Critical Care Nephrology: Core Curriculum 2009

Kathleen D. Liu, MD, PhD, MAS

INTRODUCTION

In the inpatient setting, a high proportion of nephrology consultations are requested for patients in the intensive care unit (ICU). These patients may have acute kidney injury (AKI) or may be critically ill and have end-stage renal disease (ESRD). Thus, nephrologists need to understand recent evidence-based advances in the field of critical care, as well as areas of ongoing controversy and investigation. In this article, we summarize the diagnosis and management of shock, as well as the management of sepsis, acute lung injury/acute respiratory distress syndrome (ALI/ARDS), and fulminant hepatic failure, all of which are associated with high mortality in the critical care setting. We discuss infectious complications of critical care, including ventilator-associated pneumonia and catheter-related infections. Supportive care, including nutrition, insulin therapy, and anemia management, are reviewed. Dialysis considerations in critically ill patients are discussed. Last, we review the management of several life-threatening intoxications, many of which require early recognition and consideration of dialysis.

SHOCK

Definition: absolute hypotension (eg, systolic blood pressure $<$ 90 mm Hg or mean arterial pressure [MAP] $<$ 60 mm Hg) or relative hypotension (eg, decrease in systolic blood pressure $>$ 40 mm Hg) resulting in inadequate end-organ perfusion.[1,2]

Causes

I. Hypovolemic: hemorrhage, volume depletion due to decreased fluid intake or excessive fluid losses
II. Distributive: low systemic vascular resistance
  A. Sepsis
  B. Anaphylaxis
  C. Endocrine: adrenal insufficiency
  D. Neurogenic: spinal shock
III. Cardiogenic: acute myocardial infarction, heart failure, valvular heart disease, arrhythmias
IV. Obstructive: extracardiac disease resulting in poor cardiac function: decreased cardiac filling (eg, tamponade, mechanical ventilation with high positive end-expiratory pressure resulting in decreased venous return) or increased cardiac afterload (massive pulmonary embolism)

Diagnosis[3]

I. Echocardiography: transthoracic or transesophageal
II. Invasive hemodynamic monitoring
  A. Central venous catheter
    1. Central venous pressure (CVP) may be artificially high in patients on mechanical ventilation and high levels of positive end-expiratory pressure (increases intrathoracic pressure)
    2. Superior vena cava oxygen saturation ($ScVo_2$) as a correlate of mixed venous oxygen saturation (which can be measured only with a pulmonary artery catheter)
      a. Correlation with mixed venous oxygen saturation somewhat controversial[4]
  B. Pulmonary artery catheter
    1. Pulmonary artery occlusion pressure/pulmonary capillary wedge pressure reflects left atrial pressure in the absence of significant valvular heart disease

Originally published online as doi: 10.1053/j.ajkd.2008.12.018 on March 23, 2009.

Address correspondence to Kathleen D. Liu, MD, PhD, MAS, Division of Nephrology, Department of Medicine, Critical Care Medicine, Department of Anesthesia, Box 0532, University of California, San Francisco, San Francisco, CA 94133. E-mail: kathleen.liu@ucsf.edu

0272-6386/09/5305-0025$36.00/0
doi:10.1053/j.ajkd.2008.12.018

Table 1. Hemodynamics in Various Shock States

	CVP	Cardiac Output	SVR
Cardiogenic	High	Low	High
Hypovolemic	Low	Low	High
Distributive	Low	High	Low

Abbreviations: CVP, central venous pressure; SVR, systemic vascular resistance.

2. Cardiac output monitoring: Fick or thermodilution
   a. Thermodilution cardiac output monitoring unreliable with triscupid valve disease
   b. Fick cardiac output monitoring uses mixed venous oxygen saturation (obtained from the pulmonary artery) to calculate cardiac output; assumes normal oxygen consumption

C. Cardiac output, systemic vascular resistance, and CVP can be used to distinguish between the different types of shock (Table 1)

D. Pulmonary artery catheterization has not been shown to be of benefit in critically ill or surgical populations.[5-7] In general, CVP monitoring is sufficient. Pulmonary artery catheters may be associated with complications, including infection, arrhythmias, and pulmonary artery rupture. However, in cases of mixed shock (eg, septic and cardiogenic), invasive cardiac output monitoring may be useful to tailor vasopressor therapy. Echocardiography also may be useful in the management of complex (eg, mixed cause) shock or shock in a patient with known heart failure

III. Other methods to monitor cardiac output (partial carbon dioxide rebreathing, pulse contour analysis) are less well validated

A. Arterial catheter
   1. Allows for beat-to-beat blood pressure monitoring
   2. Radial, femoral, or dorsalis pedis sites preferred
   3. Perform Allen test before radial arterial catheter placement to confirm adequate collateral circulation
   4. Avoid ulnar and brachial arteries because of greater risk of limb ischemia

IV. Serum tryptase levels can be useful in anaphylaxis

Treatment

I. Treat underlying cause of shock (infection, myocardial infarction)

II. Volume resuscitation for hypovolemia

A. Data do not support the use of colloids (albumin, hydroxyethyl starch) over isotonic crystalloid solutions[8,9]

B. In patients with sepsis, hydroxyethyl starch administration has been associated with an increased incidence of AKI and should be avoided[10]

