Chronic Kidney Disease in the Intensive Care Unit

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Before You Start: Facts You Need to Know

- CKD patients have a high prevalence of comorbid disease compared to non-CKD patients; however, CKD patients have reasonable short-term outcomes following ICU admission compared to non-CKD patients.
- The most common diagnoses contributing to ICU admission in CKD patients are sepsis and septic shock and decompensated cardiovascular disease.
- AKI is a common complication of critical illness, most often precipitated by sepsis, and remains a strong negative modifier of short- and long-term survival.
- CKD is an important and independent non-modifiable risk factor for development of AKI and long-term accelerated loss of kidney function among CKD survivor of critical illness.
- While numerous factors influence the decision to start renal replacement therapy, the most common initial modality prescribed after ICU admission worldwide remains continuous renal replacement therapy, particularly for hemodynamically unstable patients, and this may be associated with higher likelihood of recovery of renal function and dialysis independence.

32.1 Introduction

The worldwide prevalence and incidence of chronic kidney disease (CKD) and end-stage renal disease (ESRD) are increasing substantially, largely attributable to an aging population coupled with large increases in the rates of hypertension, type 2 diabetes mellitus, and obesity.

CKD patients are characterized by a higher burden of comorbid illness, including coronary artery disease, heart failure, diabetes mellitus, hypertension, and cerebrovascular disease, and generally have higher health services utilization, including rates of hospitalization, when compared to non-CKD critically ill patients. Moreover, CKD patients, in particular for the subset with

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ESRD, have a several-fold higher risk of developing critical illness. When considering these features, coupled with rising prevalence rates, the demand for intensive care unit (ICU) support for CKD patients is expected to increase. This will likely present challenges for clinicians working in resource-limited settings regarding decision-making for ICU support for CKD patients.

32.1.1 Epidemiology of CKD and ESRD in ICU

There is limited data available on the prevalence of CKD among all critically ill patients supported in ICU settings, and most studies have focused on the subset of dialysis-dependent patients with ESRD [1]. Available data would suggest the proportion of patients admitted to ICU with ESRD ranges between 1 and 9 %. The reported variability in ESRD admissions across studies is likely accounted for by differences in practice patterns, availability of ICU resources, patient case-mix, and study design. ESRD patients have consistently been shown to have an estimated 25–30-fold higher annual likelihood of admission to ICU when compared with the non-ESRD general population.

ESRD patients admitted to ICU have several notable differences in baseline characteristics when compared with non-ESRD patients. ESRD patients are generally younger, have more comorbid disease, more likely medical (i.e., nonoperative admissions), and have higher illness severity scores compared with non-ESRD patients. However, these observations may be susceptible to selection bias. Available epidemiologic surveys of ESRD patients admitted to ICU are limited by not accounting for those patients referred and refused ICU admission.

32.1.2 Precipitants for Critical Illness in CKD and ESKD

The most common precipitants of critical illness prompting ICU admission among ESRD patients are sepsis/septic shock and decompensated cardiovascular disease including cardiogenic shock, myocardial ischemia/infarction, arrhythmic complications, and heart failure/pulmonary edema. Cardiac arrest and cardiopulmonary resuscitation (CPR) are more common events occurring among ESRD patients compared with non-ESRD prior to ICU admission. This may relate to several factors including a higher prevalence of comorbid cardiovascular disease and diminished cardiopulmonary reserve, a higher incidence of primarily arrhythmic complications, and the unique pathophysiologic stress of dialysis (i.e., rapid fluid-/electrolyte-related shifts).

32.1.3 Outcomes for CKD and ESRD in ICU

Surprisingly, the early mortality for critically ill ESRD patients is lower than for those with acute kidney injury (AKI), suggesting that the prognosis is driven largely by acute illness severity rather than baseline comorbidities. However, ESRD patients have consistently higher short-term mortality rates (9–44 %) when compared to non-AKI critically ill patients and an age- and sex-matched general population. Factors that have been shown to be associated with ICU mortality in ESRD patients are older age, higher illness severity score (i.e., APACHE II or SAPS II), burden of nonrenal organ dysfunction/failure, medical or nonsurgical admission type, and provision and duration of life-sustaining technologies (i.e., mechanical ventilation, vasopressor therapy).

Studies reporting long-term survival among ESRD patients show a trend for an increased mortality rate within the first 6 months after ICU discharge, with a relatively stable but increased risk for mortality thereafter. At 2 years after ICU admission, survival is generally poor. Observational studies estimate only 1/3 of ESRD patients admitted to ICU were still alive. Although long-term mortality in ESRD patients is several times higher when compared to the general population, the presence of ESRD does not appear to independently predict long-term mortality, suggesting short-term prognosis is

more related to the acute illness severity rather than CKD and dialysis dependence.

It has been increasingly recognized that CKD influences the risk of developing AKI and that AKI per se contributes to CKD progression and incidence of ESRD. Around 50 % of patients who survive an episode of AKI requiring RRT show significant loss of glomerular filtration rate (GFR) resulting in dialysis dependence after hospital discharge in approximately 10 % of patients. The most important risk factor for incident ESRD and dialysis dependence among survivors of critical illness is prior CKD. This would suggest continued surveillance of kidney function among survivors of critical illness is vital.

Data on changes to functional status and health-related quality of life (HRQL) for ESRD patients surviving an episode of critical illness are currently lacking. However, in non-ESRD critically ill patients surviving critical illness, in particular for those with severe AKI requiring acute RRT, long-term reductions in HRQL and impaired functional status are common. These data coupled with the reduced HRQL for ESRD patients imply this may be a significant issue for survivors of critical illness.

CKD, in particular ESRD patients, consume more health resources in association with admission to ICU compared with non-CKD patients. These patients have longer durations of ICU stay, longer duration of hospitalization, and higher rates of short-term rehospitalization. Moreover, these patients often remain chronically ill following ICU discharge due to issues related to cardiovascular comorbidity, malnutrition, and deconditioning. These likely reflect diminished physiologic reserve and increased vulnerability to further adverse events.

32.1.4 Prognostic Scoring for CKD and ESRD in ICU

ICU prognostication using ICU-specific illness severity or organ failure scores (i.e., APAHCE II, SAPS III, SOFA) can be challenging among patients with ESRD. Most scoring systems have not been specifically validated for ESRD patients, and their performance routinely overestimates the risk of death [1]. This may contribute to the perceived lack of benefit of ICU support for CKD/ESRD patients referred for ICU support.

32.2 ICU Support of the Patient with Chronic Kidney Disease

The pathological changes accompanying CKD, although frequently not clinically evident until later stages of kidney disease, can present unique challenges for CKD patients presenting with critical illness. Details of some of the unique challenges in the acute management of CKD patients in the ICU are detailed in Table 32.1.

There is a paucity of data with respect to the specificity of the management of CKD patients in the ICU especially in the early stages of the disease. CKD patients should receive the same standard of care as the general population while accounting for some of the unique challenges that patients with CKD/ESRD may pose to ICU management.

32.2.1 Hemodynamic Monitoring and Mechanical Ventilation Support

The general principles for support and management of critically ill patient in the ICU focus on advanced hemodynamic and physiologic monitoring and multimodal organ support to guide restoration of tissue perfusion and oxygen delivery (Table 32.2).

The majority of patients have intravascular placement of arterial catheter for continuous blood pressure monitoring, due either to the presence of hemodynamic instability or to monitoring resuscitation (i.e., fluid therapy or titration of vasoactive therapy) or need for frequent blood sampling. Arterial catheters display systolic, diastolic, and mean arterial pressure readings along with a continuous waveform. Analysis of the pressure waveform may provide useful information regarding a patient's clinical status. Variability on pulse contours is related to the

Table 32.1 Selected challenges to the ICU management of critically ill patients with CKD and ESRD

Parameter	Issue	Consequence
Comorbid disease	High prevalence of DM, hypertension, CVD, frequent exclusion from RCT of ICU-specific interventions	Increased susceptibility to poor wound healing, compromised perfusion to vital organs/organ dysfunction, low-quality evidence base for many aspects of management
Volume homeostasis	Reduced GFR and relative oliguria	Fluid accumulation, diuretic resistance, susceptibility to fluid overload complications
Dry weight evaluation	Unmeasured fluid losses and muscle wasting	Inaccurate estimation for determined fluid removal targets for RRT
Electrolyte homeostasis	Reduced GFR, reduced capacity to excrete free water and K^+, PO_4^{3-}, Mg^+, and other electrolytes	Increased susceptibility to hyponatremia, hyperkalemia, and other electrolyte abnormalities
Hemostasis	Alternations in vWF complex, platelet activation/aggregation, and NO metabolism	Increased susceptibility to bleeding
Anemia	Relative EPO deficiency, functional iron deficiency, reduced RBC lifespan, anemia chronic disease	Increased incidence of anemia, greater susceptibility to transfusion
Immunology/ inflammatory response	Impaired T-cell activity, deficient antibody production, altered opsonization/ phagocytosis, chronic increased production of inflammatory cytokines/mediators	Increased susceptibility to infection, blunted response to infection
Antimicrobial therapy	Altered pharmacokinetics (reduced clearance, altered Vd, extracorporeal clearance), multiple prior antimicrobial exposures	Increased prevalence/susceptibility to ARO, increased susceptibility to treatment failure/ toxicity
Vascular access	Vascular calcification, PD or CVC present, multiple prior central venous catheters	Difficulty obtaining arterial and venous access, susceptibility to catheter-related infection, risk of vessel stenosis

