic drug monitoring because antibiotic concentrations for therapeutic drug monitoring are usually measured in blood samples and almost certainly overestimate concentrations at the site of infection.[29-31]

Volumes of distribution in acute kidney injury may be severely deranged from published population estimates derived from healthy individuals. First, hospitalized inpatients may have been obese and far heavier than ideal body weight at time of admission, leading to overestimation of total body water if weight-based nomograms are used. Subsequent fluid overload and extracellular fluid volume expansion in turn increase volumes of distribution for hydrophilic drugs such as aminoglycosides. Acutely ill patients frequently have decreased plasma protein concentrations; additionally, uremic solutes such as hippurate and indoxyl sulfate alter drug binding to albumin in chronic kidney failure and might do so in acute kidney failure, although this has not been tested.[32,33] The free fraction of many drugs (eg, phenytoin, digoxin, and others) is increased in kidney failure, even though the volume of distribution for total drug may increase because of movement of unbound drug into interstitial or total body water.[34,35] Failure to adjust drug doses to account for these changes can result in unexpected toxicity, as total drug remains the same but the free concentration is higher than expected.

Clearance, Metabolism, and Excretion

Clearance is a concept familiar to most nephrologists that needs little further discussion in the context of pharmacokinetics. Creatinine clearance, commonly used as an easily calculated surrogate for glomerular filtration rate (GFR), includes creatinine removed from blood by glomerular filtration and tubular secretion, although in individual patients the relative contributions of each are generally not known. The same is true for drugs that may be filtered and either reabsorbed or secreted by the tubule. In kidney failure, filtration and secretion are reduced, and it is usually assumed that reduced drug clearance by the kidney occurs in proportion to reductions in GFR.

In consideration of drug clearance, metabolism of the drug is usually significant and sometimes dominates the disappearance of drug from plasma. Metabolism may take the form of chemical modification of the drug by catalysis or hydrolysis or the addition of groups (eg, glucuronidation) that enhance excretion of the drug by modifying its solubility. The drug may also be secreted in bile and then eliminated unchanged in stool. Nonkidney drug disposition is not independent of kidney failure. Uremia and/or azotemia change hepatobiliary drug metabolism, possibly through product inhibition by accumulated metabolites.[36] Cytochrome P450 expression by the liver is reduced in chronic uremia, and in vitro studies of rodent hepatocytes suggest that a dialyzable factor contributes to the suppression.[37]

Extracorporeal clearance by the dialysis circuit occurs in parallel with endogenous clearance. Only the unbound or free drug is removed by the dialysis circuit, as the plasma proteins (albumin) to which the drug is bound are too large to pass through the pores of the dialysis membrane. CRRT has dialysate/effluent flow-limited small-solute clearance (blood flow [Qb] >> dialysate flow [Qd]), and CRRT urea clearance is generally close to the effluent flow rate, typically 2 to 3 L/h or 33 to 50 mL/min. Sustained low-efficiency dialysis (SLED) (Qd > Qb, Qb 100 ~ mL/min) and hemodialysis (Qd > Qb; Qb ~ 350-400 mL/min) have Qb-limited small-solute clearance, and barring significant recirculation or clotting in the fiber bundle, urea clearance is close to the Qb rate. Peritoneal dialysis is only rarely used in acute kidney failure and drug kinetics in acute peritoneal dialysis is not well studied. In CRRT, SLED, and conventional hemodialysis, middle molecule clearance is appreciably less than urea clearance and may be negligible.[38,39]

Typical antibiotic dosing adjustments in CRRT involve estimating ongoing extracorporeal clearance (eg, 15 mL/min) and dosing the antibiotic according to the guidelines for the equivalent creatinine clearance. Typical adjustments to dose in intermittent dialysis involve estimating drug removal in the course of a single session, frequently from the published literature rather than individualized data, and then supplementing the regular antibiotic dosing schedule with additional doses after each dialysis session. Anecdotal evidence suggests that individual institutions vary widely in their adherence to supplemental dosing.

Pharmacodynamics

Antimicrobial antibiotics fall into several broad classes of agents (Table 1) that exert their selective effect on microbes by targeting enzymes that are not shared with their mammalian host. Each class of agent is thought to have a particular preferred concentration-time profile that optimizes microbial killing while minimizing side effects. Drugs are usually classed as time dependent, meaning that time—or percentage of the dosing interval—greater than some threshold concentration influences kill rates to a greater extent than does the magnitude

Table 1. Antimicrobial Properties

Class	Example	Mechanism of Action	Microbial Killing Profile
β-Lactams	Penicillin, ceftriaxone, meropenem	Irreversible binding to enzymes necessary for peptidoglycan synthesis in bacterial cell wall	Time dependent[63,64]
Macrolides	Erythromycin	Bind 50S subunit of ribosome and block peptide chain elongation and protein synthesis	Time dependent[65]
Aminoglycosides	Gentamicin	Bind 30S ribosome and interfere with peptide chain elongation, but individual agents may have additional effects	Concentration dependent[66]
Fluoroquinolones	Ciprofloxacin	Inhibits DNA gyrase and blocks protein synthesis	Concentration dependent[67]
Tetracyclines	Doxycycline	Bind 30S ribosome and prevent transfer RNA from binding, thus preventing peptide chain elongation and blocking protein synthesis	Understudied Concentration dependent[68]
Glycopeptides	Vancomycin	Inhibits cell wall synthesis	Time dependent[69]
Lipopeptides	Daptomycin	Depolarizes cell membrane	Concentration dependent[70]
Polyenes	Nystatin, amphotericin B	Binds to ergosterol component of fungal cell membrane and increases membrane permeability	Concentration dependent[71]
Triazoles	Fluconazole	Blocks synthesis of ergosterol component of fungal cell membrane	Time dependent[72,73]
Echinocandins	Caspofungin	Inhibits B-(1,3)-glucan synthase and interrupts fungal cell wall synthesis	Concentration dependent[74]

of the peak concentration observed; conversely, concentration-dependent agents show more dependence on the magnitude of the peak concentration than on how long the concentration exceeded some multiple of the microbial minimum inhibitory concentration. Several agents exhibit a potent postantibiotic or postantifungal effect caused by the irreversible binding of the drug to bacterial or fungal cellular machinery. The pharmacokinetic processes (distribution and clearance) described earlier cause the concentration-time profile at the site of infection to differ from the concentration-time curve in plasma so that plasma concentrations may or may not be close to concentrations at the site of infection. Optimization of the plasma concentration profile to achieve a desired tissue concentration-time profile is an active area of research.

Antibiotic Dosing in Acute Kidney Injury

Unlike cancer chemotherapy agents or antiepileptic drugs, most antibiotics have large therapeutic indices—toxic doses far exceed therapeutic doses and dose-limiting toxicities are rare. For example, vancomycin toxicity is frequently reported at concentrations in excess of the therapeutic concentration by tenfold.[40,41] Commonly encountered exceptions include aminoglycosides and amphotericin B, which concentrate in the kidney cortex, causing AKI. Several azoles and macrolides are CYP3A4 inhibitors, and accumulation in kidney failure may cause elevations in other drugs, especially immunosuppressants and antiarrhythmic agents, such as amiodarone, that are metabolized by CYP3A4. β-Lactam antibiotics, especially carbapenems, have epileptogenic neurotoxicity that may be exacerbated by kidney failure.[42] Because of these direct and indirect toxicities, practitioners have been keen to avoid overdose when prescribing antibiotics for patients with kidney failure.

Dose adjustment in kidney failure is usually based on the present level of kidney function; however estimation of kidney function in AKI is a challenging proposition that is becoming its own field of study.[43-47] GFR estimates that are based on creatinine or urea levels, such as the Modification of Diet in Renal Disease estimating equation, are confounded by several factors.[48] First, not all individuals generate wastes at the same rate. Second, measurements of serum levels always assess kidney function "in arrears," as they reflect accumulation of the solute in the hours and days after the change in GFR occurred. Third, in AKI, the volume of distribution of these solutes is likely also to be changing rapidly so that changes in plasma levels arise not just from changes in generation and clearance but also from changes in total body water. Several tools have been developed to quantify AKI injury in a repeatable fashion, and most well known are the RIFLE (Risk, Injury, Failure, Loss, End-stage renal disease) and AKIN (Acute Kidney Injury Network) criteria.[49,50] These tools were developed to standardize definitions and stages of AKI for research purposes, as previous studies of AKI were difficult to compare side by side because of widely varying definitions of AKI. These scoring systems are relatively blunt instruments with limited utility in bedside medical decision making, although they are extremely helpful to the clinician's sense of risk stratification and anticipatory guidance to family and friends of the patient. In this background context of extraordinary difficulty in estimating kidney function in the critically ill patient, rapid turnaround use of existing laboratory assays can be immensely useful. Four-hour creatinine clearance, eg, can give insight into a patient's kidney function during the interval between administration of a loading dose and the first maintenance dose.[51] These real-time assessments of actual creatinine clearance may prove helpful in estimating GFR when the patient's clinical condition is evolving.[51]

Antibiotic Dosing in Extracorporeal Renal Replacement

In this section, I discuss the literature on antibiotic dosing in kidney failure requiring support and focus exclusively on continuous therapies. For intermittent dialysis, several published guides suggest supplemental doses to replace dialytic losses.[52] SLED has had limited penetration in the United States despite the highly attractive financial implications of using low-cost disposables in the intensive care unit setting. Of more than 10,000 RRT treatments in the Acute Renal Failure Trial Network study, less than 300 were SLED; in the RENAL (Randomized Evaluation of Normal vs Augmented Levels of Renal Replacement Therapy) study, all patients received venovenous hemodiafiltration after dilution.[2,3] That said, the majority of the literature on SLED in AKI has been published in the past 3 to 4 years, so drug dosing guidelines in sustained low-efficiency treatments are likely to be increasingly important and will require extensive research efforts to develop optimal dosing strategies for SLED.[53]

The primary difficulty in applying the published literature on antibiotic dosing in CRRT to bedside clinical decision making stems from the ongoing evolution of the standard of care in CRRT and significant heterogeneity in CRRT prescribing patterns. This article focuses on 1 very commonly used combination antibiotic, piperacillin-tazobactam, and reviews the previous literature as an example of the difficulties encountered by the practitioner attempting to devise a rational dosing scheme for an individual patient. Many if not all of the challenges discussed are applicable to other antimicrobial agents in AKI. The literature spans nearly 2 decades, involves relatively small numbers of subjects, and reports very different CRRT prescriptions (Table 2).