III. Vasoactive agents (Table 2)[2]

A. Vasopressors increase vascular tone, which in turn increases MAP

B. Inotropes increase cardiac contractility and therefore cardiac output

C. Commonly used medications include:
   1. Phenylephrine (neosynephrine): pure α agonist
   2. Dopamine: dopamine receptor, β and α agonist (dose dependent)
   3. Dobutamine: β1 and β2 agonist, use can be associated with hypotension; often used to increase cardiac output in patients with cardiogenic shock caused by congestive heart failure
   4. Epinephrine: β1 greater than α1, β2 receptor agonist
   5. Norepinephrine (Levophed): α1 and β1 agonist, associated with less tachycardia than epinephrine
   6. Vasopressin: has been used as a second-line pressor for refractory septic shock; use can be associated with significant mesenteric ischemia
   7. Milrinone/amrinone: phosphodiesterase inhibitors with inotropic and vasodilatory effects; used along with dobutamine for the treatment of patients with cardiogenic shock in the setting of congestive heart failure

IV. Early goal-directed therapy for sepsis (see Sepsis IV)

Table 2. Summary of Vasopressor and Inotropic Agents

Vasopressors	Comments
α Agonists	
Phenylephrine (neosynephrine)	High doses can be associated with reflex bradycardia
Mixed α/β agonists	
Norepinephrine (Levophed)	Causes less tachycardia than epinephrine
Epinephrine	
Dopamine agonists	
Dopamine	Like epinephrine, associated with significant tachycardia
Other	
Vasopressin	Increases vascular smooth muscle receptor tone via V1 receptor
Inotropes	
β Agonists	
Dobutamine	Use can be associated with hypotension
Phosphodiesterase inhibitors	
Milrinone	
Amrinone	

V. Corticosteroids for adrenal insufficiency (see Sepsis VI)
VI. Anaphylaxis: epinephrine, H1 and H2 blockers, steroids
VII. Supportive care: intubation and mechanical ventilation if needed

SEPSIS

Diagnosis[11]

I. Systemic inflammatory response syndrome (SIRS): characterized by the presence of: (1) temperature greater than 38°C or less than 36°C, (2) heart rate greater than 90 beats/min, (3) respiratory rate greater than 20 breaths/min or need for support with mechanical ventilation, and (4) white blood cell count greater than 12,000 cells/μL or less than 4,000 cells/μL
II. Sepsis: suspected or documented infection in association with 2 or more SIRS criteria
III. Severe sepsis: sepsis with acute organ dysfunction
IV. Septic shock: severe sepsis with hypotension despite adequate fluid resuscitation

Prognosis[12]

I. Approximately 750,000 cases/y in the United States, resulting in approximately 200,000 deaths
II. Mortality rate approximately 30% to 40%, but greater in sicker populations
III. Major risk factor for AKI

Treatment[11]

I. Appropriate broad-spectrum antibiotics and control of source of infection (eg, debridement, removal of infected catheter)
II. Volume resuscitation
III. Vasopressors as needed
   A. Data supporting choice of first vasopressor limited
   B. Norepinephrine/Levophed may be reasonable because it will increase systemic vascular resistance and increase cardiac output[13]
   C. A recent clinical trial does not support the use of vasopressin as a first-line agent in combination with norepinephrine (Vasopressin and Septic Shock Trial [VASST])[14]
IV. Early goal-directed therapy: refers to the combination of volume resuscitation/vasopressors and inotropes/transfusion guided by CVP (target CVP, 8 to 12 mm Hg), arterial blood pressure (MAP $>$ 65 mm Hg), $ScVo_2$ ($ScVo_2 > 70\%$), and evidence of end-organ perfusion (urine output $>$ 0.5 mL/kg/h)
   A. A single-center randomized clinical trial showed mortality benefit with early institution of these interventions (within 6 hours of diagnosis)[15]
      1. A multicenter clinical trial (Protocolized Care for Early Septic

Shock [PROCESS]) is ongoing to confirm results of the initial study and try to better correlate these interventions with benefit

V. Activated protein C was shown to have mortality benefit for patients with severe sepsis with Acute Physiology and Chronic Health Evaluation (APACHE) II score of 25 or higher in a large randomized multicenter clinical trial[16]
   A. Activated protein C has not been shown to be of benefit in children or less critically ill adults[17,18]
   B. A clinical trial of critically ill adults with refractory shock (PROWESS-SHOCK) is ongoing[19]

VI. Role of steroids for relative adrenal insufficiency is controversial[20]
   A. Diagnosis of relative adrenal insufficiency should be considered with refractory shock after volume resuscitation
   B. Both basal cortisol level and response to high-dose corticotropin (ACTH) stimulation test have been used to define adrenal insufficiency in the critically ill,[21] although criteria for adrenal insufficiency are controversial
   C. Annane et al[22] showed a mortality benefit with hydrocortisone/fludrocortisone treatment for 7 days in patients with relative adrenal insufficiency and early septic shock in a multicenter placebo-controlled randomized clinical trial
   D. However, in a subsequent multicenter placebo-controlled randomized clinical trial, low-dose hydrocortisone therapy did not improve survival in patients with septic shock[23]
      1. Treatment with hydrocortisone was associated with a shorter time on vasopressor therapy, but also with an increase in new sepsis and new septic shock
      2. Differing results may be attributable to differences in duration of septic shock, severity of illness, steroid administration (patients in study by Annane et al[22] randomly assigned earlier, had higher severity of illness scores, and received fludrocortisone and hydrocortisone)
   E. In both studies, patients were randomly assigned after the ACTH stimulation test, but before results were available; thus, patients should be treated empirically with steroids if there is a concern for relative adrenal insufficiency, rather than waiting for results of the stimulation test

VII. Other supportive care as warranted by the clinical condition: intubation and mechanical ventilation, nutrition, glycemic control

VIII. Data for some of the Surviving Sepsis guidelines are limited

ALI/ADULT RDS

Diagnosis[24]

