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SPECIAL FEATURE

Preventive Tactics and Management of Acute Kidney Injury in the ICU

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Acute kidney injury (AKI) is a sudden decline in renal function due to nephron dysfunction and/or damage that results in nitrogenous waste product accumulation and acid-base, electrolyte, and fluid disturbances. It is estimated to occur in 16-67% of critically ill patients admitted to the ICU. Common inciting causes include major surgery, iatrogenic interventions, and sepsis. Advanced age and comorbidities increase kidney susceptibility to various exposures and insults.[1] Severe AKI requiring renal replacement therapy (RRT) is associated with a 10-fold increase in mortality and increases length of stay an average of 5.7 days.[2] Preventive tactics and RRT remain the cornerstones of AKI management in critically ill patients.

IDENTIFY HIGHER-RISK PATIENTS

Prevention starts with identifying patients at higher risk for AKI. Common associated risk factors include age, gender, genetic predisposition, and multiple comorbid medical conditions, such as heart failure, diabetes, hypertension, and chronic kidney disease (CKD).[3] Patients > 65 years of age are twice as likely to sustain AKIs as patients 50-64 years of age. Patients > 75 years of age sustain AKIs three times as often as others. Interestingly, this finding is much more strongly associated with male gender.[4] Although ethnicity does not seem to affect AKI development, some studies suggest African Americans are at greater risk, perhaps because of the CKD prevalence in this population.[3]

Preexisting CKD or estimated glomerular filtration rate (eGFR) < 60 mL/min carries a high risk for AKI development.[3,4] The effects of age, gender, and race appear to be attenuated in higher stages of CKD. It is unclear if these factors play less of a biological role or if the risk for AKI in patients with advanced CKD is so great that contributions from other factors become insignificant.[5] Patients with CKD are more likely to experience progression of their disease after episodes of AKI. Those patients

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with a baseline eGFR < 45 mL/min were 30% more likely to die or progress to end-stage renal disease (ESRD).[6] Patients with proteinuria (albuminuria > 300 mg/g creatinine) are at a 2.5-fold risk of AKI compared to patients with undetectable urine albumin levels.[5]

Chronic liver disease and heart failure with reduced ejection fraction also are associated with a higher risk of AKI. Rates of AKI in cirrhosis range from 20-50%, depending on aggravating factors such as hypotension, hypoalbuminemia (< 3 g/dL), and spontaneous bacterial peritonitis.[7] AKI has been described in up to 60% of patients admitted with decompensated systolic heart failure and is associated with a greater need for renal replacement therapy.[8] A history of hypertension increases the risk for AKI by an overall odds ratio of 2 and in various settings, including contrast administration, lung resection, severe aortic dissection, and abdominal surgery.[9] Diabetes confers only a mild risk of developing AKI, but the contribution of this comorbidity is established most strongly in the setting of iodinated contrast administration and cardiovascular surgery. In comparison with nondiabetic subjects, patients with type 1 and type 2 diabetes undergoing coronary bypass graft surgery had an odds ratio of 4.9 and 1.3 to develop AKI, respectively.[10]

The risk of AKI and AKI progressing to ESRD after a major cardiac and vascular surgery is highest in patients with advanced CKD.[11] The incidence of AKI requiring RRT following cardiac surgery can be 30% higher in CKD patients, especially in the setting of complex disease (i.e., left main coronary disease) and postsurgical cardiogenic shock.[12] Longer cardiopulmonary bypass or cross-clamp time and "off-pump" procedures also strongly increase the risk of AKI.[13] Vascular surgery may carry an even higher risk for AKI than cardiac surgery, with severe AKI rates from 15-75% in patients who require thoracic and abdominal aortic interventions (depending on baseline renal function).[14]

Risk assessment models have been developed and validated to predict AKI in specific populations. Using information from the National Cardiovascular Data Registry CathPCI Registry, Tsai et al identified 11 variables associated with AKI in patients undergoing cardiac catheterization. *(See Table 1.)* ST-elevation myocardial infarction presentation, cardiogenic shock, and severe baseline CKD were the strongest predictors for AKI.[15] These variables were used to develop the risk prediction model that has demonstrated good subsequent performance to predict AKI incidence (C-statistic, 0.76) and need for dialysis (C-statistic, 0.92).[16]

