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Critical Care Nephrology: Core Curriculum 2009

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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. Lastly, we review the management of several life-threatening intoxications, many of which require early recognition and consideration of dialysis.

SHOCK

Definition: Absolute hypotension (e.g. systolic blood pressure less than 90 mm Hg or mean arterial pressure less than 60 mm Hg) or relative hypotension (e.g. fall in systolic blood pressure of more than 40 mm Hg) resulting in inadequate end-organ perfusion^{1, 2}

Etiologies:

- Hypovolemic: Hemorrhage, volume depletion due to decreased fluid intake or excessive fluid losses
- Distributive: low systemic vascular resistance
 - Sepsis
 - Anaphylaxis
 - Endocrine: adrenal insufficiency
 - Neurogenic: spinal shock
- Cardiogenic: Acute myocardial infarction, heart failure, valvular heart disease, dysrhythmias

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- Obstructive: Extracardiac disease resulting in poor cardiac function: decreased cardiac filling (e.g. tamponade, mechanical ventilation with high positive end-expiratory pressure resulting in decreased venous return) or increased cardiac afterload (massive pulmonary embolism)

Diagnosis³

- Echocardiography: transthoracic or transesophageal
- Invasive hemodynamic monitoring
 - Central venous catheter
 - ◆ Central venous pressure monitoring may be artificially high in patients on mechanical ventilation and high levels of positive end-expiratory pressure (increases intrathoracic pressure)
 - ◆ Superior vena cava O₂ saturation (ScVO₂) as a correlate of mixed venous O₂ saturation (which can only be measured with a pulmonary artery catheter)
 - ◆ Correlation with mixed venous O₂ saturation somewhat controversial⁴
 - Pulmonary artery catheter
 - Pulmonary artery occlusion pressure/pulmonary capillary wedge pressure reflects left atrial pressure in the absence of significant valvular heart disease
 - Cardiac output monitoring: Fick or thermodilution
 - ◆ Thermodilution cardiac output monitoring unreliable with tricuspid valve disease
 - ◆ Fick cardiac output monitoring uses the mixed venous oxygen saturation (obtained from the pulmonary artery) to calculate cardiac output; assumes normal O₂ consumption
 - Cardiac output, systemic vascular resistance and central venous pressure can be used to distinguish between the different types of shock

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

- Pulmonary artery catheterization has not been shown to be of benefit in critically ill or surgical populations.^{5–7} In general, central venous pressure 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 may also be useful in the management of complex (eg, mixed etiology) shock or shock in the patient with known heart failure.
- Other methods to monitor cardiac output (partial CO₂ rebreathing, pulse contour analysis) are less well validated

- Arterial catheter
 - Allows for beat-to-beat blood pressure monitoring
 - Radial, femoral or dorsalis pedis sites preferred
 - Perform Allen test prior to radial arterial line placement to confirm adequate collateral circulation
 - Avoid ulnar and brachial arteries due to higher risk of limb ischemia
- Serum tryptase levels can be useful in anaphylaxis

Treatment

- Treat underlying cause of shock (infection, myocardial infarction)
- Volume resuscitation for hypovolemia
 - Data does not support use of colloids (albumin, hextend, hydroxyethyl starch) over isotonic crystalloid solutions^{8, 9}
 - In patients with sepsis, hydroxyethyl starch administration has been associated with an increased incidence of acute kidney injury and should be avoided¹⁰
- Vasoactive agents (Table 1)²
 - Vasopressors increase vascular tone, which in turn increases mean arterial pressure
 - Inotropes increase cardiac contractility, and therefore cardiac output
 - Commonly used medications include:
 - ◆ Phenylephrine (neosynephrine): pure α agonist
 - ◆ Dopamine: Dopamine receptor, β and α agonist (dose-dependent)
 - ◆ Dobutamine: β_1 and β_2 agonist, use can be associated with hypotension; often used to increase cardiac output in cardiogenic shock due to congestive heart failure
 - ◆ Epinephrine: $\beta_1 > \alpha_1$, β_2 receptor agonist
 - ◆ Norepinephrine (Levophed): α_1 and β_1 agonist, associated with less tachycardia than epinephrine
 - ◆ Vasopressin: Has been used as a second line pressor for refractory septic shock; use can be associated with significant mesenteric ischemia
 - ◆ Milrinone/amrinone: Phosphodiesterase inhibitors with inotropic and vasodilatory effects; used along with dobutamine for the treatment of cardiogenic shock in the setting of congestive heart failure
 - Early goal directed therapy for sepsis (see below)
 - Corticosteroids for adrenal insufficiency (see below)
 - Anaphylaxis: Epinephrine, H1 and H2 blockers, steroids
 - Supportive care: Intubation and mechanical ventilation if needed