Acute onset (<7 days) of:

I. Hypoxemia: Pao_2/fraction of inspired oxygen (Fio_2) less than 300 for ALI, less than 200 for ARDS
II. Bilateral infiltrates on chest radiograph
III. No clinical evidence of left atrial hypertension

Risk Factors[25]

I. Infection: pneumonia, sepsis
II. Aspiration
III. Trauma
IV. Transfusion

Prognosis[26]

I. Mortality rate 25% to 40% in most recent studies

Treatment

I. Lung protection with a low tidal volume ventilation strategy has mortality benefit for patients with ALI/ARDS[27]
   A. Tidal volume, 6 mL/kg ideal body weight (versus 12 mL/kg ideal body weight)
   B. Ideal body weight: $50 + 2.3 \times$ (height in inches $- 60$) for men, $45.5 + 2.3 \times$ (height in inches $- 60$) for women
   C. Plateau pressure less than 30 mm H_2O
   D. Goal Pao_2, 55 to 80 mm Hg
   E. Target pH, 7.30 to 7.45

1. For moderate acidosis (pH, 7.15 to 7.30), can increase respiratory rate (not to exceed 35) until pH 7.35 or $Paco_2$ less than 25 mm Hg
2. For severe acidosis (pH < 7.15), can increase respiratory rate (not to exceed 35), increase tidal volume, or administer intravenous bicarbonate

F. Permissive hypercapnia/respiratory acidosis may be problematic in patients with concomitant AKI or chronic kidney disease who may have concurrent metabolic acidosis[28]

II. A fluid conservative management strategy increases ventilator-free days in patients with ALI/ARDS[29]
   A. Patients with ESRD or AKI requiring dialysis at the time of study enrollment were excluded from the fluid management study
   B. The fluid conservative management strategy was not associated with an increased requirement for dialysis
   C. Patients in the fluid-conservative group received diuretics to achieve a target CVP of 4 to 8 mm Hg or pulmonary artery occlusion pressure of 8 to 12 mm Hg provided they: (1) were out of shock for 12 hours, (2) had effective circulation based on cardiac index or physical examination, and (3) were not oliguric, defined as urine output less than 0.5 mL/kg/h
III. Higher levels of positive end-expiratory pressure do not appear to have mortality benefit for patients with ALI[30-32]
IV. Rescue therapies include:
   A. Extracorporeal membrane oxygenation (ECMO)
   B. High-frequency ventilation
   C. Partial liquid ventilation with a perfluorocarbon
   D. Inhaled nitric oxide
   E. Prostacyclin
V. Animal studies suggest that injurious mechanical ventilation (eg, high tidal volume) and lung injury can lead to AKI,[33-35] although the molecular mechanisms have not been fully elucidated. Similarly, AKI may lead to or exacerbate existing lung injury in animal models

VENTILATOR-ASSOCIATED PNEUMONIA[36]

I. Clinical suspicion of infection: new fevers, leukocytosis or purulent respiratory secretions, worsening respiratory failure/increased ventilator support
II. Culture: gold-standard methods are unclear
   A. Many ways to obtain culture specimens, including such quantitative methods as bronchoalveolar lavage and protected specimen brush, as well as nonquantitative cultures and endotracheal aspirates
   B. Although bronchoalveolar lavage and protected brush specimens with quantitative cultures may allow for more rapid antibiotic deescalation, superiority to nonquantitative methods is not clear[37-39]
III. Appropriate empiric initial antibiotic therapy is key: antibiotics should be tailored to known local antimicrobial resistance patterns
IV. Patients with ventilator-associated pneumonia are at high risk of sepsis and associated AKI

CATHETER-RELATED INFECTIONS

Definitions[40]

I. Catheter colonization: presence of bacteria or fungi in a quantitative or semiquantitative culture of catheter material, but without signs of local or systemic infection. Microorganisms grow in a biofilm that coats the surface of the catheter
II. Exit-site/insertion-site infection: erythema, tenderness, induration, or purulence at the site the catheter exits the skin
III. Tunnel infection: erythema, tenderness, induration, or purulence in the tract where a venous catheter is tunneled under the skin
IV. Catheter-related bloodstream infection: bacteremia in the presence of positive cultures from the catheter itself (see Diagnosis section)

Incidence

I. Catheter-related bloodstream infections are more common with nontunneled than tunneled central catheters
II. Major risk factors for infection include duration of catheter use, number of catheter

lumens (multilumen catheters carry greater risk of infection), poor technique at the time of catheter insertion, use of total parenteral nutritition (TPN)[41]

III. Although subclavian catheters generally are associated with lower risk of infections compared with internal jugular and femoral catheters, these should be avoided in patients with AKI or ESRD because of the risk of subclavian stenosis

IV. Although the internal jugular site generally is believed to be associated with less risk of infection than the femoral site, a recent randomized clinical trial suggests that the risk of infection is similar with nontunnelled femoral and internal jugular dialysis catheters in critically ill immobilized patients.[42] However, in patients in the highest tertile of body mass index (>28.4 kg/m^2), femoral catheters were associated with increased risk of infection compared with internal jugular catheters. Furthermore, these results cannot be generalized to mobile non–critically ill individuals

Diagnosis[43]

I. Differential time to positivity: if a blood sample drawn from the catheter is positive more than 2 hours before the peripheral-blood culture, this is highly suggestive of catheter-related bloodstream infection

II. Quantitative blood cultures: if a blood sample drawn through the catheter has a greater concentration (≥5:1 ratio) of microorganisms than the peripheral-blood culture, this is highly suggestive of catheter-related bloodstream infection

