Critical Care Nephrology: Core Curriculum 2020

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The intensive care unit (ICU) is a common source of high-acuity nephrology consultations. Although advanced chronic kidney disease is associated with increased ICU mortality, the prognosis of acute kidney injury (AKI) requiring renal replacement therapy is far worse, with short-term mortality rates that often exceed 50%. As such, it is essential that practicing nephrologists be comfortable caring for critically ill patients. This Core Curriculum article emphasizes the developments of the last decade since the last Core Curriculum installment on this topic in 2009. We focus on some of the most common causes of AKI in the critical care setting and use these AKI causes to delve into specific topics most relevant to critical care nephrology, including acute respiratory distress syndrome, extracorporeal membrane oxygenation, evolving concepts in fluid management, and shock. We conclude by reviewing the basics of palliative care nephrology and dialysis decision making in the ICU.

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The Core Curriculum aims to give trainees in nephrology a strong knowledge base in core topics in the specialty by providing an overview of the topic and citing key references, including the foundational literature that led to current clinical approaches.

Introduction

Epidemiology of Acute Kidney Injury in the Intensive Care Unit

Acute kidney injury (AKI) is common and associated with substantial morbidity, mortality, and medical costs. AKI is currently defined by KDIGO (Kidney Disease: Improving Global Outcomes) criteria and is divided into 3 stages based on increases in serum creatinine level or decreases in urine output. A recent multinational study with more than 1,800 patients from 97 intensive care units (ICUs) reported that AKI of any stage developed within 1 week of admission in 57% of patients. Severe (stage 2 or 3) AKI occurred in 39%, and 13.5% required renal replacement therapy (RRT).

AKI in the ICU is an independent risk factor for death. Mortality rates of AKI requiring RRT (AKI-RRT) range from 40% to 55%, higher than mortality rates reported for myocardial infarction in the ICU (20%), sepsis without AKI (15%-25%), and acute respiratory distress syndrome (ARDS) requiring mechanical ventilation (30%-40%). In addition to mortality, AKI survivors are more likely to develop significant morbidity such as chronic kidney disease (including kidney failure) and functional impairment necessitating discharge to short- or long-term care facilities.

AKI Risk Stratification in the ICU

Determining a patient's risk for developing AKI or progressing to AKI-RRT is an important step for prognosis and for early implementation of preventative measures. Much attention has focused on novel biomarkers, including [TIMP-2] × [IGFBP-7] (the product of tissue inhibitor of metalloproteinase 2 and insulin-like growth factor binding protein 7) and NGAL (neutrophil gelatinase-associated lipocalin). However, equally important are risk stratification tools that allow biomarkers to be interpreted within the appropriate clinical context. Like cardiac troponins, AKI biomarkers are most useful in patients with high pretest probabilities and lose sensitivity and specificity if checked indiscriminately. Common risk stratification tools and novel AKI biomarkers are summarized in Table 1. The field of risk stratification and the role of biomarkers are both rapidly evolving, and the reader should review the most current literature for additional information.

Causes of Death in AKI

Long-established AKI complications include electrolyte abnormalities, volume overload, and uremia. These "traditional" complications can be managed with dialysis and account for only 3% of AKI-related deaths in the ICU. A growing literature suggests that the high attributable mortality from AKI stems from systemic effects on distant organs, including the lung, heart, liver, brain, and immune system (Fig 1). AKI has been shown in animal studies and studies of humans to increase susceptibility to infection, double the rate of respiratory failure, and directly and indirectly impair cardiac function. Although the mechanisms of these systemic effects remain to be fully elucidated, given that the mortality of AKI remains high despite RRT, it appears that it is not the loss of renal clearance but rather AKI's association with multiorgan dysfunction that makes AKI so deadly.

Additional Readings

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Common Causes of AKI in the ICU

Case 1: *A 68-year-old woman with a history of hypertension presents to the emergency department with fever, nausea, vomiting, and confusion. Vital signs include temperature, 39.3°C; heart rate, 98 beats/min; blood pressure (BP), 130/59 mm Hg; respiratory rate, 26 breaths/min; and arterial oxygen saturation (Sa_{O_2}), 92% while breathing room air. Examination is notable for disorientation and right-sided costovertebral angle tenderness. Laboratory test results are notable for white blood cell count of 22 ×10³/μL; serum creatinine level, 2.3 (baseline, 0.7) mg/dL, and >50 white blood cells/high-power field on urine microscopy. Imaging includes noncontrast computed tomography of the abdomen and pelvis with right perinephric stranding but no stones or hydronephrosis bilaterally. Blood and urine cultures are obtained, ceftriaxone therapy is initiated, and she is admitted to the ICU.*

Question 1: Which of the following statements about this patient's AKI is most correct?

(a) The patient's AKI is likely due to ischemic acute tubular necrosis as a result of decreased blood flow.
(b) Her AKI is unlikely to be attributable to sepsis because she does not meet the current consensus definition of sepsis.
(c) Her AKI is unlikely to be attributable to sepsis given her normal BP.
(d) The patient's AKI puts her at increased risk for secondary infections during her hospitalization.
(e) Given her stage 3 AKI in the setting of sepsis, she would likely benefit from pre-emptive RRT before the development of an urgent indication.

For the answer to the question, see the following text.

Common causes of AKI in the ICU are outlined in Table 2. In this article, we focus on sepsis-associated AKI (SA-AKI), cardiac surgery–associated AKI (CSA-AKI), and AKI associated with acute liver failure (ALF). We also discuss interactions between respiratory and kidney failure and the role of abdominal compartment syndrome (ACS) as a cause and consequence of AKI. Other causes of AKI, including malignancy-associated AKI and cardiorenal syndrome, have been discussed in recent Core Curriculum installments from Cohen et al and House et al, and we refer the reader to those articles for more information.

Sepsis

Definition

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) defines sepsis as "life threatening organ dysfunction caused by a dysregulated host response to infection," with organ dysfunction defined as an increase in Sequential Organ Failure Assessment (SOFA) score ≥ 2 points. A screening tool, the quick SOFA, can be used in which sepsis is suggested by the presence of 2 of 3 features: (1) respiratory rate ≥ 22 breaths/min, (2) altered mental status, and (3) systolic BP ≤ 100 mm Hg. Thus, for Question 1, answer (b) is incorrect.

Epidemiology

SA-AKI occurs in 10% to 20% of all patients admitted to the ICU due to infection and in 50% to 70% of those with septic shock. SA-AKI is the most common cause of AKI in the ICU, accounting for ~50% of cases. SA-AKI is associated with dramatically worse outcomes, with relative mortality rates nearly 50% greater than for those without AKI. Furthermore, increasing data suggest that AKI is a risk factor for subsequent sepsis or secondary infections. A secondary analysis of the PICARD study showed that 56% of ICU patients with nonseptic AKI developed sepsis after a median of 5 days. Similarly, in a study of 24,660 cardiac surgery patients, 23.7% of patients with postoperative AKI developed infection compared with 3.3% of non-AKI patients. The relationship between AKI and sepsis is therefore now thought to be bidirectional; thus, the best answer to Question 1 is (d).

Pathophysiology

The pathophysiology of SA-AKI is incompletely understood. In the past, SA-AKI was thought to be a form of acute tubular necrosis stemming from global hypoperfusion. However, animal studies demonstrate that renal blood flow (RBF) is unchanged and may even increase during sepsis. Although the few RBF studies in humans paint a more complex picture, postmortem studies of patients with SA-AKI show that renal histology is usually well preserved without evidence of acute tubular necrosis. Furthermore, SA-AKI can occur in the absence of hypotension (the reason that answer (c) is incorrect for Question 1). More recent data point to microvascular dysfunction, inflammation, oxidative stress, and endothelial dysfunction as contributors to SA-AKI. One unifying theory is that SA-AKI is an adaptive energy-conserving response of tubular endothelial cells (Fig 2). Although an

Table 1. Risk Stratification Is Important to Determine Which Patients Are at High Risk for Progression to AKI, Which Can Allow for Closer Monitoring and Earlier Intervention

Risk Stratification Tool	Clinical Utility	Key Readings
Clinical risk prediction scores	Used to give greater context to a patient's clinical situation; eg, analogous to cardiac angina, "renal angina" is a concept intended to identify patients at high risk for AKI. Risk factors (eg, advanced age, hypertension, DM, CKD) and exposures (eg, volume depletion, nephrotoxins, sepsis) are combined with symptoms (eg, reduced urine output, volume overload, creatinine elevation). Malhotra et al developed a risk score based on acute and chronic factors to predict AKI development in ICU patients. Understanding a patient's baseline risk (pretest probability) allows for better interpretation of biomarker data and furosemide stress test results.	Chawla et al (*Crit Care* 2015; https://doi.org/10.1186/s13054-015-0779-y) Malhotra et al (*NDT* 2017; https://doi.org/10.1093/ndt/gfx026)
Computer algorithms	Machine learning algorithms have been used to identify patients at high risk for AKI or for requiring RRT. These complicated models can predict AKI with greater precision than risk prediction scores and can be used in real time to screen for AKI in the ICU and have been shown to detect AKI up to 6 h earlier than laboratory markers (Automated Continuous Acute Kidney Injury Prediction and Surveillance: A Random Forest Model, Chiofolo et al, *Mayo Clin Proc* 2019)	Koyner et al (*Crit Care* 2018; https://doi.org/10.1097/CCM.0000000000003123)
Furosemide stress test	Like a cardiac stress test, this functional test is meant to further stratify patients at intermediate risk of AKI progression. The patient is given IV furosemide at 1.0 mg/kg (if furosemide-naive) or 1.5 mg/kg (if previously exposed). Urine output < 200 mL over the next 2 h has 87% sensitivity and 84% specificity to predict progression to stage 3 AKI.	Koyner et al (*JASN* 2015; https://doi.org/10.1681/ASN.2014060535)

AKI Biomarker	Source	Function	Clinical Utility	Key Readings
[TIMP-2] × [IGFBP-7]	Urine	21- and 29-kDa proteins, respectively, involved in G_1 cell cycle arrest	Best at AKI prediction in the ICU setting out of 340 candidates evaluated in the Discovery Trial; FDA approved for marketing in 2014	Malhotra et al (*CJASN* 2017; https://doi.org/10.2215/CJN.01300216) Kashani et al (*Clin Chem Lab Med* 2017; https://doi.org/10.1515/cclm-2016-0973)
NGAL	Urine or serum	25-kDa protein that binds to iron-siderophore complexes and has a bacteriostatic function via the sequestering of iron during infection	Systemic levels are elevated in sepsis and severe inflammation, so clinical use is limited in the adult ICU setting	
Cystatin C	Urine or serum	13-kDa protein in the family of cysteine protease inhibitors, produced in all nucleated cells	In serum, marker of GFR similar to creatinine; in urine, because it is normally absorbed and fully degraded in the proximal tubule, urinary cystatin C is a marker of tubular dysfunction	
KIM-1	Urine	Transmembrane protein thought to participate in both kidney injury and healing processes	FDA approved for detection of drug-induced AKI in preclinical studies; unreliable in the setting of inflammation	
IL-18	Urine	Cytokine that regulates innate and adaptive immunity	Has not been well evaluated in the adult ICU setting	

Note: Novel AKI biomarkers have the potential to add clinically useful prognostic information; however, like troponin for acute cardiac syndromes, it is important to use these biomarkers in the appropriate clinical contexts. Indiscriminate use may cause sensitivity and specificity to decrease significantly.
Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; DM, diabetes mellitus; FDA, US Food and Drug Administration; GFR, glomerular filtration rate; ICU, intensive care unit; IL-18, interleukin 18; IV, intravenous; KIM-1, kidney injury marker 1; NGAL, neutrophil gelatinase-associated lipocalin; RRT, renal replacement therapy; [TIMP-2] × [IGFBP-7], product of tissue inhibitor of metalloproteinase 2 and insulin-like growth factor binding protein 7.

in-depth examination of SA-AKI pathophysiology is outside the scope of this article, it is important to note that SA-AKI pathophysiology is unique and should not be considered simply a subtype of ischemic injury (thus, answer (a) is incorrect for Question 1).

