UCSF
UC San Francisco Previously Published Works

Title
Critical Care Nephrology: Core Curriculum 2020

Permalink
https://escholarship.org/uc/item/08v027nj

Journal
American Journal of Kidney Diseases, 75(3)

ISSN
0272-6386

Authors
Griffin, Benjamin R
Liu, Kathleen D
Teixeira, J Pedro

Publication Date
2020-03-01

DOI
10.1053/j.ajkd.2019.10.010

Peer reviewed

eScholarship.org Powered by the California Digital Library
University of California

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

Am J Kidney Dis. Author manuscript; available in PMC 2021 March 01.

Published in final edited form as:

Am J Kidney Dis. 2020 March ; 75(3): 435–452. doi:10.1053/j.ajkd.2019.10.010.

Critical Care Nephrology: Core Curriculum 2019

Benjamin R. Griffin[1], **Kathleen D. Liu**[2], **J. Pedro Teixeira**[3]

[1]Division of Nephrology, Department of Medicine, University of Iowa, Iowa City, IA

[2]Division of Nephrology, Department of Medicine, and Division of Critical Care Medicine, Department of Anesthesia, University of California, San Francisco, San Francisco, CA

[3]Division of Nephrology and Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, University of New Mexico School of Medicine, Albuquerque, NM

Abstract

The intensive care unit (ICU) is a common source of high-acuity nephrology consultations. While end-stage 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 emphasizes the developments of the last decade since the last Critical Care Nephrology Core Curriculum in 2009. We focus on some of the most common causes of AKI in the critical care setting and use these AKI etiologies 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.

Epidemiology of Acute Kidney Injury in the Intensive Care Unit

Acute kidney injury (AKI) is common and associated with significant morbidity, mortality, and cost of care. AKI is currently defined by the Kidney Disease Improving Global Outcomes (KDIGO) criteria and is divided into 3 stages based on increases in serum creatinine or decreases in urine output. A recent multinational study with over 1,800 patients from 97 intensive care units (ICUs) reported that AKI of any stage developed within one 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 40–55%, higher than the 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

Corresponding Author: Benjamin R Griffin, **Address:** 12700 E 19th Ave, Campus Stop C-281, University of Colorado, Aurora, CO 80045, Benjamin.Griffin@ucdenver.edu.

Financial Disclosures

The authors declare that they have no financial conflicts of interest.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

addition to mortality, AKI survivors are more likely to develop significant morbidity including chronic kidney disease (CKD), end-stage kidney disease (ESKD), and functional impairment requiring discharge to short- or long-term care facilities.

AKI Risk Stratification in the ICU

Determining a patient's risk of 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 the product of tissue inhibitor of metalloproteinase 2 and insulin-like growth factor binding protein 7 (TIMP-2*IGFBP-7) and neutrophil gelatinase associated lipocalin (NGAL). 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 (Figure 1). AKI has been shown in human and animal studies to increase susceptibility to infection, double the rate of respiratory failure, and to directly and indirectly impair cardiac function. While 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

- Faubel S, Shah PB. Immediate Consequences of Acute Kidney Injury: The Impact of Traditional and Nontraditional Complications on Mortality in Acute Kidney Injury. Adv Chronic Kidney Dis. 2016;23(3):179–185.
- Hoste et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive Care Med. 2015 Aug;41(8):1411–23.
- Koyner JL, Davison DL, Brasha-Mitchell E, et al. Furosemide Stress Test and Biomarkers for the Prediction of AKI Severity. J Am Soc Nephrol. 2015;26(8):2023–2031.
- Malhotra R, Siew ED. Biomarkers for the Early Detection and Prognosis of Acute Kidney Injury. Clin J Am Soc Nephrol. 2017;12(1):149–173.
- Matsuura R, Srisawat N, Claure-Del Granado R, et al. Use of the Renal Angina Index in Determining Acute Kidney Injury. Kidney Int Rep. 2018;3(3):677–683.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Common Etiologies of AKI in the ICU

Common etiologies of AKI in the ICU are outlined in Table 2. In this curriculum we focus on sepsis-associated AKI, cardiac surgery-associated, and AKI associated with acute liver failure. We also discuss the interactions between respiratory and renal failure and the role of abdominal compartment syndrome 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 features, and we refer the reader to those curricula for more information.

Case #1: A 68-year old woman with a history of hypertension presents to the Emergency Department (ED) with fever, nausea, vomiting, and confusion. Vital signs include temperature 39.3°C, heart rate 98/min, blood pressure (BP) 130/59, respiratory rate 26/min, and SaO_2 92% on room air. Exam is notable for disorientation and right sided costovertebral angle tenderness. Labs are notable for WBC 22,000/mm^3, serum creatinine 2.3 mg/dL (baseline 0.7 mg/dL), and >50 WBCs/hpf on urine microscopy. Imaging includes non-contrast CT of the abdomen and pelvis with right perinephric stranding but no stones or hydronephrosis bilaterally. Blood and urine cultures are obtained, ceftriaxone 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 (ATN) as a result of decreased blood flow.
- **b.** Her AKI is unlikely to be attributable to sepsis as 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 preemptive RRT prior to development of an urgent indication.

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 of ≥2 points. A screening tool, the quick SOFA (qSOFA), can be used in which sepsis is suggested by the presence of 2 of 3 features: (1) respiratory rate ≥22 breaths/minute, (2) altered mental status, and (3) systolic blood pressure ≤100 mmHg (Q1: answer B is incorrect).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Epidemiology

Sepsis-associated AKI (SA-AKI) occurs in 10–20% of all patients admitted to the ICU due to infection and in 50–70% of those with septic shock. SA-AKI is the most common etiology of AKI in the ICU, accounting for about 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 non-septic AKI developed sepsis after a median of 5 days. Similarly, in a study of 24,660 cardiac surgery patients, 23.7% of patients with post-operative AKI developed infection compared to 3.3% of non-AKI patients. The relationship between AKI and sepsis is therefore now thought to be bidirectional (Q1: D is the correct answer).

Pathophysiology

The pathophysiology of SA-AKI is incompletely understood. In the past, SA-AKI was thought to be a form of ATN stemming from global hypoperfusion. However, animal studies demonstrate that renal blood flow (RBF) is unchanged and may even increase during sepsis. While the few RBF studies in humans paint a more complex picture, post-mortem studies of patients with SA-AKI show that renal histology is usually well preserved without evidence of ATN. Furthermore, SA-AKI can occur in the absence of hypotension (Q1: answer C is incorrect). 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 (Figure 2). While an in-depth examination of SA-AKI pathophysiology is outside the scope of this curriculum, it is important to note that SA-AKI pathophysiology is unique and should not be considered simply a subtype of ischemic injury (Q1: answer A is incorrect).

Management

Along with timely administration of antibiotics and source control, appropriate volume resuscitation remains an important determinant of outcomes in septic patients (see Shock and IV Fluids in the ICU below). Finally, though one single-center randomized controlled trial (RCT) suggested benefit from pre-emptive RRT in ICU patients with stage 2 AKI, two subsequent larger multicenter trials, including one of specifically SA-AKI, showed no benefit from preemptive RRT (Q1: answer E is incorrect; see Table 3 and CRRT section below).

Essential Reading

- Poston JT, Koyner JL. Sepsis associated acute kidney injury. BMJ. 2019 Jan 9;364:k4891

Additional Readings

- Gomez H, Ince C, De Backer D, Pickkers P, Payen D, Hotchkiss J, Kellum JA. A unified theory of sepsis-induced acute kidney injury: inflammation, microcirculatory dysfunction, bioenergetics, and the tubular cell adaptation to injury. Shock. 2014 Jan;41(1):3–11

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Case #2: A 62-year-old woman is seen in clinic with cough, fever, and hypoxemia. A nasopharyngeal swab comes back positive for influenza A, and she is initiated on oseltamivir. She is seen in the ED 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-liter (30 cc/kg) bolus of crystalloid and appropriate antibiotic treatment, the patient develops progressive hypotension. A central venous catheter (CVC) is placed via the right internal jugular vein, after which the patient's mean arterial pressure (MAP) is 45 mm Hg, CVP is 11 mm Hg, central venous oxygen saturation ($ScVO_2$) is 89%. Arterial lactate is 10.2 mmol/L, and urine output is 10 cc/hr.