Table 2. Pharmacokinetic/Pharmacodynamic Studies of Piperacillin-Tazobactam in CRRT

Reference	N	CRRT Prescription
Joos et al[75]	8	CVVH 13 mL/min
van der Werf[76]	9	CVVH 26 mL/min
Capellier et al[77]	10	CVVH 840 mL/h
Valtonen et al[55]	6	CVVH 1 L/h or CVVHDF 2 L/h
Mueller et al[57]	8	CVVHD 1.5 L/h
Arzuaga et al[56]	14	CVVH 20-30 mL/min
Seyler et al[8]	16	CVVH and CVVHDF 45 mL/kg/h
Bauer et al[10]	42	CVVH and CVVHDF 26 mL/kg/h

Abbreviations: CRRT, continuous renal replacement therapy; CVVH, continuous venovenous hemofiltration; CVVHDF, continuous venovenous hemodiafiltration.

As discussed by Trotman and colleagues in their excellent review article on antibiotic dosing in CRRT, mode and dose of CRRT vary quite widely from center to center and from report to report, making it very difficult to create generally applicable dosing guidelines.[54]

Pharmacokinetic parameters for piperacillin in my group's study resembled those reported by Seyler and colleagues[8] and differ notably from those published in a commonly used prescribing guide *The Green Book*.[52] Protein binding was lower, volume of distribution was higher, and half-life was longer than described in this prescribing guide.[52] Half-lives measured in my group's study resembled those measured by Valtonen and colleagues for 2 L/h of effluent but were shorter than those reported by Arzuaga and associates.[55,56] Total and extracorporeal clearance was higher in my group's study (74 mL/min vs 50 mL/min; 30.8 mL/min vs 11.45 mL/min, respectively) than that reported by Arzuaga and associates for patients with severe kidney failure receiving continuous venovenous hemofiltration (CVVH).[56] Arzuaga used similar equipment, but in predilution continuous hemofiltration with much lower effluent rates than use in the patients reported here. In comparison to Mueller's measurements, the patients in my group's study had slightly longer half-lives and lower elimination rate constants for both piperacillin and tazobactam.[57] At this point, a side note regarding β-lactam/β-lactamase inhibitor combinations is warranted in that the pharmacokinetics of the 2 components may be quite different; in my group's study, tazobactam had a larger volume of distribution and a longer half-life than did piperacillin.[10]

Our pharmacodynamic data resembled those of others, suggesting that the proportion with target attainment (or proportion reaching >50% T > MIC64 μg/mL) was not 100%.[8,58,59] Measurements of tissue levels for β-lactams are generally at best half to a quarter of plasma levels, and possibly much lower in patients with sepsis.[29,58,60,61] The relatively low proportion with target attainment raises significant concerns regarding response to infections and development of antimicrobial resistance.

My group has developed data for carbapenems similar to those reported by Seyler and coworkers, suggesting that not all pharmacodynamic targets are reached in plasma let alone in tissue.[8]

The literature is presented for piperacillin-tazobactam because they are among the most widely used antibiotics in the critical care environment, and it highlights the challenges confronting the practitioner who seeks evidence-based dosing guidelines. Piperacillin-tazobactam is a mainstay in treatment of gram-negative sepsis, and as such it is among the best studied in AKI. As is evident, even for this extensively used drug, the literature supporting dosing recommendations is based on remarkably few patients and heterogeneous RRT prescriptions. The same is evident for other kidney dose adjustments.

Given that the CRRT prescriptions in the literature vary widely and practice patterns evolve, it seems unwise to adjust antibiotics doses according to a set recommendation for dialysis and CRRT. Instead, in the last section of this article, a generally applicable strategy for dose adjustment in kidney failure and dialysis is presented.

Practice Recommendations for Inpatient Acute Kidney Injury

What dose adjustment recommendations can be provided to the practitioner today? First, if prescribed CRRT doses are similar to those of the ATN and RENAL studies, ie, between 25 and 35 mL/kg/h, there is a very real possibility that antibiotics will be underdosed if older dose adjustments are followed. This is reflected in Aronoff and associates' book, in which piperacillin dose recommendations were increased between the fourth and fifth editions.[52,62] Except in cases in which a particular dose-related side effect is a known concern, practitioners may prefer to err on the side of higher not lower doses. Trotman and colleagues' article is an excellent source of information for volumes of distribution and protein binding that will guide initial and subsequent doses.[54] There are little if any data to support reduction of the initial antibiotic dose solely on the basis of kidney failure; the most obvious influences on the volume of distribution of the free drug tend to cancel each other: hypoalbuminemia tends to increase the free fraction of drug, whereas extracellular fluid volume expansion dilutes that free fraction more than in a normovolemic patient. Aminoglycosides and vancomycin will continue to require weight-based dosing and therapeutic drug monitoring whenever possible. The more complicated aspect of dosing lies in scheduling subsequent doses. Concentration-dependent agents, such as fluoroquinolones, aminoglycosides, daptomycin, and amphotericin, generally are adjusted by altering the length of the dosing interval, whereas for time-dependent agents such as β-lactams and triazoles, the dosing interval is kept constant or nearly so, and the dose is reduced. Individual hospitals' prescribing practices often combine both approaches.

Although some references categorize drugs as being cleared by either the kidney or the liver,[54] the reality is that nearly all drugs undergo a combination of major, minor, and codominant elimination pathways. Micromedex, Lexi-Comp, Epocrates, and other online or mobile databases offer extensively referenced, continuously updated, and easily available data on an extensive library of drugs. A quick look at the pharmacokinetic or absorption, distribution, metabolism, and elimination sections of a drug monograph can help the practitioner quickly decide if kidney dose adjustment is necessary. Highly similar drugs in the same class cannot be assumed to share common pharmacokinetics and elimination. An example familiar to nephrologists is the difference between atenolol and metoprolol. Atenolol is excreted 85% unchanged in urine, whereas metoprolol is metabolized in the liver and undergoes negligible clearance by the kidney. Once the practitioner has identified that clearance by the kidney is a dominant or codominant mechanism of elimination, he or she needs to estimate the aggregate kidney and extracorporeal drug elimination in the individual patient. Typical dose adjustments categorize kidney function roughly into <10 mL/min, 10 to 20 mL/min, 30 to 60 mL/min, or >60 mL/min; many variations on this theme exist but the concept is uniform. Clearance by the kidney can be assumed to be nearly zero in anuric patients, and in patients with some urine output a rapid assessment of function with a 4-hour creatinine clearance test can broadly assign a patient's kidney function to 1 of the categories in the dosing guide. CRRT drug clearance for most antibiotics can be estimated as the unbound fraction (derived from a drug reference such as Micromedex or other) or from Trotman and colleague's review[54] multiplied by the effluent rate (ie, dialysate plus ultrafiltrate).

Thus for piperacillin in a 100-kg anuric patient receiving 25 mL/kg/h continuous venovenous hemodiafiltration (CVVHD), our own data measured a free fraction as 81%.[10] CRRT clearance could be estimated as 0.81×100 kg $\times$ 25 mL/(kilograms $\times$ hours) $\times$ 1 h/60 min or about 35 mL/min. Looking in any of several references for dose adjustments for a creatinine clearance of 35 mL/min, we find 3 g IV every 8 hours (Micromedex), 2.25 g piperacillin-tazobactam IV every 6 hours (Lexi-Comp), which are very similar, either 8 or 9 g of piperacillin over a 24-hour period. These also correspond exactly to the dosing at the 2 sites in our study.[10] By aggregating measured kidney and calculated extracorporeal clearance into a single number, the practitioner has a surrogate for creatinine clearance that allows application of the more commonly available dose adjustments for chronic kidney disease to patients with AKI with or without residual kidney function and any renal replacement strategy, bearing in mind that most drugs undergo multiple clearance mechanisms, and this approach accounts for only the component of clearance by the kidney.

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Enhanced Poison Elimination in Critical Care

Marc Ghannoum and Sophie Gosselin

Nephrologists and critical care physicians are commonly involved in the treatment of severely poisoned patients. Various techniques exist presently to enhance the elimination of poisons. Corporeal treatments occur inside of the body and include multiple-dose activated charcoal, resin binding, forced diuresis, and urinary pH alteration. Extracorporeal treatments include hemodialysis, hemoperfusion, peritoneal dialysis, continuous renal replacement therapy, exchange transfusion, and plasmapheresis. This review illustrates the potential indications and limitations in the application of these modalities as well as the pharmacological characteristics of poisons amenable to enhanced elimination.