Management

Along with timely administration of antibiotics and source control, appropriate volume resuscitation remains an important determinant of outcomes in septic patients (see the sections on shock and intravenous fluids in the ICU). Finally, though 1 single-center randomized controlled trial (RCT) suggested benefit from pre-emptive RRT in ICU patients with stage 2 AKI, 2 subsequent larger multicenter trials, including 1 specifically of SA-AKI, showed no benefit (hence, answer (e) is incorrect for Question 1; see Table 3 and continuous RRT [CRRT] section below).

Additional Readings

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Shock

Case 2: *A 62-year-old woman is seen in the clinic with cough, fever, and hypoxemia. A nasopharyngeal swab comes back positive for influenza A, and she is initiated on oseltamivir treatment. She is seen in the emergency department 24 hours later and is admitted to the ICU with high-grade fever, multifocal opacities on chest x-ray, and respiratory failure requiring intubation. Blood cultures and bronchoscopy with bronchoalveolar lavage are performed and methicillin-resistant Staphylococcus aureus is isolated from both. Despite an initial 2-L (30 mL/kg) bolus of crystalloid and appropriate antibiotic treatment, the patient develops progressive hypotension. A central venous catheter is placed through the right internal jugular vein, after which the patient's mean arterial pressure (MAP) is 45 mm Hg, central venous pressure (CVP) is 11 mm Hg, and central venous oxygen saturation ($ScVo_2$) is 89%. Arterial lactate level is 10.2 mmol/L, and urine output is 10 mL/h.*

Question 2: Which of the following statements is correct about the next step in management?

(a) The next best option is to initiate norepinephrine treatment and perform a passive leg raise to assess whether she is likely to respond to additional fluids.
(b) The next best option is to initiate dopamine treatment.
(c) The next best option is to continue to administer intravenous fluids until CVP is ≥12 cm H_2O.
(d) Because of the dangers associated with volume overload, the patient should not have been treated with a 30-mL/kg fluid bolus and should receive no further fluids.
(e) Because $ScVo_2$ is >70%, oxygen delivery to her tissues is adequate and therefore no additional treatment is warranted.

For the answer to the question, see the following text.

Definition and Causes

Shock is defined as circulatory failure that results in inadequate cellular oxygen utilization with evidence of tissue hypoperfusion. Hypotension is typically accompanied by tachycardia and can be either absolute (typically systolic BP < 90 mm Hg or MAP < 70 mm Hg) or relative (eg, 40 mm Hg below baseline). Physical signs of tissue hypoperfusion include oliguria, altered mental status, and cold, mottled, or cyanotic skin. Elevated serum lactate level is the primary laboratory parameter suggesting hypoperfusion but is not specific. Shock can be mechanistically classified as: (1) hypovolemic or hemorrhagic, (2) distributive, (3) cardiogenic, or (4) obstructive (Table 4).

Management

Treatment should be directed to the underlying cause of shock. Beyond that, treatment of shock typically includes a combination of intravenous fluids and/or vasoactive medications. Fluid administration in shock was traditionally guided by invasive hemodynamic monitoring of CVP and pulmonary artery occlusion pressure. A series of RCTs showed no overall benefit from pulmonary artery catheter use and increased risk for significant catheter-related morbidity from infection, arrhythmia, or pulmonary artery rupture. Pulmonary artery catheters are reserved for specific scenarios such as severe pulmonary hypertension and/or right ventricular failure. Similarly, though central venous catheters continue to be routinely used to administer vasopressors, the use of strict CVP or $ScVo_2$ targets to guide fluid administration in septic shock is no longer advocated. In contrast to the original 2001 Rivers early goal-directed therapy trial, 3 recent large multicenter RCTs (ARISE, ProCESS, and ProMISe) did not show a benefit to fluid resuscitation strategies guided by CVP and $ScVo_2$ in septic shock (accordingly, answers (c) and (e) are incorrect for Question 2). High (>85%) $ScVo_2$, rather than a reassuring finding in sepsis, has been associated with worse prognosis in multiple studies, possibly indicating impaired oxygen utilization by tissues.

In contrast to static measures (eg, CVP, $ScVo_2$, or pulmonary artery occlusion pressure), dynamic measures of volume responsiveness—in which the response to a transient or small change in cardiac filling in assessed—appear to be more useful. For example, variations in stroke volume (or a surrogate such as pulse pressure) as assessed by pulse contour analysis, transthoracic or esophageal Doppler, or bioimpedance in response to changes in intrathoracic pressure during the respiratory cycle or to a passive leg raise, appear to be useful. A recent review suggested that passive leg raise may be the most useful dynamic measure (so for Question 2, (a) is the best answer). However, every method has inherent limitations, and no technology has proved unequivocally superior. Ultimately, fluid management in patients with shock requires consideration and integration of all available data.

Vasoactive agents used to treat shock include vasopressors that increase systemic vascular resistance or inotropic agents that increase cardiac output. In the setting of heart failure or cardiogenic shock, agents may be used that decrease systemic vascular resistance. Figure 3 summarizes properties of the most commonly used vasoactive agents.

Norepinephrine has emerged as the first-line agent for septic shock due to trials and meta-analyses showing that norepinephrine causes fewer tachyarrhythmias (mostly atrial fibrillation) and may be associated with decreased overall mortality compared to dopamine (disqualifying (b) as the correct answer to Question 2). Vasopressin, which causes vasoconstriction through V_1-receptor activation, appears useful for shock refractory to catecholamines. It has been specifically validated as an effective vasopressor for vasodilatory shock after cardiac surgery and as a second-line "catecholamine-sparing" agent in septic shock. Vasopressin also appears to cause less atrial fibrillation than catecholamines. An increased risk for

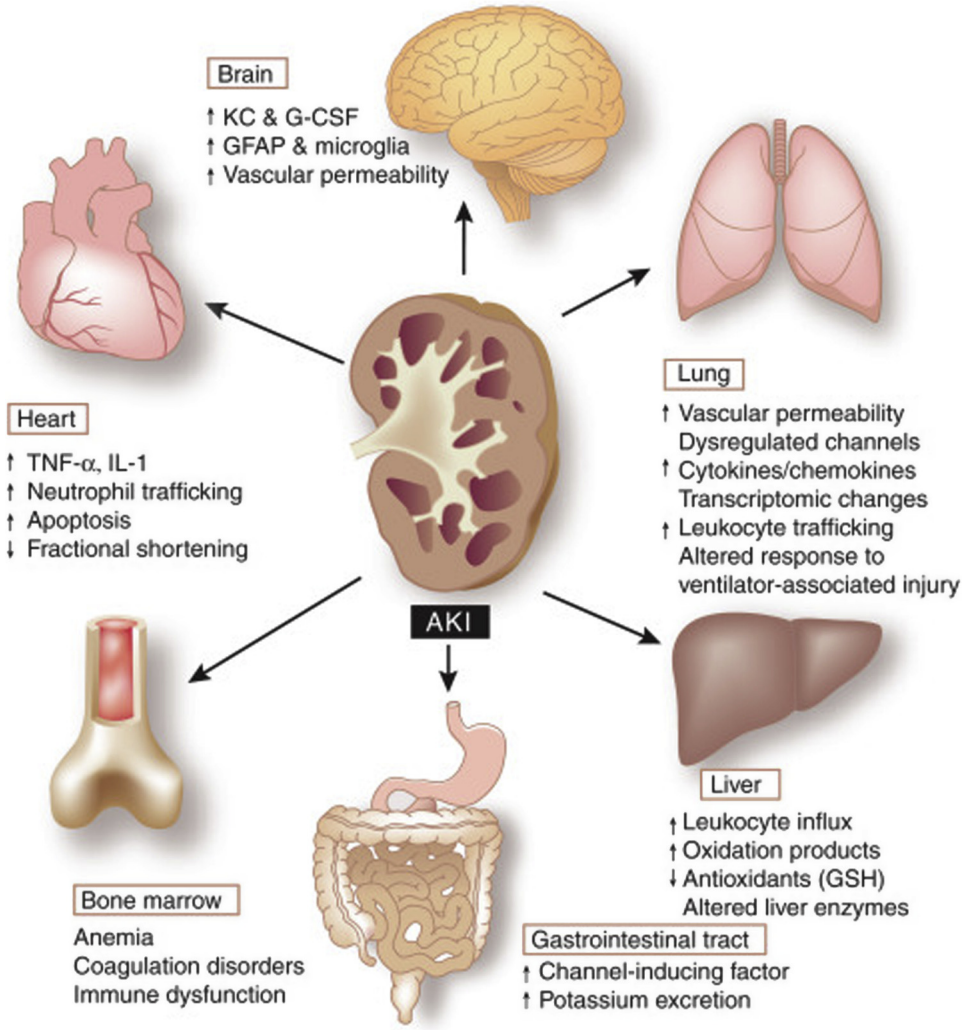

Figure 1. Acute kidney injury (AKI)-induced distant organ effects, including changes to brain, lungs, heart, liver, gastrointestinal tract, and bone marrow. Changes may include alterations in organ function, microvascular inflammation and coagulation, cell apoptosis, transporter activity, oxidative stress, and transcriptional responses. Abbreviations: G-CSF, granular colony-stimulating factor; GFAP, glial fibrillary acidic protein; GSH, glutathione; IL-1, interleukin 1; KC, keratinocyte-derived chemokine; TNF-α, tumor necrosis factor α. Reproduced from Scheel et al (Uremic lung: new insights into a forgotten condition. *Kidney Int.* 2008;74(7):849-51) with permission of Elsevier; original image © 2008 International Society of Nephrology.

hyponatremia from V_2-receptor activation has not been observed in clinical studies. The VANISH trial, a recent large RCT of the effect of vasopressin (vs norepinephrine) on kidney function, suggested that vasopressin reduced the need for RRT, but this secondary outcome requires further validation.