Abbreviations: *DM* diabetes mellitus, *CVD* cardiovascular disease, *GFR* glomerular filtration rate, *NO* nitric oxide, *Vd* volume of distribution, *ARO* antimicrobial-resistant organisms, *RCT* randomized controlled trial, *ICU* intensive care unit, *PD* peritoneal dialysis, *CVC* central venous catheter, *vWF* von Willebrand factor, *RBC* red blood cells, *NO* nitric oxide

elasticity, amplification, and distortion of smaller peripheral arterioles. CKD patients with significant peripheral vascular disease and/or arteriolar calcification may have reduced vessel elasticity (i.e., arterial stiffness) and exacerbated amplification that results in relative increases in systolic pressure and low diastolic pressure with rapid diastolic runoff (i.e., widened pulse pressure). ESRD patients with a fistula or graft will have accelerated diastolic runoff and as a consequence lower diastolic and mean arterial pressure. In addition, given the prevalence of comorbid conditions in CKD such as cardiac valvular disease, ventricular hypertrophy (LVH), or pulmonary hypertension, arterial catheters may have misleading instantaneous accuracy, though likely have preserved trending [2].

Additional static hemodynamic measures, such as central venous pressure (CVP) and pulmonary artery occlusion pressure (PAOP), have focused on providing an estimate of left ventricular preload to guide fluid resuscitation. The challenge with these fixed pressure-derived measures is their lack of predictability to determine whether a patient will positively response to a fluid challenge (i.e., show improvement in cardiac output and performance associated with a fluid bolus). These measures are confounded by alterations in ventricular wall compliance (i.e., LVH in ESRD). Both CVP and PAOP lack precision in individual patients and should not be used in isolation to guide resuscitation. This may contribute to excessive and inappropriate fluid prescription. The central venous oxygenation ($ScVO_2$) is generally accepted surrogate for the venous oxygen saturation (S_vO2) and reflects the adequacy of global cardiac output and oxygen delivery.

Functional dynamic metrics that utilize the observed variability in left ventricular filling

Table 32.2 Methods for monitoring and support of organ failure in critically ill patients

Organ system	Monitoring	Support
Circulatory	Indwelling arterial catheter, central venous catheter, pulmonary artery catheter, respiratory variation in pulse pressure or stroke volume (LiDCO, PiCCO, FloTrac/Vigileo), echocardiography, impedance cardiography, cardiac-specific troponin, b-type natriuretic peptide	Fluid therapy, vasoactive therapy (inotropes, vasopressors), pacemaker, indwelling mechanical support (intra-aortic balloon pump, Impella, ventricular assist device), extracorporeal support (venoarterial extracorporeal membrane oxygenation)
Respiratory	Pulse oximetry, arterial blood gas, end-tidal CO_2, flow-volume loops on mechanical ventilator, chest radiography	Noninvasive mechanical ventilation (nasal, mask, helmet CPAP, or BIPAP), conventional mechanical ventilator, oscillator, extracorporeal support (venovenous extracorporeal membrane oxygenation)
Renal	Routine blood/urine biochemistry, urine microscopy, urine output, fluid balance, novel urine or plasma kidney damage-specific biomarkers (NGAL, KIM-1, IL-18, L-FABP, NAG), renal ultrasound, renal Doppler resistive index	Renal replacement therapy (CRRT, SLED, IRRT)
Gastrointestinal	Feeding tolerance, diarrhea, routine blood biochemistry, abdominal radiography	Enteric nutrition, parenteral nutrition, glycemic control, micronutrient supplementation
Liver	Routine blood biochemistry (liver enzymes, lactate, glucose, ammonia)	Molecular adsorbent circulation system
Hematologic/ inflammatory	Clinical examination, complete blood count/ smear, C-reactive protein, procalcitonin	Blood transfusion, early/broad-spectrum antimicrobials, extracorporeal blood purification
Neurologic	Neurologic examination, CSF examination, brain radiology (CT, MRI, angiography), EEG, brain damage-specific biomarkers (neuron-specific enolase, S100β, myelin basic protein), invasive ICP monitoring, cerebral microdialysis	Sedation, antiepileptic therapy, intracranial hypertension management, intraventricular drain

Abbreviations: *CO_2* carbon dioxide, *CPAP* continuous positive airway pressure, *BIPAP* bilevel positive airway pressure, *NGAL* neutrophil-associated lipocalin, *KIM-1* kidney injury molecule-1, *IL-18* interleukin-18, *FABP* fatty acid binding protein, *MARS* molecular adsorbent circulation system, *NAG* N-acetyl-β-D-glucosaminidase, *CRRT* continuous renal replacement therapy, *SLED* sustained low-efficiency dialysis, *IRRT* intermittent renal replacement therapy, *ICP* intracranial pressure

across the respiratory cycle, measured as the variation in pulse pressure (PPV) or stroke volume (SVV), have been shown to better predict fluid responsiveness in mechanically ventilated critically ill patients (Box 32.1). The premise is that variations in systolic blood pressure and stroke volume are greater in hypovolemic states due to the increase collapsibility of the vena cava, increased transmural effect on the right atrium, and the relationship between stroke volume and preload being on the steep portion of the Frank–Starling curve. Large variation in SVV or PPV (>12 %) indicates fluid administration will translate into improved cardiac output. There are important limitations to the use of PPV/SVV and measures are susceptible to errors in states where patients are not adapted to controlled mechanical ventilation (i.e., breathing spontaneously, variable tidal volume [Vt]) or are not in sinus rhythm (i.e., atrial fibrillation). Variation in the inferior vena cava diameter during respiration as seen by echocardiography is additional functional dynamic measure of fluid responsiveness. In spontaneously breathing patients, only passive leg raising (PLR) has been shown to reliably predict fluid responsiveness. PLR involves transient elevation of the lower extremities above the heart of a recumbent patient, mimicking the effect of a large fluid bolus on the central circulation.

Box 32.1. Definitions of Functional Hemodynamic Metrics

Pulse pressure variation (PPV): Defined as the maximum pulse pressure minus the minimum pulse pressure, divided by the average of these two pressures over a mechanically delivered breath. PPV is based on the premise of pulsus paradoxus, the changes in arterial pressure during inspiration and expiration. PPV is not a true measure of preload or volume status, but an indicator of the position of the Frank–Starling relationship curve between stroke volume and preload to predict fluid responsiveness:

$$\mathrm{PPV}(\%) = \left(\mathrm{PP}_{\max} - \mathrm{PP}_{\min}\right) / \left[\left(\mathrm{PP}_{\max} + \mathrm{PP}_{\min}\right) / 2\right] \times 100$$

Stroke volume variation (SVV): Defined as the percentage of change between the maximum and minimum stroke volumes over a certain interval. Similar to PPV, SVV is not a true measure of volume status or preload but rather an assessment of response to fluid resuscitation:

$$\mathrm{SVV} = \left(\mathrm{SV\ maximum} - \mathrm{SV\ minimum}\right) / \left[\left(\mathrm{SV\ maximum} + \mathrm{SV\ minimum}\right) / 2\right]$$

Table 32.3 Common modes of invasive mechanical ventilation in the ICU

Mode	Description	Advantages	Disadvantages
VCV	Machine delivered, patient triggered, flow targeted, frequency equal to minimum set rate; present Vd (volume limited)	Ensures the delivery of a minimum Vt and total ventilation	May be uncomfortable if high inspiratory flow needed by patient, may predispose to dynamic hyperinflation (auto-PEEP), may predispose to VILI
PCV	Machine delivered, patient triggered, pressure targeted, frequency equal to minimum set rate; breath terminated by present Ti (pressure limited)	Pressure limited; control of plateau/mean airway pressure; better patient comfort	Vt variable; does not ensure delivery of minimum ventilation
PSV	Patient triggered and pressure targeted Vt; breath terminated by present inspiratory flow rate; patient determined Vt, Ti, and frequency	Better patient–ventilator synchrony; augments patients' breather; better patient comfort; used commonly to wean	Vt, Ti, frequency variable; does not ensure delivery of minimum ventilation; unsuitable for patients with impaired respiratory drive
SIMV	Machine-delivered synchronized breaths at present Vt, flow or pressure targeted; preset minimum rate; patient can breathe spontaneously with PSV between machine-delivered breaths	Ensures the delivery of a minimum Vt and total ventilation, allows some spontaneous breathing	May be uncomfortable, may increase work of breathing, may prolong weaning
CPAP	Machine set PEEP; patient triggered; patient determined Vt, Ti, and frequency	Augments spontaneous breathing; reduced inspiratory work; patient comfort; used commonly to wean	Vt, Ti, frequency variable; does not ensure delivery of minimum ventilation; may increase work of breathing