Key Words: Poisoning, Critical care, Toxicity, Overdose, Enhanced elimination

Introduction

Poisonings account for a significant portion of health-related admissions to hospitals across the world. The U.S. National Poison Data System reported nearly 2.5 million toxic human exposures in 2010, 5% of which required admission in an intensive care unit.[1] Nephrologists and critical care physicians are involved in the treatment of acute poisonings in various roles either as consultants or treating physicians. Knowledge of toxicological principles is therefore important to ensure that optimal management is offered to poisoned patients.

After the initial resuscitation and stabilization of the patient, a risk assessment must be performed. It is a distinct cognitive step in which the variables of the poisoning for a specific individual are comprehensively analyzed to determine the risk benefit of potential interventions. In most poisoned patients, risk assessment will confirm that general supportive measures will usually suffice. These include airway management and protection, ventilatory support, fluid resuscitation, correction of electrolyte and acid-base disorders, and management of poison-related hypo/hyperthermia. The management of poison-induced seizures and arrhythmias warrants a specific approach focused on pathophysiological mechanisms.[2,3] Poison-specific antidotes can rapidly reverse life-threatening symptoms, but they are only available for a minority of cases. Other treatments may include competitive receptor agonism or antagonism to mitigate the effect of the poison.

When a patient presents early after ingestion or when the poison is still expected to be in the gastrointestinal (GI) tract, the potential benefit for GI decontamination with gastric lavage, single-dose activated charcoal, or whole-bowel irrigation must be evaluated. Many patients unfortunately present after the ideal window for GI decontamination, usually accepted to be within 1 hour of ingestion; however, decontamination also can be considered after exposure to xenobiotics that undergo extended-release, delay gastric emptying, or cause bezoar formation, even after the "golden hour." Moreover, skin decontamination of poisons with significant dermal absorption (pesticides, hydrofluoric acid) is often overlooked.

Interventions in which the physician can potentially make a difference in outcome and/or decrease the duration of toxicity are those centered on decreasing the body burden of a given absorbed poison by increasing its elimination. These measures are usually divided between corporeal and extracorporeal treatments. Corporeal treatments occur inside of the body whereas extracorporeal treatments take place outside of the body, usually via an extracorporeal circuit (Table 1). The frequency of some of these interventions in the United States is presented in Figure 1.[1] The description, application, and indications of techniques susceptible to enhanced poison elimination will be summarized in the following section.

Corporeal Treatments

Intestinal Exsorption

Multiple-Dose Activated Charcoal

Activated charcoal can be given to enhance elimination of certain poisons. This is in contrast to the administration of single-dose activated charcoal to prevent systemic absorption of large ingestions, bezoars, or sustained-release preparations (decontamination). Multiple-dose activated charcoal (MDAC) promotes clearance of poisons by two possible mechanisms: by interrupting enterohepatic circulation of xenobiotics secreted in bile or by promoting the passive diffusion of poisons down a concentration gradient from the intestinal capillaries to the intraluminal gut space, a process also described as "exsorption". The intestinal mucosa serves as a dialysis membrane, and the term "gut dialysis" seems to have first been introduced by Levy when commenting on the work of Berg.[4,5]

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Literature on MDAC is heterogeneous: the evidence includes animal experiments, human volunteer studies, case reports, as well as very few randomized-controlled trials. This disparity in patient selection and study designs makes the interpretation of the published results complex and controversial for different poisons.

To add to the difficulty in comparing clearance data, MDAC regimens are not uniform in their dose, frequency, and duration. Most centers recommend 1 g/kg of aqueous activated charcoal given every 4 hours or 0.5 g/kg every 2 hours until improvement in status or decline in poison concentrations in the blood. Efficacy appears unaltered by different dosing regimens.[6] Ideal toxicokinetic properties of poisons amenable to MDAC therapy include a small volume of distribution, low protein binding, prolonged half-life, low intrinsic clearance, and a nonionized state at physiologic pH, although the data are conflicting.[7,8]

Contraindications to MDAC include an altered level of consciousness with an unprotected airway, protracted vomiting unresponsive to antiemetic therapy, and intestinal occlusion. Complications such as aspiration pneumonitis, appendicitis, or charcoal bezoar with MDAC have also been reported infrequently. The incidence of these complications seems to increase with the amount of activated charcoal doses given.[9-11]

At present, MDAC has been shown to increase total body clearance for a few poisons (Table 1), although it is unclear if this affects clinical outcomes. In a study of carbamazepine poisoning, duration of coma and need for mechanical ventilation were decreased in patients receiving MDAC.[12] In another randomized controlled trial of oleander seed poisoning, MDAC for 72 hours yielded fewer deaths and dysrhythmias.[13] In 1999, a joint initiative by the American Association of Clinical Toxicology (AACT) and the European Association of Poison Centres and Clinical Toxicologists (EAPCCT) published guidelines for the use of MDAC and recommended its use for life-threatening poisoning with five substances: theophylline, dapsone, carbamazepine, phenobarbital, and quinine.[14]

CLINICAL SUMMARY

- Use of elimination enhancement techniques is an integral part of the general management of poisoned patients.
- The major corporeal techniques are multiple-dose activated charcoal and urine alkalinization.
- Hemodialysis is the most commonly favored extracorporeal technique in poisoning situations because of its availability, cost, and safety profile.
- In the absence of good clinical studies demonstrating the efficacy of elimination techniques, consensus-based recommendations are needed to ensure better management care for poisoned patients.

Resins

Sodium Polystyrene Sulfonate. Sodium polystyrene sulfonate (SPS) is a cation exchange resin usually administered for the treatment of hyperkalemia. SPS can also bind other cations such as thallium and iron.[15] Animal studies have shown that SPS can bind lithium (Li) in the GI tract and enhance elimination of already absorbed Li. Furthermore, this effect is dose dependent.[16] In one retrospective human study of 48 patients, apparent Li half-life was decreased nearly 50% in patients who received SPS, although fecal Li measurements were lacking to document the contribution of SPS on total body Li clearance.[17] Complications associated with SPS include hypokalemia and intestinal necrosis, although its true incidence and its association with sorbitol remain controversial.[18]

Prussian Blue. The crystal structure of the Prussian blue (PB) molecule binds potassium, but it has higher affinity for cesium and thallium. It is given orally and it is not absorbed by the GI tract. PH is currently used for decontamination and fecal exsorption of radiocesium and thallium.[19–22] PB comes in two formulations: insoluble and soluble salts. Radiocesium poisoning has been more often reported with soluble PB whereas the insoluble form of PB has been used with thallium poisoning. It is unclear if both can be used interchangeably for these two poisonings.[23]

Cholestyramine. The use of cholestyramine, a lipid-lowering resin, has been used with success, although anecdotally, to enhance elimination for the following poisons: digoxin, digitoxin,[24,25] ibuprofen,[26] meloxicam,[27] methotrexate,[28] mycophenolate mofetil,[29] perfluorinated compounds,[30] piroxicam,[31] tenoxicam,[31] and warfarin.[32] In the case of digoxin poisoning, the idea of resin binding has been largely supplanted by the use of digoxin-specific Fab fragments. The role of cholestyramine in digoxin poisoning when digoxin-specific Fab fragments are unavailable remains unclear.

Renal Elimination

Forced Diuresis

The principle behind forced diuresis is to promote poison elimination by using a large volume of intravenous crystalloids to which loop diuretics can be added. The role of forced diuresis has been advocated for substances with kidney excretion such as cyclophosphamide, thallium, isoniazid, meprobamate, fluoride, iodide, 5-fluorouracil, cisplatin, bromides, barium, chromium, Li, salicylates, and ethylene glycol. The efficacy of this technique has not been demonstrated. In the case of salicylate poisoning, urine alkalinization is much more effective than

Table 1. Types and Mechanisms of Elimination Enhancement Techniques

Extracorporeal Treatments	Corporeal Treatments
Diffusion-based	Intestinal diffusion (exsorption) or enterohepatic binding
HD	MDAC
PD	Resins (SPS, PB, cholestyramine)
Convection-based	Renal elimination
HF	Forced diuresis
	Urine alkalinization
	Urine acidification
Adsorption-based	
HP	

HD, hemodialysis; PD, peritoneal dialysis; HP, hemoperfusion; HF, hemofiltration; MDAC, multiple dose activated charcoal; SPS, sodium polystyrene sulfonate; PB, Prussian blue.

forced diuresis.[33] Furthermore, forced saline diuresis has not been shown to enhance elimination of Li compared with aggressive fluid repletion.[34] Finally, complications such as fluid overload, pulmonary edema, cerebral edema, hypernatremia, and hypokalemia are deterrents for its application.

Urinary Alkalinization

Alteration in urine pH is used to alter undissociated acid or base in the tubular lumen to its ionized form. Because charged particles diffuse poorly from the renal tubular lumen back to blood, their urinary elimination is enhanced. Poisons for which urinary clearances are likely to be increased with alkalinization need to be predominantly eliminated by kidneys, distributed in the extracellular compartment, be weak acids with a pKa in the range of 3.0-7.0, and minimally protein-bound. Because pH is a logarithmic value, each 1.0 increment in urine pH will increase elimination 10-fold; therefore, urine pH should be kept between 7.5 and 8.5 for maximal efficacy.