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

- **a.** The next best option is to initiate norepinephrine and perform a passive leg raise (PLR) to assess whether she is likely to respond to additional fluids.
- **b.** The next best option is to initiate dopamine.
- **c.** The next best option is to continue to administer IV 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 cc/kg fluid bolus and should receive no further fluids.
- **e.** Because the $ScVO_2$ is >70%, oxygen delivery to her tissues is adequate and therefore no additional treatment is warranted.

Shock

Definition and Etiologies

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 mmHg or MAP <70 mmHg) or relative (e.g., 40 mmHg below baseline). Physical signs of tissue hypoperfusion include oliguria, altered mental status, and cold, mottled, or cyanotic skin. Elevated serum lactate 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, the 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 (PAOP). A series of RCTs showed no overall benefit from pulmonary artery (PA) catheter use and increased risk of significant

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

catheter-related morbidity from infection, arrhythmia, or PA rupture. PA catheters are reserved for specific scenarios such as severe pulmonary hypertension and/or right ventricular (RV) failure. Similarly, though CVCs 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, three recent large multicenter RCTs (ARISE, ProCESS, and ProMISe) did not show any benefit to fluid resuscitation strategies guided by CVP and ScVO2 in septic shock (Q2: answers C and E are incorrect). 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 (e.g. CVP, $ScVO_2$, or PAOP), dynamic measures of volume responsiveness—in which the response to a transient or small change in cardiac filling are 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 PLR, appear to be useful. A recent review suggested that PLR may be the most useful dynamic measure (Q2: A is the correct answer). However, every method has inherent limitations, and no technology has proven 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 (SVR) or inotropic agents that increase cardiac output (CO). In the setting of heart failure or cardiogenic shock, agents may be used that decrease SVR. 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 (Q2: A, not B, is the correct answer). Vasopressin, which causes vasoconstriction via 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 of 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 renal 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 requiring RRT, but the significance of this secondary outcome requires additional investigation. Of note, there may be an increased risk of thrombotic events with angiotensin II administration.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

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.

Essential Readings

- Asfar P, Meziani F, Hamel JF, et al. High versus low blood-pressure target in patients with septic shock. N Engl J Med. 2014;370(17):1583–1593.
- Bentzer P, Griesdale DE, Boyd J, MacLean K, Sirounis D, Ayas NT. Will This Hemodynamically Unstable Patient Respond to a Bolus of Intravenous Fluids? JAMA. 2016;316(12):1298–1309.
- Marik PE, Monnet X, Teboul JL. Hemodynamic parameters to guide fluid therapy. Ann Intensive Care. 2011;1(1):1.

Additional Readings

- Gordon AC, Mason AJ, Thirunavukkarasu N, et al. Effect of Early Vasopressin vs Norepinephrine on Kidney Failure in Patients With Septic Shock: The VANISH Randomized Clinical Trial. JAMA. 2016;316(5):509–518.
- Jentzer JC, Coons JC, Link CB, Schmidhofer M. Pharmacotherapy update on the use of vasopressors and inotropes in the intensive care unit. J Cardiovasc Pharmacol Ther. 2015;20(3):249–260.
- Tumlin JA, Murugan R, Deane AM, et al. Outcomes in Patients with Vasodilatory Shock and Renal Replacement Therapy Treated with Intravenous Angiotensin II. Crit Care Med. 2018;46(6):949–957.
- Vincent JL, De Backer D. Circulatory shock. N Engl J Med. 2013;369(18):1726–1734.

IV Fluids in the ICU

Colloids versus Crystalloids

The use of colloid solutions was reviewed in detail in the 2018 AKI Core Curriculum. 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, when compared to balanced salt solutions such as lactated ringers (LR) or Plasma-Lyte (PL, Baxter), may increase the risk of 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. One evaluated patients admitted from the ED to a non-ICU setting (SALT-ED, n >13,000), and

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

the other evaluated ICU patients (SMART, n >15,000). In both trials, the use of balanced solutions resulted in an approximately 1% absolute reduction in the rate of "MAKE-30," a composite outcome of death, need for RRT, or persistent doubling of creatinine at 30 days. In the SMART trial, the prespecified subgroup with sepsis had an absolute reduction in 30-day mortality of over 4%. In the SALT-ED trial, the benefit of balanced solutions was greatest in those who presented with an already-elevated serum creatinine. Some have called for caution in interpreting the SMART and SALT-ED trials, while others have concluded that "routine use of saline, especially in large doses, should now be abandoned." Additional large clinical trials are ongoing. Importantly, saline 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 on the kidneys remains unclear, but it is thought to be related to the high chloride content. Proposed mechanisms include reduced GFR via 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 are 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 renal dysfunction, lower odds of renal recovery, and increased mortality. The negative impact of fluid overload on renal 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 renal function and was associated with a trend towards decreased mortality.

Given the potential for both benefit and harm (Figure 4) from IV 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 on, by 36 to 48 hours a transition to a conservative approach and ultimately to a deresuscitative strategy, may benefit most patients (Figure 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 of harm from over- or under-resuscitation, mortality was lowest in those provided with adequate initial fluid resuscitation followed by conservative fluid management (Q2: answer D is incorrect).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Essential Readings

- Murphy CV, Schramm GE, Doherty JA, et al. The importance of fluid management in acute lung injury secondary to septic shock. Chest. 2009;136(1):102–109.
- Semler MW, Self WH, Wanderer JP, et al. Balanced Crystalloids versus Saline in Critically Ill Adults. N Engl J Med. 2018;378(9):829–839.

Additional Readings

- Boyd JH, Forbes J, Nakada TA, Walley KR, Russell JA. Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure are associated with increased mortality. Crit Care Med. 2011;39(2):259–265.
- Hjortrup PB, Haase N, Bundgaard H, et al. Restricting volumes of resuscitation fluid in adults with septic shock after initial management: the CLASSIC randomised, parallel-group, multicentre feasibility trial. Intensive Care Med. 2016;42(11):1695–1705.
- Prowle JR, Kirwan CJ, Bellomo R. Fluid management for the prevention and attenuation of acute kidney injury. Nat Rev Nephrol. 2014;10(1):37–47.
- Self WH, Semler MW, Wanderer JP, et al. Balanced Crystalloids versus Saline in Noncritically Ill Adults. N Engl J Med. 2018;378(9):819–828.
- Silversides JA, Major E, Ferguson AJ, et al. Conservative fluid management or deresuscitation for patients with sepsis or acute respiratory distress syndrome following the resuscitation phase of critical illness: a systematic review and meta-analysis. Intensive Care Med. 2017;43(2):155–170.

Cardiac Surgery-Associated AKI

Epidemiology

Cardiac surgery-associated AKI (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 20–30% of cases.

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 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 below).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Prevention

Since the timing of the renal insult can be anticipated, numerous studies have evaluated preoperative 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 a urinary TIMP-2*IGFBP7 >0.3 ng/mL^2/1000 were randomized to receive usual care or a KDIGO-based care bundle (minimization of nephrotoxic agents, discontinuation of ACE 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.

Essential Reading:

- Wang Y, Bellomo R. Cardiac surgery-associated acute kidney injury: risk factors, pathophysiology and treatment. Nat Rev Nephrol. 2017 Nov;13(11):697–711

Additional Readings

- Meersch M, Schmidt C, Hoffmeier A, Van Aken H, Wempe C, Gerss J, Zarbock A. Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers: the PrevAKI randomized controlled trial. Intensive Care Med. 2017 Nov;43(11):1551–1561
- Ortega-Loubon C, Fernandez-Molina M, Carrascal-Hinojal Y, Fulquet-Carreras E. Cardiac surgery-associated acute kidney injury. Ann Card Anaesth. 2016;19(4):687–698.