Abbreviations: *VCV* volume-controlled ventilation, *PCV* pressure-controlled ventilation, *PSV* pressure support ventilation, *SIMV* synchronized intermittent mandatory ventilation, *Vt* tidal volume, *PEEP* positive end-expiratory pressure, *VILI* ventilator-induced lung injury, *Ti* inspiratory time

Mechanical ventilation is a core life-sustaining technology that largely defined the modern practice of critical care. Most critically ill patients require mechanical ventilation, whether for lung-specific indications (i.e., acute lung injury), systemic indications (i.e., shock), or postoperative support. A summary of the most common modes of mechanical ventilation provided in the context of critical illness is shown in Table 32.3. Epidemiologic data have shown an increased

utilization of mechanical ventilation for critically ill patients in recent years. These patients are generally burdened with a high prevalence of comorbid disease, in particular CKD, representing up to one quarter of all mechanically ventilated patients.

Kidney disease, both acute and chronic, can present unique challenges with respect to respiratory physiology, lung–kidney interaction, and mechanical ventilation support [3]. First, CKD/ESRD patients often have high prevalence of comorbid respiratory illness such as restrictive or obstructive defects, pleural disease, pulmonary calcification, sleep apnea, or dialysis-associated hypoxemia. Patients receiving PD have chronically elevated intra-abdominal pressure and diminished functional residual capacity. These factors predispose to limited pulmonary reserve. Second, CKD/ESRD patients often have diminished cardiac reserve and all have compromised capacity to excrete solute and water. Acute cardiac events and/or fluid accumulation (i.e., noncompliance with diet, inappropriate dry weight prescription, missed dialysis) can predispose to acute cardiorenal syndrome and pulmonary edema. Third, the development of acute injury to the kidney can induce a systemic inflammatory response with distant pathophysiologic effects in the lung (i.e., alterations in alveolar permeability and aquaporin expression). Fourth, the positive pressure applied during mechanical ventilation acts to increase intrathoracic, intrapleural, and intra-abdominal pressures both during inspiration and for the duration of the respiratory cycle (i.e., PEEP) with the aim to improve and maintain adequate gas exchange. This can stimulate an array of hemodynamic, neural, and hormonal responses that can negatively impact kidney perfusion and further inhibit excretory function. This is observed as immediate and reversible declines in urine output and fluid retention, contributing to worsening fluid accumulation. Finally, mechanical ventilation may provoke ventilator-induced lung injury (VILI) leading to an exacerbating cascade of systemic inflammation that may have distant injurious effects on the kidney [3]. Data have also shown the development of AKI may delay weaning from mechanical ventilation [4]. This is likely multifactorial and related to greater difficulties with volume and acid–base homeostasis in AKI. By extension, CKD/ESRD patients are similarly likely to encounter prolonged weaning from mechanical ventilation.

The most severe form of respiratory failure is acute respiratory distress syndrome (ARDS), defined as rapid-onset (1 week) respiratory symptoms and hypoxemia associated with bilateral opacities resulting in respiratory failure not fully explained by cardiac failure or fluid overload. The incidence of milder forms of ARDS is 78.9/100,000 person-years while more severe ARDS occurs at a rate of 58.7/100,000 person-years. The most common predisposing factor is pulmonary and non-pulmonary sepsis. The mortality remains significant, in the range of 35–40 %, and long-term morbidity among survivors remains severely burdensome. The development of AKI or worsening kidney function in the setting of ARDS is common, occurring in excess of 35 %, and has an important modifying impact on increasing mortality risk (60–80 %) [4]. It is believed part of the attributable mortality in ARDS has been related to the development of secondary harm associated with the mechanical ventilator (i.e., VILI). Accordingly, a number of "lung protective" strategies for improving outcome in ARDS have been evaluated (Table 32.4). The advent of open lung low tidal volume ventilation to prevent alveolar overdistension, cyclic collapse, and barotrauma may be associated with iatrogenic alveolar hypoventilation and hypercarbic respiratory acidosis. This may be poorly tolerated in patients with AKI or CKD/ESRD with loss of renal compensation and inability to buffer the accumulated CO_2. These patients are likely to require early initiation of RRT to mitigate severe acidemia and excessive fluid accumulation.

32.2.2 Fluid, Electrolyte, and Acid–Base Management

Patients with CKD/ESRD are more susceptible to fluid and metabolic complications due to impaired fluid, electrolyte, and acid–base homeostasis.

Table 32.4 Ventilation and other supportive therapies in ARDS

Strategy	Description	Comment
Lung protective ventilation	Target tidal volume 4–6 mL/kg ideal body weight; set positive end-expiratory pressure (PEEP) to avoid alveolar collapse; maintain plateau pressure <30 cm H_2O; may precipitate permissive hypercapnia	The "low tidal" volume and "open" lung ventilatory strategy are aimed at minimizing iatrogenic injury from mechanical ventilation (i.e., ventilator-induced lung injury [VILI]). VILI is induced by volutrauma, barotrauma, atelectrauma, and biotrauma. Level I evidence has shown utilizing lung protective ventilation has shown reductions in mortality, durations of ventilation, and durations in ICU
Recruitment maneuvers (RM)	The rationale for utilizing RM in ARDS is to improve alveolar recruitment and gas exchange. RM are generally a series of continuously applied (20–40 s) high levels of PEEP (30–40 cm H_2O)	RM can improve oxygenation in suitable ARDS candidates with recruitment of alveolar segments; however, it can be associated with hemodynamic instability. No level I evidence
Neuromuscular blockade (NMB)	Early short-term use of continuous NMB (<48 h) in severe ARDS may improve gas exchange and reduce VILI	Recent level I evidence found lower 28-day and hospital mortality associated with a strategy of early short-term continuous infusion of NMB in severe ARDS and no increase in the rate of ICU-acquired weakness
Daily sedation interruption	A strategy of daily interruption or minimal sedation has been advocated to reduce duration of ventilation, duration of ICU stay, and the incidence of delirium	These patients did not necessarily have ARDS. Recent level I evidence did not show evidence of reduced duration of ventilation or delirium associated with daily sedation interruption among ventilated patients receiving a sedation protocol
Conservative versus liberal fluid therapy strategy	The rationale for a conservative fluid management strategy is based on the premise of minimizing nonessential fluid and active removal of excess fluid once physiologic stability was achieved	Recent level I evidence found that a conservative fluid strategy, compared with a liberal fluid strategy, resulted in a nonsignificant reduction in mortality and significant shorter durations of mechanical ventilation, ICU stay, and trends for lower utilization of RRT. These findings were similar for the subgroup with AKI
Prone positioning	ARDS is often a heterogeneous syndrome with worse air space consolidation in basal (dependent) lung segments. The rationale for prone positioning is to improve V/Q matching and reduce VILI by having patients in prone position for 12–16 h per day	Prior trials have found prone positioning improves oxygenation; and recent level I evidence found a strategy of early prone positioning was associated with improved survival at 28 and 90 days. Prone positioning should be protocolized
Inhaled vasodilators (iNO, prostacyclin)	The rationale for inhaled vasodilators, by reducing PVR and improving V/Q matching in ARDS, can improve oxygenation	Meta-analyses of small randomized trials have found no improvement in mortality with inhaled vasodilators for ARDS; however, it was associated with transient improvements in oxygenation and increased risk of AKI. Inhaled vasodilators are a reasonable salvage therapy for refractory hypoxemia
High-frequency oscillatory ventilation (HFOV)	The premise for HFOV is to utilize sub-anatomical tidal volumes, high mean airway pressures, and high respiratory rates to maintain open lung ventilation, minimize the risk of VILI, and allow lungs injury to recover	Recent level I evidence found early utilization of HFOV, compared with standard lung protective ventilation, was associated with increased in-hospital mortality, greater use of sedation, neuromuscular blockade, and vasoactive therapy. HFOV should be reserved for salvage therapy in those with refractory hypoxemia
Extracorporeal membrane oxygenation (ECMO)	Candidates should have potentially reversible respiratory failure, severe hypoxemia (Murray score >3.0), ideally venovenous circuit via dual-lumen catheter, early referral to experienced centers	ECMO has generally been reserved as salvage therapy for adult patients; however, recent level I evidence from randomized trials and observational data during the pH1N1 pandemic found reasonable survival

Table 32.4 (continued)

Strategy	Description	Comment
Ineffective or harmful interventions	Surfactant, antioxidants/glutamine supplementation, N-acetylcysteine, ibuprofen, ketoconazole	Numerous high-quality randomized trials in adults have no clear evidence of benefit for these therapies

Abbreviations: *AKI* acute kidney injury, *ARDS* acute respiratory distress syndrome, *ECMO* extracorporeal membrane oxygenation, *HFOV* high-frequency oscillatory ventilation, *iNO* inhaled nitric oxide, *NMB* neuromuscular blockade, *PVR* pulmonary vascular resistance, *RM* recruitment maneuvers, *VILI* ventilator-induced lung injury

Fluid therapy is perhaps the most common intervention received by critically ill patients. The key concept for dosing fluid therapy in critically ill patients is to actively address ongoing losses coupled with constant reassessment of need for further hemodynamic support. While the optimal endpoints for fluid therapy during resuscitation remain controversial, increasing evidence suggests that resuscitation needs to be individualized and that the integration of functional hemodynamic measures to guide fluid responsiveness are superior to static measures of volume status.