Angiotensin II, similar to vasopressin, is a potent non-adrenergic vasoconstrictor that has recently been approved for use in septic shock after being shown to effectively increase BP in vasodilatory shock. A post hoc analysis suggested that angiotensin II may be particularly beneficial to patients with septic shock and AKI-RRT, but the significance of this secondary outcome requires additional investigation. Of note, there may be an increased risk for thrombotic events with angiotensin II administration.

Vasoactive agents are typically titrated to an initial MAP goal of ≥65 mm Hg. A recent RCT of a higher MAP goal in patients with septic shock showed no overall mortality difference. However, subgroup analysis showed that patients with chronic hypertension may benefit from a higher MAP goal with a decreased need for RRT, although this came with a higher rate of atrial fibrillation.

Additional Readings

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Table 2. Summary of Common Causes of AKI in the ICU Setting

Cause	Definition	Epidemiology	Pathophysiology	Management	One Key Reading
Sepsis	KDIGO AKI in the setting of "life threatening organ dysfunction caused by a dysregulated host response to infection"; SOFA score increase ≥ 2 points or qSOFA ≥ 2	Most common cause of AKI (accounts for 50% of AKI cases in the ICU); incidence is 10%-20% of septic patients overall, 50%-70% in septic shock	No longer thought to be primarily ischemic/hypotensive in nature; key factors are: (1) Microvascular dysfunction (2) Endothelial dysfunction (3) Inflammation (4) Oxidative stress	Early fluid resuscitation	Poston & Koyner (*BMJ* 2019; https://doi.org/10.1136/bmj.k4891)
Cardiac surgery	No consensus definition, but KDIGO criteria are becoming standard	Second most common cause of AKI in the ICU; incidence ranges from 5%-42% depending on AKI definition used	Multifactorial; extracorporeal circulation and hemolysis are unique contributors to CSA-AKI	PrevAKI trial showed adhering to KDIGO guideline reduced AKI rates by 30% in a high-risk population	Wang & Bellomo (*Nat Rev Nephrol* 2017; https://doi.org/10.1038/nrneph.2017.119)
Acute liver failure	(1) Hepatic encephalopathy of any severity, (2) INR ≥ 1.5 (3) Onset of illness < 26 wk (4) No evidence of cirrhosis	50% of ALF cases due to acetaminophen toxicity; 70% develop AKI, 30%-70% require RRT	(1) Renal hypoperfusion from decreased MAP and increased renal vasoconstriction (2) Direct tubular toxicity from offending agent (acetaminophen most commonly)	"Early" RRT; expedited liver transplant	Leventhal & Liu (*Adv Chronic Kidney Dis* 2015; https://doi.org/10.1053/j.ackd.2015.06.006)
Intra-abdominal HTN	IAH defined as IAP > 12 mm Hg; ACS defined as IAP > 20 mm Hg associated with new organ dysfunction	Interestingly, IAH—likely via renal venous congestion—has been associated with both HRS and CRS; AKI rate may be as high as 40%	Decreased perfusion mediated by elevations in renal vein pressure and renal parenchymal pressure (rather than by decreased cardiac output or ureteral compression)	(1) Decompressive laparotomy (2) Adequate sedation and analgesia to control abdominal muscle tone	Mohmand & Goldfarb (*JASN* 2011; https://doi.org/10.1681/ASN.2010121222)
Hepatorenal syndrome	(1) Presence of cirrhosis & ascites (2) Scr increase ≥ 0.3 mg/dL (3) No improvement in Scr after 48 h of diuretic withdrawal & volume expansion with albumin (4) Absence of shock (5) No nephrotoxic drugs (6) Absence of proteinuria, hematuria, or US findings	HRS type 1 has a 2-wk mortality of 80%; HRS type 2 has a median survival of 6 mo; in patients awaiting liver transplant, rate of HRS is nearly 50%	Primarily due to intense renal vasoconstriction without structural kidney damage	(1) Midodrine and octreotide (2) Terlipressin (outside the US) (3) TIPS (4) Liver transplant	Kidney Disease in the Setting of Liver Failure: Core Curriculum 2013
Malignancy	KDIGO-defined AKI in the setting of malignancy	18% in first y following cancer diagnosis; mortality in AKI-RRT is 66%-88%	Cancer-specific causes include: (1) Nephrotoxic chemotherapy (2) Cast nephropathy (3) Lymphomatous infiltration (4) Hepatic sinusoidal obstruction syndrome (5) TMA	(1) Discontinue offending agent if possible (2) Treatment of underlying condition (3) RRT	Onco-Nephrology: Core Curriculum 2015
Cardiorenal syndrome	Type 1: Acute cardiac dysfunction leading to decreased kidney function; Type 3: Acute worsening of kidney function causing cardiac dysfunction; Type 5: Systemic conditions causing simultaneous dysfunction of the heart and kidney	45%-65% of patients with HF with reduced ejection fraction will develop concomitant kidney disease	Type 1: Kidney arterial underfilling and increased venous congestion due to systolic dysfunction; Type 3: Incompletely understood; Type 5: Sepsis is the most common example in the ICU	Diuresis; stepped pharmacologic therapy is superior to ultrafiltration for the preservation of kidney function	Management of Heart Failure in Advancing CKD: Core Curriculum 2018

Abbreviations: ACS, abdominal compartment syndrome; AKI, acute kidney injury; ALF, acute liver failure; CRS, cardiorenal syndrome; CSA-AKI, cardiac surgery–associated acute kidney injury; HF, heart failure; HRS, hepatorenal syndrome; HTN, hypertension; IAH, intra-abdominal hypertension; IAP, intra-arterial pressure; ICU, intensive care unit; INR, international normalized ratio; KDIGO, Kidney Disease: Improving Global Outcomes; MAP, mean arterial pressure; qSOFA, quick Sequential Organ Failure Assessment; Scr, serum creatinine; SOFA, Sequential Organ Failure Assessment; TIPS, transjugular intrahepatic portosytemic shunt; TMA, thrombotic microangiopathy.

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Intravenous Fluids in the ICU

Colloids Versus Crystalloids

The use of colloid solutions was reviewed in detail in the 2018 Core Curriculum on AKI. Despite theoretical advantages, these solutions are expensive and multiple large RCTs have been negative. In addition, there is evidence of harm (increased rates of AKI) with hetastarch solutions, which should generally be avoided.

Saline Versus Balanced Solutions

Epidemiologic data suggest that 0.9% saline solution, when compared with balanced salt solutions such as lactated Ringers or Plasma-Lyte (Baxter), may increase the risk for AKI, need for RRT, and mortality in ICU patients. Two recent large, single-center, pragmatic, unblinded, multiple-crossover trials examined the use of balanced crystalloids versus 0.9% saline solution. One evaluated patients admitted from the emergency department to a non-ICU setting (SALT-ED; $n > 13{,}000$), and the other evaluated ICU patients (SMART; $n > 15{,}000$). In both trials, the use of balanced solutions resulted in an ~1% absolute reduction in the rate of "MAKE-30," a composite outcome of death, need for RRT, or persistent doubling of creatinine level at 30 days. In the SMART trial, the prespecified subgroup with sepsis had an absolute reduction in 30-day mortality of >4%. In the SALT-ED trial, the benefit of balanced solutions was greatest in those who presented with an already elevated serum creatinine level. Some have called for caution in interpreting the SMART and SALT-ED trials, while others have concluded that standard use of saline solution, particularly in large doses, should be discontinued. Additional large clinical trials are ongoing. Importantly, saline solution should be the fluid of choice in patients with specific electrolyte derangements, such as hypovolemic hypochloremic metabolic alkalosis.

The pathophysiology underlying the purported negative effect of saline solution on the kidneys remains unclear, but it is thought to be related to the high chloride content. Proposed mechanisms include reduced glomerular filtration rate (GFR) through activation of tubuloglomerular feedback triggered by increased chloride delivery to the macula densa, vasoconstriction caused by chloride-induced thromboxane release, and increased inflammatory cytokine expression induced by acidosis.

Harms of Fluid Overload and the Importance of Timing of Fluid Administration:

There is an increasing number of observational studies showing that volume overload in patients with AKI, ARDS, sepsis, and critical illness in general is independently associated with progressive decreases in kidney function, lower odds of renal recovery, and increased mortality. The negative impact of fluid overload on kidney function may be due to venous congestion, which can lead to renal venous hypertension, increased renal interstitial pressure, and ultimately reduced RBF and GFR. Emerging prospective data also suggest that fluid restriction may be beneficial to patients with critical illness such as ARDS (see below) or sepsis. For example, in a recent feasibility trial of patients with septic shock, fluid restriction (after initial resuscitation) improved kidney function and was associated with a trend toward decreased mortality.

Given the potential for both benefit and harm (Fig 4) from intravenous fluids, thoughtful assessment of volume status is of paramount importance in critically ill patients. In addition, fluid management should consider the temporal context—the so-called ebb and flow—of a patient's critical illness. Specifically, while aggressive resuscitation is usually warranted early, by 36 to 48 hours a transition to a conservative approach and ultimately to a deresuscitative strategy may benefit most patients (Fig 5). For example, in a study of patients presenting with the combination of ARDS and septic shock (with or without AKI), a group at risk for harm from over- or under-resuscitation, mortality was lowest in those provided with adequate initial fluid resuscitation followed by conservative fluid management (which is why (d) is an incorrect answer to Question 2).