A direct relationship has been shown between urinary salicylate concentrations and urine pH[35] (Fig 2). Coma duration was shortened by 50% in phenobarbital-

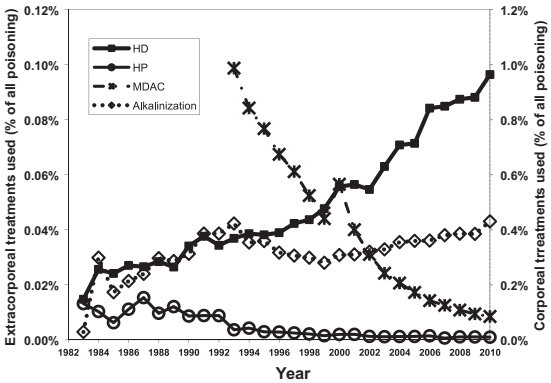

Figure 1. Elimination enhancement trends in the United States. HD + HP on left axis; MDAC + alkalinization on the right axis.[34] HD, hemodialysis; HP, hemoperfusion; MDAC, multiple dose activated charcoal.

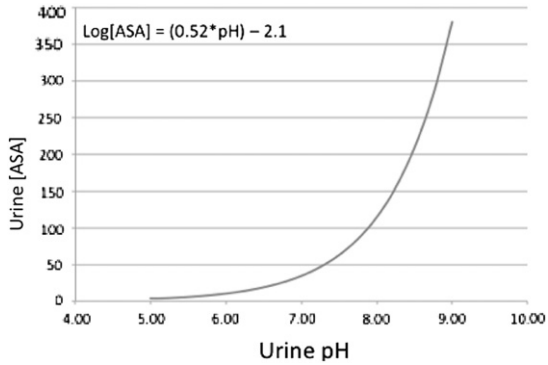

Figure 2. Urinary [ASA] relationship to urinary pH. Adapted with permission from Hoffman RS, Goldfrank LS, et al. *Goldfrank's Toxicologic Emergencies* (10th ed.). New York, NY: McGraw Hill. (In press.)

poisoned patients who received urinary alkalinization,[36] although MDAC is usually preferred in this context[37,38] despite the absence of clinical benefit in one prospective randomized trial.[39]

In 2004, the AACT and EAPCCT published a joint position statement on urine alkalinization.[39a] They recommended its use as first-line therapy for salicylate poisoning in patients who do not meet criteria for hemodialysis. Other poisons for which urinary alkalinization has been proposed are listed in Table 2, but clear evidence for their clinical efficacy is lacking. Hypokalemia is the most common complication of alkalinization, but it can be corrected by giving potassium supplements. Alkalotic tetany is reported occasionally, but overt hypocalcemia is rare.

Urinary Acidification

On the other hand, weak bases will have their kidney excretion promoted in acid urine. Urinary acidification with ammonium chloride or ascorbic acid has been proposed in amantadine, amphetamine, quinidine, or phencyclidine poisoning. However, it is no longer recommended because of modest elimination enhancement and the significant risk associated with metabolic acidosis, particularly in poisoned patients.

A summary of poisons that can potentially be significantly eliminated by corporeal treatments are presented in Table 2.

Extracorporeal Treatments

Extracorporeal treatments (ECTRs) are only used in approximately 0.1% of poisonings treated in the United StatesS[35]; however, this percentage is on the rise and suggests that the indications of these techniques are either increasing or are becoming better understood. Although ECTRs are often viewed as more efficient than corporeal treatments, they are also more invasive, more costly, and require transfer to a specialized center.

Although ECTR can undoubtedly remove certain poisons from the body, it is unclear if this equates to

Table 2. Poisons Which are Amenable to Corporeal Elimination Enhancement

Urinary alkalinization	MDAC	Cholestyramine
2,4-Dichlrophenoxyacetic acid	Acetaminophen[8]	Digoxin
Chlorpropamide[58]	Amatoxin[59]	Digitoxin
Diflunisal	Amitriptyline[60]	Ibuprofen
Fluoride	Carbamazepine[61,*]	Meloxicam
Methotrexate[42]	Cyclosporine	Methotrexate
Phenobarbital	Dapsone*	Mycophenolate mofetil
Primidone	Digitoxin[62,63]	Perfluorinated compounds
Salicylates*	Digoxin	Piroxicam
Sulfonamides	Nadolol	Tenoxicam
	Nortriptyline	Warfarin
	Phenobarbital[39,*]	
	Phenylbutazone	
	Piroxicam[43]	
	Propoxyphene	
	Quinine*	
	Salicylates[64,65]	
	Thallium[66]	
	Theophylline[8,*]	
	Vancomycin	
	Yellow oleander[13,67]	

Abbreviation: MDAC, multiple dose activated charcoal.
*Supported as first-line therapy by AACT/EAPCCT position papers.

a favorable outcome. Almost all of the current evidence comprises case reports and case series. In the rare observational studies, study design and interpretation of the results are often flawed. In one notable example, the result from one study in Li poisoning suggested no positive effect of dialysis, although the presence of confounding by indication might have suggested an opposite interpretation. This has reinforced the respective positions of advocates and opponents of ECTR in poisoning.[40]

In the absence of unbiased comparative clinical studies, potential benefits of ECTR should be weighed against costs and side effects. Unfortunately, complications of ECTR are poorly studied in the context of poisoning. Because hemodialysis is seen as an indispensable treatment for acute kidney injury (AKI) and end-stage renal disease (ESRD), inevitable complications are considered acceptable. In poisoning, in which indications of ECTR are more debatable and where alternative treatments exist, the risk-benefit ratio is undeniably higher. Although the data in poisoning are uncertain, most complications appear to be associated with catheter placement and include pneumothorax, arterial puncture, and bleeding, with reported incidence varying from 1 to 5%.[15,41] The incidence of hypotension during ECTR is unknown, but is probably more often induced by the xenobiotic itself than by the extracorporeal technique.

Specific ECTRs

ECTR removal of any specific poison can be predicted by its physicochemical properties and by the specific mechanism offered by the respective ECTR. Because ECTR only removes solutes from the blood compartment, poisons that have a large volume of distribution (ie, confined mostly in the extravascular compartments) will not be significantly removed by ECTR. In poisons that undergo high endogenous clearance (>4 mL/min/kg), ECTR clearance will be respectively less impressive than in poisons in which metabolism and elimination are low. Likewise, alteration of normal elimination pathways (kidney or hepatic failure) may induce a lower threshold for ECTR.

Hemodialysis

Hemodialysis (HD) remains the technique most often used for the treatment of ESRD and AKI. Solute elimination is based on diffusion through a semipermeable membrane. The molecular cutoff of most conventional dialyzers today is approximately 5000 Da, with poisons of small size being preferentially eliminated. Therefore, the circuit cannot remove poisons that are very large or are bound to proteins. However, because protein binding sites may be saturated in overdose, a larger portion of unbound poison is present that can then be eliminated (eg, valproic acid[42]). Even highly bound poisons can be removable by HD if the dissociation constant to protein is small enough, permitting elimination of a constant pool of unbound poison (eg, phenytoin[43]). The advent of high-efficiency, high-flux dialyzers has rendered other techniques such as HP almost obsolete.[44] HD has added value of rapidly correcting electrolyte and acid-base disturbances and is an additional benefit in metformin poisoning, for example.

Hemofiltration

Hemofiltration (HF) is based on the principle of convection, in which convective forces or solvent drag removes

water and particles. Although most often dispensed continuously in the intensive care unit (as continuous veno-venous HF), several centers in Europe and North America are now offering this as an intermittent therapy for ESRD.[45] Because of the high permeability of hemofilters, HF can clear larger molecules than HD (up to 50,000 Da).

Hemoperfusion

In hemoperfusion (HP), blood passes through a charcoal or resin column to which poisons are adsorbed. HP can remove small- and large-sized poisons (including those that are highly protein bound). Compared with HD, HP is associated with more complications than HD (namely hypocalcemia, thrombocytopenia, leucopenia, hypoglycemia)[46,47] as well as superior cost and early saturation of columns.

Exchange Transfusion

In exchange transfusion (ET), blood is exchanged milliliter per milliliter. It has the advantage of eliminating poison tightly bound to erythrocytes. Although clearances obtained with ET are lower than with other ECTRs, this technique can be performed without the complex apparatus needed for HD. ET is also easier to operate in neonates and has been used for poisoning due to theophylline and salicylates in this population.[48,49] ET is beneficial in poisoned-induced hemolysis, which can follow exposure to xenobiotics such as in chromium, dapsone, and arsine.[50]

Peritoneal Dialysis

In peritoneal dialysis (PD), a solution is inserted in the peritoneal cavity for a short dwell during which poison can diffuse freely from capillaries to the dialysate. Although technically occurring inside of the body, PD can be quickly performed in patients after insertion of a peritoneal catheter, but it does not provide equivalent efficacy compared with HD. Clearances obtained with PD are 15-20 mL/minute at best, compared with 200-250 mL/minute in HD. However, PD may be considered when other more efficient ECTRs are unavailable, in the neonatal patient where PD might be easier to perform than HD, and in poisoning of marginal severity affecting patients already undergoing PD.