Fluid therapy also represents a central cornerstone for the prevention and/or the management of AKI. Of the numerous strategies evaluated to date for prevention of AKI, only fluid therapy has been shown to be consistently effective. Importantly, however, *there is no evidence that fluid therapy will reverse AKI once established*. Reduced urine output is common and often precedes overt AKI; however, it lacks specificity. Oliguria in the absence of clear hypovolemia or fluid responsiveness is not necessarily an indication for a fluid challenge. The distinction is important. In the context of hypovolemia and/or reduced arterial filling, fluid therapy would appear appropriate. However, there is no evidence to support a fluid challenge in the resuscitated patient with oliguric AKI. While such a fluid challenge may be intended to promote diuresis, dilute tubular toxins, and attenuate tubular obstruction from casts, there is no data to suggest it attenuates the severity of AKI or improves clinical outcome. Instead, the liberal use of fluid therapy in these circumstances may exacerbate fluid overload and lead to harm. Fluid accumulation can also mask the presence and severity of AKI by increasing the total body water and hemodiluting creatinine. Recent evidence suggests that classifying AKI after correcting creatinine concentration for the volume of fluid administered improves the ability to classify AKI and predict mortality. Unnecessary fluid accumulation and overload are associated with clear increases in morbidity, including worsening AKI and delayed renal recovery, and mortality, in particular in patients with compromised kidney function across a range of clinical settings [5]. Diuretic therapy should be reserved for mitigating fluid overload in responsive patients rather than for preventing AKI or promoting recovery of kidney function. In patients whose fluid balance cannot be managed adequately with conservative fluid administration or diuretic therapy, RRT should be considered. In addition, the routine practice of providing "maintenance" of unmeasured fluid deficits such as "third space losses" for the majority of critically ill patients is questionable, in particular for those with CKD/ESRD, and often contributes unnecessary fluid accumulation.

In addition, the types of fluid administrated are increasingly recognized as having dose-dependent qualitative toxic effects. Colloids are commonly used for acute resuscitation in critically ill patients. Synthetic colloids, such as hydroxyethyl starch (HES), have appeal for resuscitation fluids based on the premise that they attenuate the inflammatory response, mitigate endothelial barrier dysfunction, improve microcirculatory flow, and contribute to more rapid hemodynamic stabilization; however, accumulated data have now suggested use of these fluids in critical illness is associated with dose-dependent risk for severe AKI requiring RRT, bleeding complications, and death (Box 32.2). In addition, these solutions are prohibitively more

expensive when compared with crystalloids. Albumin is routinely used for resuscitation in liver failure patients with spontaneous bacterial peritonitis for prevention of hepatorenal syndrome and limited clinical data suggest albumin may improve outcome in severe sepsis.

Resuscitation with high chloride concentration solutions (i.e., 0.9 % saline – strong ion difference: 0 mEq/L) can directly contribute to iatrogenic hyperchloremic metabolic acidosis. The physiologic stress with large volume resuscitation of chloride-rich solutions may be less tolerated in CKD patients. Recent data have compared resuscitation with saline (0.9 %) to balanced crystalloid solutions (i.e., Ringer's lactate, Plasma-Lyte). Preferential use of these balanced solutions with a lower "chloride load" that more closely mimic the chloride content and strong ion difference of plasma has been associated with fewer metabolic complications (i.e., metabolic acidosis, hyperkalemia, hypernatremia), reduced blood product utilization, reduced AKI, and need for RRT and cost savings [6] (Box 32.3).

There is uncertain benefit for supplemental intravenous bicarbonate therapy for treatment of metabolic acidosis. Bicarbonate is commonly used in critical illness when confronted by severe metabolic acidosis (i.e., pH <7.15); however, its use is guided by limited clinical evidence. Bicarbonate supplementation intended to treat loss of bicarbonate from the buffer pool (i.e., renal tubular acidosis) would appear logical; however, its use to treat acidosis due to elevated lactate has been associated with increased mortality. Bicarbonate administration (1–2 mEq/kg) can transiently increase serum pH and serum bicarbonate; however, it may precipitate untoward adverse effects including worsening intracellular acidosis, extracellular accumulation of CO_2,

Box 32.2. What the Guidelines Say You Should Do: Fluid Resuscitation in Critically Ill Patients

- Do not use HES in patients with severe sepsis or at risk of AKI.
- Gelatin should not be used in patients at risk for AKI.
- Do not use HES or gelatin in organ donors.
- Do not use synthetic colloids in patients with head injury or intracranial bleeding.
- Albumin may be used for resuscitation in severe sepsis.
- Do not use albumin in patients with head injury.
- Hyperoncotic solutions should not be used for fluid resuscitation.
- New colloid should be introduced into clinical practice only after patient safety parameters are established.

Source: Reproduced with kind permission from Springer Science and Business Media: Reinhart et al. [7]

Box 32.3. Definition and Calculation of the Strong Ion Difference

The strong ion difference is the difference between the sums of concentrations of the strong cations and strong anions dissolved in plasma. In normal plasma with preserved serum protein content, the SID is approximately 40 mEq/L.

Strong ion difference (SID): $[Na^+] + [K^+] + [Ca^+] + [Mg^+] - [Cl^-] - [\text{other strong anions}]$

Solution	$[Cl^-]$ (mEq/L)	SID (mEq/L)
Plasma	95–105	40
0.9 % Saline	154	0
Plasma-Lyte	98	50

Chloride is the predominant strong anion capable of modifying serum pH. Increases in serum chloride concentration (0.9 % saline administration) will reduce SID and contribute to metabolic acidosis with normal anion gap.

Accumulation of organic acids (i.e., lactate, keto acids) will increase other strong anions and induce metabolic acidosis by lowering SID with a normal serum chloride concentration and elevated anion gap.

and hypocalcemia. The current Surviving Sepsis Guidelines do not recommend use of bicarbonate for serum pH >7.15 in patients with lactic acidosis associated with severe sepsis. When bicarbonate is administered, consideration should be given for a slow infusion, allowance for adequate CO_2 removal, and correction of hypocalcemia along with reversal of the underlying contributing factor for the acidosis.

32.2.3 Nutritional Support

Malnutrition is an important contributor to increased morbidity and mortality in critical illness. Critically ill patients, in particular those with premorbid comorbid disease such as CKD and those with acute organ dysfunction such as AKI, can often present nutritionally at risk or overtly malnourished at the time of admission. Critical illness is a physiologic state characterized by widespread system inflammation, metabolic derangement, and catabolism. In these circumstances, critically ill patients, in particular those already malnourished, may be unable to adequately absorb or utilize nutrients. This may be further compounded by added clearance of nutrients during RRT.

The goal in critical illness is to provide sufficient nutritional support as to maintain homeostatic and metabolic needs without precipitating complications. Importantly, determination of the optimal caloric intake for critically ill patients ideally should involve the interdisciplinary contributions of a dietician. Dieticians can assist with ensuring optimal nutritional prescription for critically ill patients with AKI or CKD/ESKD as their course and therapies evolve (i.e., resolving organ dysfunction, recovering kidney function, transition from continuous to intermittent RRT). Early nutritional support in critical illness will not be significantly modified by the presence of CKD; however, in patients with advanced CKD or ESRD not supported with RRT, specialized enteric formulas are available that are more caloric dense (2 kcal/mL), low in electrolytes (i.e., K^+, PO_4^-, Mg^+), and fluid restricted. The intent of these specialized formulations is to provide adequate nutritional support while mitigating the development of metabolic complications or unnecessary fluid accumulation in patients with reduced GFR. In patients with AKI, one of the few interventions proven to improve renal recovery is delivery of adequate nutritional support, and therefore, more recent guidelines discourage protein restriction in critically ill patients with AKI and supplement protein further in patients receiving RRT [8].