SEPSIS

Diagnosis¹¹

- Systemic Inflammatory Response Syndrome (SIRS): Characterized by the presence of (1) temperature $> 38^{\circ}\text{C}$ or $< 36^{\circ}\text{C}$ (2) heart rate > 90 beats/minute (3) respiratory rate > 20 breaths/minute or the need for support with mechanical ventilation (4) white blood cell count $> 12,000$ cells/mm³ or < 4000 cells/mm³
- Sepsis: Suspected or documented infection in association with 2 or more of the SIRS criteria
- Severe sepsis: Sepsis with acute organ dysfunction
- Septic shock: Severe sepsis with hypotension despite adequate fluid resuscitation

Prognosis¹²

- Approximately 750,000 cases/year in the United States, resulting in approximately 200,000 deaths
- Mortality rate approximately 30–40%, but higher in sicker populations
- Major risk factor for acute kidney injury

Treatment¹¹

- Appropriate broad spectrum antibiotics and control of source of infection (e.g. debridement, removal of infected catheter)
- Volume resuscitation
- Vasopressors as needed
 - Data supporting choice of first vasopressor limited
 - Norepinephrine/levophed may be reasonable, since it will increase systemic vascular resistance and increase cardiac output¹³
 - A recent clinical trial does not support the use of vasopressin as a first-line agent in combination with norepinephrine (VASST)¹⁴
- Early goal directed therapy: Refers to the combination of volume resuscitation/vasopressors and inotropes/transfusion guided by central venous pressure (target CVP 8–12 mm Hg), arterial blood pressure (MAP > 65 mm Hg), superior vena cava oxygen saturation (ScVO₂ $> 70\%$) and evidence of end-organ perfusion (urine output > 0.5 cc/kg/hour)
 - A single center randomized clinical trial showed mortality benefit with early institution of these interventions (within 6 hours of diagnosis)¹⁵
 - ◆ A multicenter clinical trial (PROCESS) is ongoing to confirm the results of the initial study and to try to better correlate these interventions with benefit
- Activated protein C was shown to have mortality benefit for severe sepsis with APACHE II score ≥ 25 in a large, randomized, multicenter clinical trial¹⁶
 - Activated protein C has not been shown to be of benefit in children or in less critically ill adults^{17, 18}
 - A clinical trial in critically ill adults with refractory shock (PROWESS-SHOCK) is ongoing¹⁹

- Role of steroids for relative adrenal insufficiency remains controversial²⁰
 - Diagnosis of relative adrenal insufficiency should be considered with refractory shock after volume resuscitation
 - Both basal cortisol level and response to high-dose adrenocorticotrophic hormone (ACTH) stimulation test have been used to define adrenal insufficiency in the critically ill²¹, although criteria for adrenal insufficiency remain controversial
 - Annane et al demonstrated 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 trial²²
 - However, in a subsequent multicenter, placebo controlled randomized clinical trial, low dose hydrocortisone therapy did not improve survival in patients with septic shock²³
 - ◆ Treatment with hydrocortisone was associated with a shorter time on vasopressors but also with an increase in new sepsis and new septic shock
 - ◆ Differing results may be attributable to differences in duration of septic shock, severity of illness, steroid administration (patients in Annane study randomized earlier, had higher severity of illness scores, received fludrocortisone and hydrocortisone)
 - In both studies, patients were randomized after the ACTH stimulation test but before the results were available; thus patients should be empirically treated with steroids if there is a concern for relative adrenal insufficiency, rather than waiting for the results of the stimulation test
- Other supportive care as warranted by the clinical condition: intubation and mechanical ventilation, nutrition, glycemic control
- Data for some of the Surviving Sepsis guidelines is limited