Additional Readings

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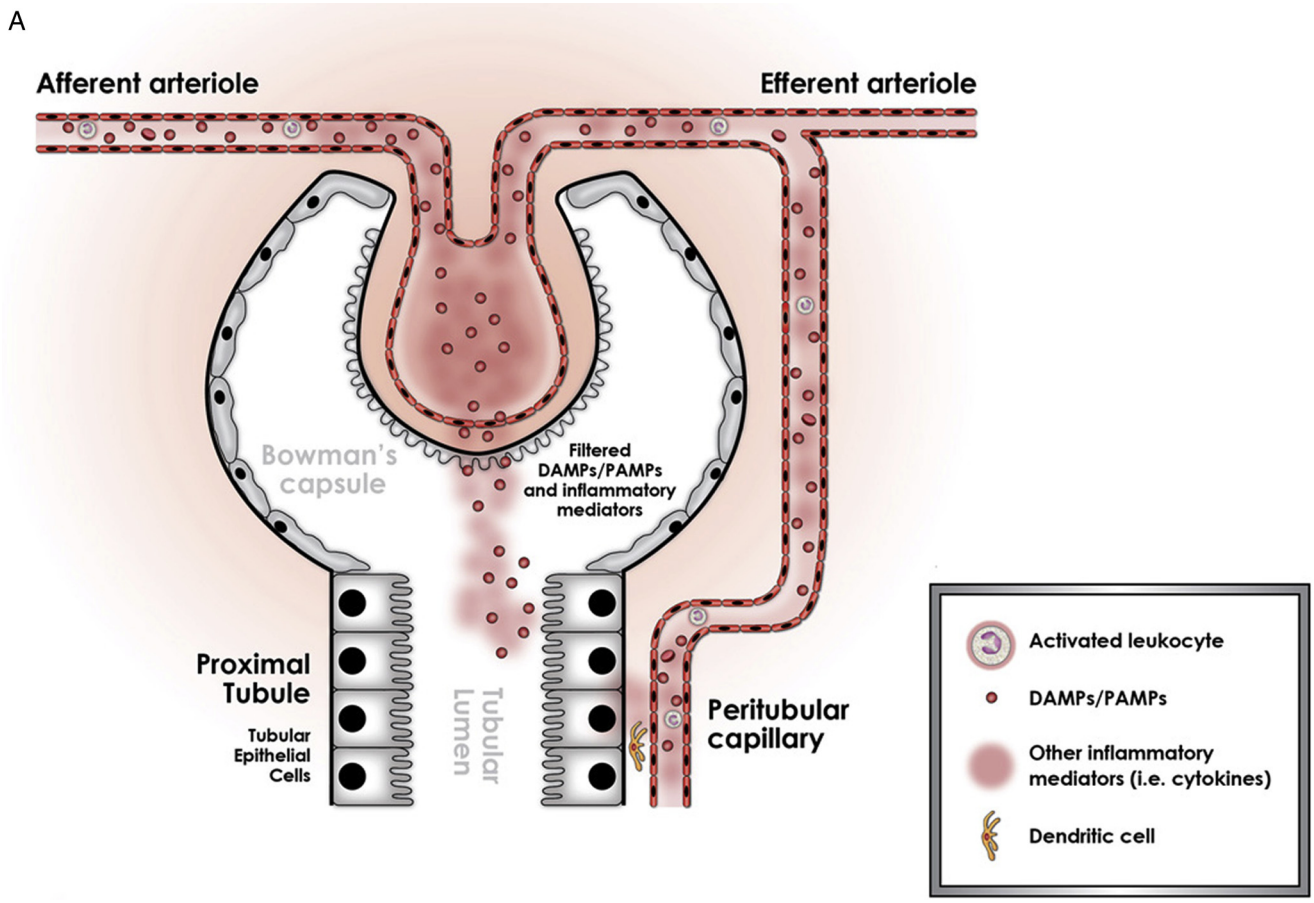

Figure 2. (A) Sepsis results in the release of damage- (DAMPs) and pathogen-associated molecular patterns (PAMPs), which are filtered at the glomeruli. (B) These "danger signals" can lead to significant microcirculatory dysfunction, which is manifest by heterogeneity of flow. A number of capillaries begin to exhibit sluggish flow, which may lead to amplification of the danger signals in these areas and lead to increased oxidative stress. Also, expression of tumor necrosis factor (TNF) receptors in the S2 segment tubular cells has inspired the proposal that secretion of TNF-α by S1 cells may signal distal segments in a paracrine fashion. There is some evidence that this paracrine signal may also include mediators of cell cycle arrest, namely tissue inhibitor of metalloproteinase 2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP-7). (C) Paracrine stimulation from S1 segment tubular epithelial cells triggers an "oxidative outburst" in the S2 and S3 segment tubular epithelial cells. This oxidative outburst may affect mitochondrial function by uncoupling respiration, thereby causing energetic imbalance, production of radical oxygen and nitrogen species (ROS/RNS), and loss of mitochondrial membrane potential. Apoptosis may be avoided through reduced energy utilization, mitophagy, and cell-cycle arrest. Finally, downregulated apical ionic transport leads to chloride accumulation which triggers tubuloglomerular feedback (TGF) and subsequent constriction of the afferent arteriole, leading to decreased glomerular filtration rate. Abbreviations: AMP, adenosine monophosphate; ATP, adenosine triphosphate; ICAM, intercellular adhesion molecule; NHE1, sodium-hydrogen antiporter 1; VCAM, vascular cell adhesion molecule. Figure panels adapted from Gomez et al (A unified theory of sepsis-induced acute kidney injury: inflammation, microcirculatory dysfunction, bioenergetics, and the tubular cell adaptation to injury. *Shock*. 2014;41(1):3-11) with permission of Wolters Kluwer Health, Inc; original images © 2013 by the Shock Society.

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Cardiac Surgery–Associated AKI

Epidemiology

CSA-AKI is the second most common cause of AKI in the ICU. CSA-AKI is defined inconsistently in the literature, but generally refers to AKI occurring within 2 to 7 days of surgery. Consequently, the reported incidence of CSA-AKI ranges widely, but by KDIGO criteria, it occurs in about 20% to 30% of cases.

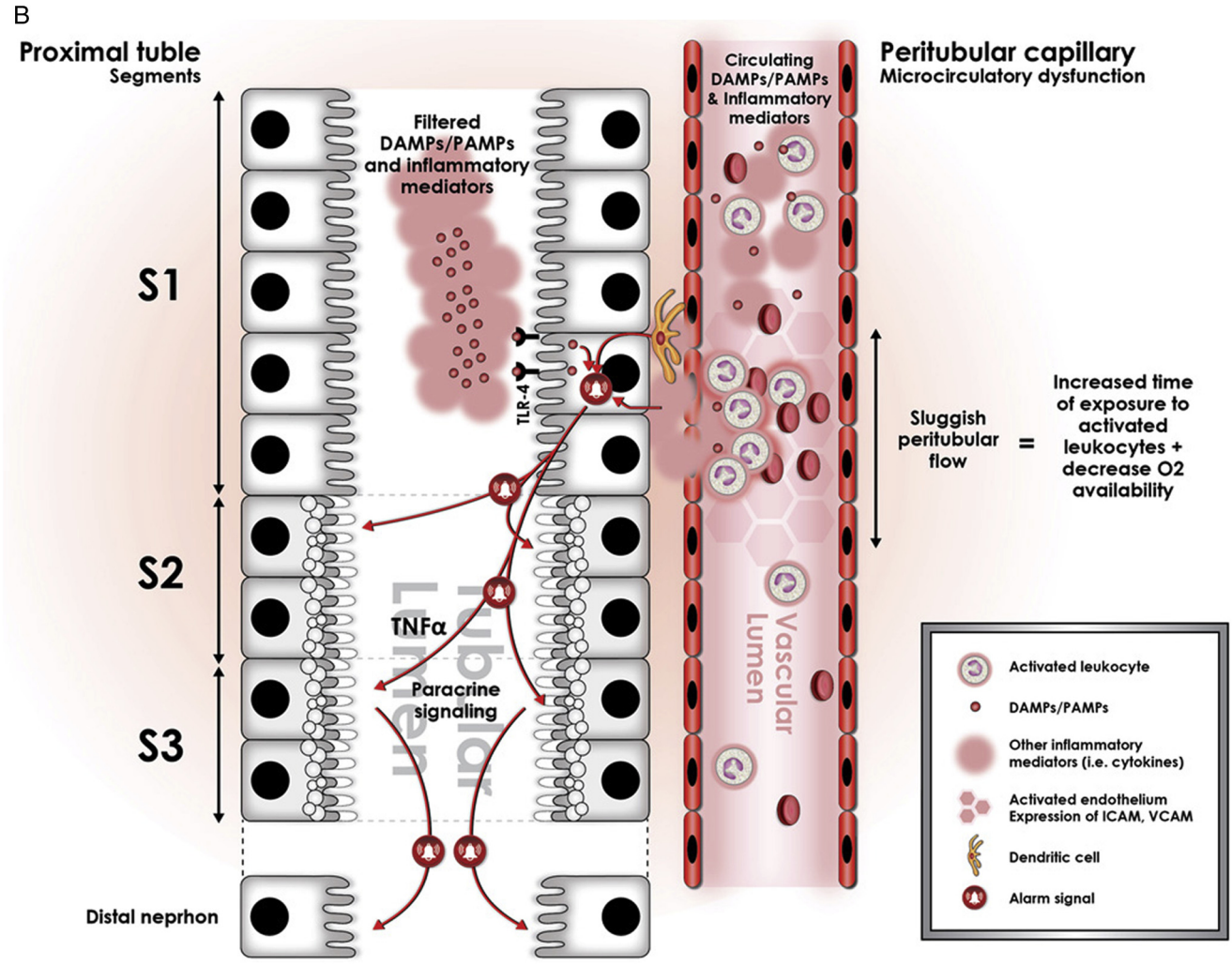

Figure 2. *Continued.*

Pathophysiology

The pathophysiology of CSA-AKI is multifactorial. Renal hypoperfusion, inflammation, oxidative stress, atheroembolism, and nephrotoxins may all contribute. Unique to CSA-AKI are mechanical factors, particularly the use of cardiopulmonary bypass (CPB). Time on CPB is one of the strongest predictors of AKI, and CPB has been associated with increases in levels of damage-associated urinary biomarkers. In addition, both left ventricular assist device (LVAD) placement and extracorporeal membrane oxygenation (ECMO) can precipitate hemolysis and pigment-associated nephropathy (see ECMO section).

Prevention

Because the timing of the renal insult can be anticipated, numerous studies have evaluated pre- or intraoperative interventions to prevent CSA-AKI. Many of these, such as statin use, have not been of benefit. Use of renal-protective fluids (balanced crystalloid solutions) and avoidance of starch solutions have been shown in studies to reduce rates of AKI, although the literature specific to CSA-AKI is not definitive.

Minimizing CPB time and using off-bypass techniques are associated with reduced CSA-AKI. Use of a KDIGO-based AKI bundle has also been shown to reduce AKI in a single-center study. In PrevAKI, patients who underwent CPB and had an elevated urinary [TIMP-2] × [IGFBP-7] were randomly assigned to receive usual care or a KDIGO-based care bundle (minimization of nephrotoxic agents, discontinuation of angiotensin-converting enzyme inhibitors, avoidance of hyperglycemia, and volume optimization). Rates of AKI were significantly reduced in those who received bundled care (55.1% vs 71.7%; $P = 0.004$). The trial detected no mortality difference, but it was not powered to do so. Larger clinical trials are ongoing.

Management

The mainstay of CSA-AKI management is prevention. When prevention fails, treatment is supportive.