The preferred method for delivery of nutritional support is by the enteric route. This should be started early after ICU admission (within 24–48 h). The rationale for prioritizing enteric delivery of nutrition (EN) is based on the premise that it will preserve gut mucosal integrity, reduce bacterial and endotoxin translocation, and reduce the risk of gastrointestinal bleeding. However, critical illness, coupled with baseline susceptibilities (i.e., diabetes mellitus), may be associated with enteric feeding intolerance from gut dysmotility (i.e., medications, electrolyte disorders, comorbid disease) and suboptimal absorption (i.e., gut wall edema). Two recent trials in critically ill patients have shown no incremental outcome benefit for a strategy of "trophic" feeds (i.e., 10–25 mL/h) during the first few days of critical illness. Likewise, high-quality evidence to support a strategy of intentional "permissive hypofeeding" (target 60–70 % total caloric intake) is currently lacking and cannot be recommended. Measures to improve the success of enteric nutritional support include use of prokinetic agents (i.e., dose-adjusted metoclopramide, domperidone), advancement of small bowel feeding tubes, elevation of the head of the bed (~30–45°), and not using specified gastric residual thresholds that often result in suboptimal delivery of targeted feeds.

If there remains intolerance to EN and failure to meet nutritional targets with EN, or there are other medical or surgical reasons to avoid EN, current evidence would suggest starting total parenteral nutrition (TPN) after a period of several days.

The optimal amount of protein supplementation in AKI is unknown. Current practice guideline recommendations are to avoid protein

restriction in critically ill patients if the intent is to prevent worsening azotemia with the goal of preventing or delaying the initiation of RRT. Indeed, patients with AKI are often catabolic and require protein supplementation, in particular to account for the added clearance of amino acids while receiving RRT.

There is insufficient data to suggest the use of routine micronutrient supplementation [6]. In fact, there is an increased risk of mortality associated with the use of glutamine in patients with multiorgan failure.

The acute stress of critical illness coupled with nutritional support can often precipitate stress-induced hyperglycemia. The avoidance of significant hyperglycemia, hypoglycemia, and variation in glycemic control is associated with improved outcomes. However, recent trials have suggested that tight glycemic control (TGC) with intensive insulin therapy (IIT) (BG 4.4–6.0 mmol/L) may be associated with increased risk for hypoglycemia and worse outcome. Accordingly, current practice guidelines recommend a more pragmatic and less intensive strategy targeting glycemic control between 6.1 and 10.0 mmol/L (110–180 mg/dL) (Box 32.4).

32.2.4 Sepsis

Sepsis is an important precipitant of critical illness and commonly prompts acute hospitalization and admission to ICU. Data from the USRDS suggest infection is the leading cause of death among patients with ESRD. CKD patients may be more susceptible to development of infectious complications and sepsis for a number of reasons including:

- Presence and repeated access to indwelling central venous catheters (CVC) and arteriovenous fistulas (AVP) for dialysis access
- Acquired immunodeficiency related to primary etiology of kidney disease
- Immune dysregulation related to retention of uremic toxins (i.e., defective host responses in phagocytic cells, lymphocytes, and antigen processing, dysbiosis of gut microflora)
- Repeated episodes of systemic inflammation related to altered gut permeability and bacterial/endotoxin translocation during dialysis

This risk is further modified by additional factors such as comorbid disease (i.e., peripheral vascular disease and diabetes mellitus, smoking) and frequent interaction with health-care services (i.e., colonization with antimicrobial-resistant

Box 32.4. What the Guidelines Say You Should Do: Nutritional Support in Critically Ill Patients

- Initiate nutritional support via the enteral over parenteral route.
- Initiate early enteral nutrition (EN) (within 24–48 h).
- If there is intolerance, or inability to meet caloric needs or contraindications with EN, parenteral nutrition (PN) should be started after 5–7 days.
- In critically ill patients, initial caloric and protein targets should be 20–30 kcal/kg/day and 0.6–1.7 g/kg/day adapted to catabolism levels and individual needs.
- Protein restriction is not recommended during the early catabolic phases of critical illness for patients with AKI, CKD, or ESRD. Additional protein supplementation is needed for patients receiving RRT.
- Glycemic control with insulin is recommended for target blood glucose between 6.1 and 10.0 mmol/L (110–180 mg/dL). Hyperglycemia, hypoglycemia, and wide variations in blood glucose should be avoided.
- Do not use glutamine supplementation in patients with severe sepsis or multiorgan dysfunction.
- Indications for PN in AKI/CKD are similar to non-AKI/non-CKD patients.
- Interdisciplinary consultation with critical care dietician is recommended.

Source: Reprinted from Cano et al. [8]. Copyright 2009, with permission from Elsevier

organisms [MRSA, VRE] and frequent exposure to antimicrobials).

The utilization of indwelling access catheters is a significant source of bloodstream infection and sepsis in CKD/ESRD patients, is directly related to the duration of usage, is most commonly caused by gram-positive organism (coagulase-negative staphylococcus, *Staphylococcus aureus*), and is associated with considerably higher risk of morbidity and mortality. The risk is two- to threefold higher for non-tunneled (most commonly inserted in the ICU) compared with tunneled catheters. For ESRD patients receiving dialysis via tunneled catheters, the risk of bloodstream infection, infection-related hospitalization, and infection-related death is further two- to threefold higher than for those receiving hemodialysis via arteriovenous fistulas or grafts. Important morbidity from temporary catheters arises from the risk of development of metastatic foci of infection from highly virulent bacteria, such as *Staphylococcus aureus*, and includes endocarditis, septic arthritis, osteoarthritis, and epidural abscess.

The most common sources of non-dialysis-related infections among CKD/ESRD patients are:

- Upper and lower respiratory tract infections (i.e., community and/or hospital-acquired)
- Genitourinary infections (i.e., pyocystis, pyelonephritis, perinephric infection)
- Cellulitis/osteomyelitis
- Gastrointestinal infections (i.e., *Clostridium difficile*, cholangitis, hepatitis, gastroenteritis, diverticulitis, cholangitis)
- Central nervous systems infections (i.e., mucormycosis)
- Other infections: HIV and tuberculosis

Pneumonia is a common contributor to morbidity and mortality in CKD/ESRD patients. The risk of developing pneumonia is 3–5 times higher among CKD/ESRD patients compared with matched population with normal kidney function and is associated with a higher likelihood of ICU admission and 4–6 times the total duration of hospitalization.

The prevalence of asymptomatic pyuria among CKD/ESKD patients with residual urine production is common (30–40 %) but of undetermined significance, and the diagnosis of genitourinary infection mandates the presence of a positive culture result. Indeed, genitourinary infections may be the most common source of nosocomial infection occurring in hospitalized CKD/ESRD patients due primarily to urinary catheterization. These sources of infection may predispose to bloodstream infection in susceptible CKD/ESRD patients and necessitate ICU referral for resuscitation and hemodynamic support. In anuric ESRD patients, urinary catheterization except for diagnostic indications should be avoided.

Cellulitis is a common precipitant of infection in CKD/ESRD patients often predisposed by poor peripheral circulation (i.e., diabetes mellitus, peripheral vascular disease) coupled with extravascular peripheral edema or infection introduced through repeated puncture of the native vascular access. By extension, suboptimally treated cellulitis may result in osteomyelitis of adjacent bony structures. Severe cellulitis may present with bloodstream infection in susceptible CKD/ESRD patients and prompt ICU admission.

The incidence of common gastrointestinal infections in CKD/ESRD patients is similar to the general population; however, their physiologic reserve to withstand these infections may be severely blunted and further predispose to added morbidity. The exceptions include susceptibility to infectious hepatitis (hepatitis B and C virus), peritonitis among patients receiving peritoneal dialysis, and *Clostridium difficile* colitis due to frequent antimicrobial exposure and interaction with health services.

Sepsis is defined as the presence of infection together with systemic manifestations of inflammation. Severe sepsis is defined as sepsis plus sepsis-induced organ dysfunction or tissue hypoperfusion, and septic shock is defined as severe sepsis plus hypotension not reversed with fluid resuscitation [9]. The diagnostic criteria for sepsis and sepsis-related organ dysfunction are shown in Box 32.5. It is important to recognize that many of these criteria may be modified due to CKD/ESRD and its treatment alone (i.e., dialysis-induced endotoxemia or hypotension) or due to concomitant comorbid disease

(i.e., reduced cardiac reserve due to cardiorenal syndrome, autonomic dysfunction due to diabetes mellitus), drug therapy (i.e., β-blockers, Coumadin), or not being applicable (i.e., serum creatinine elevation or oliguria in anuric ESKD).