ACUTE LUNG INJURY/ADULT RESPIRATORY DISTRESS SYNDROME

Diagnosis²⁴

Acute onset (< 7 days) of

- Hypoxemia: $\text{PaO}_2/\text{FiO}_2 < 300$ for Acute Lung Injury (ALI), < 200 for Adult Respiratory Distress Syndrome (ARDS)
- Bilateral infiltrates on chest radiograph
- No clinical evidence of left atrial hypertension

Risk factors²⁵

- Infection: pneumonia, sepsis
- Aspiration
- Trauma
- Transfusion

Prognosis²⁶

- Mortality rate 25–40% in most recent studies

Treatment

- Lung protection with a low tidal volume ventilation strategy has mortality benefit for ALI/ARDS²⁷
 - Tidal volume 6 cc/kg ideal body weight (versus 12 cc/kg ideal body weight)
 - Ideal body weight: $50 + 2.3 * (\text{height in inches} - 60)$ for men, $45.5 + 2.3 * (\text{height in inches} - 60)$ for women
 - Plateau pressure < 30 mm H₂O
 - Goal PaO₂ 55–80 mm Hg
 - Target pH 7.30–7.45
 - ◆ For moderate acidosis (pH 7.15–7.30), can increase respiratory rate (not to exceed 35) until pH 7.35 or PaCO₂ < 25
 - ◆ For severe acidosis (pH < 7.15), can increase respiratory rate (not to exceed 35), increase tidal volume, or administer intravenous bicarbonate
 - Permissive hypercapnia/respiratory acidosis may be problematic in patients with concomitant acute kidney injury or chronic kidney disease who may have concurrent metabolic acidosis²⁸
- A fluid conservative management strategy increases ventilator free days in patients with ALI/ARDS²⁹
 - Patients with ESRD or AKI requiring dialysis at the time of study enrollment were excluded from the fluid management study
 - The fluid conservative management strategy was not associated with an increased requirement for dialysis
 - Patients in the fluid conservative group received diuretics to achieve a target CVP of 4–8 mm Hg or pulmonary artery occlusion pressure of 8–12 mm Hg, provided that 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 as defined by urine output of less than 0.5 cc/kg/hour
- Higher levels of positive end-expiratory pressure does not appear to have mortality benefit for patients with ALI^{30–32}
- Rescue therapies include
 - Extracorporeal membrane oxygenation (ECMO)
 - High frequency ventilation
 - Partial liquid ventilation with a perfluorocarbon
 - Inhaled nitric oxide
 - Prostacyclin
- Animal studies suggest that injurious mechanical ventilation (eg, high tidal volume) and lung injury can lead to acute kidney injury,^{33–35} although the molecular

mechanisms have not been fully elucidated. Similarly, acute kidney injury may lead to or exacerbate existing lung injury in animal models.

VENTILATOR ASSOCIATED PNEUMONIA³⁶

- Clinical suspicion of infection: New fevers, leukocytosis or purulent respiratory secretions, worsening respiratory failure/increased ventilator support
- Culture: Gold standard methods remain unclear
 - Many ways to obtain culture specimens, including quantitative methods such as bronchoalveolar lavage and protected specimen brush, as well as nonquantitative cultures and endotracheal aspirates
 - Although bronchoalveolar lavage and protected brush specimen with quantitative cultures may allow for more rapid antibiotic-de-escalation, superiority to nonquantitative methods is not clear^{37–39}
- Appropriate empiric initial antibiotic therapy is key: antibiotics should be tailored to known local antimicrobial resistance patterns
- Patients with ventilator associated pneumonia are at high risk for sepsis and associated acute kidney injury