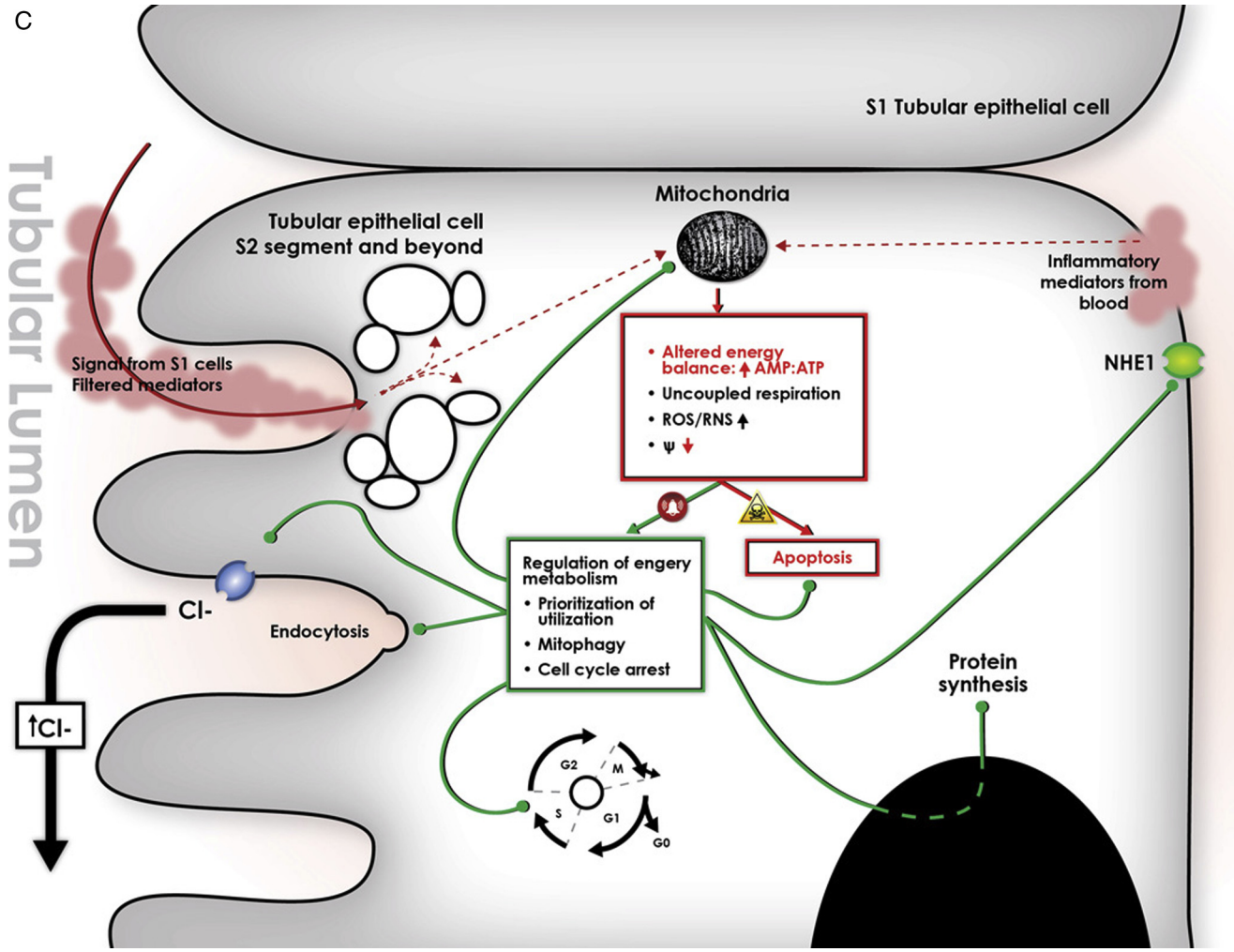

Figure 2. *Continued.*

Additional Readings

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Extracorporeal Membrane Oxygenation

Overview

The use of ECMO in adults has grown exponentially since the 2009 H1N1 influenza outbreak, with overall ECMO use more than tripling between 2008 and 2014. An ECMO circuit is essentially a simplified CPB machine that can provide support for days to weeks. All circuits include 2 vascular cannulae and a blood pump. Blood from the venous system is passed through a membrane oxygenator, where an air-oxygen gas mixture runs countercurrent to the blood, resulting in oxygen delivery and carbon dioxide (CO_2) removal. The blood flow depends on the pump rate, which is adjustable and set in rotations per minute. The amount of oxygen delivered can be increased either by increasing the oxygen content of the oxygenator gas or by increasing the pump rotations per minute to achieve higher flow. CO_2 elimination can be adjusted by altering the flow rate of the oxygenator gas, known as the "sweep," which typically runs from 1 to 6 L/min. Higher sweep will eliminate more CO_2 and result in lower arterial P_{CO_2}.

There are 2 basic types of ECMO circuits, which differ in whether the oxygenated blood is returned to the venous or arterial system (Fig 6). Venovenous ECMO can effectively replace the gas exchange function of the lungs but requires intact cardiac function to pump the blood and is used to treat isolated respiratory failure. Venoarterial (VA)-ECMO is used to treat cardiac failure with or without respiratory failure, often used as a bridge to either cardiac transplantation or a long-term cardiac support device such as an LVAD.

Table 3. Comparison of Randomized-Controlled Studies Evaluating the Timing of RRT Initiation

	AKIKI (n = 619)	ELAIN (n = 231)	IDEAL ICU (n = 488)	STARRT AKI (target n = 2,866)
Study site	Multicenter (France)	Single surgical ICU (Germany)	Multicenter (France)	Multicenter (international)
Inclusion criteria	KDIGO stage 3 AKI and on ventilator (85%) or pressors (85%) (with septic shock in 56%)	(1) KDIGO stage 2 AKI, (2) plasma NGAL > 150 ng/mL, and (3) severe sepsis, pressors, fluid overload despite diuretics, and/or nonrenal SOFA > 2	RIFLE-F AKI in early septic shock (100% on pressors)	KDIGO stage 2 AKI
Significant exclusion criteria	Severe AHRF (Fio_2 ≥ 50%)	—	Pulmonary edema despite diuretics	—
Early RRT	Within 6 h of stage 3 AKI	Within 8 h of stage 2 AKI	Within 12 h of stage 3 AKI	Within 12 h of randomization
Indications for RRT in delayed arm	SUN > 112 mg/dL, K > 6 mmol/L, pH < 7.15, severe pulmonary edema, oliguria > 72 h	Stage 3 AKI or SUN > 100 mg/dL, K > 6 mmol/L, organ edema, urine output < 200 mL/d	At 48 h unless recovery or K > 6.5 mmol/L, pH < 7.15, or pulmonary edema	K ≥ 6.0 mmol/L, pH ≤ 7.20, bicarbonate ≤ 12 mmol/L, Pao_2/Fio_2 ≤ 200, persistent AKI > 72 h
Receipt of RRT (early vs late)	98% vs 51%	100% vs 91%	97% vs 62%	Awaiting results
Spontaneous recovery (in late-start group)	49%	9%	38%	
RRT modality	55% IHD, 45% CRRT	100% CVVHDF	55% CRRT, 45% IHD	
60-d mortality (early vs late)	48.5% vs 49.7% (P = 0.79)	38.4% vs 50.4% (P = 0.07)	—	
90-d mortality (early vs late)	—	39.3% vs 54.7% (P = 0.03)	58% vs 54% (P = 0.38)	
ICU LOS in survivors	13 d in both groups (NS)	19 vs 22 days (NS)	12 d in both groups (NS)	
MV (early vs late)	7 vs 6 d free of MV (NS)	125 vs 181 h (P = 0.002)	2 vs 3 d free of MV (NS)	

Abbreviations: AHRF, acute hypoxemic respiratory failure; AKI, acute kidney injury; CRRT, continuous renal replacement therapy; CVVHDF, continuous venovenous hemodiafiltration; Fio_2, fraction of inspired oxygen; ICU, intensive care unit; IHD, intermittent hemodialysis; KDIGO, Kidney Disease: Improving Global Outcomes; LOS, length of stay; MV, mechanical ventilation; NGAL, neutrophil gelatinase-associated lipocalin; NS, not significant; RIFLE, Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease; RRT, renal replacement therapy; SOFA, Sequential Organ Failure Assessment; SUN, serum urea nitrogen.

Because of the high flows typically used in ECMO circuits (3-6 L/min), the venous blood chamber (eg, inferior vena cava) being emptied is constantly under significant negative pressure (eg, −60 mm Hg). As a result, ECMO circuits are sensitive to decreases in effective circulating volume. Relatively modest hypovolemia can generate enough negative pressure to produce vibrations in the ECMO tubing, which are referred to as "chugging" or "chattering." With more severe hypovolemia, the walls of the inferior vena cava may temporarily fully collapse around the drainage cannula, causing a sudden severe decrease in flow called a "suck-down" event. Depending on the cause, treatments for chattering or suck-down include volume expansion, decreases in pump rate, and cannula repositioning. Analogous to a failing heart, VA-ECMO is also very sensitive to afterload, so hemodynamic intolerance of hypertension is common. Some recommend that hypertension be aggressively treated in all ECMO patients, but this approach is largely extrapolated from data from adult LVAD or pediatric ECMO patients in whom hypertension is strongly associated with increased risk for stroke and bleeding.

Major complications include bleeding or clotting events. To prevent clotting of the circuit, patients are typically treated with systemic anticoagulation with heparin. This is particularly important for patients receiving VA-ECMO, in which thrombi that form in the circuit could cause strokes or other arterial embolic events.

AKI on ECMO

Up to 80% of adults receiving ECMO develop AKI, with ~45% of patients receiving ECMO ultimately requiring RRT. Not surprisingly, AKI appears to be more common in those receiving VA-ECMO for cardiac failure. There are limited observational data suggesting that pre-emptive RRT can prevent or mitigate volume overload. Fluid overload in ECMO patients appears to be independently associated with an increased risk for mortality, and guidelines suggest targeting euvolemia with diuretics or

Table 4. Typical Hemodynamics in Various Shock States and Their Differential Diagnosis

	CVP or Preload	CO	SVR	Examples
Distributive	↓	↑	↓↓	• Septic • Neurogenic • Anaphylaxis • Adrenal insufficiency
Hypovolemic or hemorrhagic	↓↓	↓	↑	• Hemorrhagic • Other volume depletion (diarrhea, vomiting, overdiuresis, inadequate intake)
Cardiogenic	↑	↓↓	↑	• Acute myocardial infarction • Heart failure • Valvular disease • Post cardiopulmonary bypass • Arrhythmia
Obstructive	NA	↓↓	↑	• Massive pulmonary embolism • Tamponade • Tension pneumothorax • Mechanical ventilation with excess PEEP

Note: The 3 primary categories of shock can be classified by the primary mechanism (double arrows) of hypotension through the relationship MAP = CO × SVR and the concept of preload. Note that more than 1 type of shock can coexist in a given patient (eg, combined septic and cardiogenic shock in a patient with prominent myocardial depression of sepsis; combined obstructive and hypovolemic shock in a trauma patient with tamponade). Obstructive shock, like cardiogenic shock, will typically cause high CVP along with low CO and high SVR but depending on the underlying cause (ie, the site of obstruction), can have variable effects on right or left ventricular preload. Adrenal insufficiency can cause shock by both distributive and hypovolemic mechanisms.
Abbreviations: CO, cardiac output; CVP, central venous pressure; MAP, mean arterial pressure; NA, not applicable; PEEP, positive end-expiratory pressure; SVR, systemic vascular resistance.

RRT when hemodynamically stable to optimize cardiopulmonary function.