Extracorporeal Membrane Oxygenation

The use of extracorporeal membrane oxygenation (ECMO) in adults has grown exponentially since the 2009 H1N1 influenza outbreak, with overall ECMO usage 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 two 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 (RPMs). The amount of oxygen delivered can be increased either by increasing the oxygen content of the oxygenator gas or by

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

increasing the pump RPMs to achieve a 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 pCO_2.

There are two basic types of ECMO circuits, which differ in whether the oxygenated blood is returned to the venous or arterial system (Figure 6). Venovenous (VV) 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 transplant or a long-term cardiac support device such as an LVAD.

Because of the high flows typically used in ECMO circuits (3–6 L/min), the venous blood chamber (e.g., IVC) being emptied is constantly under significant negative pressure (e.g., −60 mmHg). 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 IVC may temporarily fully collapse around the drainage cannula, causing a sudden, severe drop 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 which hypertension is strongly associated with increased risk of stroke and bleeding.

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

AKI on ECMO

Up to 80% of adults on ECMO develop AKI, with roughly 45% of patients on 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 preemptive RRT can prevent or mitigate volume overload. Fluid overload in ECMO patients appears to be independently associated with an increased risk of mortality, and guidelines suggest targeting euvolemia with diuretics or RRT once 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 non-pulsatile blood flow in the case of VA-ECMO. Excess circuit-related hemolysis can cause development of pink urine or RRT effluent. When hemolysis is suspected, plasma free hemoglobin levels should be measured.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

For patients with AKI on ECMO, CRRT is the preferred modality. CRRT can be provided by placing a separate dialysis catheter or by connecting the CRRT circuit directly to the ECMO circuit (Figure 6). A separate dialysis circuit may lower the risk of embolism in the ECMO circuit. Separate circuits also have the practical advantage that problems with one circuit will not interfere with the other. On the other hand, placing a dialysis catheter may carry an elevated risk of air embolism, as the substantial negative pressure generated by the ECMO pump can entrain air into in the venous system. It may be beneficial to temporarily decrease ECMO pump rates during the highest risk portions of catheter placement (e.g., 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 of air entrainment. The CRRT outflow should be connected to the pre-oxygenator 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. As 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 over the past two 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 towards baseline. However, GFR may not improve in those with intrinsic renal disease. Like ECMO patients, LVAD patients are at elevated risk of AKI throughout their course, and AKI (particularly AKI-RRT) is associated with poor outcomes. LVAD-specific causes of AKI include hemolysis, RV failure, and possibly non-pulsatile blood flow. An in-depth discussion of LVADs is beyond the scope of this review, but those interested are directed towards the additional readings.

Essential Reading

- Razo-Vazquez AO, Thornton K. Extracorporeal Membrane Oxygenation-What the Nephrologist Needs to Know. Adv Chronic Kidney Dis. 2016;23(3):146–151.

Additional Readings

- Kielstein JT, Heiden AM, Beutel G, et al. Renal function and survival in 200 patients undergoing ECMO therapy. Nephrol Dial Transplant. 2013;28(1):86–90.
- Lyu L, Long C, Hei F, et al. Plasma Free Hemoglobin Is a Predictor of Acute Renal Failure During Adult Venous-Arterial Extracorporeal Membrane Oxygenation Support. J Cardiothorac Vasc Anesth. 2016;30(4):891–895.
- Roehm B, Vest AR, Weiner DE. Left Ventricular Assist Devices, Kidney Disease, and Dialysis. Am J Kidney Dis. 2018;71(2):257–266.
- Ross DW, Stevens GR, Wanchoo R, et al. Left Ventricular Assist Devices and the Kidney. Clin J Am Soc Nephrol. 2018;13(2):348–355.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

- Schmidt M, Bailey M, Kelly J, et al. Impact of fluid balance on outcome of adult patients treated with extracorporeal membrane oxygenation. Intensive Care Med. 2014;40(9):1256–1266.
- Seczynska B, Krolikowski W, Nowak I, Jankowski M, Szuldrzynski K, Szczeklik W. Continuous renal replacement therapy during extracorporeal membrane oxygenation in patients treated in medical intensive care unit: technical considerations. Ther Apher Dial. 2014;18(6):523–534.

Acute Liver Failure

Kidney disease complicating liver cirrhosis is reviewed in detail in the Kidney Disease in the Setting of Liver Failure: Core Curriculum 2013, so we instead will focus on acute liver failure (ALF).

Definition and Etiologies

LF, previously known as fulminant hepatic failure, is defined by (1) hepatic encephalopathy of any severity, (2) INR ≥1.5, (3) onset of illness <26 weeks, and (4) no evidence of cirrhosis. Though at times difficult to discern, the distinction between ALF and chronic liver disease is critical as some of the complications (particularly intracranial hypertension) and management options (e.g., consideration of “early” RRT and expedited liver transplant) 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 U.S. cohorts, acetaminophen toxicity alone accounts for approximately 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 multi-organ failure.

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

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

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

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 of intracranial hypertension. In contrast to chronic liver failure, RRT may have a role in specifically treating hyperammonemia in ALF, although this remains controversial.

Essential Readings

- Leventhal TM, Liu KD. What a Nephrologist Needs to Know About Acute Liver Failure. Adv Chronic Kidney Dis. 2015;22(5):376–381.

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, Group USALFS. Continuous renal replacement therapy is associated with reduced serum ammonia levels and mortality in acute liver failure. Hepatology. 2017.
- Davenport A, Will EJ, Davidson AM. Improved cardiovascular stability during continuous modes of renal replacement therapy in critically ill patients with acute hepatic and renal failure. Crit Care Med. 1993;21(3):328–338.
- Murphy N, Auzinger G, Bernel W, Wendon J. The effect of hypertonic sodium chloride on intracranial pressure in patients with acute liver failure. Hepatology. 2004;39(2):464–470.

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 a PaO_2 of 130 mm Hg on 100% FiO_2. Bedside echocardiography shows normal left ventricular (LV) 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 of dialysis-requiring AKI.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

AKI and Respiratory Failure

AKI in the setting of respiratory failure is particularly deadly. AKI is an independent risk factor for respiratory failure and vice versa, with a 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 down-regulation 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

Acute Respiratory Distress Syndrome (ARDS) is defined by four 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; 4) Hypoxemia with PaO_2/FiO_2 (P/F) ≤300 mm Hg (P/F ≤200 mm Hg for moderate ARDS and ≤100 mm Hg for severe ARDS). Common risk factors for ARDS include primary pulmonary processes (e.g., pneumonia, aspiration, contusion, drowning) and systemic insults (e.g., sepsis, pancreatitis, transfusion). Despite improvements in care, the mortality of ARDS remains significant at 30–40% 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 a lower pH (i.e., 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 in order to prevent severe acidemia during permissive hypercapnia.

Another important component of supportive care for patients with ARDS is careful management of fluid balance. The Fluids and Catheters Treatment Trial (FACTT) showed that a “conservative” strategy results in more ventilator and ICU-free days without an effect on mortality (Q3: D is correct, A and C are incorrect). There was a trend for *less* RRT need with the conservative strategy (Q3: E is incorrect). 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 LV function (Q3: B is incorrect).

Essential Reading

- National Heart L, Blood Institute Acute Respiratory Distress Syndrome Clinical Trials N, Wiedemann HP, et al. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med. 2006;354(24):2564–2575.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Additional Readings

- Teixeira JP, Ambruso S, Griffin BR, Faubel S. Pulmonary Consequences of Acute Kidney Injury. Semin Nephrol. 2019;39(1):3–16.
- Thompson BT, Chambers RC, Liu KD. Acute Respiratory Distress Syndrome. N Engl J Med. 2017;377(6):562–572.