The general principles and initial management of sepsis in CKD/ESRD patients are similar to the acute resuscitation of patients with suspected sepsis and AKI without kidney disease (Boxes 32.6 and 32.7). Early "bundled" resuscitation coupled with prompt broad-spectrum antimicrobial therapy and source control should be established in accordance with clinical practice guidelines [9]. If there is suspicion that the source of sepsis is a vascular access catheter, this should be promptly removed once further central venous access has been confirmed.

32.2.5 Acute Kidney Injury

Acute kidney injury (AKI) is a common complication encountered in hospitalized patients, particularly in the setting of critical illness, occurring in up to two-thirds of patients [13].

Recently, the KDIGO Clinical Practice Guidelines for Acute Kidney Injury published updated consensus criteria for the diagnosis and staging of AKI [11] (Table 32.5). These criteria do not currently integrate evolving novel diagnostic biomarkers specific for kidney damage (i.e., NGAL, KIM-1, IL-18, L-FABP). Yet, these novel biomarkers show significant promise to improve the capacity for early diagnosis, prognostication, and informed decision-making in AKI by helping to better discriminate etiology of loss of kidney function (i.e., AKI vs. CKD), risk of worsening AKI and need for RRT, and long-term risk of CKD.

Development of AKI portends a worse clinical prognosis in critically ill patients and predicts such adverse outcomes as need for renal replacement therapy (RRT), prolonged ICU and hospital stay, and increased mortality risk [14]. Importantly, for the CKD patients developing acute-on-chronic AKI, the risk of worsened CKD and accelerated decline in function toward ESRD is increased several fold. More severe forms of AKI are also associated with gradient increases in the risk of death and/or non-recovery of kidney function and dialysis dependence [15].

Box 32.5. Diagnostic Criteria for Sepsis Syndrome and Sepsis-Related Organ Dysfunction

Infection (confirmed or suspected) plus some of the following criteria:
General variables
Fever (>38.3 °C) or hypothermia (<36.0 °C)
Heart rate >90/min or more than 2 standard deviations above normal for age
Tachypnea
Altered mental status
Significant edema or positive fluid balance (>20 mL/kg over 24 h)
Hyperglycemia (blood glucose >7.7 mmol/L) in the absence of DM
Inflammatory variables
Leukocytosis (WBC >12,000/μL) or leukopenia (WBC <4,000/μL) or >10 % immature forms
Plasma C-reactive protein more than 2 standard deviations above the normal value
Plasma procalcitonin more than 2 standard deviations above the normal value
Hemodynamic variables
Arterial hypotension (SBP <90 mm Hg, MAP <70 mm Hg, or SBP decrease >40 mm Hg or less than 2 standard deviations below normal for age)
Organ dysfunction variables
Arterial hypoxemia ($PaO_2/FiO_2 < 300$)
Acute oliguria (urine output <0.5 mL/kg for 2 h despite fluid resuscitation)
Creatinine increase (>44.2 μmol/L)
Coagulation abnormalities (INR >1.5, aPTT >60s)
Ileus (absent bowel sounds)
Thrombocytopenia (platelet count <100,000/μL)
Hyperbilirubinemia (plasma bilirubin [total] >70 μmol/L)
Tissue perfusion variables
Hyperlactatemia (>1 mmol/L)
Decrease capillary refill or mottling

Source: Reproduced with kind permission from Springer Science and Business Media: Dellinger et al. [9]

Box 32.6. What the Guidelines Say You Should Do? Surviving Sepsis Campaign Guideline: Sepsis "Bundles"

To be completed within 3 h

- Measure serum lactate.
- Obtain blood cultures prior to administration of antimicrobials.
- Administer broad-spectrum antimicrobials.
- Administer 30 mL/kg crystalloid for hypotension or lactate ≥4 mmol/L.

To be completed within 6 h

- Administer vasopressors (for hypotension not responsive to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥65 mmHg.
- Measure central venous pressure (CVP) and central venous oxygenation ($ScVO_2$) and resuscitate to target CVP ≥8 cmH_2O and $ScVO_2$ ≥70 %.
- Remeasure serum lactate if initial value was elevated and resuscitate to target normalization.

Antimicrobial therapy and source control

- Aim to administer broad-spectrum "effective" intravenous antimicrobial therapy within the first 1 h of recognition of sepsis. Each 1 h delay in administration of appropriate antimicrobials during the first 6 h is associated with an 8 % decrease in survival.
- Initial short-term (3–5 days) administration of empiric combination antimicrobial therapy should be undertaken for severe sepsis/septic shock or difficult-to-treat sources of infection or suspicion of multidrug-resistant organisms.
- Evaluation for a specific anatomical diagnosis of infection should be undertaken for consideration for emergent (within 6–12 h) source control measures (i.e., surgical for septic arthritis, catheter removal for bloodstream infection, chest thoracostomy tube insertion for empyema). Delay to source control when present is also associated with significant decrease in survival.

Source: Reproduced with kind permission from Springer Science and Business Media: Dellinger et al. [9]

Box 32.7. Relevant Clinical Practice Guidelines

1. *Chronic kidney disease:* Kidney Disease: Improving Global Outcomes (KDIGO) Chronic Kidney Disease Working Group. KDIGO 2012 Clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013;3(1):1–163 [10]. Available at: http://kdigo.org/home/guidelines/ckd-evaluation-management/
2. *Acute kidney injury:* Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO 2012 Clinical practice guideline for acute kidney injury. Kidney Int Suppl. 2012;2:1–141 [11]. Available at: www.kdigo.org/clinical_practice_guidelines/index.php
3. *Sepsis:* Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med. 2013;41(2):580–637 [9]. Available at: www.survivingsepsis.org/Pages/default.aspx
4. *Fluid therapy:* Reinhart K, Perner A, Sprung CL, Jaeschke R, Schortgen F, Johan Groeneveld AB, Beale R, Hartog CS; European Society of Intensive Care Medicine. Consensus statement of the ESICM task force on colloid volume therapy in critically ill patients. Intensive Care Med. 2012;38(3):368–83 [7].
5. *Nutritional support:* Critical Care Nutrition – Canadian Clinical Practice Guidelines [12]. Available at: www.criticalcarenutrition.com/index.php

AKI is a syndrome with a spectrum of contributing factors. The risk factors for development of AKI are often multidimensional and are related to synergy between premorbid susceptibility (i.e., older age, CKD, diabetes mellitus, hypertension, liver disease) and factors contributing to critical illness (i.e., sepsis, shock states, diagnostic procedures involving contrast media, major surgery) [13, 14]. The diagnostic evaluation of AKI should

Table 32.5 KDIGO diagnostic criteria and severity staging for AKI

AKI is defined as any of the following:		
Increase in serum creatinine ≥26.5 μmol/L (≥0.3 mg/dL) within 48 h		
Increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days		
Urine volume <0.5 mL/kg/h for 6 h		
AKI staging	**Serum creatinine**	**Urine output**
Stage I	Increase of 1.5–1.9 times baseline or ≥26.5 μmol/L (≥0.3 mg/dL)	<0.5 mL/kg/h × 6–12 h
Stage II	Increase of 2.0–2.9 times baseline	<0.5 mL/kg/h × ≥12 h
Stage III	Increase of ≥3.0 times baseline or ≥ 353.6 μmol/L (≥4.0 mg/dL) or start of RRT	<0.3 mL/kg/h × ≥24 h or anuria ≥12 h

Source: Reprinted by permission from Macmillan Publishers Ltd: Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group [11], copyright 2012. Available at: http://www.nature.com/kisup/index.html

integrate routine biochemistry, urinalysis and imaging where indicated to rule out immediately reversible etiologies (i.e., post-obstructive) or those requiring specialized interventions (i.e., vasculitis).

An understanding of the pathophysiology of AKI is important to provide appropriate management for these patients. Our current understanding of the pathophysiologic mechanisms contributing to AKI remains incomplete; however, contrary to the conventional view, recent data argue against ischemia–reperfusion as the predominant pathophysiologic mechanism contributing to AKI. The causal role of alternations in renal blood flow, microcirculation, and endothelial function, immune cell infiltration and activation, immune-mediated toxic injury and apoptosis, and inflammatory mediator-induced organ cross talk is only beginning to be better understood.

The general strategies for prevention and management of AKI are similar for those with and without CKD [16] (Table 32.6). Specific interventions for prevention and treatment of established AKI are few and most have focused on preventing development of contrast-induced AKI in susceptible patients such as those with CKD. Several specific examples of mitigating risk of developing AKI or its complications are outlined in Table 32.7 [11, 16].