CATHETER RELATED INFECTIONS

Definitions⁴⁰

- Catheter colonization: Presence of bacteria or fungi in a quantitative or semi-quantitative culture of catheter material but without signs of local or systemic infection. Microorganisms grow in a bio-film that coats the surface of the catheter
- Exit site/insertion site infection: Erythema, tenderness, induration or purulence at the site where the catheter exits the skin
- Tunnel infection: Erythema, tenderness, induration or purulence in the tract where a venous catheter is tunneled under the skin
- Catheter related blood stream infection: Bacteremia in the presence of positive cultures from the catheter itself (see Diagnosis section)

Incidence

- Catheter related blood stream infections are more common with non-tunneled than with tunneled central lines
- Major risk factors for infection include duration of catheter use, number of catheter lumens (multilumen catheters carry a higher risk of infection), poor technique at the time of catheter insertion, use of total parenteral nutrition⁴¹
- Although subclavian catheters are generally associated with a lower risk of infections compared to internal jugular and femoral catheters, these should be avoided in patients with acute kidney injury or end-stage renal disease due to the risk of subclavian stenosis.
- While the internal jugular site is generally thought 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 nontunneled femoral and internal jugular dialysis catheters in critically ill, immobilized patients.⁴² However, in patients in the highest tertile of body mass index (BMI > 28.4), femoral lines were associated with an increased risk

of infection compared to internal jugular lines. Furthermore, these results cannot be generalized to mobile, noncritically ill individuals.

Diagnosis⁴³

- 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 blood stream infection
- Quantitative blood cultures: If a blood sample drawn through the catheter has a higher concentration ($\geq 5:1$ ratio) of microorganisms than the peripheral blood culture, this is highly suggestive of catheter related blood stream infection
- Quantitative culture of catheter segment or catheter tip: Requires removal of central venous catheter

Treatment⁴⁴

- Empiric broad spectrum antibiotics; staphylococci are common pathogen
- 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 (4) type of infection/pathogen
- 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

- Patients who are critically ill are frequently hypermetabolic/hypercatabolic and therefore are at increased risk for nutritional complications⁴⁵
- Calorie requirements can be estimated using predictive equations (Harris-Benedict or Mifflin-St Jeor for obesity) or measured using indirect calorimetry (in which O₂ consumption and CO₂ generation are measured in expired gas and used to calculate resting energy expenditure and the respiratory quotient)
 - Indirect calorimetry is less accurate as oxygen requirements increase and is generally not useful when the patient requires a fraction of inspired O₂ of more than 0.60
 - Indirect calorimetry also allows for calculation of the respiratory quotient (RQ); a high RQ (≥ 1.0) suggests overfeeding (of either total calories or carbohydrates) or a hypermetabolic state
- Nitrogen balance can be used to determine whether the provision of nutrition therapy (particularly protein) is adequate
 - Protein requirements of patients with acute kidney injury will vary based on the underlying cause of AKI and the type of renal support provided (both intermittent hemodialysis and continuous renal replacement therapy associated with ongoing protein losses)⁴⁶
 - Patients on continuous renal replacement therapy (CRRT) will likely require at least 1.6–1.8 g/kg/day of amino acids and in some studies have received up to 2.5 g/kg/day without complications
- Serum markers for nutritional adequacy in the critically ill remain controversial⁴⁵

- Although serum albumin is a valuable prognostic indicator of morbidity and mortality, serum albumin levels decrease with metabolic stress as well as with specific disease states that are common in the ICU such as liver failure
- Transferrin, prealbumin, and retinol binding protein may be superior markers of nutritional status; however, in critical illness, synthesis of these proteins may decrease due to preferential production of acute phase reactants (i.e., C reactive protein)
- Prealbumin may be falsely elevated in patients with kidney failure due to reduced clearance and in patients on high-dose steroids
- Trend of prealbumin and C-reactive protein may be more useful than absolute values to follow response to nutrition therapy
- In an observational cohort study, critically ill patients with acute kidney injury did not have significantly more major gastrointestinal complications (vomiting, diarrhea, abdominal distention) nor more infectious complications (aspiration pneumonia)⁴⁷
- Total parenteral nutrition is associated with an increased risk of infection and should only be used if efforts to provide enteral nutrition have failed or if the patient has a strict contraindication to enteral feeding