Plasmapheresis

In plasmapheresis (PP), plasma (and all of its solutes) is separated from blood and replaced by either 5% albumin or fresh frozen plasma during one or more sessions. PP can usually eliminate very large poisons (up to 3,000,000 Da) such as dextran and rituximab.[51,52] However, most known poisons are small and are therefore better removed by other ECTRs. Compared with HD, PP is also less available and carries more complications.[53]

Liver Dialysis

Liver dialysis (such as single-pass albumin dialysis) is becoming more available for the treatment of hepatic failure, sometimes as a bridge for liver transplantation. Because liver dialysis can remove protein-bound poisons, it has been used for treatment of various poisonings, such as for *Amanita phalloides* and calcium-channel blockers.[54,55] Although promising, these techniques are expensive and have yet to show better toxicokinetic advantages than either PP or even HD.

Combined ECTRs

ECTRs can be combined to optimize the respective advantages of convection, diffusion, and adsorption. For example, HP and HP have been used in series.

Continuous Versus Intermittent Techniques

Continuous techniques are usually dispensed continuously over 24 hours whereas intermittent techniques are usually performed over a standard 4- to 6-hour period (although they can be performed for much longer without expected additional problems). In the critical care setting, continuous techniques are often used for the treatment of oliguric AKI and preferred over conventional HD. This is explained, amongst other reasons, by the possibility to remove fluid over longer periods of time, reducing the risk of hypotension. However, in poisoned patients, fluid removal is rarely necessary, making the potential benefit of CRRT in this context less likely. Because of lower blood and effluent/dialysate flow in CRRT, hourly clearances are at least 2-3 times less than

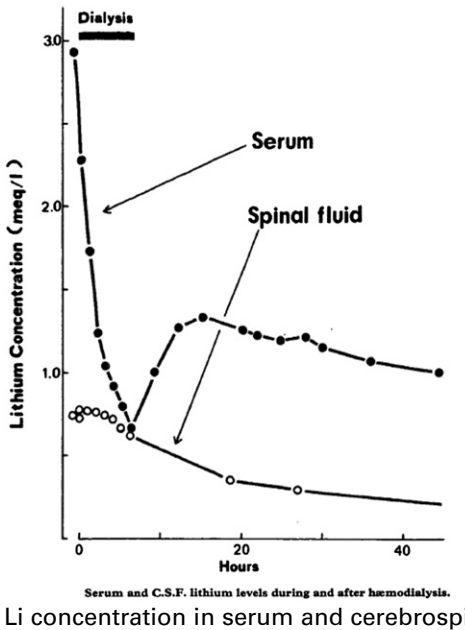

Figure 3. Li concentration in serum and cerebrospinal fluid during dialysis. Reproduced with permission from Science Direct from Amdisen A, Skjoldborg H. Haemodialysis for lithium poisoning. *Lancet*. 1969;2:213.

what can be achieved with intermittent dialysis. Because of its lower efficacy, CRRT is therefore only really preferred in situations when intermittent HD is unavailable, when technical/admission logistics clearly favor CRRT, or in situations of hypotension with coexisting oliguric AKI.

Several authors also mention the added advantage of avoiding plasma rebound with CRRT. Plasma rebound refers to an increase in serum concentration of a poison after interruption of ECTR. This is explained by transfer of poison from central compartments to blood after the procedure. Although this rebound may appear dramatic, this does not necessarily result in increased poison burden in the toxic compartment. As seen in Figure 3, after dialysis, Li concentration increases in the plasma, but this is paralleled by a decrease in Li in the central nervous system (which is where toxicity occurs). A second dialysis then presents an added opportunity to remove more Li. This situation has to be contrasted to situations in which serum rebound occurs because of prolonged absorption of poison, in which case prolonged or repeated ECTR may be indicated.

ECTR can potentially enhance elimination of many poisons and should be considered in life-threatening exposures to barbiturates, ethylene glycol, isopropanol, Li, methanol, methotrexate, salicylates, theophylline, and valproic acid.

Despite the use of ECTR in medical practice for over 60 years, comprehensive guidelines are currently lacking to guide physicians treating poisonings. To provide uniform recommendations, the EXtracorporeal TReatments In Poisoning (EXTRIP) workgroup was formed as an international collaboration of experts representing diverse specialties (nephrology, clinical toxicology, critical care, pharmacology) and supported by over 30 professional societies. For every poison, the clinical benefit of ECTR is weighed against associated complications, alternative therapies, and costs. Rigorous methodology was developed, international literature was reviewed, and pertinent clinical and toxicokinetic data of ECTR were extracted. Rationale, background, objectives, and complete methods of this endeavor were reported previously.[56,57] In the absence of good evidence, rigorous consensus-based recommendations are proposed. Clinical recommendations are expected to be finalized in 2012 and published in early 2013.

Conclusion

Enhanced elimination techniques can effectively decrease the body burden of many toxins, but well-designed studies are currently lacking to quantify their benefits. Corporeal techniques such as resins, urine alkalinization, or MDAC do not usually offer elimination rates similar to ECTR, but they can be instituted in almost every medical facility without delay. ECTRs are more labor-intensive and require transfer to a specialized center. The risk-benefit ratio of elimination enhancement in poisoning appears lowest when the poison is associated with significant morbidity, when alternative therapies are lacking (eg, Fab for digoxin poisoning), and when the poison is amenable to elimination by corporeal or extracorporeal techniques (ie, they contribute to a large proportion to total body elimination).

If any enhanced elimination modality is considered, contact with a regional poison center is recommended to discuss management issues applicable to the poison. Amongst the various ECTRs available, intermittent HD provides the best expected removal for most poisons with the lowest incidence of complication and should therefore be the preferred modality in most cases. Clinical application of ECTR in poisoning should be facilitated by the future publications of recommendations.

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Considerations in the Critically Ill ESRD Patient

Balazs Szamosfalvi and Jerry Yee

ESRD patients are admitted more frequently to intensive care units (ICUs) and have higher mortality risks than the general population, and the main causes of critical illness among ESRD patients are cardiovascular events, sepsis, and bleeding. Once in the ICU, hemodynamic stabilization and fluid-electrolyte management pose major challenges in oligoanuric patients. Selection of renal replacement therapy (RRT) modality is influenced by the outpatient modality and access, as well as severity of illness, renal provider experience, and ICU logistics. Currently, most patients receive intermittent hemodialysis or continuous RRT with temporary vascular access catheters. Acute peritoneal dialysis (PD) is less frequently utilized, and utility of outpatient PD is reduced after an ICU admission. Thus, preservation of current vascular accesses, while limiting venous system damage for future access creations, is relevant. Also, dosing of small-solute clearance with urea kinetic modeling is difficult and may be supplanted by novel online clearance techniques. Medication dosing, coordinated with delivered RRT, is essential for septic patients treated with antibiotics. A comprehensive, standardized approach by a multidisciplinary team of providers, including critical care specialists, nephrologists, and pharmacists, represents a nexus of care that can reduce readmission rates, morbidity, and mortality of vulnerable ESRD patients.

Key Words: Intermittent hemodialysis, Sustained low-efficiency dialysis, Online clearance monitor, Access recirculation monitor, Optical oxygen saturation sensor

Introduction

The incidence of developing dialysis-requiring ESRD is approximately 400 patients per million population in the United States.[1] ESRD patients are several fold more frequently hospitalized and admitted to the intensive care unit (ICU) than patients with normal kidney function. The major causes of admission to the ICU are sepsis,[2] particularly in patients on hemodialysis (HD) using a catheter access, and cardiovascular (CVS) events (eg, acute myocardial infarction, cardiac arrest, congestive heart failure, and cerebrovascular accident), with other common problems including HD access complications and gastrointestinal bleeding.[3] The most important causes of mortality are CVS events and sepsis.[1,4] When compared with patients with normal kidney function, ESRD patients in the ICU have an increased risk of mortality, mostly because of more severe comorbidity burden. ESRD survivors of an ICU admission often remain chronically ill after discharge and remain at a higher risk of mortality, new CVS events, malnutrition, and hospital re-admission for several months.[3,5-7] This review will discuss select aspects of caring for dialysis-dependent patients including the evolving concepts of measuring the delivered dialysis dose, ultrafiltration (UF) monitoring, and anticoagulation. Electrolyte and medication management issues were the subject of another recent review[8] and will be discussed only to a lesser extent here.

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Financial Disclosure: The authors are inventors of the automated regional citrate anticoagulation technology described in U.S. patents.