MAXIMIZE RENAL PERFUSION

Intravascular volume expansion to maintain renal perfusion in high-risk patients is the best demonstrated tactic to prevent AKI. Fluid administration has been shown to decrease AKI risk in several clinical settings, including myoglobinuric or hemoglobinuric AKI, radiocontrast nephropathy, and aminoglycoside- and amphotericin-associated nephrotoxicity. Fluids also have been shown to decrease the risk of intratubular obstruction from crystal deposition in tumor lysis syndrome and drug-induced crystalline nephropathies.[17] Isotonic crystalloids are preferred, as multiple clinical studies have proven synthetic colloids to be nephrotoxic.[18] Recent evidence suggests the use of balanced crystalloids (Ringer's lactate or PlasmaLyte) instead of saline is associated with a lower risk of AKI.[19]

As AKI progresses, one of the earliest consequences is the loss of normal autoregulation of renal blood flow during blood pressure fluctuations. Rapid hemodynamic stabilization, optimization of cardiac output, and maintenance of renal perfusion (generally by maintaining a mean arterial pressure > 65 mmHg) is essential to prevent further renal injury. However, once the injury is established, the potential benefit of further volume expansion must be balanced with the unwanted consequence of fluid accumulation and overload.[20] A large randomized trial comparing dopamine to norepinephrine as initial vasopressors in patients with septic shock showed no significant differences between groups regarding renal function or mortality, although norepinephrine was associated with less arrhythmias and was superior regarding survival in patients with cardiogenic

shock.[21] In clinical trials, vasopressin increases blood pressure and enhances diuresis in hypotensive oliguric patients with sepsis, but it has not yet been proven to enhance survival nor been shown to prevent or ameliorate AKI.[22]

MINIMIZE NEPHROTOXIC MEDICATIONS AND IODINATED CONTRAST

Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and nonsteroidal anti-inflammatory medications increase the risk of AKI in critically ill patients. Their harmful effects are worse in the setting of advanced age, sepsis, volume depletion, eGFR < 45 mL/min, impaired systolic function, postcardiac surgery, and advanced cirrhosis. As their primary effect is on renal hemodynamics and only results in tubular damage with prolonged use, most patients recover renal function within three to five days after discontinuation of these agents.

Antibiotics such as vancomycin, aminoglycosides, and beta-lactams are associated with more selective damage to tubular and interstitial cells and have been associated with both severe AKI and the need for RRT. Elevated vancomycin trough levels (> 35 µg/mL) have been strongly associated with acute tubular necrosis and AKI.[23] Aminoglycoside toxicity is related primarily to duration of therapy and typically develops after five to seven days of treatment (earlier in the presence of CKD). Preceding signs of renal toxicity include concentrating defects, low-grade proteinuria, granular casts in the urine sediment, elevated fractional excretion of sodium (FENa), and urinary loss of potassium and magnesium. Prolonged exposure to high-dose, broad-spectrum beta-lactams (e.g., piperacillin-tazobactam, cefepime, or ampicillin-sulbactam) have been associated with increased AKI risk. Several recent reports have raised concerns about the risk of AKI with the combination therapy of piperacillin-tazobactam and vancomycin. In our institution, a short course (< 72 hours) of piperacillin/tazobactam plus vancomycin was not associated with an increased risk of AKI or long-term adverse renal outcomes compared to other empiric broad-spectrum antibiotics commonly used in the ICU.[24]