INTENSIVE INSULIN THERAPY

- A large, randomized clinical trial of surgical patients demonstrated mortality benefit and decreased length of ICU stay in patients who received intensive insulin therapy (target blood glucose 80 to 110 mg/dL [4.4–6.1 mmol/L])⁴⁸
- A subsequent randomized clinical trial of medical patients did not show the same mortality benefit⁴⁹
 - However, patients who had longer ICU stays (defined as 3 or more days) did have decreased in-hospital and ICU mortality with intensive insulin therapy
- Intensive insulin therapy is associated with an increased incidence of severe hypoglycemia⁵⁰
- It remains unclear if the benefit is from glycemic control or a direct effect of the insulin itself
- A pooled analysis of the large medical and surgical clinical trials suggested that patients with better glycemic control had lower mortality rates; however, it is unclear if this was as a result of the improved glycemic control or due to differences in severity of illness⁵¹
- Similarly, a pooled analysis of the two large clinical trials and a meta-analysis suggest that intensive insulin therapy has a renoprotective effect^{52, 53}
- However, a recent meta-analysis of 29 clinical trials (total of 8432 patients) did not demonstrate a difference in mortality or need for dialysis between patients randomized to tight versus usual glucose control.⁵⁴ There was a decreased incidence of bacteremia and a marked increase in the incidence of hypoglycemia (glucose < 40 mg/dL [2.2 mmol/L]) in the tight control group. Of note, the target glucose level in the tight control group varied across these studies from less than 100 mg/dL to less than 144 mg/dL (<5.6–<8.0 mmol/L).
- Thus, the optimum target glucose in critically ill patients remains unclear at present.

ANEMIA MANAGEMENT

Target hemoglobin in critically ill patients

- A large, randomized clinical trial suggested that a restrictive transfusion strategy (transfusions only when the hemoglobin concentration fell below 7 g/dL) was safe and associated with a trend towards improved clinical outcomes when compared to a liberal transfusion strategy (transfusions when the hemoglobin concentration fell below 10 g/dL)⁵⁵
- Of note, patients with chronic anemia (hemoglobin < 9 g/dL) and patients with active bleeding were excluded. In addition, the authors note that the results may be less applicable to patients with active myocardial ischemia, since a higher 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

- In a recent placebo controlled, randomized clinical trial, recombinant erythropoietin did not decrease the number of transfusions needed or the proportion of patients transfused⁵⁶ Erythropoietin therapy was associated with an increased number of thrombotic events
- Given recent findings of significant complications associated with erythropoiesis-stimulating agents in clinical trials of chronic kidney disease and oncology patients,^{57, 58} use in the critical care setting cannot be recommended at this time in the absence of kidney disease

DIALYSIS CONSIDERATIONS

Modality

- Intermittent dialysis and continuous renal replacement therapy can be considered equivalent modalities for the treatment of patients with AKI^{59, 60}
- There may be a subset of patients who are critically ill with refractory hypotension or elevated intracranial pressure (e.g. patients with fulminant hepatic failure) in whom CRRT is preferable
 - CRRT: continuous fluid/volume management and slow clearance
 - ◆ Arterio-venous (AV) and veno-venous (VV) modalities, now primarily VV modalities
 - ◆ Continuous veno-venous hemofiltration (CVVH): convective clearance
 - ◆ Continuous veno-venous hemodialysis (CVVHD): diffusive clearance
 - ◆ Continuous veno-venous hemodiafiltration (CVVHDF): convective and diffusive clearance
 - CRRT may necessitate anticoagulation to prolong the half life of the filter
 - Anticoagulation typically administered pre-filter to minimize systemic anticoagulation
 - ◆ Heparin and citrate are most common types of therapy