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Assessment of the ESRD Patient in the ICU

In addition to the acute illness precipitating the ICU admission, ESRD patients may have a multitude of comorbidities, and it may be helpful if the nephrologist follows a comprehensive "checklist" on initial evaluation (Table 1). The ICU admitting diagnosis, evaluation, and treatment plan should be ascertained. The etiology and duration of ESRD; the outpatient dialysis modality and prescription; and any prior documentation of code status, end-of-life wishes, and circumstances under which dialysis withdrawal is desired should be assessed from the history and records. If residual kidney function is present, strategies should be used to preserve it, which is of particular importance in peritoneal dialysis (PD) patients. The hepatitis B surface antigen status should be established, and surface antigen-positive patients must be dialyzed in isolation with dedicated equipment. The PD catheter and exit site should be meticulously cared for by an experienced provider. The HD access should be examined daily for patency and signs of infection and, in the case of an arteriovenous fistula (AVF) or graft (AVG), the extremity should be protected from blood pressure cuffs, venipuncture, and the placement of an arterial catheter. This requirement should be emphasized to the ICU team and clearly documented in the patient's chart. The central veins draining the access arm should also be protected from venous catheters. The use of central venous catheters (CVCs) in the subclavian vein and of peripherally inserted CVCs via veins that could be used in the future for AVF or AVG creation should be avoided if possible. Ultrasound guided placement of a triple lumen CVC in the left internal jugular vein and preservation of the right internal jugular vein for HD access might be a practical approach that also avoids the use of femoral CVCs less preferred because of the increased risk of infection and thrombosis and decreased mobility. Systemic blood samples often can be

obtained during renal replacement therapy (RRT) or from the arterial catheter, reducing the need for venipuncture blood sampling. The extracellular and intravascular fluid volume status should be evaluated at least daily using a combination of physical examination, strict intake and output records, daily weight trends, and, when available, hemodynamic monitoring data trends. UF goals should then be established in close communication with the ICU team. The adequacy of small-solute clearance and electrolyte and acid-base control with dialysis should be monitored closely. The medication administration record must be reviewed daily and when the RRT prescription is changed to avoid the use of medications unsafe in ESRD (eg, succinylcholine, meperidine) and to ensure that drug dosing is adjusted for residual kidney function and delivered RRT. Antibiotic dosing in particular has to be coordinated with RRT and discussed frequently with the pharmacist. Medications unique to this population (eg, erythropoiesis stimulating agents, vitamin D compounds, and phosphate binders) should also be reviewed and used as warranted. Adequate nutrition should be ascertained daily, preferably by enteral feeding using a potassium- and phosphate-restricted formula or diet. Citrate-antibiotic dialysis catheter locking solutions are increasingly applied to prevent catheter infection. The ICU team should be warned to aspirate these before using the catheter during resuscitation to avoid temporary ionized hypocalcemia in the right atrium and ventricle. Finally, the appropriateness of continued aggressive ICU support in light of the patient's clinical course and previously stated advance directives (if available) should be evaluated periodically together with the ICU team and the patient or the surrogate decision-maker.

CLINICAL SUMMARY

- ESRD patients are more frequently admitted to the ICU and have a higher mortality than patients with normal kidney function.
- The delivered dose of hemodialysis may be monitored using online clearance to ensure correction of acid-base and electrolyte changes and inform antibiotic dosing in the ICU.
- Ultrafiltration goals should be defined together with the ICU team to achieve protocol-driven optimization of hemodynamics including central venous O_2 saturation.
- Novel dialysis systems with simple single-needle access and automated citrate anticoagulation may enable the safe use of sustained low-efficiency dialysis with arteriovenous fistula access in the future.

RRT

Dialysis Modality Selection

The proportion of ESRD patients maintained on PD may vary by country and region, resulting in varying utilization of PD in the ICU. Continued use of PD in the ICU may be difficult because of many factors, including the lack of cycler equipment and/or continuous ambulatory peritoneal dialysis (CAPD)-trained ICU nurses, particularly during nocturnal shifts. On the other hand, PD use in the ICU is prevalent and represents a successful, lower-cost alternative to extracorporeal blood purification in developing countries.[9] Usually, patients receive CAPD with 4-6 exchanges a day with volume in the range of 2-3 L adjusted to provide acceptable control of serum chemistry. However, continuing PD may be difficult or contraindicated in patients with severe Gram-negative, polymicrobial, or fungal peritonitis; in patients who require abdominal surgery; in patients with severe respiratory failure in which abdominal distension may further impair gas exchange; and in severely catabolic patients in which CAPD may not provide sufficient acid-base and electrolyte control. As a result, survival of the PD technique during and after an ICU stay is markedly limited.[10] Therefore, the remainder of this section will cover in more detail the more prevalent HD techniques used to support ESRD patients in the ICU.

Most ESRD patients are maintained on 3-times-a-week intermittent hemodialysis (IHD) as outpatients and stay on this modality when admitted to the ICU. IHD machines are designed to deliver 200-300 mL/minute diffusive urea clearance (Kurea) and operate at a blood flow (QB) of 300-500 mL/minute and a dialysate flow (QD) of 400-1000 mL/minute over a period of 3-5 hours.[11] Critically ill ESRD patients may not tolerate such intense therapy well, and the use of gentler, continuous renal replacement therapy (CRRT) may be considered. CRRT machines that use prepackaged, sterile dialysate and/or replacement fluids deliver 25-100 mL/minute diffusive and/or convective Kurea and operate at a QB of 100-300 mL/minute and a dialysate and/or replacement fluid flow of 25-100 mL/min 24 hours a day. Sustained low-efficiency dialysis (SLED) is a so-called hybrid therapy that is usually intermittent and uses an IHD machine to deliver 90-250 mL/minute diffusive Kurea operating at a QB of 200-300 mL/minute and a QD of 100-300 mL/minute over a prolonged period of 8-16 hours.[12]

Most ESRD patients rely on an AVF or AVG for HD access. This is cannulated with an arterial needle to withdraw uremic blood and a venous needle to return dialyzed blood to the patient during IHD, and the operator stays at the bedside to continuously monitor the patient. In the event of a return needle disconnect, life-threatening blood loss could occur in 2-5 minutes. There is no commercial technology that would provide 100% protection against this complication, although some recently approved monitoring systems may reduce the

Table 1. Problem-Focused Evaluation of the ESRD Patient in the ICU

Critical illness	Cause of admission to the ICU with evaluation and management plan.
ESRD history	Cause and duration of ESRD; hepatitis B surface-antigen status; outpatient dialysis prescription including outpatient urea kinetic volume of distribution (V), activated vitamin D and erythropoietin dose, code status, end-of-life wishes, and advance directives for dialysis withdrawal in ICU.
RRF protection	Particularly important in PD patients. Limit IV radiocontrast dye and nephrotoxic medication (eg, aminoglycoside) exposure as feasible.
Dialysis access	Assess for signs of infection. Document the patency of AVF or AVG daily. Ensure proper care of the PD catheter and exit site. Confirm that blood flow is sufficient to achieve the goals of therapy. ICU teams should avoid placing a blood pressure cuff, arterial- or central venous lines, or doing venipuncture on the access arm.
Vein preservation	Obtain blood samples with dialysis or from existing IV- or arterial lines to minimize venipuncture. Limit placement of peripherally inserted CVCs and subclavian venous catheters as feasible.
Volume status and UF	Assess patient weight and fluid intake and output at least daily. Monitor absolute value and trend of central venous pressure and central venous oxygen saturation ($ScVO_2$) as well as invasive arterial blood pressure and computerized pulse waveform analysis data when available.
IVFs	Use isotonic IVFs when possible. Calculate the hyponatremic effects of the free water load from certain IV antibiotics, vasopressors drips, and *N*-acetylcysteine infusions usually provided in 5% dextrose water.
Laboratory studies	Monitor at least daily chemistry profile, albumin, calcium, magnesium, phosphate, and complete blood count. Monitor blood cultures and cardiac laboratory tests as indicated.
Dialysis adequacy	Measure the delivered dose of small-solute clearance (OLC) with every IHD session and deliver at least 1.2 Kt/V (using outpatient or estimated V) 3 times per week. Provide extra treatments as needed for optimal volume and solute control.
Antibiotic dosing	Dose antibiotics in close coordination with the pharmacist, considering drug levels, residual kidney function, delivered small-solute clearance, and clearance of the drug with the modality of RRT and dialyzer utilized.
Other medications	Verify and adjust as needed the dose of blood pressure drugs, digoxin, seizure, and other medications with limited clearance in ESRD.

risk.[13] As a result, double-needle access of AVF and AVG cannot be recommended for safe use to provide either SLED or traditional CRRT in which the ICU nurse operator is not expected to stay at the bedside all of the time. In the absence of a clear survival advantage of CRRT over IHD (plus extrapolating from neutral studies in the acute kidney injury [AKI] population[14]) and considering the need for temporary catheter access for the former, ESRD patients with working AVF and AVG usually receive IHD in the ICU. ESRD patients with pre-existing HD catheter access may conveniently receive any RRT modality. In patients with AVF or AVG who have indications for CRRT (eg, severe hemodynamic instability on vasopressors, marked fluid overload requiring high daily cumulative fluid removal, or high risk of developing increased intracranial pressure [eg, with fulminant liver failure]) the possible complications of placing a temporary HD catheter to allow CRRT use must be weighed against the risks of continued use of IHD with the AVF or AVG. In the near future, machines with novel blood pumps[15] may become available enabling safe, single-plastic-needle access of AVF or AVG for 10- to 12-hour SLED. Compared with traditional CRRT, SLED is associated with important cost savings[16,17] and still allows for gentler solute and volume removal than IHD. Taken together, these developments may favor SLED over traditional CRRT and IHD use in ICU ESRD patients in the future.

Assessment of the Adequacy of HD in the ICU

In the AKI ICU literature, several recent, large, randomized, and controlled studies have failed to confirm that the delivered dose of small-solute clearance has an effect on survival in a broad dosing range once a minimally sufficient dose of uremic clearance is provided.[18,19] Likewise, a large, randomized, and controlled study in the stable outpatient HD population failed to show that increasing the dose of small-solute clearance beyond current Kidney Disease Outcomes Quality Initiative guidelines would lead to better survival.[20] Taken together, these data make it implausible that a simple escalation of delivered small-solute clearance beyond outpatient targets would lead to better outcomes in the critically ill ESRD patient. In the absence of strong evidence-based guidelines for small-solute clearance dosing targets in the ICU ESRD population, the authors believe that the recently published Kidney Disease: Improving Global Outcomes dosing guidelines for IHD and CRRT for ICU AKI patients[21] may also be applied as reasonable and simple dosing goals for ESRD patients.