The risk of contrast-induced nephropathy (CIN) ranges from 1-25%. The strongest predictor for CIN is kidney function at the time of exposure, but contrast (volume, osmolarity, arterial vs. venous infusion) and patient factors (hypotension, sepsis, diabetes, heart failure, advanced age, concomitant nephrotoxins) are additional strong contributors to severe CIN and the need for RRT. The authors of multiple studies have shown that administration of isotonic crystalloids prior to and following contrast exposure reduces the risk of AKI and is most beneficial in patients with an eGFR < 30mL/min.[25] The authors of the recent PRESERVE trial, a comparison of commonly applied tactics to prevent CIN, showed there was no benefit of IV sodium bicarbonate vs. IV sodium chloride or oral acetylcysteine vs. placebo to prevent a composite outcome of death, need for dialysis, or persistent decline in kidney function at 90 days or for the prevention of CIN.[26] Notably, higher-risk patients, including those undergoing emergency procedures more typical of the critically ill, were excluded from this trial.

Table 1: Variables Associated With Acute Kidney Injury in Patients Undergoing Percutaneous Coronary Intervention

- Age
- Baseline chronic kidney disease (mild/moderate/severe)
- Prior cerebrovascular disease
- Chronic heart failure
- Prior percutaneous coronary intervention
- ST-elevation myocardial infarction
- Diabetes
- Chronic lung disease
- Hypertension
- Cardiac arrest
- Anemia
- Heart failure on presentation
- Cardiogenic shock
- Use of intra-aortic balloon pump

URINE BIOMARKERS

Creatinine is recognized as an insensitive biomarker for AKI. Recently, the FDA approved the NephroCheck Test, a quick, quantitative measurement of the cell cycle arrest biomarkers tissue inhibitor of metalloproteinase-2 and insulin-like growth factor binding protein 7. These urinary biomarkers increase in response to renal tubule cell stress or early injury due to exposures known to cause AKI. A primary clinical cutoff value (0.3) for the NephroCheck Test is both specific to AKI (i.e., not caused by other comorbidities such as CKD or sepsis) and identifies critically ill patients at imminent risk of developing moderate to severe AKI in the next 12 hours.[27] A second, high-specificity cutoff (2.0) was selected and verified in patients at the highest risk of AKI. Both cutoff values underwent confirmatory validation in a multisite study that used clinical adjudication to determine the primary endpoint of moderate-severe AKI. A positive test identifies patients who may be candidates for kidney-sparing management tactics that are outlined in the Kidney Disease Improving Global Outcomes (KDIGO) guidelines for high-risk patients.[28,29]

ELECTRONIC MEDICAL RECORD DECISION SUPPORT

Consistently applying best evidence-based practices to bedside practice is a challenge for many common critical care conditions, and AKI is no exception.

Electronic alert systems to notify intensivists about nephrotoxic side effects of drugs prescribed for septic patients and to recommend hydration protocols in at-risk patients undergoing contrast studies have demonstrated impressive reductions in the development of AKI.[30] More recently, a clinical decision support system that alerts physicians of creatinine changes and/or early stages of AKI using KDIGO criteria with a suggested management approach has been shown to reduce the need for RRT, hospital length of stay, and mortality.[31]

DIAGNOSTIC APPROACH

Urine analysis is a priority in any suspected case of AKI. A normal urine sediment suggests either a prerenal or postrenal etiology, although hematuria, pyuria, or crystalluria also may be seen in obstructive uropathy. Proteinuria and urinary sediment containing abundant cells or casts suggests an intrinsic process. The presence of many renal tubular epithelial cells, epithelial cell casts, or pigmented (muddy brown) granular casts suggests the diagnosis of acute tubular necrosis (ATN) and a higher risk for severe AKI and RRT.

In the appropriate clinical setting, the presence of white blood cells (WBCs) and WBC casts suggests acute interstitial nephritis.[32] Although eosinophiluria also may be seen in association with interstitial nephritis, the specificity and sensitivity of this finding is very limited (< 40%). Urine eosinophils can be seen with ATN, atheroembolic disease, and urinary tract infections.[33] The use of FENa or urine Na excretion to help distinguish the etiology of AKI carries poor specificity and sensitivity. Such use should be considered only in the setting of oliguria without recent loop diuretics, radiocontrast, glomerulonephritis, myoglobinuria, or sepsis. FE-urea (< 35% for prerenal and > 65% for ATN) and FE-uric acid (< 7% for prerenal AKI and > 20% for ATN) both offer better sensitivity and specificity. Injury biomarkers detect AKI 36-48 hours earlier than serum creatinine and urine output.