Intraabdominal Hypertension and Abdominal Compartment Syndrome

Definitions, Epidemiology, and Risk Factors

Intraabdominal hypertension (IAH) and abdominal compartment syndrome (ACS) have been increasingly recognized as common causes of renal dysfunction in ICU patients. Normal intraabdominal pressure (IAP) is 5–7 mmHg. IAH is defined by a sustained elevation in IAP ≥12 mmHg, and ACS is defined as sustained IAP >20 mmHg associated with new organ dysfunction. IAH has been reported in 30–50% of mixed medical and surgical ICU patients, with ACS occurring in 5–12%. Risk factors for IAH include trauma, major burns, abdominal surgery, mechanical ventilation, obesity, ascites, hemoperitoneum, gastric or bowel distention, large volume resuscitation, and pancreatitis.

Diagnosis

Physical exam is unreliable for diagnosis, so transduction of bladder pressure via a Foley catheter is used to estimate IAP. The ideal frequency of testing is unclear, but some experts suggest serial measurement of IAP every 4–6 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 CO, impaired ventilation, and increased intracranial pressure. The kidneys are particularly sensitive to the effects of IAH such that ACS is felt by some to be unlikely in the absence of oliguria. Renal dysfunction from IAH appears to be due to decreased perfusion mediated primarily by elevations in renal venous and parenchymal pressures (rather than by decreased CO 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 via paracentesis or nasogastric suction.

Fluid management is complex in the setting of IAH. Some of the physiologic disturbances of ACS—namely decreased CO—can be aggravated by intravascular hypovolemia, but positive fluid balance is clearly associated with increased risk of IAH. Inferior vena cava (IVC) 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

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

without renal failure remains unclear. When providing RRT to patients with IAH, the femoral vein should likely be avoided for dialysis catheter placement as IAH may lead to recirculation and impaired clearance.

Essential Readings

- 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.

Additional Readings

- Dalfino L, Tullo L, Donadio I, Malcangi V, Brienza N. Intra-abdominal hypertension and acute renal failure in critically ill patients. Intensive Care Med. 2008;34(4):707–713.
- 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.
- 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.

Continuous Renal Replacement Therapy and Prolonged Intermittent Renal Replacement Therapy

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

Prolonged Intermittent Renal Replacement Therapy (PIRRT) is another RRT option in the ICU. PIRRT consists of treatment over 6–12 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 PIRRT is outside the scope of this review, but interested readers are directed to the readings.

Additional Reading

- 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.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

- Edrees F, Li T, Vijayan A. Prolonged Intermittent Renal Replacement Therapy. Adv Chronic Kidney Dis. 2016;23(3):195–202.

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 antibiotics and requires intubation. Shortly afterwards he is initiated on norepinephrine and vasopressin due to worsening hypotension despite IV fluids. Over the next 72 hours, the patient's creatinine rises from 1.0 to 4.4, and his urine output decreases to 0–5 mL/hr. A family meeting is planned to discuss the initiation of CRRT.

Question 4: Which off the following is most correct?

a. Palliative care consultation would be inappropriate because he has AKI rather than CKD.

b. A goals-of-care discussion is not indicated as 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 pre-hospitalization 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.

Palliative Care Nephrology in the ICU

Many associate palliative care (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 ESKD. Nonetheless, the limited data available suggest that the PC needs of AKI patients are significant (Q4: A is incorrect). In a recent study of over 90,000 AKI-RRT patients from the US National Inpatient Sample dataset, only 8% received PC services. Given the high mortality associated with AKI-RRT in the ICU, the need for RRT should routinely prompt a 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 a QoL comparable to death (Q4: C is incorrect).

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 (Q4: B is incorrect). Elderly patients and nursing home residents also have increased risk of poor outcomes with RRT initiation. A series of prognostic tools have been developed

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

for predicting mortality in AKI patients, 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 non-renal 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 (Q4: D is incorrect).

In such cases, time limited trials (TLTs) of RRT may be a useful, patient-centered approach to dialysis decision-making (Q4: E is the best answer). TLTs 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(ies) being trialed are stopped. In the case of RRT, the goals of TLTs can include global factors (e.g., resolution of shock, extubation) or tolerance of RRT (e.g., hemodynamic tolerance of IHD in a patient with advanced heart disease). Data to support the use of TLTs are limited, but they are recommended by the Renal Physicians Association's *Clinical Practice Guideline on Shared Decision-Making in the Appropriate Initiation of and Withdrawal from Dialysis*.

Essential Readings

- Scherer JS, Holley JL. The Role of Time-Limited Trials in Daily sis Decision Making in Critically Ill Patients. Clin J Am Soc Nephrol. 2016;11(2):344–353.

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.
- Renal Physicians Association: Clinical Practice Guideline. Shared Decision-Making in the Appropriate Initiation of and Withdrawal From Dialysis. 2nd ed. Rockville, MD: Renal Physicians Association; 2010.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Acknowledgments

Support

BG is supported by a National Research Service Award (NRSA) Institutional Predoctoral Training Grant (T32), grant number T32 DK 007135. KDL is supported by NIDDK K24113381.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

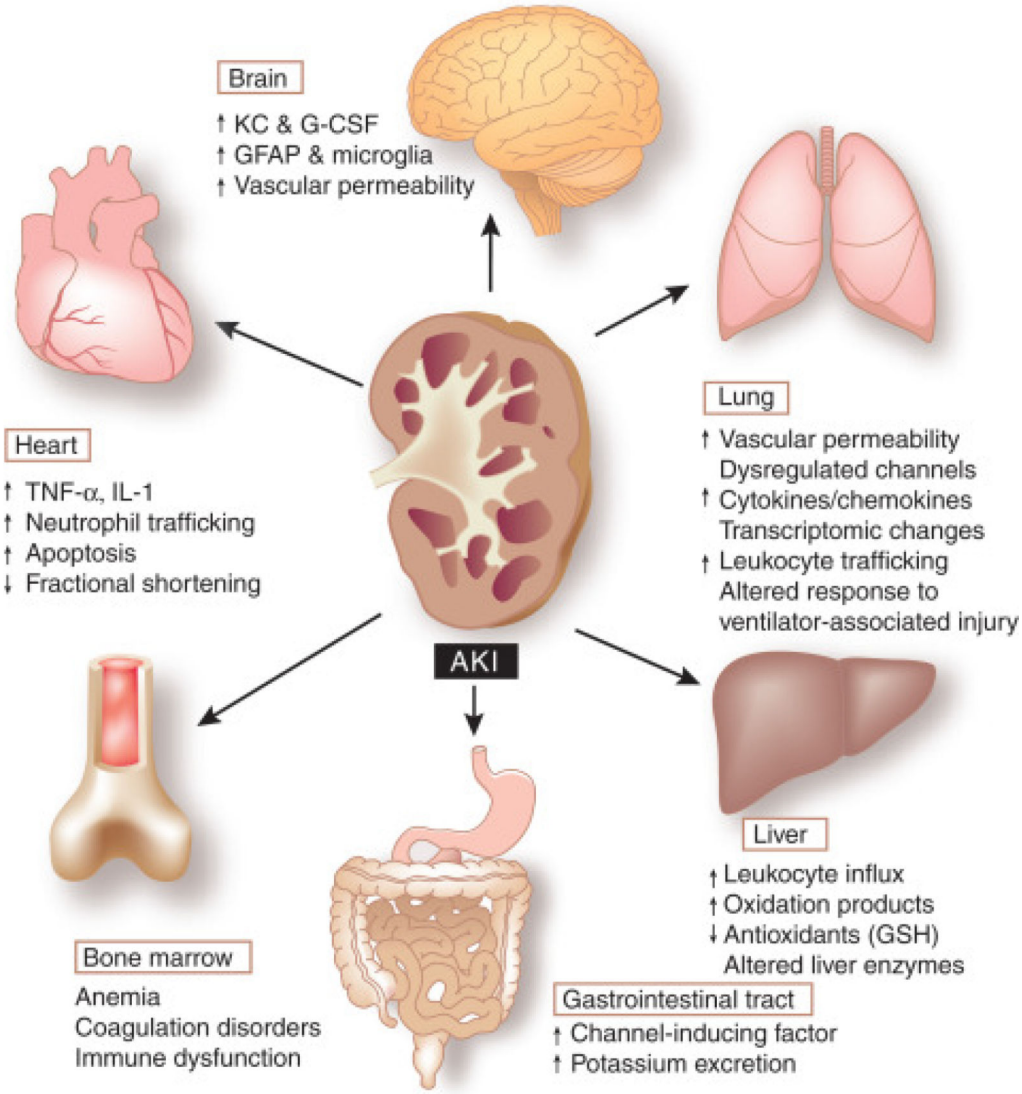


Figure 1.