III. Quantitative culture of catheter segment or catheter tip: requires removal of central venous catheter

Treatment[44]

I. Empiric broad-spectrum antibiotics; staphylococci are common pathogens

II. Removal of central venous catheter; however, this decision will depend on: (1) ongoing need for central venous access, (2) ability to replace the catheter at another site, (3) clinical status of the patient, and (4) type of infection/pathogen

III. Indications for catheter removal include: septic shock, presence of a tunnel infection, polymicrobial bacteremia, gram-negative rod bacteremia, fungemia, evidence of distant infection (abscesses, endocarditis), and failure to respond to antibiotic therapy

NUTRITION/TPN

I. Patients who are critically ill frequently are hypermetabolic/hypercatabolic and therefore at increased risk of nutritional complications[45]

II. Calorie requirements can be estimated by using predictive equations (Harris-Benedict or Mifflin-St Jeor for obesity) or measured by using indirect calorimetry (in which oxygen consumption and carbon dioxide generation are measured in expired gas and used to calculate resting energy expenditure and the respiratory quotient [RQ])
   A. Indirect calorimetry is less accurate as oxygen requirements increase and generally is not useful when the patient requires an F_{IO_2} greater than 0.60
   B. Indirect calorimetry also allows for calculation of the RQ; a high RQ (≥1.0) suggests overfeeding (of either total calories or carbohydrates) or a hypermetabolic state

III. Nitrogen balance can be used to determine whether provision of nutrition therapy (particularly protein) is adequate
   A. Protein requirements of patients with AKI vary based on the underlying cause of AKI and type of renal support provided (both intermittent hemodialysis and continuous renal replacement therapy [CRRT] associated with ongoing protein losses)[46]
   B. Patients on CRRT likely will require at least 1.6 to 1.8 g/kg/d of amino acids and, in some studies, have received up to 2.5 g/kg/d without complications

IV. Serum markers for nutritional adequacy in the critically ill are controversial[45]
   A. Although serum albumin level is a valuable prognostic indicator of morbidity and mortality, serum albumin levels decrease with metabolic stress and with specific disease states that are common in the ICU, such as liver failure

   B. Transferrin, prealbumin, and retinol-binding protein levels may be superior markers of nutritional status; however, in patients with critical illness, synthesis of these proteins may decrease because of preferential production of acute-phase reactants (ie, C-reactive protein)
   C. Prealbumin level may be falsely increased in patients with kidney failure because of reduced clearance and in patients on high-dose steroid therapy
   D. Trends of prealbumin and C-reactive protein levels may be more useful than absolute values to follow up response to nutrition therapy
V. In an observational cohort study, critically ill patients with AKI did not have significantly more major gastrointestinal complications (vomiting, diarrhea, abdominal distention) or more infectious complications (aspiration pneumonia)[47]
VI. TPN is associated with increased risk of infection and should be used only if efforts to provide enteral nutrition have failed or the patient has a strict contraindication to enteral feeding

INTENSIVE INSULIN THERAPY

I. A large randomized clinical trial of surgical patients showed mortality benefit and decreased length of ICU stay in patients who received intensive insulin therapy (target blood glucose, 80 to 110 mg/dL [4.4 to 6.1 mmol/L])[48]
II. A subsequent randomized clinical trial of medical patients did not show the same mortality benefit[49]
   A. However, patients who had longer ICU stays (defined as ≥3 days) had decreased in-hospital and ICU mortality with intensive insulin therapy
III. Intensive insulin therapy is associated with an increased incidence of severe hypoglycemia[50]
IV. It is unclear whether the benefit is from glycemic control or a direct effect of the insulin itself
V. A pooled analysis of the large medical and surgical clinical trials suggest that patients with better glycemic control had lower mortality rates; however, it is unclear whether this was a result of the improved glycemic control or differences in severity of illness[51]
VI. Similarly, a pooled analysis of the 2 large clinical trials and a meta-analysis suggest that intensive insulin therapy has a renoprotective effect[52,53]
VII. However, a recent meta-analysis of 29 clinical trials (8,432 patients) did not show a difference in mortality or need for dialysis therapy between patients randomly assigned to tight versus usual glucose control.[54] There was a decreased incidence of bacteremia and marked increase in the incidence of hypoglycemia (glucose < 40 mg/dL [<2.2 mmol/L]) in the tight-control group. Of note, target glucose level in the tight-control group varied across these studies from less than 100 to less than 144 mg/dL (<5.6 to <8.0 mmol/L)
VIII. Thus, the optimum target glucose level in critically ill patients is unclear at present

ANEMIA MANAGEMENT

Target Hemoglobin in Critically Ill Patients

I. A large randomized clinical trial suggested that a restrictive transfusion strategy (transfusions only for hemoglobin < 7 g/dL) was safe and associated with a trend toward improved clinical outcomes compared with a liberal transfusion strategy (transfusions for hemoglobin < 10 g/dL)[55]
II. Of note, patients with chronic anemia (hemoglobin < 9 g/dL) and those with active bleeding were excluded. In addition, the investigators noted that results may be less applicable to patients with active myocardial ischemia because a greater proportion of these patients were not enrolled in the trial because of refusal on the part of the treating physician to allow study participation

Role of Erythropoietin Therapy in Critically Ill Patients

I. In a recent placebo-controlled randomized clinical trial, recombinant erythropoietin did not decrease the number of transfusions needed or the proportion of patients who received transfusions[56]

II. Erythropoietin therapy was associated with an increased number of thrombotic events
III. Given recent findings of significant complications associated with erythropoiesis-stimulating agents in clinical trials of patients with chronic kidney disease and oncology patients,[57,58] routine use in the critical care setting cannot be recommended at this time in the absence of kidney disease