Although not validated for clinical use, urine and/or plasma neutrophil gelatinase-associated lipocalin (NGAL) has been reported to be an effective early marker of AKI in sepsis, postcardiac surgery, and drug-induced renal damage. Plasma NGAL > 150-200 ng/dL has been used in numerous AKI trials as an early and specific marker for AKI and has shown a good correlation with impaired renal recovery, need for RRT, and increased mortality.[34-36] The furosemide stress test is another important functional evaluation tool. A positive test (< 200 mL urine two hours after IV furosemide 1-1.5 mg/kg) in patients with AKI stage 1 is highly predictive of progression to AKI stage 3 (area under the curve, 0.87).[37]

STARTING RENAL REPLACEMENT THERAPY

The decision to start RRT should be individualized, integrating baseline clinical information (i.e., CKD, injury and functional biomarkers, renal reserve), acute diagnosis, illness severity, nonrenal organ dysfunction, and physiologic and laboratory data to determine the patient trajectory in the dynamic setting of critical illness.

Among patients facing life-threatening AKI complications, the decision to start RRT generally is clear. Severe hyperkalemia refractory to medical therapy, marked metabolic acidosis with a persistent bicarbonate < 12 mEq/L or pH < 7.15, symptoms of uremia and/or blood urea nitrogen > 110-120 mg/dL, and/or fluid overload > 10% of basal body weight or resulting in high FiO_2 that is difficult to wean are commonly accepted indications to initiate RRT treatment.[17]

Unfortunately, outside these urgent indications, the best method and timing of RRT remains elusive. There are many postulated benefits of continuous RRT (CRRT) in the critically ill. CRRT does not affect blood pressure as much, reducing the need for escalation in vasopressors in critically ill patients. CRRT may confer more rapid correction of electrolyte and acid-base derangements, better control of azotemia, and improved fluid balance homeostasis when initiated early.

In select patients at high risk for worsening AKI, early CRRT could prevent overt complications of fluid overload, which may be independently associated with mortality. CRRT may unload a damaged kidney by providing added solute clearance, reducing metabolic demand, limiting exposure to nephrotoxins or unnecessary diuretics, and perhaps facilitating repair and recovery. CRRT also may modulate inflammation/immune function in sepsis and attenuate subsequent cardiac complications, platelet dysfunction, and lung injury.

Unfortunately, these theoretical benefits have not been demonstrated consistently in trials comparing CRRT to intermittent hemodialysis. The ELAIN trial is the most recent to suggest significant improvements in mortality, renal recovery, inflammatory markers, days free of mechanical ventilation, and length of stay in ICU.[36]

A conservative tactic consisting of supportive management resulted in spontaneous recovery of renal function without RRT in 25-49% of patients with AKI stage 3 who were randomized to standard or delayed initiation of RRT for acute indications.[38-40] Late RRT initiation in the AKIKI[39] and IDEAL-ICU[40] trials showed no difference in

mortality at 28-90 days, length of ICU stay, days free of vasopressor or mechanical ventilation support, and dependence on RRT at 30 days vs. patients who received early RRT initiation. Patients who received conservative management or delayed initiation of CRRT demonstrated earlier spontaneous diuresis, a lower risk of catheter related-bloodstream infections, thrombosis, iatrogenic episodes of hemodynamic instability, less hypophosphatemia and hypocalcemia, and reduced lower muscle weakness because of fewer barriers to mobilization.[38-40] RRT also can remove metabolic and nutritional factors such as hydrosoluble vitamins, microelements (copper, zinc, selenium), amino acids, and free-unbound hormones. The impact of this effect on outcomes of critical illness is still unknown.