AKI-induced distant organ effects. AKI leads to changes in distant organs, including brain, lungs, heart, liver, gastrointestinal tract, and bone marrow. Changes have been described in organ function, microvascular inflammation and coagulation, cell apoptosis, transporter activity, oxidative stress, and transcriptional responses. Abbreviations: AKI, acute kidney injury; 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.

Originally published by Scheel et al., Kidney Int. 2008

Author Manuscript
Author Manuscript
Author Manuscript
Author Manuscript

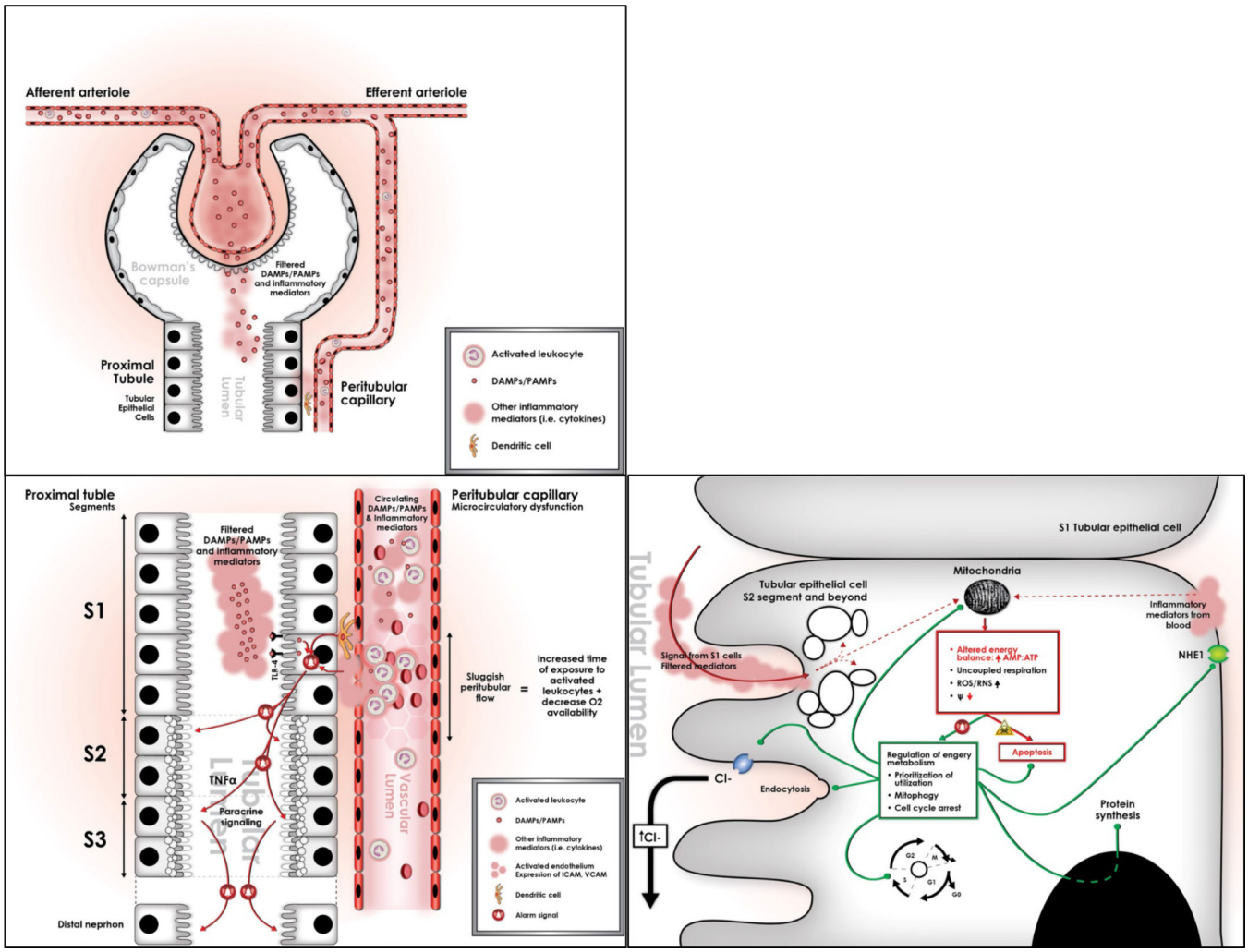


Figure 2.

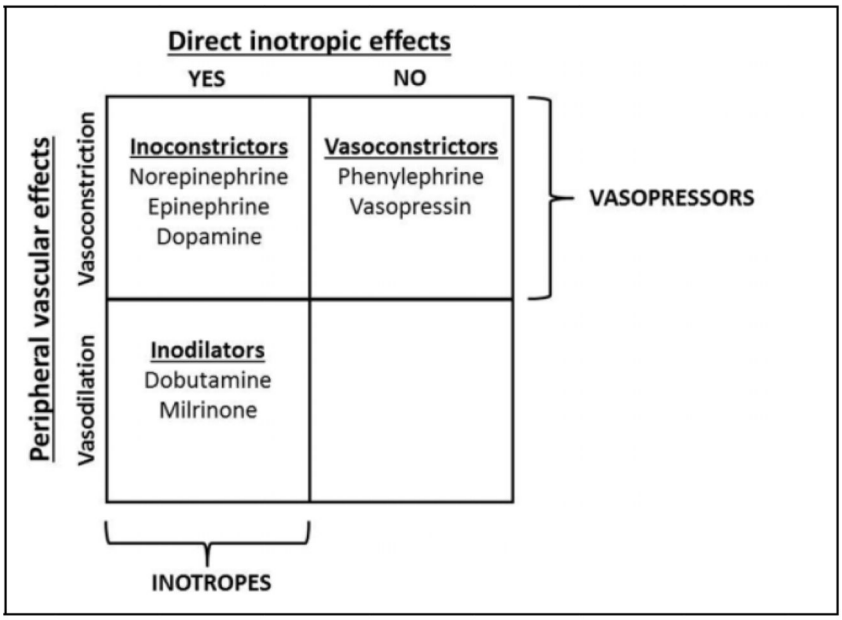
(A) Sepsis results in the release of damage- and pathogen-associated molecular patterns (DAMPs and PAMPs) which are filtered at the glomeruli. (B) These “danger signals” can lead to significant microcirculatory dysfunction, which is manifest by heterogeneity of flow. A number of capillaries begin to exhibit sluggish flow, which may lead to amplification of “danger signals” in these areas and lead to increased oxidative stress. In addition, expression of TNF receptors in the S2 segment tubular cells has led to the hypothesis that S1 cells may signal distal segments in a paracrine fashion through secretion of TNF-alpha. Finally, there is also data suggesting that this paracrine signal may also include mediators of cell cycle arrest, namely TIMP-2 and IGFBP-7. (C) Paracrine stimulation from S1 segment tubular epithelial cells produces an oxidative outburst in the S2 and S3 segment tubular epithelial cells. This oxidative outburst can potentially alter mitochondrial function by uncoupling respiration, which in turn leads to energetic imbalance, radical oxygen and nitrogen species (ROS/RNS) production, and loss of mitochondrial membrane potential. Apoptosis may be avoided through reduced energy utilization, mitophagy, and cell cycle arrest. Finally, down-regulated 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. Figures adapted from Gomez et al., Shock. 2014

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

a.



b.