The mechanism of AKI on ECMO is thought to be multifactorial due to inflammation, disordered coagulation, pigment injury from hemolysis, and nonpulsatile blood flow in the case of VA-ECMO. Excess circuit-related hemolysis can cause the development of pink urine or RRT effluent. When hemolysis is suspected, plasma-free hemoglobin levels should be measured.

For patients with AKI on ECMO, CRRT is the preferred modality. CRRT can be provided by placing a separate dialysis catheter or connecting the CRRT circuit directly to the ECMO circuit (Fig 6). A separate dialysis circuit may lower the risk for embolism in the ECMO circuit. Separate circuits also have the practical advantage that problems with one circuit will not interfere with the other. However, placing a dialysis catheter may carry an elevated risk for air embolism because the substantial negative pressure generated by the ECMO pump can entrain air into the venous system. It may be beneficial to temporarily decrease ECMO pump rates during the highest risk portions of catheter placement (eg, dilation). If connecting the CRRT circuit directly to the ECMO circuit, it may be preferable to connect the CRRT inflow to a post-pump segment of the ECMO circuit to minimize the risk for air entrainment. The CRRT outflow should be connected to the preoxygenator segment of the ECMO circuit, where the oxygenator can serve as a filter that prevents air or clots from the CRRT circuit from reaching the ECMO return cannula. Because the pressures of an ECMO circuit are more extreme than the pressures typical of a CRRT circuit, the pressure alarm settings in the CRRT machine often need to be adjusted.

AKI and LVADs

Like ECMO, the use of LVADs to treat end-stage heart failure has grown dramatically during the past 2 decades. On average, LVAD placement produces an initial improvement in GFR, which likely reflects improved renal perfusion in patients with type 2 cardiorenal syndrome (kidney injury due to chronic cardiac dysfunction), followed by a gradual decline back toward baseline. However, GFRs may not improve in those with intrinsic kidney disease. Like ECMO patients, LVAD patients are at elevated risk for AKI throughout their course, and AKI (particularly AKI-RRT) is associated with poor outcomes. LVAD-specific causes of AKI include hemolysis, right ventricular failure, and possibly nonpulsatile blood flow. An in-depth discussion of LVADs is beyond the scope of this review, but those interested are directed toward the additional readings.

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Acute Liver Failure

Kidney disease complicating liver cirrhosis is reviewed in detail in a 2013 Core Curriculum article on kidney disease in the setting of liver failure, so we instead focus on ALF.

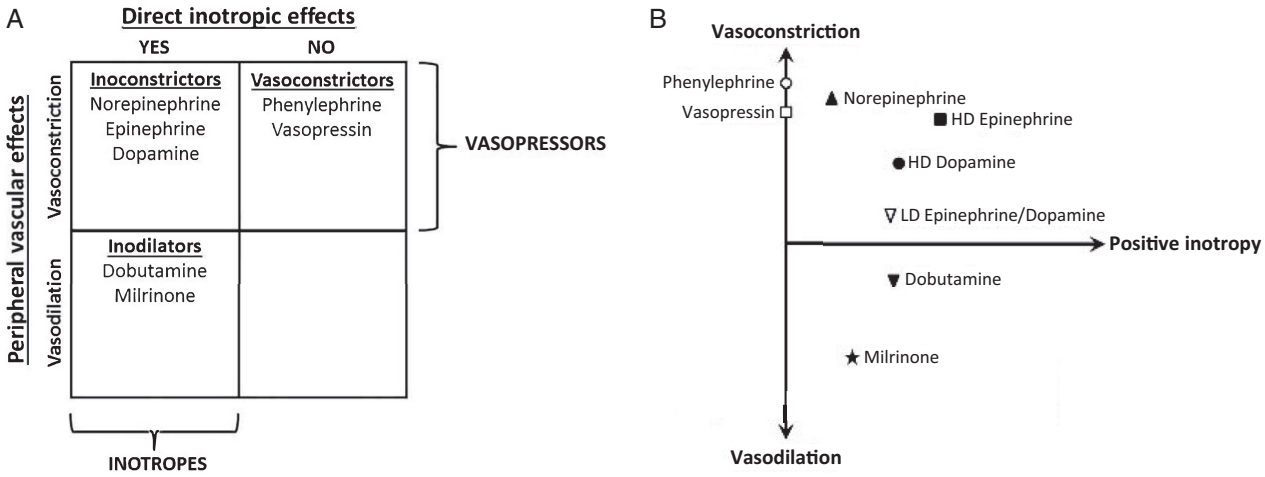

Figure 3. Proposed classification of (A) vasoactive agents and (B) schematic of the type and strength of the vascular response each produces. Adrenergic inoconstrictors stimulate β_1 and α_1 receptors to induce increased inotropy and vasoconstriction, respectively. Of note, epinephrine, in addition to β_1 and α_1 activity, has significant β_2 activity, but nonetheless acts as a vasoconstrictor due to the dominant effect of α_1-mediated vasoconstriction; however, β_2-mediated relaxation of smooth muscle by epinephrine is clinically important in the setting of anaphylaxis, where it acts to induce bronchodilation. Pure vasoconstrictors include the pure α_1 agonist phenylephrine and the nonadrenergic agent vasopressin, which acts on V_1 receptors on vascular smooth muscle cells; angiotensin II (not depicted) is a second recently approved nonadrenergic pure vasoconstrictor that acts on AT_1 receptors on vascular smooth muscle. Inodilators include dobutamine, which increases inotropy via β_1 stimulation and induces vasodilation via vascular β_2 receptors; milrinone is another inodilator that acts similarly via phosphodiesterase 3 inhibition. Effects in the case of epinephrine and dopamine depend in part on dose (LD, low-dose; HD, high-dose). Adapted from Jentzer et al (Pharmacotherapy update on the use of vasopressors and inotropes in the intensive care unit. *J Cardiovasc Pharmacol Ther.* 2015;20(3):249-60) with permission of SAGE Publications; original figures © Jentzer et al 2014.

Definition and Causes

ALF, previously known as fulminant hepatic failure, is defined by: (1) hepatic encephalopathy of any severity, (2) international normalized ratio ≥ 1.5, (3) onset of illness less than 26 weeks, and (4) no evidence of cirrhosis. Though at times difficult to discern, the distinction between ALF and chronic liver disease is critical because some of the complications (particularly intracranial hypertension) and management options (eg, consideration of "early" RRT and expedited liver transplantation) apply more specifically to ALF.

The most common causes of ALF can be divided into: (1) toxic insults, most often acetaminophen; (2) acute viral hepatitis; and (3) ischemic or vascular injury. In modern US cohorts, acetaminophen toxicity alone accounts for ~50% of cases.

Prognosis and Complications

Though some cases (especially acetaminophen related) will spontaneously resolve, mortality of ALF is high with supportive care alone. Complications of ALF include AKI, encephalopathy, coagulopathy and bleeding, hypoglycemia, sepsis, and multiorgan failure.

In contrast to cirrhosis, severe encephalopathy from ALF is frequently accompanied by cerebral edema with progressive intracranial hypertension and risk for herniation. Cerebral edema accounts for 20% to 25% of deaths in modern ALF cohorts. First-line treatment for confirmed or suspected intracranial hypertension includes mannitol, though its use may be limited by decreased kidney function. Hypertonic saline solution to achieve a serum sodium level of 145 to 155 mEq/L is recommended in patients with or at high risk for cerebral edema.

AKI in the setting of ALF may be due to renal hypoperfusion (eg, bleeding and hepatorenal physiology), intrinsic injury (eg, direct tubular toxicity of acetaminophen), or complications of ALF (eg, sepsis) and appears to be associated with further increase in risk for cerebral edema.

Management

Patients with ALF may require RRT relatively early in the course of AKI. CRRT is preferred to intermittent hemodialysis (IHD) because CRRT reduces the risk for intracranial hypertension. In contrast to chronic liver failure, RRT may have a role in specifically treating hyperammonemia in ALF, although this remains controversial.

Additional Readings

- Canalese J, Gimson AE, Davis C, Mellon PJ, Davis M, Williams R. Controlled trial of dexamethasone and mannitol for the cerebral oedema of fulminant hepatic failure. *Gut.* 1982;23(7):625-629.
- Cardoso FS, Gottfried M, Tujios S, Olson JC, Karvellas CJ; US Acute Liver Failure Study Group. Continuous renal replacement therapy is associated with reduced serum ammonia levels and mortality in acute liver failure. *Hepatology.* 2017.

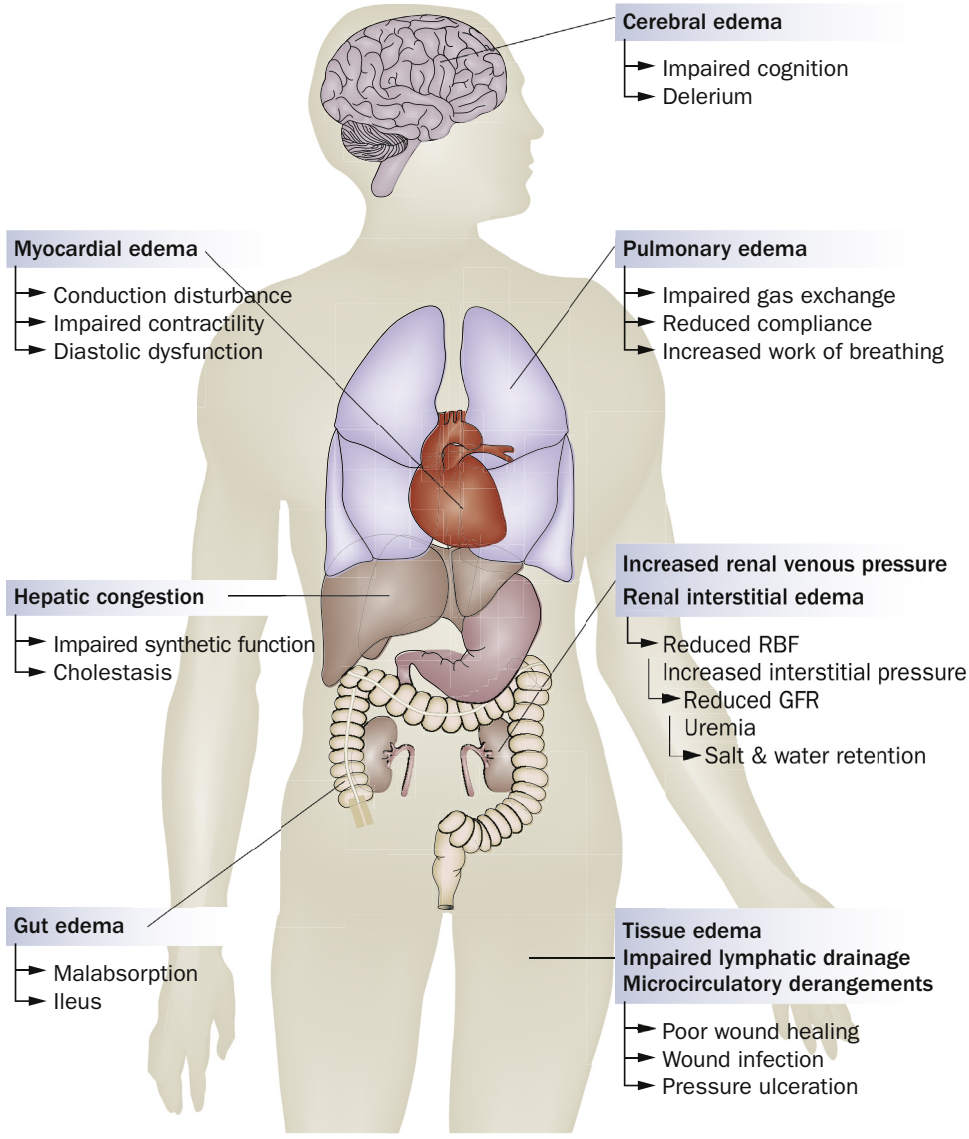

Figure 4. Pathologic sequelae of fluid overload in organ systems. Abbreviations: GFR, glomerular filtration rate; RBF, renal blood flow. Reproduced from Prowle et al (Fluid balance and acute kidney injury. *Nat Rev Nephrol*. 2010;6(2):107-15) with permission of Springer Nature; original image © 2010 Macmillan Publishers Limited.