SUMMARY

There is a frustrating patchwork of conflicting clinical studies in this area. Best critical care practices must focus on systematic efforts and computer-based decision support to identify patients at high risk for AKI. Further, these practices must minimize the risk of this common and significant disorder through diligent efforts to maximize renal perfusion, minimize unnecessary exposure to nephrotoxins, and judiciously administer balanced crystalloid solutions, especially prior to contrast exposure. When AKI occurs, urine sediment analysis, FE-urea, FE-uric acid, the furosemide stress test, and the NephroCheck Test all can help identify individuals at a higher risk of progressing to severe disease and RRT.

Although there are many hypothetical benefits to CRRT in the critically ill, evidence supporting the best mode and timing of RRT remains elusive. Treatment is individualized in the absence of life-threatening indications that have failed medical management. ■

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ABSTRACT & COMMENTARY

Finding a Consensus on ARDS Diagnostics and Determining a Relationship to Hospital Mortality

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Mr. Kallet reports he is a major stockholder in the Asthma & Allergy Prevention Company, is a consultant for Getinge Group, and receives grant/research support from Nihon-Kohden.

SYNOPSIS: Critical care physicians reviewed more than 700 mechanically ventilated patients with acute hypoxemia and reached a consensus on the presence of acute respiratory distress syndrome (ARDS) in 15% of patients and nonconsensus on the presence of ARDS in an additional 14% of cases. Hospital mortality was not different between these cohorts (37% and 35%, respectively).

SOURCE: Sjoding MW, Hofer TP, Co I, et al. Difference between patients in whom physicians agree and disagree about the diagnosis of ARDS. *Ann Am Thorac Soc* 2018; Oct 15. doi: 10.1513/AnnalsATS.201806-434OC. [Epub ahead of print].

In a single-center retrospective study, a panel of 13 critical care physicians (seven advanced pulmonary critical care fellows and six critical care faculty, three of whom had been involved in ARDS clinical trials) reviewed 738 mechanically ventilated patients with acute onset hypoxemia (an arterial oxygen tension to inspired oxygen fraction [PaO_2/FiO_2] < 300 mmHg) for the presence of ARDS using the Berlin Definition during the first week of hospitalization. All available electronic data were reviewed, including chest radiographs and CT scans. Clinicians used a standardized evaluation tool for identifying ARDS. Overall variation in ARDS diagnosis was examined according to variations in clinician assessments and differences between subject presentations.

Based on results of physician reviews, patients received an estimated probability of ARDS depending on the degree of physician agreement; patients with greater agreement that ARDS was present had a higher estimated ARDS probability. Patients were categorized as consensus-ARDS (probability of

ARDS, > 80%), disagreement (probability of ARDS, 20-80%), and no ARDS (probability of ARDS, < 20%).

The panel performed more than 1,800 reviews. Individual members varied widely in their determination of ARDS (8-47%). However, between clinicians there was 69-83% agreement on the presence of ARDS. Only 7% of the total variation in diagnosing ARDS was attributable to clinicians vs. patient attributes. Nonetheless, in half the patients diagnosed with ARDS, there was substantial disagreement between critical care physicians. The highest rate of ARDS diagnosis occurred among faculty who had participated in ARDS clinical trials (34%), followed by other critical care faculty (30%) and fellows (20%).

Statistically significant patient characteristics distinguishing consensus vs. disagreement on the diagnosis of ARDS included the presence of pneumonia (75% vs. 49%, respectively), noncardiogenic shock (62% vs. 43%, respectively), and bilateral "airspace disease" on chest radiograph (70% vs. 23%, respectively). Smaller differences in the presence of nonpulmonary sepsis (35% vs. 32%, respectively) were not significant. Overall, derived decision rules based on these results indicated that the combination of pneumonia, noncardiogenic shock, and a nadir PaO_2/FiO_2 < 120 mmHg revealed the highest consensus (63%) and lowest nonconsensus (16%) for diagnosing ARDS. The only significant differences in clinical outcomes between consensus and nonconsensus cohorts diagnosed with ARDS were mean days of severe hypoxemia (3.2 days vs. 2.0 days, respectively) as well as ventilator-free days (14 days vs. 16 days, respectively).