DIALYSIS CONSIDERATIONS

Modality

I. Intermittent dialysis and CRRT can be considered equivalent modalities for the treatment of patients with AKI[59,60]
II. There may be a subset of patients who are critically ill with refractory hypotension or increased intracranial pressure (eg, patients with fulminant hepatic failure) in whom CRRT is preferable
    A. CRRT: continuous fluid/volume management and slow clearance
        1. Arteriovenous (AV) and venovenous (VV) modalities, now primarily VV modalities
        2. Continuous VV hemofiltration (CVVH): convective clearance
        3. Continuous VV hemodialysis (CVVHD): diffusive clearance
        4. Continuous VV hemodiafiltration (CVVHDF): convective and diffusive clearance
    B. CRRT may necessitate anticoagulation to prolong the half-life of the filter
    C. Anticoagulation typically administered prefilter to minimize systemic anticoagulation
        1. Heparin and citrate are most common types of therapy
        2. Citrate chelates calcium, a necessary cofactor in the coagulation cascade
            a. Major risk of citrate anticoagulation is hypocalcemia
            b. Can also be associated with metabolic alkalosis (1 molecule of citrate is converted to 3 molecules of bicarbonate)
    D. Drug dosing: in general, medications should be dosed for a creatinine clearance of 10 to 50 mL/min; if possible, follow up drug levels to optimize dosing
III. Slow low-efficiency dialysis (SLED): 8 to 12 h/treatment, 6 treatments/wk; hybrid technique with improved hemodynamic tolerance

Access

I. For critically ill patients with ESRD, CRRT modalities require placement of a temporary or tunneled catheter

Membrane

I. Biocompatible membranes are in more common use and may be associated with improved survival and shorter time to renal recovery[61]
II. Cuprophane membranes can lead to complement activation and infiltration of the kidneys by inflammatory cells, including neutrophils, which may increase renal injury and thereby delay renal recovery

Dose

I. A recent large multicenter randomized clinical trial (Acute Renal Failure Trial Network [ATN] study) suggested there was no benefit with more intensive dialysis (CVVHDF with effluent flow rate of 35 mL/kg/h or intermittent hemodialysis 6 times/wk with Kt/V of 1.2/session) compared with less intensive dialysis (CVVHDF with effluent flow rate of 20 mL/kg/h or 3 times/wk intermittent hemodialysis)[62]
    A. Patients with chronic kidney disease (defined as creatinine $>$ 2.0 mg/dL [$>$177 μmol/L] in men and 1.5 mg/dL [133 μmol/L] in women) were excluded
II. These results are supported by a large single-center study comparing 2 doses of CRRT[63]; a multicenter study of 2 doses of CVVHDF is ongoing
III. Conversely, single-center clinical trials suggested mortality benefit with greater doses of CVVH and intermittent dialysis
    A. For the CRRT study, there may have been differences in the characteristics of patients treated and treatment characteristics[64] (including a greater proportion of surgical patients, fewer patients with sepsis, and inclusion of patients with chronic kidney disease, as well as use of lactate-based replacement fluid and postfilter replacement fluid administration)

B. For the intermittent hemodialysis (IHD) study, doses of dialysis provided per treatment were lower than in the ATN study[65]

Timing

I. Optimum timing of the initiation of dialysis therapy for patients with AKI is unclear, although observational studies have suggested potential benefit to earlier initiation of dialysis therapy[66,67]
II. A number of the critical care practices described in this article may impact on the metabolic parameters that trigger the decision to initiate dialysis therapy.[28] Specifically, low tidal volume ventilation and permissive hypercapnia may exacerbate acidemia in a patient with AKI and associated metabolic acidosis. Early goal-directed therapy may ultimately result in volume overload, and, depending on the fluid selected for resuscitation, hyperchloremic metabolic acidosis. Steroid administration for relative adrenal insufficiency may exacerbate azotemia and volume retention. Thus, these changes in critical care practice may necessitate earlier initiation of dialysis therapy in selected patients

FULMINANT HEPATIC FAILURE

I. Common causes: medications/toxins (acetaminophen, *Amanita phalloides* mushroom poisoning, other drug reactions), acute viral infections (hepatitis B, hepatitis A), vascular causes (portal vein thrombosis, hepatic vein thrombosis = Budd-Chiari syndrome), metabolic diseases (Wilson disease, acute fatty liver of pregnancy, Reye syndrome), cryptogenic[68,69]
II. Orthotopic liver transplantation is definitive therapy
III. Mortality high with supportive care alone
IV. Common complications include:
    A. Hepatic encephalopathy
    B. Cerebral edema: can lead to increased intracranial pressure and brain stem herniation
        1. Major cause of mortality in this population
        2. Patients with compromised kidney function may require CRRT to avoid fluctuations in intracranial pressure and tight volume control (especially in setting of transfusions of large volumes of blood products)
    C. AKI: altered hemodynamics, direct toxicity
        1. Because of large volume of blood products and cerebral edema, may require support with CRRT before conventional "indications" are met[69]
    D. Coagulopathy
    E. Hypoglycemia
    F. Infection/sepsis