32.2.6 Renal Replacement Therapy

Renal replacement therapy (RRT) is a vital, life-sustaining, and organ support technology applied in approximately 4–8 % of all critically ill patients and in approximately 70 % of those with more severe forms of AKI [14].

However, RRT also increases the complexity and health resource use for critically ill patients, and recent data have suggested its utilization may be associated with higher risk of death and dialysis dependence among survivors. These data highlight the existing uncertainty regarding many aspects of the decision to initiate and process of delivery of RRT to critically ill patients.

Current guidelines recommend the utilization of an uncuffed, non-tunneled dialysis catheter for acute RRT in the ICU. The position of these acute catheters should avoid insertion in the subclavian vessels to mitigate the risk of long-term complications such as stenosis/thrombosis. Existing tunneled dialysis catheters may be used if already in situ; however, use of fistulas or grafts in acute critical care settings, in particular for CRRT, should be avoided.

The optimal time to start RRT in critically ill patients with AKI and/or CKD is currently unknown. There is general consensus that RRT should be urgently initiated in the presence of life-threatening complications related to AKI such as severe electrolyte abnormalities (i.e., hyperkalemia), acid–base disturbances (i.e., acidemia), and fluid balance (i.e., pulmonary edema); however, outside of these indications, the optimal time to start is uncertain [11] (Table 32.8). It is likely more important to

Table 32.6 Summary of strategies for initial resuscitation of critically ill patients with CKD/ESRD and for the prevention and management of AKI

Intervention	Comment
Restore/optimize arterial filling[a]	Responsiveness to a fluid challenge should be assessed using functional hemodynamic monitoring. Isotonic or balance crystalloid solutions should be used for acute resuscitation. Synthetic colloids (i.e., hydroxyethyl starch) and hyperoncotic solutions should be avoided for fluid resuscitation in those at risk for AKI
Restore/optimize cardiac output[a]	The addition of inotropic therapy should be considered for patients with absolute or relative low cardiac output states
Restore/optimize mean arterial pressure[a]	The addition of vasopressor therapy, in conjunction with fluid therapy, should be considered in patients with refractory hypotension
Restore/optimize oxygen-carrying capacity	The consideration for blood transfusion should be given for ICU patients with AKI or CKD patients with severe anemia and evidence of tissue hypoperfusion and hypoxia. No evidence to support increasing the dose of erythropoietin-stimulating agents during acute illness and possible risk of harm (increased risk of thrombosis)
Remove/avoid all nonessential nephrotoxins or perform appropriate therapeutic monitoring/dose adjustment when necessary	Avoid aminoglycosides unless there is no suitable alternative; utilize azole or echinocandin antifungals or lipid formulations of amphotericin if there is no suitable alterative to treat systemic fungal infection
Consider context-specific interventions based on current clinical practice guidelines	For contrast media exposure, hepatorenal syndrome, rhabdomyolysis, sepsis, vasculitis
Monitor for/avoid excess fluid accumulation	AKI and CKD are associated with greater risk for fluid accumulation. Monitor daily fluid intake/output and daily/cumulative fluid balance, recognizing there is some "ebb and flow" to fluid balance in critical illness
Monitor for/avoid complications of overt kidney failure	Monitor AKI and CKD patients for serious complications such as hyperkalemia, acidemia, fluid overload, and drug toxicities and appropriately plan for RRT
Maintain glycemic control	Glycemic control has been associated with reduced incidence of AKI and lower utilization of RRT. The balance of evidence now recommends maintaining glycemic control with a target blood glucose (BG) of 6.1–10.0 mmol/L (110–180 mg/dL) rather than using intensive insulin therapy (IIT) to maintain tight glycemic control, with BG of 4.4–6.0 mmol/L (80–110 mg/dL), due to the increased risk of hypoglycemia

[a]There should be early use of invasive/functional hemodynamic monitoring (i.e., arterial catheter, central venous pressure, echocardiography, pulmonary artery catheter, or methods to measure stroke volume or pulse pressure variation)

evaluate the broad clinical context of critically ill patients' admission diagnosis, illness severity, non-kidney organ dysfunction, the probability of worsening AKI or non-recovery, and additional conditions that may be modified by RRT (i.e., fluid accumulation) rather than reliance on absolute thresholds in conventional biochemical markers such as creatinine or urea. Early initiation of RRT in patients with AKI or advanced CKD has the intuitive appeal of avoiding life-threatening AKI complications while ensuring the adequate delivery of essential medications (i.e., antimicrobials) and nutrition and transfusion support without concern for excessive fluid accumulation. Recent systematic reviews have supported this concept, suggesting earlier RRT initiation may improve survival; however, studies included in these analyses were highly susceptible to bias [17, 18].

The choice of ideal RRT modality for critically ill patients has long been debated. Systematic reviews have not shown a clear survival advantage

Table 32.7 Selected examples of acute physiology and interventions with the potential for negative effects on kidney function

Intervention	Example	Action
Altered systemic hemodynamics		
Reduced arterial filling	Diuretics	Discontinue
Negative inotropic therapy	β-Blockers	Discontinue
Antihypertensive therapy	CCB	Discontinue
Altered renal hemodynamics		
Afferent arteriolar vasoconstrictors	NSAIDs	Discontinue
Efferent arteriolar vasodilators	ACEi/ARB[a]	Discontinue
Altered renal venous pressure		
Elevated intra-abdominal pressure	Excess fluid accumulation	Avoid
Nephrotoxins		
Antibiotics	Aminoglycosides, vancomycin, colistin, sulfamethoxazole, foscarnet	Discontinue, monitor, or dose-adjust
Antifungals	Amphotericin	Discontinue, monitor, or dose-adjust
Antivirals	Acyclovir, HAART	Discontinue, monitor, or dose-adjust
Immunosuppression	Tacrolimus, cyclosporine	Discontinue, monitor, or dose-adjust
Fluid therapy	Dextrans, hydroxyethyl starch	Avoid
Diagnostic imaging	Radiocontrast media	Avoid
Cytotoxic chemotherapy	Cisplatin, methotrexate	Discontinue, monitor, or dose-adjust

Abbreviations: *CCB* calcium channel blockers, *NSAIDs* nonsteroidal anti-inflammatory drugs, *ACE* angiotensin converting enzyme, *ARB* angiotensin receptor blocker, *HAART* highly active antiretroviral therapy, *IAP* intra-abdominal pressure

[a]ACEi and ARB lead to reduction in glomerular blood flow, which has beneficial effects for kidney survival in chronic kidney disease patients but may lead to worsening kidney function in patients with AKI

for one modality, continuous RRT (CRRT), slow low-efficiency dialysis (SLED), or intermittent RRT (IRRT), over another in critically ill patients with AKI [19] (Table 32.9). Ideally, the modality chosen should suit the patient's acute physiology and therapeutic objectives while avoiding treatment-related complications. CRRT is the preferred modality in hemodynamically unstable patients and those with acute brain injury or fulminant hepatic failure and at risk for intracranial hypertension and cerebral edema [11]. CRRT has also been shown superior for maintaining fluid homeostasis and mitigating fluid overload. A recent systematic review suggested that initial therapy with CRRT in critically ill patients is associated with lower rates of dialysis dependence among survivors when compared with IRRT [20]. These data may imply CRRT may be the preferred initial modality for surviving critically ill patients at increased risk for incident or worsening CKD (i.e., those with baseline CKD).

The optimal mode of CRRT to improve outcome remains uncertain. The purported advantages to hemofiltration (CVVH) compared with hemodialysis (CVVHD) are the improved convective clearance of middle molecular weight solutes such as inflammatory and toxic mediators. Recent data have suggested equivalent outcomes in terms of survival and recovery of kidney function; however, CVVH may be associated with short filter lifespan compared with CVVHD [21].

The optimal time to transition from CRRT to either SLED or IRRT is currently unknown; however, it pragmatically will coincide with physiologic stabilization and following weaning from vasoactive support.