However, different from the outpatient setting, ESRD patients in the ICU often require accurate dosing of life-saving medications (eg, antibiotics in sepsis), and measurement of the delivered solute clearance may become more relevant to outcomes if it is applied to the complex challenge of precisely dosing dialyzable drugs.[22,23] Further, when a life-threatening electrolyte disorder (eg,-severe hyperkalemia) or profound metabolic acidosis (eg, toxic alcohol ingestion) is diagnosed, being immediately able to measure the delivered small-solute clearance to confirm the efficacy of the RRT procedure in real time may be important and may allow for the detection of a dysfunctional, recirculating access sooner than possible

with the traditional method of analyzing serum chemistry trends on RRT.

Formal urea kinetic modeling, the gold standard of measuring the delivered dose of small-solute clearance during IHD in the outpatient setting, is difficult to perform in the ICU.[24] Traditional anthropomorphic equations[25] used to estimate the urea kinetic volume (V) usually do not correlate well with the much larger true V in the edematous, 10- to 20-L volume overloaded typical ICU patient. The urea generation rate may also be variable and usually increased in the critically ill catabolic patient.[26] Because ICU IHD and CRRT are not infrequently prescribed with no or reduced anticoagulation when compared with outpatient IHD, a gradual decline of the dialyzer performance during a single RRT session is possible and may also contribute to a delivered clearance lower than prescribed. All of these factors can be accounted for, and simplified equations can be used,[27] making urea kinetic modeling eventually feasible in expert academic settings.[28] However, the precise sampling and complex calculation requirements including possible considerations of cardiac output (CO) and systemic vascular resistance (SVR) in the regional blood flow model in critically ill patients may question the feasibility of this approach in routine clinical practice.[29]

Fortuitously, the delivered small-solute clearance can be measured automatically and without cost or risk to the patient using the online clearance (OLC) measurement available on several modern IHD machines.[11] The measurement requires dialysate flow above 300 mL/minute for the rapid modulation of the fresh dialysate sodium (Na) level in the range of 135-155 mEq/L and takes a few minutes to complete. The machine detects the electrical conductivity changes of the fresh and spent dialysate in response to the programmed changes in the fresh dialysate Na level. The way the technology is implemented on the market leader commercial dialysis machine limits the net amount of Na transferred between patient and dialysate to clinically negligible.[30] The effective ionic dialysance (Kecn; about equal to effective Na dialysance and effective urea clearance) is calculated in milliliters per minute; a decline of the dialyzer performance due to partial clotting and access recirculation (AR) reduce its value.[30] The blood temperature monitor (BTM; Fresenius) has multiple functions including measuring the temperature of the incoming and return limbs of the blood circuit to detect AR. For AR measurements, the IHD machine rapidly changes the temperature of the fresh dialysate, thereby indirectly changing the temperature of the venous return blood, and then senses any corresponding temperature change in the incoming blood that should only be observed if AR is present.[31] Correlating the online, automatically determined Kt with the apparent urea volume of distribution determined preferably with bioimpedance spectroscopy allows for the determination of the urea Kt/V with clinically sufficient accuracy and without the need for blood sampling and complex calculations.[32] OLC can also be obtained in 10-hour SLED using a commercial dialysis machine operating in IHD mode for 10 hours at a QB of 170 mL/minute and a QD of 400 mL/minute as recently shown by our group.[33] This approach will lessen the uncertainty about the delivered small-solute clearance during SLED, which made antibiotic dosing difficult and a plausible impediment to the wide adoption of the modality in the past.[34,35]

Finally, optical detection of ultraviolet-light-absorbing solutes in the waste dialysate with simple, low-cost technology was applied to indirectly monitor the delivered urea Kt/V in real time during IHD, and the technology is now available commercially.[36] Distinct from ionic dialysance, optical effluent sensing allows for continuous dialysate solute-level monitoring with immediate detection of changes. Application of this sensor to IHD and intermittent SLED in the ICU may be desirable, but it requires validation. However, because the Kt/V calculations rely on time-dependent reductions in effluent solute concentrations during intermittent therapy, the technology as described would be inapplicable during 24-hour CRRT with constant effluent solute levels in steady state.

In summary, ascertaining the delivered dose of small-solute clearance is feasible now with commercially available OLC technology. Further research in the ICU ESRD population is needed to confirm if OLC can be used to guarantee the delivery of a minimum dose of dialysis equivalent to the Kidney Disease Outcomes Quality Initiative-recommended outpatient 3-times-per-week 1.2 Kt/V HD dose, to immediately detect ineffective dialysis due to AR or partial dialyzer clotting, especially when patients with emergent electrolyte and acid-base changes are treated, and to precisely estimate the dialytic removal of important medications, particularly of drugs for which laboratory measurements are not readily available.

Once the delivered Kt/V is measured, the optimal fresh dialysate Na, potassium (K), and bicarbonate concentration may be adjusted during the RRT session, taking into consideration the patient's kinetic volume and predialysis chemistry and the rate of development of hyperkalemia and acidosis (or in rare clinical scenarios alkalosis) to result in an optimal postdialysis serum electrolyte profile. Generally, postdialysis hypokalemia and metabolic alkalosis should be avoided to lessen the risk of cardiac arrhythmias; therefore, when a large Kt/V is delivered (eg, with prolonged IHD or SLED), fresh dialysate Na, bicarbonate, and K levels should approximate normal plasma chemistry values. It may also be prudent to use a fresh dialysate Na level (possible range on the market leader dialysis machine 130-155 mEq/L) within 10 mEq/L of the patient's predialysis serum Na concentration to avoid an unduly large magnitude and rapid rate of correction of preexisting hyponatremia or hypernatremia, which may also be predicted based on

estimates of total body water and online-measured electrolytic conductivity clearance (Kecn).[37] ESRD patients with serum Na below 120 or above 165 meq/L are rarely encountered; such patients initially may require CRRT with custom-prepared replacement fluid Na levels to avoid unduly rapid correction of their severe dysnatremias. A fair estimate of the bicarbonate delivery during RRT may also be calculated from the delivered ionic dialysance and the average bicarbonate gradient between the patient's systemic plasma and the fresh dialysate. This information may be important to the ICU team to clearly define the severity of ongoing metabolic acidosis, which may be completely masked by several hundred millimoles of bicarbonate provided by the RRT session. The most common example is the development of lactic acidosis during SLED; this sometimes may go unnoticed unless the anion gap is corrected for hypoalbuminemia and trended and/or a dedicated lactate measurement is ordered.

Hemodynamic Optimization including Fluid Therapy and UF

Fluid Administration to ESRD Patients

ESRD patients admitted to the ICU may have low effective arterial blood volume and hemodynamic instability due to any combination of cardiac dysfunction, sepsis, severe liver disease, gastrointestinal bleeding, volume depletion, and third spacing after extensive surgery with or without overall extracellular fluid (ECF) volume reduction. Restoration of intravascular volume and circulation may require the administration of large volumes of intravenous fluids (IVFs). In the absence of ESRD patient-specific guidelines, the authors believe it is reasonable to assume that the principles of early goal-directed therapy[38] may also be applicable to the ESRD population with the obvious caveat that excess fluid infusion is more difficult to correct in anuric patients. However, by definition, anuric ESRD patients are unable to regulate their ECF tonicity without urine output, and even patients who have RRF are unlikely to be able to generate a significant medullary osmotic gradient and thereby variable urine tonicity. Therefore, to maintain a normal serum Na concentration and tonicity, the use of isotonic IVFs is usually required. In these patients, the effect on an ECF Na concentration of 1 L of IVF gained or 1 L of body fluid lost with a specific Na and K content can be reliably calculated and predicted.[39,40] The hyponatremic effect of hypotonic infusions (eg, vasopressors, *N*-acetylcysteine) and certain antibiotics administered in 5% dextrose-water IVF commonly used in the ICU should be predicted and if needed mitigated with the use of a higher Na fresh dialysate. When such calculations are omitted (eg, when a small ESRD patient receives 5-6 L of 0.45% half-isotonic saline perioperatively), clinically dangerous hyponatremia will develop, inexorably necessitating emergent dialytic correction. Even when ECF expansion is achieved while maintaining normotonicity, it is very difficult clinically to avoid "overshoot" and the development of varying degrees of ECF overload with or without pulmonary congestion in this usually anuric population. Finally, even if meticulous attention is paid to hemodynamic monitoring during IVF administration, pulmonary edema may develop with the resolution of the initial systemic inflammatory response syndrome (SIRS) causing rapid mobilization of third-spaced ECF volume, again requiring extra session(s) of or CRRT.