INTOXICATIONS

I. Acetaminophen
    A. *N*-Acetylcysteine
    B. Supportive care for fulminant hepatic failure, including metabolic acidosis (hepatocyte necrosis and inability to metabolize lactate can result in severe lactic acidosis)
    C. AKI, may be direct effect of acetaminophen leading to acute tubular necrosis or hepatorenal syndrome; usually recovers spontaneously, but may require dialytic support
    D. 5-Oxoprolinuria and associated metabolic acidosis may occur in susceptible individuals, even when only recommended doses of acetaminophen are administered[70]
        1. Consider in a patient with recent acetaminophen use, unexplained metabolic acidosis, altered mental status
        2. *N*-Acetylcysteine may increase glutathione levels and be of benefit
II. Salicylates[71]
    A. Classically presents with respiratory alkalosis and anion gap metabolic acidosis
    B. Symptoms include tinnitus, altered mental status, nausea/vomiting
    C. Activated charcoal for gut decontamination
    D. Glucose should be administered if the patient has altered mental status because aspirin can cause central nervous system (CNS) hypoglycemia, even with normal serum glucose concentrations

E. Sodium bicarbonate to promote mobilization of salicylates from tissue stores to plasma and urinary excretion
F. Hemodialysis: altered mental status, volume overload, plasma salicylate concentration greater than 100 mg/dL

III. Methanol/ethylene glycol[72,73]
A. Present with anion gap acidosis and osmolar gap
B. Early recognition is critical
C. Visual changes, including blurry vision, central scotomata, blindness, retinal edema, and hyperemia of the optic disk, are characteristic of methanol poisoning
D. Oliguria and calcium oxalate crystals in urine are characteristic of ethylene glycol toxicity; can use UV light (Woods lamp) to look for fluorescence in urine (fluorescein added to most antifreeze)
E. Fomepizole/ethanol competitively inhibit alcohol dehydrogenase and prevents the formation of toxic metabolites (methanol is converted to formate, ethylene glycol is converted to glycolate/glyoxylate/oxalate)
F. Dialysis will remove both the alcohols and toxic metabolites
1. Should not wait for confirmatory testing result to initiate treatment
2. Consider empiric therapy in a patient with unexplained anion gap acidosis, osmolar gap, and suspected ingestion/evidence of end-organ dysfunction
G. Additional supportive care, including folate/thiamine

IV. Lithium[74]
A. Presents with altered mental status, neuromuscular excitability, tremors, nausea, vomiting, seizures
B. Consider dialysis based on absolute level and symptoms
C. Slow equilibration between intracellular and extracellular lithium may lead to plasma rebound and necessitate extended dialysis sessions (8 to 12 hours)

V. Metformin[75]
A. Can be associated with life-threatening lactic acidosis, in particular, when used in patients with reduced kidney function or hepatic dysfunction, heart failure, history of lactic acidosis, or ongoing hypoperfusion or hemodynamic instability
B. Metformin should be held if a patient requires parenteral contrast for a computed tomographic scan for at least 48 hours poststudy to ensure normal kidney function
C. In patients with life-threatening acidosis, dialysis will remove metformin and allow for the provision of bicarbonate to treat the acidosis

VI. Other toxicities to consider for treatment with hemodialysis: paraquat, isopropanol, theophylline (cleared by means of dialysis, but more efficiently cleared by using charcoal hemoperfusion)

SPECIAL ACID-BASE AND ELECTROLYTE ABNORMALITIES

I. Propofol can be associated with life-threatening metabolic acidosis, especially in children[76]
II. Lorazepam (Ativan) infusions contain polyethylene glycol as a carrier agent and can be associated with anion gap acidosis[76]
III. Cerebral salt wasting with CNS disease (subarachnoid hemorrhage, postneurosurgery) can lead to profound hyponatremia[77]
A. Can be differentiated from CNS-associated syndrome of inappropriate antidiuretic hormone (SIADH) by volume status: cerebral salt wasting leads to hypovolemia, patients with SIADH are euvolemic

ACKNOWLEDGEMENTS

Support: Dr Liu is supported by National Institutes of Health/National Center for Research Resources/Office of the Director University of California, San Francisco Clinical and Translational Science Institute Grant No. KL2 RR024130.

Financial Disclosure: None.

REFERENCES

1. Parrillo J: Approach to the patient with shock, in Goldman L, Ausiello D (eds): Cecil Medicine (ed 23), chap 107. Philadelphia, PA, Saunders Elsevier, 2007

2. Herget-Rosenthal S, Saner F, Chawla LS: Approach to hemodynamic shock and vasopressors. Clin J Am Soc Nephrol 3:546-553, 2008

3. Davison D, Junker C: Advances in critical care for the nephrologist: Hemodynamic monitoring and volume management. Clin J Am Soc Nephrol 3:554-561, 2008

4. Chawla LS, Zia H, Gutierrez G, Katz NM, Seneff MG, Shah M: Lack of equivalence between central and mixed venous oxygen saturation. Chest 126:1891-1896, 2004

5. Sandham JD, Hull RD, Brant RF, et al: A randomized, controlled trial of the use of pulmonary-artery catheters in high-risk surgical patients. N Engl J Med 348:5-14, 2003

6. Wheeler AP, Bernard GR, Thompson BT, et al: Pulmonary-artery versus central venous catheter to guide treatment of acute lung injury. N Engl J Med 354:2213-2224, 2006

7. Richard C, Warszawski J, Anguel N, et al: Early use of the pulmonary artery catheter and outcomes in patients with shock and acute respiratory distress syndrome: A randomized controlled trial. JAMA 290:2713-2720, 2003

8. Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R: A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med 350:2247-2256, 2004

9. Perel P, Roberts I: Colloids versus crystalloids for fluid resuscitation in critically ill patients. Cochrane Database Syst Rev 17:CD000567, 2007

10. Brunkhorst FM, Engel C, Bloos F, et al: Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med 358:125-139, 2008

11. Bone RC, Balk RA, Cerra FB, et al: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest 101:1644-1655, 1992

12. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR: Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs of care. Crit Care Med 29:1303-1310, 2001