■ COMMENTARY

One of the most vexing and contentious issues in ARDS is that clinicians often cannot agree on which patients actually have the syndrome. This can substantially affect how these patients are managed and their ultimate outcomes. This problem has existed for as long as the syndrome has been formally recognized. One is reminded of Petty's famous editorial "Confessions of a Lumper," which described misuse of the designation, although he personally considered it "a desirable lumping of a variety of pulmonary insults."[1] In this context, the lack of appreciable differences in hospital mortality between consensus and nonconsensus cohorts is the most meaningful result of this study. ARDS is an acute, hyperinflammatory process that at onset almost invariably is associated with nonpulmonary organ dysfunction regardless of severity.[2] Historically, 90% of ARDS mortality results from progressive multiorgan dysfunction. The emerging picture over the past two decades suggests that common clinical interventions (e.g., use of physiologic tidal volume) that reduce the inflammatory process (rather than exacerbate it) are associated with fewer organ dysfunction episodes and better outcomes. Therefore, from a practical standpoint, clinicians should be less concerned about the certainty of diagnosing ARDS. Rather, our focus should be on whether patients are in a hyperinflammatory state and whether chest mechanics suggest the presence of either stretch-related or shear-related lung injury. In essence, once engaged, the hyperinflammatory state (and associated multiorgan injury) does not cease upon reaching arbitrary cutoffs in PaO_2/FiO_2. Our management tactics not succumb to that illusion.

An insightful finding of the Sjoding et al study was the influence of clinician experience. The highest rates of ARDS diagnosis were made by physicians who participated in clinical trials of ARDS, whereas the lowest was among critical care fellows. This suggests that clinicians whose practices largely focus on the detection of ARDS may be more attuned to the subtlety of syndrome presentation as well as an awareness of the multitude of less common mechanisms that produce ARDS. ■

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2. Kallet RH, Lipnick MS, Zhou H, et al. Characteristics of nonpulmonary organ dysfunction at onset of acute respiratory distress syndrome based on the Berlin definition. *Respir Care* 2018; [in press].

CME/CE INSTRUCTIONS

To earn credit for this activity, please follow these instructions:

1. Read and study the activity, using the provided references for further research.

2. Log on to **ReliasMedia.com** and click on My Account. First-time users must register on the site using the eight-digit subscriber number printed on their mailing label, invoice, or renewal notice.

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CME/CE QUESTIONS

1. **The goal of the furosemide stress test in the ICU is to:**
   a. diagnosis early acute kidney injury (AKI) in a patient with a normal estimated glomerular filtration rate (eGFR).
   b. predict the progression of AKI stage 1 to AKI stage 3.
   c. identify recovery of renal function in patients with AKI stage 3.
   d. evaluate the benefits of additional volume resuscitation.

2. **A 65-year-old male with chronic kidney disease (CKD) stage 3 (eGFR 35 mL/min) is admitted with septic shock. NephroCheck on admission is 3.5 ng^2/mL^2. This result suggests:**
   a. the need for emergent renal replacement therapy.
   b. the need for aggressive fluid resuscitation.
   c. a current diagnosis of AKI stage 3.
   d. a high risk of developing AKI stage 3.

3. **Which of the following interventions is associated with a lower risk for AKI in critically ill patients?**
   a. Early use of angiotensin-converting enzyme inhibitors
   b. Use of synthetic colloids, such as gelatin, for volume expansion
   c. Close monitoring of creatinine and urine output in CKD patients
   d. High doses of furosemide before iodinated contrast

4. **Which statement is true regarding the diagnosis of acute respiratory distress syndrome (ARDS) in the Sjoding et al study?**
   a. Critical care fellows diagnosed ARDS more frequently than attending physicians.
   b. Attending physicians who participated in ARDS trials diagnosed the fewest number of ARDS cases.
   c. There was substantial disagreement between critical care physicians in half the patients diagnosed with ARDS.
   d. None of the above

CME/CE OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- identify relevant topics in the practice of critical care medicine;
- utilize recommendations from current clinical guidelines; and
- manage common critically ill patient and ICU administration scenarios.