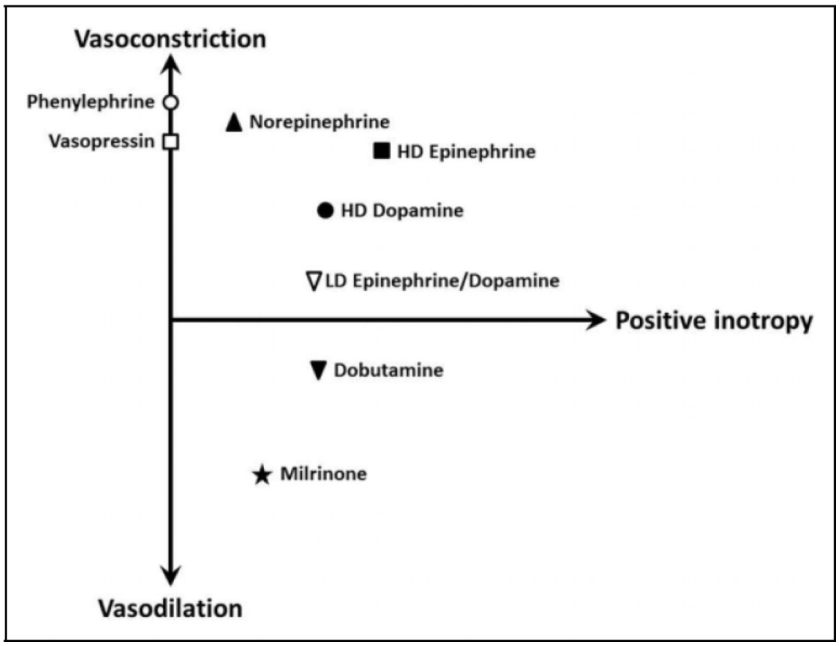


Figure 3.

Proposed classification of vasoactive agents (3a) and schematic of the type and strength of the vascular response each produces (3b). 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

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

the pure α_1 agonist phenylephrine and the non-adrenergic agent vasopressin, which acts on V_1 receptors on vascular smooth muscle cells; angiotensin II [not-depicted] is a second recently approved non-adrenergic 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 which 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). Figures adapted from Jentzer et al.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

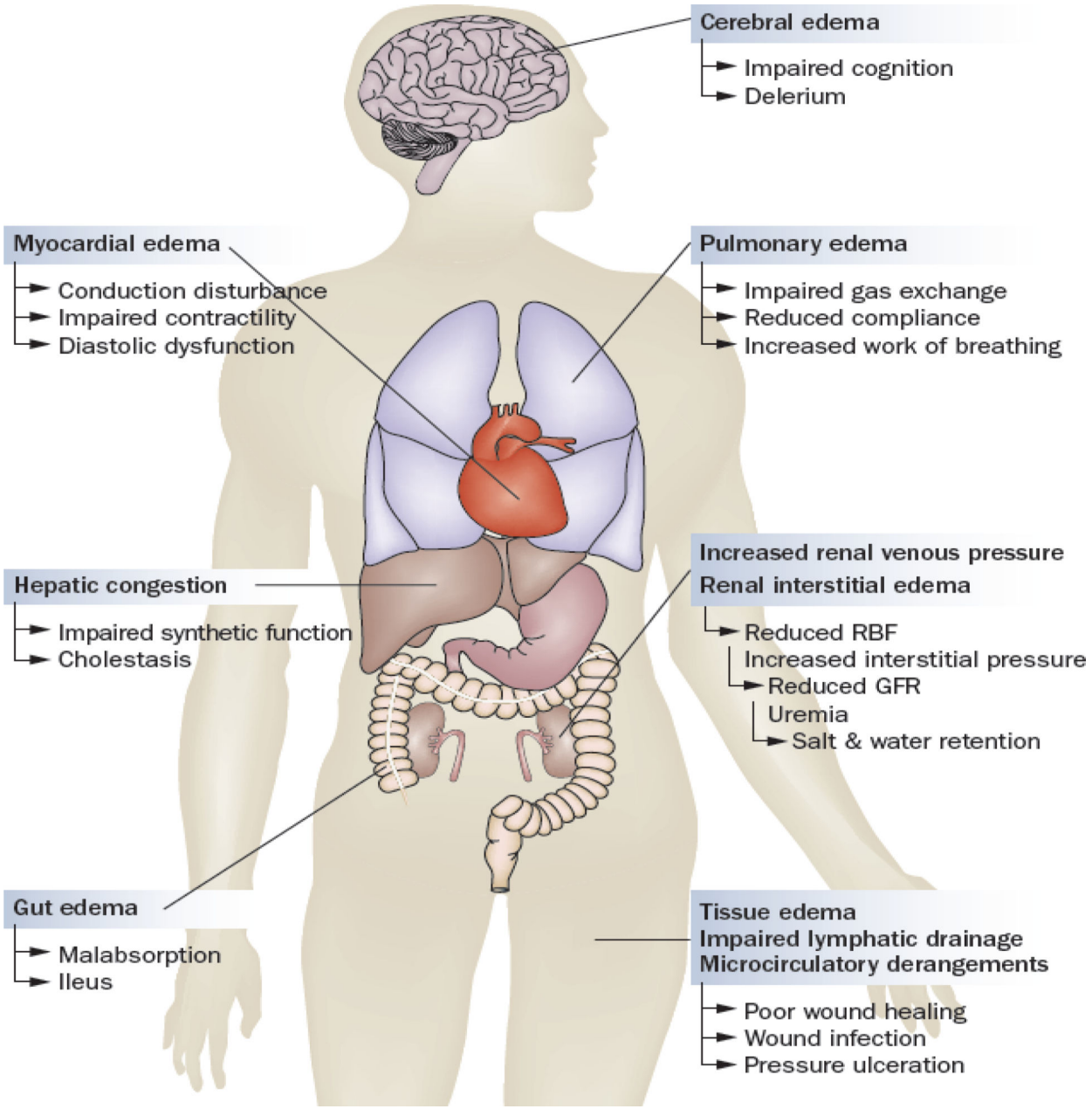


Figure 4.

Pathological sequelae of fluid overload in organ systems. Prowle et al., Nature Reviews Nephrology 2010

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

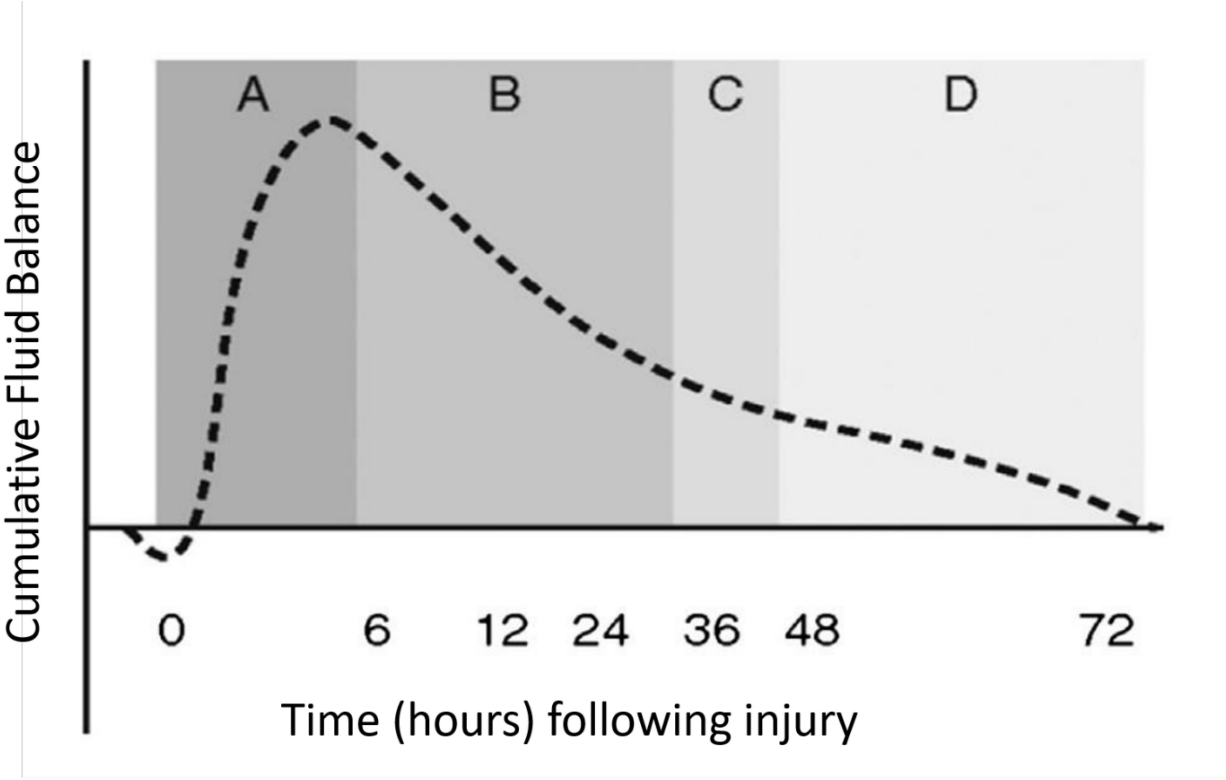


Figure 5:

Changing fluid resuscitation strategies parallel the phases of critical illness and the immune response to sepsis or another injury. Phase A (0 to 6 hours): initial aggressive volume resuscitation (e.g., 30 cc/kg of IV crystalloid), also known as the ebb phase of critical illness. Phase B (6 to 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 to 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 auto-diurese, pharmacologic diuresis or ultrafiltration can be provided to achieve euvolemia. The time at which a given patient transitions from one phase to the next may be variable and multiple insults can substantially disrupt this sequence. Adapted from Godin et al.

Author Manuscript
Author Manuscript
Author Manuscript
Author Manuscript

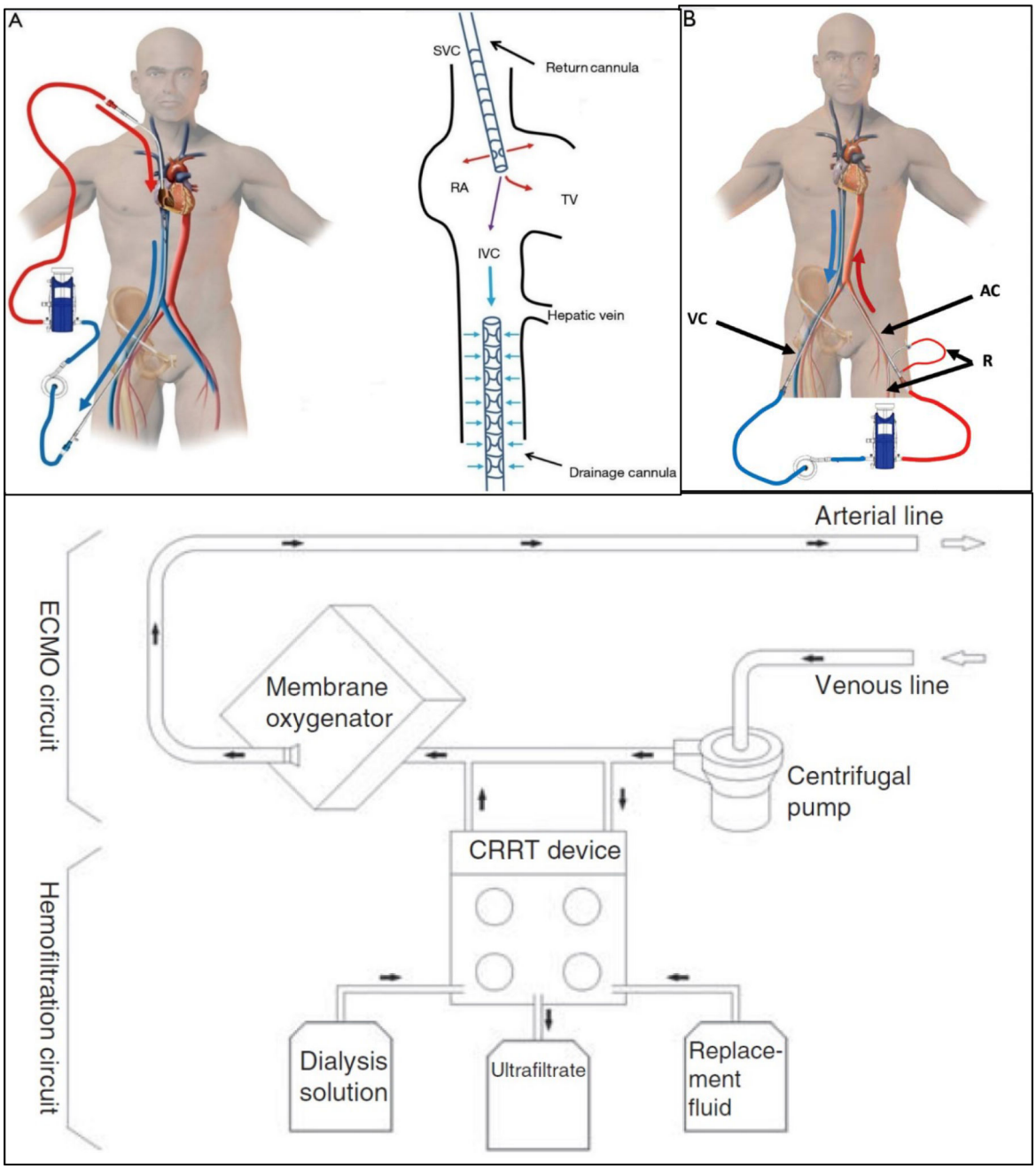


Figure 6.

Schematics of (A) VV-ECMO, (B) VA-ECMO, and (C) integrated ECMO and CRRT circuits. In VV-ECMO (A), venous drainage is via a large multiport cannula introduced via the femoral vein and advanced to the hepatic IVC just below the IVC-RA junction. The blood then passes through a centrifugal pump followed by a membrane oxygenator prior to returning to the body via a catheter that is placed through the right internal jugular and SVC and terminates in the RA. In VV-ECMO, the tips of the two cannulae must be maintained a minimum distance apart to prevent recirculation (inset). In VA-ECMO (B), oxygenated blood is returned via the left femoral artery and travels retrograde up the aorta towards the

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

great vessels and mixes with blood leaving the LV. 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. (C) The inflow to a separate CRRT device is ideally connected to a post-pump segment of the ECMO circuit so that the risk of 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 pre-oxygenator segment of the ECMO circuit to allow the oxygenator to filter out any air or clots coming from the CRRT device. Figures A and B are adapted from Banfi et al. Figure C is adapted from Santiago et al. Abbreviations: AC, arterial cannula; IVC, inferior vena cava; LV, left ventricle; R, reperfusion cannula; RA, right atrium; SVC, superior vena cava; TV, tricuspid valve; VC, venous cannula.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

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. 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 the sensitivity and specificity to drop significantly.