13. Martin C, Viviand X, Leone M, Thirion X: Effect of norepinephrine on the outcome of septic shock. Crit Care Med 28:2758-2765, 2000

14. Russell JA, Walley KR, Singer J, et al: Vasopressin versus norepinephrine infusion in patients with septic shock. N Engl J Med 358:877-887, 2008

15. Rivers E, Nguyen B, Havstad S, et al: Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 345:1368-1377, 2001

16. Bernard GR, Vincent JL, Laterre PF, et al: Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 344:699-709, 2001

17. Abraham E, Laterre PF, Garg R, et al: Drotrecogin alfa (activated) for adults with severe sepsis and a low risk of death. N Engl J Med 353:1332-1341, 2005

18. Nadel S, Goldstein B, Williams MD, et al: Drotrecogin alfa (activated) in children with severe sepsis: A multicentre phase III randomised controlled trial. Lancet 369:836-843, 2007

19. Barie PS: "All in" for a huge pot: The PROWESS-SHOCK trial for refractory septic shock. Surg Infect (Larchmt) 8:491-494, 2007

20. Marik PE, Pastores SM, Annane D, et al: Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: Consensus statements from an international task force by the American College of Critical Care Medicine. Crit Care Med 36:1937-1949, 2008

21. Cooper MS, Stewart PM: Adrenal insufficiency in critical illness. J Intensive Care Med 22:348-362, 2007

22. Annane D, Sebille V, Charpentier C, et al: Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA 288:862-871, 2002

23. Sprung CL, Annane D, Keh D, et al: Hydrocortisone therapy for patients with septic shock. N Engl J Med 358:111-124, 2008

24. Bernard GR, Artigas A, Brigham KL, et al: The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 149:818-824, 1994

25. Ware LB, Matthay MA: The acute respiratory distress syndrome. N Engl J Med 342:1334-1349, 2000

26. Liu KD, Matthay MA: Advances in critical care for the nephrologist: Acute lung injury/ARDS. Clin J Am Soc Nephrol 3:578-586, 2008

27. Brower RG, Shanholtz CB, Fessler HE, et al: Prospective, randomized, controlled clinical trial comparing traditional versus reduced tidal volume ventilation in acute respiratory distress syndrome patients. Crit Care Med 27: 1492-1498, 1999

28. Liu KD, Matthay MA, Chertow GM: Evolving practices in critical care and potential implications for management of acute kidney injury. Clin J Am Soc Nephrol 1:869-873, 2006

29. Wiedemann HP, Wheeler AP, Bernard GR, et al: Comparison of two fluid-management strategies in acute lung injury. N Engl J Med 354:2564-2575, 2006

30. Brower R, Lanken P, MacIntyre N, et al: Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. N Engl J Med 351:327-336, 2004

31. Meade MO, Cook DJ, Guyatt GH, et al: Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: A randomized controlled trial. JAMA 299:637-645, 2008

32. Mercat A, Richard JC, Vielle B, et al: Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: A randomized controlled trial. JAMA 299:646-655, 2008

33. Imai Y, Parodo J, Kajikawa O, et al: Injurious mechanical ventilation and end-organ epithelial cell apoptosis and organ dysfunction in an experimental model of acute respiratory distress syndrome. JAMA 289:2104-2112, 2003

34. Choi WI, Quinn DA, Park KM, et al: Systemic microvascular leak in an in vivo rat model of ventilator-induced lung injury. Am J Respir Crit Care Med 167:1627-1632, 2003

35. Kuiper JW, Groeneveld AB, Slutsky AS, Plotz FB: Mechanical ventilation and acute renal failure. Crit Care Med 33:1408-1415, 2005

36. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-

associated pneumonia. Am J Respir Crit Care Med 171:388-416, 2005

37. Shorr AF, Sherner JH, Jackson WL, Kollef MH: Invasive approaches to the diagnosis of ventilator-associated pneumonia: A meta-analysis. Crit Care Med 33:46-53, 2005

38. Kollef MH: Diagnosis of ventilator-associated pneumonia. N Engl J Med 355:2691-2693, 2006

39. The Canadian Critical Care Trials Group: A randomized trial of diagnostic techniques for ventilator-associated pneumonia. N Engl J Med 355:2619-2630, 2006

40. Mermel LA, Farr BM, Sherertz RJ, et al: Guidelines for the management of intravascular catheter-related infections. Clin Infect Dis 32:1249-1272, 2001

41. Safdar N, Kluger DM, Maki DG: A review of risk factors for catheter-related bloodstream infection caused by percutaneously inserted, noncuffed central venous catheters: Implications for preventive strategies. Medicine (Baltimore) 81:466-479, 2002

42. Parienti JJ, Thirion M, Megarbane B, et al: Femoral vs jugular venous catheterization and risk of nosocomial events in adults requiring acute renal replacement therapy: A randomized controlled trial. JAMA 299:2413-2422, 2008

43. Safdar N, Fine JP, Maki DG: Meta-analysis: Methods for diagnosing intravascular device-related bloodstream infection. Ann Intern Med 142:451-466, 2005

44. Band J: Treatment of central venous catheter-related infections. Up To Date March 12, 2008

45. Stralovich-Romani A, Mahutte C, Luce J: Nutritional and ethical principles in critical illness and injury, in George R, Light R, Matthay M, Matthay R (eds): Chest Medicine (ed 5). Philadelphia, PA, Lippincott Williams & Wilkins, 2005, pp 497-516