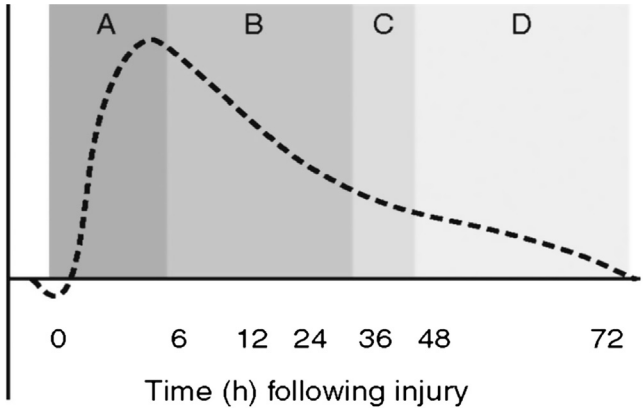

Figure 5. Changing fluid resuscitation strategies parallel the phases of critical illness and the immune response to sepsis or another injury. Phase A (0-6 hours): initial aggressive volume resuscitation (eg, 30 mL/kg of intravenous crystalloid), also known as the ebb phase of critical illness. Phase B (6-36 hours): decelerating fluid resuscitation; fluid is often still required to compensate for extravascular sequestration, but fluids should only be provided as needed to maintain organ perfusion in a targeted manner, with frequent reassessment of fluid responsiveness. Phase C (36-48 hours): equilibrium phase; fluid administration is stopped. Phase D (beyond 48 hours): mobilization, deresuscitation, or flow phase; fluids are withheld to allow for spontaneous diuresis or, in those who fail to autodiurese, pharmacologic diuresis or ultrafiltration can be provided to achieve euvolemia. The time at which a given patient transitions phases may vary and multiple insults can substantially disrupt this sequence. Reproduced from Godin et al (Clinical approach to the patient with AKI and sepsis. *Semin Nephrol*. 2015 Jan;35(1):12-22) with permission of Elsevier; original image © 2015 Elsevier Inc.

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AKI and Respiratory Failure

Case 3: *A 64-year-old man is admitted with cough, fever, and hypoxemia. Soon thereafter, he develops respiratory distress and requires endotracheal intubation. Chest x-ray shows diffuse bilateral pulmonary opacities. Blood gas reveals Pa_{O_2} of 130 mm Hg on 100% fraction of inspired oxygen (Fi_{O_2}). Bedside echocardiography shows normal left ventricular systolic function. A nasopharyngeal swab comes back positive for influenza A.*

Question 3: Which of the following statements is correct about management of this patient's fluid balance?

(a) There are no data to guide fluid management in patients with ARDS.
(b) Fluid removal (with diuretics or ultrafiltration) should only be attempted in patients with ARDS and impaired cardiac function.
(c) Conservative fluid management (less fluid, more diuretics) in patients with ARDS results in decreased mortality.
(d) Conservative fluid management in patients with ARDS results in more ventilator- and ICU-free days.
(e) Conservative fluid management in patients with ARDS is associated with increased risk for dialysis-requiring AKI.

For the answer to the question, see the following text.

Pathophysiology

AKI in the setting of respiratory failure is particularly deadly. AKI is an independent risk factor for respiratory failure and vice versa, with 2- to 3-fold increased mortality when one complicates the other. The pathophysiology of lung-kidney cross-talk is complex but may involve the inflammatory effects of AKI on the lung endothelium, impaired alveolar fluid clearance due to downregulation of pulmonary sodium and water channels in the setting of AKI, and the deleterious hemodynamic effects of mechanical ventilation on RBF and microvascular flow.

Acute Respiratory Distress Syndrome Definition and Prognosis

ARDS is defined by 4 criteria: (1) onset within 1 week of a known clinical insult, (2) chest imaging with bilateral opacities, (3) pulmonary edema that cannot be fully explained by cardiac failure or fluid overload, and (4) hypoxemia with $Pa_{O_2}/Fi_{O_2} \leq 300$ mm Hg ($Pa_{O_2}/Fi_{O_2} \leq 200$ mm Hg for moderate ARDS and ≤100 mm Hg for severe ARDS). Common risk factors for ARDS include primary pulmonary processes (eg, pneumonia, aspiration, contusion, and drowning) and systemic insults (eg, sepsis, pancreatitis, and transfusion). Despite improvements in care, the mortality of ARDS remains significant at 30% to 40% in recent cohorts.Management

The cornerstone of treatment is to address the underlying cause while providing "lung-protective" mechanical ventilation. A low-tidal-volume lung-protective ventilation protocol reduced absolute mortality by 9% in a large RCT. Notably, the protocol allowed for permissive hypercapnia, in which lung protection was prioritized at the potential expense of lower pH (ie, 7.15-7.30). In the original protocol, use of intravenous bicarbonate was permitted to manage concomitant metabolic acidosis; however, in the setting of significant AKI, early hemodialysis may be required to prevent severe acidemia during permissive hypercapnia.

Another important component of supportive care for patients with ARDS is careful management of fluid balance. FACTT showed that a "conservative" strategy results in more ventilator- and ICU-free days without an effect on mortality (thus, for Question 3, (d) is the best answer, and (a) and (c) are incorrect). There was a trend for less RRT need with the conservative strategy (hence (e) is incorrect for Question 3). Though ARDS can coexist with heart failure, FACTT excluded those with clinical evidence of elevated cardiac filling pressures; thus, the study applies to patients with normal left ventricular function (accordingly, (b) is incorrect).

Additional Readings

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Intra-abdominal Hypertension and ACS

Definitions, Epidemiology, and Risk Factors

Increasingly, intra-abdominal hypertension (IAH) and ACS are recognized as common causes of decreased kidney function in ICU patients. Normal intra-abdominal pressure (IAP) is 5 to 7 mm Hg. IAH is defined as a sustained elevation in IAP ≥ 12 mm Hg, and ACS is defined as sustained IAP > 20 mm Hg associated with new organ dysfunction. IAH has been reported in 30% to 50% of mixed medical and surgical ICU patients, with ACS occurring in 5% to 12%. Risk factors for IAH include trauma, major burns, abdominal surgery, mechanical ventilation,