Pretest Probability Assessments				**Key Readings**
Clinical Risk Prediction Scores	Clinical Risk Prediction Scores are used to give greater context to a patient's clinical situation. For instance, renal angina is a concept designed to identify patients at high risk of AKI analogous to cardiac angina. Risk factors including susceptibilities (e.g., advanced age, hypertension, diabetes, CKD) and exposures (e.g., volume depletion, nephrotoxins, sepsis) are combined with symptoms (e.g., decreased 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.			Renal angina: concept and development of pretest probability assessment in acute kidney injury - Chawla et al., Crit Care 2015 A risk prediction score for acute kidney injury in the intensive care unit. - Malhotra et al., NDT 2017
Computer Algorithms	Machine learning algorithms have similarly been used to identify patients at high risk to develop AKI or the need for RRT. These complicated models are able to predict AKI with greater precision than risk prediction scores. These algorithms can be used in real time to screen for AKI in the ICU and have been shown to detect AKI up to 6 hours earlier than laboratory markers (Automated Continuous Acute Kidney Injury Prediction and Surveillance: A Random Forest Model, Chiofolo et al., Mayo Clin Proc, 2019)			The Development of a Machine Learning Inpatient Acute Kidney Injury Prediction Model - Koyner et al., Crit Care, 2018
Furosemide Stress Test	Akin to a cardiac stress test, it is a functional test used to further stratify patients at intermediate risk of AKI progression. The patient is given 1.0 mg/kg of IV furosemide if furosemide-naïve and 1.5 mg/kg if previously exposed. A urine output less than 200 mL over the next two hours was shown to have 87% sensitivity and 84% specificity to predict progression to Stage 3 AKI.			Furosemide Stress Test and Biomarkers for the Prediction of AKI Severity - Koyner et al., JASN 2015
AKI Biomarkers				
Biomarkers	Source	Function	Clinical Utility	Biomarkers for the Early Detection and Prognosis of Acute Kidney Injury. - Malhotra et al., CJASN 2017 Biomarkers of acute kidney injury: the pathway from discovery to clinical adoption - Kashani et al., Clin Chem Lab Med. 2017
TIMP2*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.	
NGAL	Urine or Serum	A 25-kDa protein that binds to iron-siderophore complexes and has a bacteriostatic function through 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	Serum – Marker of GFR similar to creatinine Urine – Because Cystatin C 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 pre-clinical 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	

NGAL - neutrophil gelatinase-associated lipocalin; TIMP2*IGFBP-7 - product of tissue inhibitor of metalloproteinase-2 and insulin-like growth factor binding protein-7; KIM-1 - kidney injury marker-1

Am J Kidney Dis. Author manuscript; available in PMC 2021 March 01.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 2.

Summary of common etiologies of AKI in the ICU setting

Etiology	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 of ≥2 points or qSOFA ≥2	Most common cause of AKI, accounting 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	Sepsis associated acute kidney injury. Poston et. al. BMJ. 2019.
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% based on AKI definition used.	Multifactorial. Extracorporeal circulation and hemolysis are unique contributors to CSA-AKI.	The PrevAKI trial showed that adherence to KDIGO guidelines reduced rates of AKI by 30% in a high-risk population.	Cardiac surgery-associated acute kidney injury: risk factors, pathophysiology and treatment. Wang et. al Nat Rev Nephrol. 2017.
Acute Liver Failure	(1) Hepatic encephalopathy of any severity, (2) INR ≥1.5 (3) Onset of illness <26 weeks (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 (APAP most commonly)	"Early" RRT Expedited Liver transplant	What a Nephrologist Needs to Know About Acute Liver Failure. Leventhal et al., Adv Chronic Kidney Dis 2015.
Intra-Abdominal HTN	IAH defined as an IAP >12 mmHg ACS is defined as IAP >20 mmHg associated with new organ dysfunction	Interestingly, IAH—likely via renal venous congestion—has been associated with both hepatorenal syndrome (HRS) and cardiorenal syndrome (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 by ureteral compression)	1) Decompressive laparotomy 2) Adequate sedation and analgesia to control abdominal muscle tone 3) Temporary neuromuscular blockade in refractory cases	Renal dysfunction associated with intra-abdominal hypertension and the abdominal compartment syndrome. Mohmand et al., JASN 2011.
Hepatorenal syndrome	1. Presence of cirrhosis and ascites; 2. Serum creatinine increase ≥0.3 mg/dL OR ≥50% increase from baseline; 3. No improvement of serum creatinine after 48 hours of diuretic withdrawal and volume expansion with albumin; 4. Absence of shock; 5. No recent treatment with nephrotoxic drugs; 6. Absence of proteinuria, hematuria, or US findings	HRS Type 1 has a 2-week mortality of 80% HRS Type 2 has a median survival of 6 months. 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 the first year following cancer diagnosis. Mortality in AKI requiring RRT is 66–88%	Cancer-specific causes include: 1) Nephrotoxic chemotherapy 2) Cast nephropathy 3) Lymphomatous infiltration of the kidney 4) Hepatic sinusoidal obstruction syndrome	1) Discontinue offending agent in possible 2) Treatment of underlying condition 3) RRT	Onco-Nephrology: Core Curriculum 2015

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Etiology	Definition	Epidemiology	Pathophysiology	Management	One Key Reading
			5) Thrombotic microangiopathy		
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 heart failure 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 renal function.	Management of Heart Failure in Advancing CKD: Core Curriculum 2018

KDIGO – Kidney Disease Improving Global Outcomes; AKI – acute kidney injury; ALF – acute liver failure; HRS – hepatorenal syndrome; TIPS – transjugular intrahepatic portosytemic shunt; IAH – Intraabdominal Hypertension; ACS – abdominal compartment syndrome.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

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=2866)**
Study Site	Multicenter (France)	Single Surgical ICU (Germany)	Multicenter (France)	Multicenter (international)
Inclusion Criteria	KDIGO Stage 3 AKI andon ventilator (85%) or pressors (85%) [with septic shock in 56%]	(1) KDIGO Stage 2 AKI, (2) plasma NGAL >150ng/ml, and (3) severe sepsis, pressors, fluid overload despite diuretics, and/or non-renal 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 hours of Stage 3 AKI	Within 8 hours of Stage 2 AKI	Within 12 hours of Stage 3 AKI	Within 12 hours of randomization.
Indications for RRT in delayed arm	BUN >112 mg/dL, K >6 mmol/L, pH <7.15, severe pulmonary edema, oliguria >72 hours	Stage 3 AKI or BUN >100 mg/dL, K >6 mmol/L, organ edema, urine output <200 ml/day	At 48 hours 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 hours
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%	
Modality RRT	55% IHD, 45% CRRT	100% CVVHDF	55% CRRT, 45% IHD	
60-day mortality (early vs. late)	48.5% vs. 49.7% (p = 0.79)	38.4% vs. 50.4% (p = 0.07)	-	
90-day mortality (early vs. late)	-	39.3% vs. 54.7% (p = 0.03)	58% vs. 54% (p = 0.38)	
ICU LOS in Survivors	13 days in both groups (NS)	19 days vs. 22 days (NS)	12 days in both groups (NS)	
Mechanical Ventilation (early vs. late)	7 vs. 6 days free of MV (NS)	125 hours vs. 181 hours (p = 0.002)	2 vs. 3 days free of MV (NS)	

AKI – Acute kidney injury; KDIGO – Kidney Disease Improving Global Outcomes; RIFLE – Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease; NGAL - neutrophil gelatinase-associated lipocalin; AHRF – Acute hypoxemic respiratory failure; CRRT – Continuous renal replacement therapy; CVVHDF – Continuous venovenous hemodiafiltration; iHD – intermittent hemodialysis; HR – Hazard ratio; CI – Confidence Interval; ICU – Intensive care unit; LOS – Length of stay; NS – Not significant; MV – Mechanical ventilation

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 4.

Typical hemodynamics in various shock states and their differential diagnosis. The three primary categories of shock can be classified by the primary mechanism (double arrows) of hypotension via the relationship MAP = CO x SVR and the concept of preload. Note that more than one type of shock can coexist in a given patient (e.g., 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 (i.e., the site of obstruction), can have variable effects on right ventricular or left ventricular preload. Adrenal insufficiency can cause shock by both distributive and hypovolemic mechanisms.
Abbreviations: CVP, central venous pressure; CO, cardiac output; MAP, mean arterial pressure; SVR, systemic vascular resistance.

	CVP or preload	CO	SVR	Examples
Distributive	↓	↑	↓↓	• Septic • Neurogenic • Anaphylaxis • Adrenal insufficiency*
Hypovolemic or hemorrhagic	↓↓	↓	↑	• Hemorrhagic • Other volume depletion (diarrhea, vomiting, over-diuresis, inadequate intake)
Cardiogenic	↑	↓↓	↑	• Acute myocardial infarction • Heart failure • Valvular disease • Post cardiopulmonary bypass • Dysrhythmia
Obstructive	*	↓↓	↑	• Massive pulmonary embolism • Tamponade • Tension pneumothorax • Mechanical ventilation with excess positive end-expiratory pressure (PEEP)