46. Liu KD, Stralovich-Romani A, Chertow GM: Nutrition support for adult patients with acute renal failure, in Merritt R (ed): American Society for Parenteral and Enteral Nutrition (ASPEN) Nutrition Support Guidelines. Silver Spring, MD, American Society for Parenteral and Enteral Nutrition, 2006, pp 281-286

47. Fiaccadori E, Maggiore U, Giacosa R, et al: Enteral nutrition in patients with acute renal failure. Kidney Int 64:999-1004, 2004

48. Van den Berghe G, Wouters P, Weekers F, et al: Intensive insulin therapy in the critically ill patient. N Engl J Med 345:1359-1367, 2001

49. Van den Berghe G, Wilmer A, Hermans G, et al: Intensive insulin therapy in the medical ICU. N Engl J Med 354:449-461, 2006

50. Schetz MRC: Classical and alternative indications for continuous renal replacement therapy. Kidney Int Suppl 66:S129-S132, 1999

51. Van den Berghe G, Wilmer A, Milants I, et al: Intensive insulin therapy in mixed medical/surgical intensive care units: Benefit versus harm. Diabetes 55:3151-3159, 2006

52. Thomas G, Rojas MC, Epstein SK, Balk EM, Liangos O, Jaber BL: Insulin therapy and acute kidney injury in critically ill patients: A systematic review. Nephrol Dial Transplant 22:2849-2855, 2007

53. Schetz M, Vanhorebeek I, Wouters PJ, Wilmer A, Van den Berghe G: Tight blood glucose control is renoprotective in critically ill patients. J Am Soc Nephrol 19:571-578, 2008

54. Wiener RS, Wiener DC, Larson RJ: Benefits and risks of tight glucose control in critically ill adults: A meta-analysis. JAMA 300:933-944, 2008

55. Hebert PC, Wells G, Blajchman MA, et al: A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. N Engl J Med 340:409-417, 1999

56. Corwin HL, Gettinger A, Fabian TC, et al: Efficacy and safety of epoetin alfa in critically ill patients. N Engl J Med 357:965-976, 2007

57. Phrommintikul A, Haas SJ, Elsik M, Krum H: Mortality and target haemoglobin concentrations in anaemic patients with chronic kidney disease treated with erythropoietin: A meta-analysis. Lancet 369:381-388, 2007

58. Bennett CL, Silver SM, Djulbegovic B, et al: Venous thromboembolism and mortality associated with recombinant erythropoietin and darbepoetin administration for the treatment of cancer-associated anemia. JAMA 299:914-924, 2008

59. 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 36:610-617, 2008

60. Vinsonneau C, Camus C, Combes A, et al: Continuous venovenous haemodiafiltration versus intermittent haemodialysis for acute renal failure in patients with multiple-organ dysfunction syndrome: A multicentre randomised trial. Lancet 368:379-385, 2006

61. Subramanian S, Venkataraman R, Kellum J: Influence of dialysis membranes on outcomes in acute renal failure: A meta-analysis. Kidney Int 62:1819-1823, 2002

62. Palevsky PM, Zhang JH, O'Connor TZ, et al: Intensity of renal support in critically ill patients with acute kidney injury. N Engl J Med 359:7-20, 2008

63. Tolwani AJ, Campbell RC, Stofan BS, Lai KR, Oster RA, Wille KM: Standard versus high-dose CVVHDF for ICU-related acute renal failure. J Am Soc Nephrol 19:1233-1238, 2008

64. Ronco C, Bellomo R, Homel P, et al: Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: A prospective randomized trial. Lancet 356:26-30, 2000

65. Schiffl H, Lang S, Fischer R: Daily hemodialysis and the outcome of acute renal failure. N Engl J Med 346:305-310, 2002

66. Liu KD, Himmelfarb J, Paganini E, et al: Timing of initiation of dialysis in critically ill patients with acute kidney injury. Clin J Am Soc Nephrol 1:915-919, 2006

67. Seabra VF, Balk EM, Liangos O, Sosa MA, Cendoroglo M, Jaber BL: Timing of renal replacement therapy initiation in acute renal failure: A meta-analysis. Am J Kidney Dis 52:272-284, 2008

68. Fontana RJ: Acute liver failure including acetaminophen overdose. Med Clin North Am 92:761-794, viii, 2008

69. Auzinger G, Wendon J: Intensive care management of acute liver failure. Curr Opin Crit Care 14:179-188, 2008

70. Humphreys BD, Forman JP, Zandi-Nejad K, Bazari H, Seifter J, Magee CC: Acetaminophen-induced anion gap meta-

bolic acidosis and 5-oxoprolinuria (pyroglutamic aciduria) acquired in hospital. Am J Kidney Dis 46:143-146, 2005

71. Kulig K: Aspirin intoxication, in Parsons P, Wiener-Kronish J (eds): Critical Care Secrets (ed 4). Philadelphia, PA, Mosby Elsevier, 2007, pp 515-518

72. Megarbane B, Borron SW, Baud FJ: Current recommendations for treatment of severe toxic alcohol poisonings. Intensive Care Med 31:189-195, 2005

73. Sivilotti M, Winchester J: Methanol and ethylene glycol poisoning. Up to Date May 15, 2008

74. Okusa MD, Crystal LJ: Clinical manifestations and management of acute lithium intoxication. Am J Med 97:383-389, 1994

75. Chu J, Stolbach A: Metformin poisoning. Up To Date October:16.3, 2008

76. Kam PC, Cardone D: Propofol infusion syndrome. Anaesthesia 62:690-701, 2007

77. Palmer BF: Hyponatremia in patients with central nervous system disease: SIADH versus CSW. Trends Endocrinol Metab 14:182-187, 2003