- ◆ Citrate chelates calcium, a necessary cofactor in the coagulation cascade
 - Major risk of citrate anticoagulation is hypocalcemia
 - Can also be associated with metabolic alkalosis (1 molecule of citrate is converted to 3 molecules of bicarbonate)
- Drug dosing: In general, medications should be dosed for a creatinine clearance of 10–50; if possible, follow drug levels to optimize dosing
- Slow, low efficiency dialysis (SLED): 8–12 hours/treatment, 6 treatments/week - hybrid technique with improved hemodynamic tolerance

Access

- For critically ill ESRD patients, continuous renal replacement therapy modalities require placement of a temporary or tunneled catheter

Membrane

- Biocompatible membranes are in more common use and may be associated with improved survival and shorter time to renal recovery⁶¹
- 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

- Recent large, multicenter randomized clinical trial (ATN study) suggested that there was no benefit with more intensive dialysis (CVVHDF with effluent flow rate of 35 cc/kg/hour or intermittent hemodialysis 6 times/week with Kt/V of 1.2/session) compared to less intensive dialysis (CVVHDF with effluent flow rate of 20 cc/kg/hour or three times/week intermittent hemodialysis)⁶²
 - Patients with chronic kidney disease (defined as a creatinine > 2.0 mg/dL [177 µmol/L] in men and 1.5 mg/dL [133 µmol/L] in women) were excluded
- These results are supported by a large, single center study comparing two doses of CRRT;⁶³ a multicenter study of two doses of CVVHDF is ongoing
- In contrast, single center clinical trials suggested mortality benefit with higher doses of CVVH and intermittent dialysis
 - For the CRRT study, there may have been differences in the characteristics of patients treated and treatment characteristics⁶⁴ (including a higher 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 post-filter replacement fluid administration)
 - For the IHD study, doses of dialysis provided per treatment were lower than in the ATN study⁶⁵

Timing

- Optimum timing of initiation of dialysis for AKI remains unclear, though observational studies have suggested potential benefit to earlier initiation of dialysis^{66, 67}

- A number of the critical care practices described in this article may impact the metabolic parameters that trigger the decision to initiate dialysis.²⁸ Specifically, low-tidal volume ventilation and permissive hypercapnia may exacerbate acidemia in a patient with acute kidney injury and an associated metabolic acidosis. Early goal directed therapy may ultimately result in volume overload, and, depending on the fluid selected for resuscitation, a 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 in selected patients.

FULMINANT HEPATIC FAILURE

- Common etiologies: medications/toxins (acetaminophen, Amanita phalloides mushroom poisoning, other drug reactions), acute viral infections (hepatitis B, A), vascular causes (portal vein thrombosis, hepatic vein thrombosis = Budd-Chiari syndrome), metabolic diseases (Wilson's disease, acute fatty liver of pregnancy, Reye's syndrome), cryptogenic^{68, 69}
- Orthotopic liver transplantation is definitive therapy
- Mortality high with supportive care alone
- Common complications include:
 - Hepatic encephalopathy
 - Cerebral edema: can lead to increased intracranial pressure and brainstem herniation
 - ◆ Major cause of mortality in this population
 - ◆ Patients with compromised kidney function may require continuous renal replacement therapy to avoid fluctuations in intracranial pressure and tight volume control (especially in setting of transfusions of large volumes of blood products)
 - Acute kidney injury: altered hemodynamics, direct toxicity
 - ◆ Due to large volume of blood products and cerebral edema, may require support with continuous renal replacement therapy before conventional "indications" are met⁶⁹
 - Coagulopathy
 - Hypoglycemia
 - Infection/sepsis

INTOXICATIONS

- Acetaminophen
 - N-acetylcysteine
 - Supportive care for fulminant hepatic failure, including metabolic acidosis (hepatocyte necrosis and inability to metabolize lactate can result in severe lactic acidosis)
 - Acute kidney injury, may be direct effect of acetaminophen leading to acute tubular necrosis or hepatorenal syndrome; usually recovers spontaneously, but may require dialytic support.