The utilization of peritoneal dialysis in critical illness may be impractical and result in insufficient solute clearance in catabolic patients and inadequate fluid removal. These factors may have contributed to the observation of higher mortality for critically ill patients treated with

Table 32.8 Indications for starting RRT in ICU

Indication	Comment
Renal replacement therapy	
Life-threatening indications	These indications have not been evaluated in trials
Hyperkalemia	Evidence of refractory elevated potassium and rapidly rising or cardiac toxicity. RRT is effective for temporarily reducing serum potassium
Acidemia	Evidence of refractory academia and inability to adequately compensate (pH <7.15). RRT can rapidly mitigate metabolic acidosis; however, correction requires targeted treatment of the precipitating disease
Pulmonary edema	Evidence of fluid overload contributing to worsening hypoxemia, contributing to need for ventilatory support or prevention of weaning from ventilatory support. RRT can effectively reduce extravascular lung water in diuretic-resistant states
Uremic complications	Pericarditis, bleeding, encephalopathy. In modern ICU practice, withholding RRT until uremic complications arise would be uncommon
Nonemergent indications	
Azotemic control	Conventional criteria evaluate blood accumulation of urea and creatinine; however, numerous additional metabolites/uremic toxins can also accumulate. Blood concentrations of these metabolites may be confounded by added factors such as nutritional status, catabolism, and volume status
Fluid overload/accumulation	Fluid overload/accumulation that is refractory to diuretics or when there are diuretic-induced electrolyte abnormalities can both be an important determinants for starting RRT
Acid–base/electrolyte abnormalities	Additional factors such as metabolic acidosis and marked electrolyte abnormalities (sodium, magnesium) can be potentially treated with RRT; however, no standardized criteria exist
Renal support	These indications in critical illness may occur separately from patients with either life-threatening complications of AKI or advanced AKI and rather can be viewed as a platform for organ support to prevent complications and facilitate treatment
Volume homeostasis	Fluid accumulation is worse in AKI and is associated with worse outcome. RRT may represent part of a strategy to mitigate excessive fluid accumulation
Nutritional support	RRT can better enable the delivery of full nutritional support (i.e., enteral or parenteral) without the concern for excessive fluid accumulation
Acid–base/electrolyte homeostasis	RRT may represent part of a strategy to enable "permissive hypercapnia" in ICU patients with severe ARDS and AKI/CKD or mitigate adverse effects from anticipated electrolyte disorders (i.e., tumor lysis syndrome)
Immunomodulation	RRT may represent a strategy for modulating and restoring immune function in sepsis and associated severe inflammatory states. Studies are ongoing
Drug delivery	RRT can better enable the delivery of essential drugs (i.e., antimicrobials) without the concern for excessive fluid accumulation

Abbreviations: *ARDS* acute respiratory distress syndrome, *ICU* intensive care unit, *RRT* renal replacement therapy

peritoneal dialysis compared with those treated with hemodialysis.

Determination of the optimal dose intensity for small solute clearance for critically ill patients with AKI has long been a clinical priority. Early randomized trials clearly favored a more intensive strategy; however, recent high-quality data have not shown a benefit with this approach. Two multicenter randomized trials, the Department of Veterans Affairs/National Institutes of Health (VA/NIH) Acute Renal Failure Trial Network (ATN) Study and the Randomized Evaluation of Normal versus Augmented Level (RENAL) Replacement Therapy Study, found no incremental benefit in critically ill patients with AKI from a more intensive (high-dose) RRT compared with a less intensive RRT strategy [22, 23]. The more intensive strategy did not decrease mortality, accelerate recovery of kidney function, or alter the rate of nonrenal organ failure. Importantly, these findings do not imply that the dose of RRT is not important, but rather, the evidence would

Table 32.9 Description of the characteristics and comparisons of RRT modalities used to treat critically ill patients

Characteristics	CRRT	SLED/EDD	IRRT
Duration (h)	20–24 h/day	8–12 h/day	3–6 h/day
Blood flow rate	100–250 mL/h	200–300 mL/h	400–500 mL/h
Dose intensity	20–25 mL/kg/h	Kt/V 1.2–1.4	Kt/V 1.2–1.4
Comparison			
Risk of hemodynamic instability	↓↓	↑/↓	↑↑
Azotemic control	↑↑	↑/↓	↓↓
Electrolyte homeostasis	↑↑	↑/↓	↓↓
Volume control	↑↑	↑/↓	↓↓
Risk of bleeding	↑↑	↑/↓	↓↓
Patient mobilization	↓↓	↑	↑↑
Immunomodulation	↑↑	↓	↓↓
Cost (per day)	↑↑	↑/↓	↓↓
Special circumstances[a]	Most suitable	Not recommended	Not recommended

Abbreviations: *CRRT* continuous renal replacement therapy, *SLED/EDD* slow low-efficiency dialysis/extended daily dialysis

[a]Shock states, severe hyponatremia, elevated intracranial pressure (i.e., traumatic brain injury, fulminant hepatic failure)

suggest there is no need to exceed a CRRT dose of 20–25 mL/kg/h effluent flow rate or IHD three times per week with delivered Kt/V_{urea} 1.2–1.4 per treatment for small solute clearance.

In general, RRT should be discontinued when it is no longer indicated due to either sufficient residual or recovering kidney function or a change in the overall goals of care of the patient. The best predictor for successful weaning from RRT for critically ill patients is the volume of spontaneous urine production in 24 h. Those capable of producing ≥450–500 mL urine per day have a higher likelihood of short-term recovery and dialysis independence. There is no evidence to suggest improved or accelerated recovery and dialysis independence with early forced diuresis with furosemide.

32.2.7 Pharmacotherapy

Drug pharmacokinetics in critical illness and AKI is significantly modified due to alterations in drug bioavailability, reduced protein binding, increased volume of distribution, altered biotransformation, and reduced intrinsic clearance and elimination. Appropriate drug dosing is further complicated by a number of factors, including baseline comorbid disease of patients (i.e., CKD), need for multiple drugs that potentially interact with vital functions, lower thresholds for toxicity, evolving illness severity and organ dysfunction (i.e., changes in GFR), and superimposed extracorporeal drug removal (Table 32.10).

In general, there are several pragmatic steps to help guide drug dosing in critically ill patients with AKI and those receiving RRT [24]. First, the literature should be reviewed for existing data on drug dose guidance for a specific drug [25]. Second, for drugs with primary renal elimination, a bedside estimate of baseline GFR and a dynamic assessment of total creatinine clearance, if applicable, should be undertaken, assuming there is no significant secretion or reabsorption. In particular, consideration should be given to patients receiving RRT who have recovering or residual renal function. Third, particularly for drugs with a narrow therapeutic index and risk of toxicity, therapeutic drug monitoring when possible should be undertaken (i.e., phenytoin, vancomycin, aminoglycosides). Fourth, several drug classes may be administered based on their observed clinical response, such as with sedatives, analgesics, or vasoactive medications. However, selected drugs have potentially toxic

Table 32.10 Summary of factors affecting drug elimination in critically ill patients receiving RRT

Factor	Comment
Drug characteristics	Molecular weight, charge, and nonrenal elimination can impact clearance
Drug availability	
Vd	Increased in critical illness and AKI, generally requires larger loading dose, and reduces drug availability for EC clearance
PB	Only unbound fraction available, reduced in critical illness and AKI, reduces drug availability for EC clearance
[plasma]	Only drug within intravascular compartment available for EC clearance
Extracorporeal therapy	
Dose intensity	Higher dose intensity, such as prescription of HVHF, will increase EC clearance; clearance impacted if large discrepancy between prescribed and delivered dose
BFR	Higher blood flow rate will deliver more drug to filter, only important at either very low or high blood flow or large discrepancy between prescribed and delivered dose
Mode (convention vs. dialysis)	EC clearance dependent on total effluent flow rate and/or dialysate flow rate
Replacement fluid	Prefilter replacement fluid administration will result in hemodilution and lower EC clearance
Filter membrane	Sieving/diffusion coefficient important, whereas surface area has limited impact on EC clearance
Organ recovery	Residual or recovery kidney function can greatly increase overall clearance during extracorporeal therapy

metabolites that can accumulate in patients with reduced kidney function. As examples, the elimination of α1-hydroxymidazolam (main metabolite of midazolam) and glucuronide metabolites of morphine are principally eliminated by the kidneys and thus may accumulate in AKI/CKD. Finally, given the complexity, there is a recognized need for a dedicated ICU pharmacist among the interdisciplinary ICU team, particularly for patients with CKD or AKI.

Conclusions

The prevalence of CKD and ESRD is increasing. These patients are burdened by high comorbid disease, are more likely to interact with critical care services, and have worse short-term and long-term outcomes compared with non-CKD patients. Short-term mortality is predominantly driven by acuity of illness rather than CKD status per se, and CKD status should likely not preclude critical care support. The pathophysiologic changes associated with CKD/ESKD and development of superimposed AKI can present unique challenges for clinicians in the ICU management of these patients.

Before You Finish: Practice Pearls for the Clinician

- CKD and specially ESRD status alone should not exclude consideration for admission in the ICU.
- Prognostic score results should be carefully considered since they routinely overestimate mortality in ESRD patients.
- The principles of management of sepsis should be applied to CKD, fluid overload being an obvious caveat.
- Fluid therapy should be considered a drug therapy and dosed accordingly.
- Long-term kidney function monitoring is mandatory after an AKI episode.
- Consider initiation of RRT ahead of absolute indications. CRRT is the preferred option for the hemodynamically unstable patient.
- Avoid nephrotoxic drugs for patients with CKD and/or at risk for AKI.
- Adjust drug regimens to kidney function, except for the loading dose of antibiotics.

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