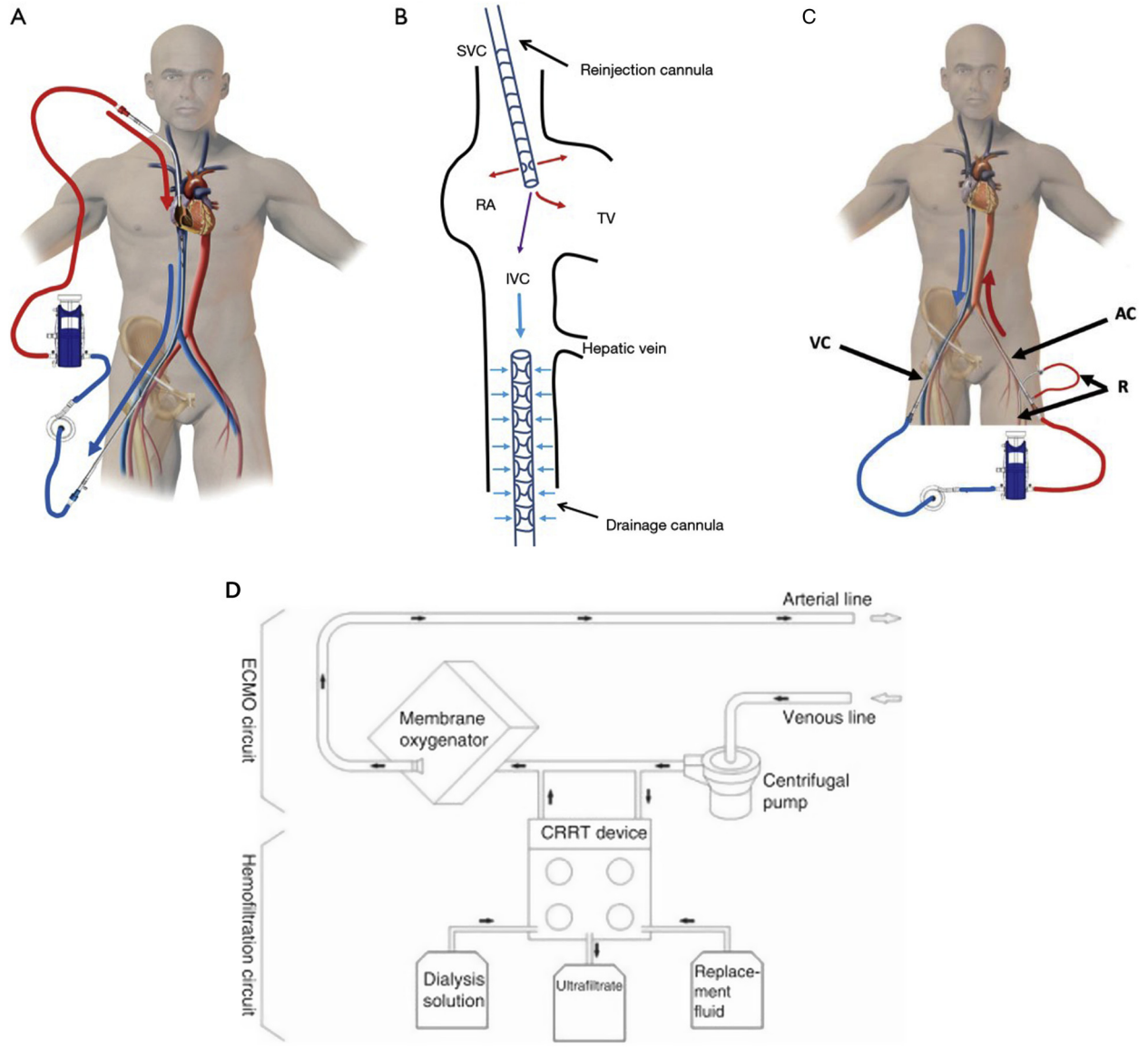

Figure 6. Schematics of (A-B) venovenous extracorporeal membrane oxygenation (VV-ECMO), (C) venoarterial ECMO (VA-ECMO), and (D) integrated ECMO and continuous renal replacement therapy (CRRT) circuits. (A) In VV-ECMO, venous drainage is through a large multiport cannula introduced via the femoral vein and advanced to the hepatic inferior vena cava (IVC) just below the IVC-right atrium (RA) junction. The blood then passes through a centrifugal pump followed by a membrane oxygenator before returning to the body through a catheter that is placed through the right internal jugular and superior vena cava (SVC) and terminates in the RA. In VV-ECMO, the tips of the 2 cannulae must be maintained a minimum distance apart to prevent recirculation (B). (C) In VA-ECMO, oxygenated blood is returned through the left femoral artery and travels retrograde up the aorta toward the great vessels and mixes with blood leaving the left ventricle. In this example, a distal reperfusion cannula (R) also carries oxygenated blood from the return cannula and infuses it into the left femoral artery beyond the cannulation site to prevent distal left lower-extremity ischemia. (D) The inflow to a separate CRRT device is ideally connected to a post-pump segment of the ECMO circuit so that the risk for entrainment of air from the CRRT circuit into the ECMO circuit is minimized by the high positive circuit pressure; the outflow from the CRRT is ideally connected to a preoxygenator segment of the ECMO circuit to allow the oxygenator to filter out any air or clots coming from the CRRT device. Abbreviations: AC, arterial cannula; TV, tricuspid valve; VC, venous cannula. Panels A and B reproduced from Banfi et al (Veno-venous extracorporeal membrane oxygenation: cannulation techniques. *J Thorac Dis*. 2016;8(12):3762-3773) and panel C adapted from Banfi et al (Veno-arterial extracorporeal membrane oxygenation: an overview of different cannulation techniques. *J Thorac Dis*. 2016;8(9):E875-E885), with permission of Nancy International Ltd (subsidiary of AME Publishing Company); original images © 2016 *Journal of Thoracic Disease*. Panel D reproduced from Santiago et al (The use of continuous renal replacement therapy in series with extracorporeal membrane oxygenation. *Kidney Int*. 2009;76(12):1289-92) with permission of Elsevier; original image © 2009 International Society of Nephrology.

obesity, ascites, hemoperitoneum, gastric or bowel distention, large-volume resuscitation, and pancreatitis.

Diagnosis

Physical examination is unreliable for diagnosis, so transduction of bladder pressure through a Foley catheter is used to estimate IAP. The ideal frequency of testing is unclear, but some experts suggest serial measurement of IAP every 4 to 6 hours in all patients with or at risk for IAH until IAP normalizes.

Pathophysiology

IAH can decrease the perfusion of any abdominal organ, and effects can be transmitted to other compartments leading to decreased cardiac output, impaired ventilation, and increased intracranial pressure. The kidneys are particularly sensitive to the effects of IAH such that ACS is thought by some to be unlikely in the absence of oliguria. Decreased kidney function from IAH appears to be due to reduced perfusion mediated primarily by elevations in renal venous and parenchymal pressures (rather than by decreased cardiac output or ureteral compression). IAH has been implicated in the pathogenesis of both hepatorenal and cardiorenal syndrome.

Management

In established ACS, decompressive laparotomy remains the treatment of choice despite its high morbidity. Less invasive measures to control IAH include adequate sedation to control abdominal muscle tone with temporary neuromuscular blockade in refractory cases, or decompression through paracentesis or nasogastric suction.

Fluid management is complex in the setting of IAH. Some of the physiologic disturbances of ACS—namely decreased cardiac output—can be aggravated by intravascular hypovolemia, but positive fluid balance is clearly associated with increased risk for IAH. Inferior vena cava ultrasound is particularly unhelpful in measuring volume status in the setting of ACS. Small case series suggest that CRRT can lower IAP, but the role for RRT for patients with IAH without kidney failure remains unclear. When providing RRT to patients with IAH, the femoral vein should likely be avoided for dialysis catheter placement because IAH may lead to recirculation and impaired clearance.

Additional Readings

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- De Waele JJ, De Laet I, Kirkpatrick AW, Hoste E. Intra-abdominal hypertension and abdominal compartment syndrome. *Am J Kidney Dis.* 2011;57(1):159-169.
- Kirkpatrick AW, Roberts DJ, De Waele J, et al. Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. *Intensive Care Med.* 2013;39(7):1190-1206.
- Mohmand H, Goldfarb S. Renal dysfunction associated with intra-abdominal hypertension and the abdominal compartment syndrome. *J Am Soc Nephrol.* 2011;22(4):615-621. ★ **ESSENTIAL READING**
- Sood P, Dass B, Bakuzonis C, Ross EA. Intra-abdominal hypertension can be monitored with femoral vein catheters during CRRT and may cause access recirculation. *Clin Nephrol.* 2010;74(3):223-228.

CRRT and Prolonged Intermittent RRT

CRRT, which was the focus of a 2016 Core Curriculum, is often preferred over IHD in the ICU because it is associated with less hemodynamic instability. Since 2016, another large RCT has evaluated the timing of RRT initiation (IDEAL-ICU). Table 3 compares large RCTs of dialysis timing.

Prolonged intermittent RRT is another RRT option in the ICU. Prolonged intermittent RRT consists of treatment over 6 to 12 hours with blood and dialysate flow rates that are higher than CRRT but lower than IHD. It may replace CRRT or be used as a bridge between CRRT and IHD for patients recovering from critical illness. A full discussion of prolonged intermittent RRT is outside the scope of this review, but interested readers are directed to the readings.

Additional Readings

- Barbar SD, Clere-Jehl R, Bourredjem A, et al. Timing of renal-replacement therapy in patients with acute kidney injury and sepsis. *N Engl J Med.* 2018;379(15):1431-1442.
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Palliative Care Nephrology in the ICU

Case 4: *A 70-year-old man is admitted with respiratory failure due to community-acquired pneumonia. Blood cultures are positive for pneumococcus. He is started on appropriate antibiotic therapy and requires intubation. Shortly afterward, he is initiated on norepinephrine and vasopressin therapy due to worsening hypotension despite intravenous fluids. Over the next 72 hours, the patient's creatinine level increases from 1.0 to 4.4 mg/dL, and urine output decreases to 0 to 5 mL/h. A family meeting is planned to discuss the initiation of CRRT.*

Question 4: Which off the following is most correct?

(a) Palliative care (PC) consultation would be inappropriate because he has AKI rather than chronic kidney disease.
(b) A goals-of-care discussion is not indicated because most patients with AKI and respiratory failure survive.
(c) If the patient is started on RRT and survives the hospitalization, his quality of life (QoL) at 60 days is likely to return to his prehospitalization baseline.
(d) CRRT should not be offered even if desired by the family because it would constitute futile care in this case.
(e) A time-limited trial of CRRT should be pursued in this case if CRRT is desired by the family.

For the answer to the question, see the following text.

Many associate PC with transition to hospice and preparation for death. However, PC is a multidisciplinary support system that assists patients and their surrogates with communication about difficult decisions, advance care planning, and prognosis. It also offers caregiver support, identifies and addresses spiritual and emotional needs, and provides focused symptom identification and management.

To date, most of the available research and initiatives in PC nephrology have focused on kidney failure. Nonetheless, the limited data available suggest that the PC needs of patients with AKI are significant (and therefore (a) is incorrect for Question 4). In a recent study of more than 90,000 AKI-RRT patients from the US National Inpatient Sample data set, only 8% received PC services. Given the high mortality associated with AKI-RRT in the ICU, the need for RRT should routinely prompt reconsideration of the overall prognosis and goals of care. AKI is also associated with lasting effects on QoL. In one large study, 25% of 60-day survivors of AKI-RRT reported QoL comparable to death (hence (c) is incorrect for Question 4).

Some experts have proposed that consideration of RRT for AKI in ICU patients should automatically trigger PC consultation. Barring such systematic change, the first step is clarification of prognosis. The features of critical illness most commonly associated with poor outcomes from AKI include liver failure, mechanical ventilation, and multiorgan failure (thus, (b) is incorrect for Question 4). Elderly patients and nursing home residents also have increased risk for poor outcomes with RRT initiation. A series of prognostic tools have been developed for predicting mortality in patients with AKI, but none of these have been prospectively validated as superior to the others or to physician impression.

If the overall prognosis appears poor, providers should reexamine whether RRT is likely to provide meaningful benefit. Unfortunately, nephrologists are often faced with a variety of challenges, including uncertainty or disagreement about the prognosis or the utility of RRT and lack of training in end-of-life care. Prognostication in ICU patients is inherently difficult. Nephrologists may feel limited in their ability to participate in goals-of-care discussions because AKI in critical illness is often secondary to a nonrenal process. Likewise, nephrologists may not feel justified in limiting RRT because despite the poor overall prognosis of AKI-RRT, many survivors report that in retrospect they would still have opted to undergo dialysis despite reductions in QoL. Offering RRT, if clearly desired by the patient or surrogates, may at times be appropriate despite an overall poor prognosis (making (d) incorrect for Question 4).

In such cases, time-limited trials of RRT may be a useful patient-centered approach to dialysis decision making (hence, for Question 4, (e) is the best answer). Time-limited trials are agreements between providers and a patient and/or surrogates to use certain medical therapies over a defined period to see if the patient improves or deteriorates according to agreed-on clinical outcomes. If the patient improves, disease-directed therapy continues; if the patient deteriorates, the therapy being trialed is stopped. In the case of RRT, the goals of time-limited trials can include global factors (eg, resolution of shock or extubation) or tolerance of RRT (eg, hemodynamic tolerance of IHD in a patient with advanced heart disease). Data to support the use of time-limited trials are limited, but they are recommended by the Renal Physicians Association's guideline document listed in the additional readings.

Additional Readings

- Chong K, Silver SA, Long J, et al. Infrequent provision of palliative care to patients with dialysis-requiring AKI. *Clin J Am Soc Nephrol.* 2017;12(11):1744-1752.
- Johansen KL, Smith MW, Unruh ML, et al. Predictors of health utility among 60-day survivors of acute kidney injury in the Veterans Affairs/National Institutes of Health Acute Renal Failure Trial Network Study. *Clin J Am Soc Nephrol.* 2010;5(8):1366-1372.
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- Scherer JS, Holley JL. The role of time-limited trials in dialysis decision making in critically ill patients. *Clin J Am Soc Nephrol.* 2016;11(2):344-353. ★ **ESSENTIAL READING**

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