- 5-oxoprolinuria and associated metabolic acidosis may occur in susceptible individuals, even when only recommended doses of acetaminophen are administered⁷⁰
 - ◆ Consider in a patient with recent acetaminophen use, unexplained metabolic acidosis, altered mental status
 - ◆ N-acetylcysteine may increase glutathione levels and be of benefit
- Salicylates⁷¹
 - Classically presents with respiratory alkalosis and anion gap metabolic acidosis
 - Symptoms include tinnitus, altered mental status, nausea/vomiting
 - Activated charcoal for gut decontamination
 - Glucose should be administered if the patient has altered mental status because aspirin can cause CNS_[A2] hypoglycemia, even with normal serum glucose concentrations
 - Sodium bicarbonate to promote mobilization of salicylates from tissue stores to the plasma and urinary excretion
 - Hemodialysis: Altered mental status, volume overload, plasma salicylate concentration > 100 mg/dL
- Methanol/ethylene glycol^{72, 73}
 - Present with anion gap acidosis and osmolar gap
 - Early recognition is critical
 - Visual changes including blurry vision, central scotomata, blindness, retinal edema and hyperemia of the optic disk are characteristic of methanol poisoning
 - Oliguria and calcium oxalate crystals in the urine are characteristic of ethylene glycol toxicity; can use UV light (Woods lamp) to look for fluorescence in the urine (fluorescein added to most antifreeze)
 - Fomepizole/ethanol competitively inhibits alcohol dehydrogenase and prevents the formation of toxic metabolites (methanol is converted to formate, ethylene glycol to glycolate/glyoxylate/oxalate)
 - Dialysis will remove both the alcohols and toxic metabolites
 - ◆ Should not wait for confirmatory testing to initiate treatment
 - ◆ Consider empiric therapy in a patient with unexplained anion gap acidosis, osmolar gap, and suspected ingestion/evidence of end-organ dysfunction
 - Additional supportive care including folate/thiamine
- Lithium⁷⁴
 - Presents with altered mental status, neuromuscular excitability, tremors, nausea, vomiting, seizures
 - Consider dialysis based on absolute level as well as symptoms

- Slow equilibration between intracellular and extracellular lithium may lead to plasma rebound and necessitate extended dialysis sessions (8–12 hours)
- Metformin⁷⁵
 - Can be associated with life-threatening lactic acidosis, in particular when used in patients with reduced kidney function or hepatic dysfunction, heart failure, prior history of lactic acidosis, or patients with ongoing hypoperfusion or hemodynamic instability
 - Metformin should be held if a patient requires parenteral contrast for a CT scan for at least 48 hours post-study to ensure normal kidney function
 - In patients with life threatening acidosis, dialysis will remove metformin and allow for the provision of bicarbonate to treat the acidosis
- Other toxicities to consider hemodialysis for: paraquat, isopropanol, theophylline (cleared by dialysis, but more efficiently cleared by charcoal hemoperfusion)

SPECIAL ACID/BASE AND ELECTROLYTE ABNORMALITIES

- Propofol can be associated with life-threatening metabolic acidosis, especially in children⁷⁶
- Lorazepam (Ativan) infusions contain polyethylene glycol as a carrier agent and can be associated with an anion gap acidosis⁷⁶
- Cerebral salt wasting with central nervous system disease (subarachnoid hemorrhage, post-neurosurgery) can lead to profound hyponatremia⁷⁷
 - Can be differentiated from CNS-associated syndrome of inappropriate antidiuretic hormone (SIADH) by volume status: CSW_[A3] leads to hypovolemia, patients with SIADH are euvolemic

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Table 1
Summary of vasopressor and inotropic agents

Vasopressors	Comments
Alpha agonists	
Phenylephrine (neosynephrine)	High doses can be associated with reflex bradycardia
Mixed alpha/beta 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	
Beta agonists	
Dobutamine	Use can be associated with hypotension
Phosphodiesterase inhibitors	
Milrinone	
Amrinone	