Hemodynamic Assessment to Guide UF Goals

Fluid overload may be present on ICU admission or may complicate the fluid therapy of critical illness in ESRD patients, and fluid overload is known to be associated with poor clinical outcomes in AKI.[41] A major goal of kidney support is to reduce the extracellular volume expansion with UF. However, it is very difficult to do this safely without compromising organ perfusion because patients are often hemodynamically unstable with insufficient intravascular refill rates that can fluctuate dramatically.[42] To guide IVF use, ICU teams often place catheters in the internal jugular vein with ultrasound guidance to monitor the absolute value and the trend of the superior vena cava O_2 saturation ($ScVO_2$) and central venous pressure in preference to the prior practice of using pulmonary artery catheters. The $ScVO_2$ is generally accepted as a useful, dynamic, surrogate marker of CO at unchanged arterial O_2 content and body O_2 consumption, with a lower value signifying a lower CO state.[43] $ScVO_2$ has also been associated with outcomes and complications after major surgery,[44] and optimization of $ScVO_2$ is a component of early goal-directed therapy for SIRS.[38] Computerized arterial pressure waveform analysis on dedicated devices may complement such monitoring because an arterial pressure line is usually in place in these patients. Obtaining a two-dimensional echocardiogram to define right and left ventricular systolic function, to detect and grade valvular heart disease, and to assess the presence of a pericardial effusion is noninvasive and may prove very helpful.

UF with Online Monitoring

Rapid net UF during IHD can lead to variable degrees of hemoconcentration and a corresponding relative reduction in the circulating blood volume with the ultimate development of hypotension and organ hypoperfusion. It is possible to detect this phenomenon in real time by integrating a low-cost, disposable optical chamber into the dialysis blood circuit prefilter and using a commercial optical hematocrit, relative blood volume, and O_2 saturation monitor. A pulse oxymeter-like sensor clips onto the

chamber from the outside and measures blood absorption of transmitted light at multiple wavelengths. The device calculates and displays the hematocrit, the hemoglobin level, and the O_2 saturation of the circuit incoming blood in real time. When the dialysis catheter tip is in the superior vena cava, the monitor essentially displays the $ScVO_2$ online at a negligible cost compared with a dedicated $ScVO_2$ monitoring catheter and device, and it may help to reduce net UF rates that are not tolerated before dangerous hemodynamic compromise develops. Conversely, blood volume monitoring was not useful to predict hypotension in the ICU,[45] but it could help detect catastrophic overultrafiltration, which rarely can and does happen due to operator error or equipment malfunction.[46] It is important to note that reliable readings during IHD and SLED may require very effective anticoagulation to prevent biofouling of the optical chamber. Once it develops, intradialytic hypotension may be treated by reducing the hourly net fluid removal rate and by small IVF or albumin boluses. The use of a slightly colder fresh dialysate temperature of approximately 35.0-35.5°C during IHD may also help lessen the incidence of hypotension by providing a mechanism to maintain the core temperature of the patient without the need for skin vasodilatation and increased perfusion for heat loss through radiation to the environment. Conversely, heat loss from the blood circuit during SLED and CRRT is essentially guaranteed because of the lower blood and dialysate or replacement fluid flows. Therefore, the use of a dialysate temperature below 36.5°C (including CRRT without a fluid warmer) is not recommended because it may lead to clinically significant hypothermia and mask a febrile state.

Anticoagulation During IHD, SLED, or CRRT

ESRD patients are at increased risk of bleeding in the ICU because of uremic platelet dysfunction and the possible presence of recent surgical wounds or gastrointestinal arteriovenous malformations. For brief (3- to 5-hour) IHD anticoagulation-free treatment sessions, saline flushes of the blood circuit may suffice. Use of acid concentrates with a final 1X dialysate content of 2.4-3 mEq/L citric acid as opposed to 3-4 mEq/L acetic acid may also have a modest anticoagulant effect. However, when using citric-acid-based dialysate, a 0.5-mEq/L higher dialysate calcium content may be necessary to achieve the same systemic ionized calcium level as with a 3- to 4-mEq/L acetic-acid-based dialysate.[47] Less thrombogenic blood circuits, catheters, and dialyzers incorporating novel surface-modifying macromolecules[48] and airless, nonturbulent blood flow pathways are in development and may be helpful in the future.

When an anticoagulant is necessary, the use of unfractionated heparin may be attempted because it is relatively short-acting and its effect can be reversed. Many other anticoagulants have been used during ICU dialysis and were recently reviewed.[49] However, all of these drugs, including heparin, have significant side effects and most importantly can increase the risk of systemic bleeding.

Regional citrate anticoagulation (RCA) is a very effective method to prevent clotting of the extracorporeal blood circuit without any systemic bleeding tendency. The procedure has gradually gained ground for CRRT and has been applied during IHD and 8- to 10-hour SLED.[17,50] RCA is now recommended in the Kidney Disease: Improving Global Outcomes Clinical Practice Guideline for Acute Kidney Injury as the method of choice for anticoagulation of CRRT circuits when citrate use is not contraindicated.[21] However, RCA use in nonexpert centers has been limited by concerns about severe electrolyte complications including hypercalcemia or hypocalcemia, hypernatremia, metabolic alkalosis, or acidosis, particularly in patients with shock and severe liver dysfunction. These complications were noted less frequently when RCA was used during intermittent SLED[17,50] and the principles of safe, near-automated delivery of RCA for IHD and SLED were described.[51] In our large ICU RRT program serving 160 ICU beds in a single center, we have been using 10- and 24-hour SLED-RCA protocols safely for many ESRD patients with catheter access even in the presence of severe liver dysfunction and/or shock.[33] Citrate accumulation and electrolyte abnormalities due to RCA are not observed, and clotting of the extracorporeal circuit is virtually never seen. In the future, 10-hour SLED-RCA may also increase the use of single-needle access of AVF and AVG in the ICU by eliminating the clotting risk inherent to the intermittent circuit blood flow.[52]

Quality Improvement Initiatives

ICU Dialysis Telemetry

In outpatient HD, telemetry collection of dialysis machine data during treatment is becoming mandatory in the United States. For example, one of the largest outpatient dialysis providers has been collecting online small-solute clearance data from its units as a proposed adequacy assessment and targeting tool for about a decade.[53,54] Computer and software technology developed for this purpose are easily adaptable to monitor IHD and SLED treatments provided in the ICU to ESRD patients.[33] Such data collection could confirm the duration of RRT, the delivered small-solute clearance, and the frequency and cause of machine alarms leading to treatment interruptions. This would be of obvious interest in the ICU, where considerably more variation in patient condition, treatment prescriptions, and complications occurs than in the outpatient setting. The wirelessly collected data can be stored on secure servers and used in real-time and post hoc quality monitoring and quality

improvement projects; we are now implementing such a program.[33]

Communication Between Providers

The importance of daily, detailed communication between the ICU team and the pharmacist was discussed earlier. A detailed report to the outpatient nephrologist about the hospital course and postdischarge care plan is also indispensable. ESRD patients may experience marked weight loss after a protracted ICU stay, which must be communicated for an immediate lowering of the estimated dry weight used in the outpatient dialysis center to correctly set net UF goals and prevent volume overload due to the use of an outdated, higher estimated dry weight. Conversely, patients may be discharged still recovering from SIRS with reduced blood pressure medications and significant ECF overload from earlier IVF therapy. Such patients may need daily outpatient HD for a few days for volume control and a gradual increase in blood pressure medications as they recover fully. Antibiotic therapy started in the ICU is often completed with postdialytic dosing in the outpatient HD unit. Detailed communication of the indication, duration, and dose of each agent is indispensable for optimal care. Changes to the outpatient medication regimen (eg, antihypertensive pills after an admission for uncontrolled hypertension) must also be communicated to allow the HD unit to monitor the effects of and compliance with the new drug schedule.

Discharge Planning to Prevent Re-Admissions

ESRD patients have an increased risk of mortality after the survival of an ICU admission, and in the United States the 30-day hospital re-admission rate of ESRD patients is very high at 36%.[1,55] Communicating in simple terms to the patient and family the cause of the hospital admission and the main treatment received is important for compliance with the care plan after discharge. In particular, compliance with the outpatient dialysis, diet, and adjusted medication regimen must be emphasized. Access to follow-up with the primary doctor and adequate insurance coverage and financial means to obtain the prescribed medications should be ascertained. Postdischarge follow-up phone calls and a home visit by a nurse can also help monitor and ensure patient compliance with the discharge plan.

Summary

ESRD patients are frequently admitted to the ICU, and their management poses many unique challenges. Meticulous attention to IVF therapy, optimization of hemodynamic status, medication dosing, and sophisticated use of multiple RRT strategies are all important elements of critical care support. Recognizing the higher risk of subsequent morbidity and mortality in ESRD patient ICU survivors and developing a comprehensive, multidisciplinary team strategy during the ICU stay and the discharge process may help improve outcomes and reduce hospital re-admissions.

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Erratum to The Rheumatology of Gout

In the article "The Rheumatology of Gout" (Sundy JS, Advances in Chronic Kidney Disease 19:404-412), page 408 incorrectly cites the dose of pegloticase (Krystexxa, Savient Pharmaceuticals, Bridgewater, NJ) as 8 mg twice weekly. The correct dose is 8 mg given as an intravenous infusion every two weeks.[1]

Reference

1. Package insert: Highlights of prescribing information, KRYSTEXXA (pegloticase). Available at: http://www.savientpharma.com/pdf/KRYSTEXXA%20Prescribing%20Information.pdf. Accessed December 10, 2012.

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Critical Care for the Nephrologist

Kathleen D. Liu, MD, PhD
Guest Editor

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Cover Image: Fluid overload is gaining increased recognition as a complication of acute kidney injury and is common in critically ill patients. "The Drowning Kidney" was created by Heather Deacon, Biographica.

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