Overview of the Medical Management of the Critically Ill Patient

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Abstract
The medical management of the critically ill patient focuses predominantly on treatment of the underlying condition (e.g., sepsis or respiratory failure). However, in the past decade, the importance of initiating early prophylactic treatment for complications arising from care in the intensive care unit setting has become increasingly apparent. As survival from critical illness has improved, there is an increased prevalence of post-intensive care syndrome—defined as a decline in physical, cognitive, or psychologic function among survivors of critical illness. The Intensive Care Unit Liberation Bundle, a major initiative of the Society of Critical Care Medicine, is centered on facilitating the return to normal function as early as possible, with the intent of minimizing iatrogenic harm during necessary critical care. These concepts are universally applicable to patients seen by nephrologists in the intensive care unit and may have particular relevance for patients with kidney failure either on dialysis or after kidney transplant. In this article, we will briefly summarize some known organ-based consequences associated with critical illness, review the components of the ABCDEF bundle (the conceptual framework for Intensive Care Unit Liberation), highlight the role nephrologists can play in implementing and complying with the ABCDEF bundle, and briefly discuss areas for additional research.

Introduction
In general, the management of critically ill patients has predominantly focused on treatment of the underlying condition. Common conditions leading to intensive care unit (ICU) admission include respiratory failure, acute myocardial infarction, cerebral infarction/intracranial hemorrhage, and sepsis (1). However, across a wide variety of conditions, common interventions are applied, including sedation, mechanical ventilation, and artificial nutrition. Until recently, consolidated evidence regarding sedation choice, mobility, and length of mechanical ventilation was scant. Over time, clinical practice guidelines focused on the management of critically ill patients have grown in scope from sedative and analgesic choices to encompass additional aspects of supportive care, including prevention/management of delirium, nutrition, and mobility (2). In 2013, the Society of Critical Care Medicine (SCCM) developed the ICU Liberation initiative to support the implementation of the Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit (3). The ICU Liberation Collaborative was a nationwide project designed by SCCM to facilitate and study the implementation of a more comprehensive bundle of care, ABCDEF (Figure 1): assess, prevent, and manage pain; both spontaneous awakening trials (SATSs) and spontaneous breathing trials (SBTs); choice of analgesia and sedation; delirium: assess, prevent, and manage; early mobility and exercise; and family engagement/empowerment.

Although several earlier clinical trials had evaluated the efficacy of these individual interventions, Balas et al. (4) were the first to demonstrate that coordinated implementation of bundled interventions could simultaneously increase ventilator-free days and mobility in the ICU while decreasing delirium. A subsequent multicenter, cohort study of over 15,000 patients (5) demonstrated even more impressive results: completion of the bundle elements was associated with significant decreases in hospital death within 7 days, ICU readmission, and discharge to a nonhome facility. On any given day, those who had all bundle elements completed had lower odds of mechanical ventilation, coma, delirium, or physical restraint use on the next hospital day. Significant pain was more often identified by patients who received all ABCDEF bundle elements, which presumably allowed for more appropriate treatment. The most recent guideline update occurred in 2018 and also included recommendations to minimize immobility and sleep disruptions (6).

The ABCDEF bundle is unique from other ICU bundles in that it is applicable to all patients admitted to the ICU. Furthermore, because it does not address a single organ group, disease, or symptom but rather is focused on improving quality of life during and post-ICU, preventing complications, and facilitating engagement of patients and families, it requires all members of the health care team to work together to facilitate each of the elements. Nephrologists are critical members of the team in terms of facilitating implementation of ICU Liberation and the A-F bundle.
ICU Liberation

ICU Liberation is the overarching philosophy and practice directed at improving care by “liberating” ICU patients from pain, oversedation, delirium, mechanical ventilation, immobility and isolation, as well as from post-discharge sequelae that can be life-altering for many patients.

2018 Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU (PADIS Guidelines)

The PADIS Guidelines provide a roadmap for developing integrated, evidence-based, and patient-centered protocols which can be implemented through the ICU Liberation Bundle.

Organ-Based Complications

To understand the importance of the A-F bundle, it is critical to acknowledge that multiple organ systems can sustain collateral damage during efforts to treat a critically ill patient. What follows is a high-level review of representative organ-based complications that can ensue after critical illness to highlight the effect on longer-term outcomes. Other articles in this series focus on cardiovascular and pulmonary dysfunction in critically ill individuals, along with kidney-related complications of critical illness. We note that there is...
significant potential for crosstalk between the kidney and other organs during critical illness, with strong links established to the pulmonary, cardiovascular, and immune systems. Finally, patients with kidney failure are also prone to critical illness and its complications.

Neurologic
The neurologic system can be irreversibly damaged during critical illness and the recovery period. Cognitive impairment in postintensive care syndrome (PICS) is well recognized, with 40% of surviving patients having global cognition scores that are comparable with those of patients with moderate traumatic brain injury 3 months after hospital discharge (7). There is a strong correlation between delirium and cognitive decline; in a meta-analysis of 23 studies, patients who experienced delirium had worse cognitive function post-ICU (8). In patients with primary sepsis, these cognitive changes have been shown to last at least 8 years (9). Although there is not a comprehensive understanding of the origins of cognitive decline, in one study, 86% of patients who experienced delirium had pathologic evidence of hypoxia in the hippocampus, pons, or striatum (10). AKI is an independent risk factor for delirium and coma in critically ill patients (11). Patients with kidney failure may have cognitive changes due to uremia. Further, a number of medications that are commonly given in critically ill patients (e.g., antibiotics) are associated with delirium or neurotoxicity in patients with kidney failure (12).

Gastrointestinal
Many patients who receive treatment in the ICU receive insufficient caloric intake. Failure to provide adequate enteral feeds can disrupt naturally occurring gastrointestinal bacteria. Approximately 70% of patients admitted to the ICU receive antibiotics, although only 50% have documented sepsis (13). Antibiotics, although often lifesaving, can also obliterate native gastrointestinal flora. The long-term effect of changes in the intestinal microbiome on physical status and function are unknown. Similarly, AKI as well as kidney failure can affect the gut microbiome, which may have direct implications for gut function as well as for the immune system (14,15).

Musculoskeletal
Immobility in the ICU is a significant contributor to weakness and critical illness myopathy (16). Indeed, ICU-acquired weakness can result in multiple negative consequences, including prolonged mechanical ventilation, longer length of stay in the ICU, higher mortality, and greater functional disability in the long term (17). Less well-studied but probable sequelae of ICU-acquired weakness include psychologic effects and effects on the patient’s family and social support network. When catabolism occurs and there is decreased muscle mass, estimating the degree of kidney dysfunction may become challenging due to decreased creatinine production in association with decreased muscle mass. In experimental models, acute sepsis decreases creatinine generation independent of changes in muscle mass (18). In this context, although cystatin C levels are independently associated with inflammation in a number of cohorts (19,20) and although inflammation is common in critical illness, cystatin C has been shown to better identify patients with eGFR <60 ml/min per m² in the ICU (21). Furthermore, the sarcopenia index (22), which is the ratio of creatinine to cystatin C, has been proposed as a measure of muscle mass; a lower sarcopenia index suggests lower muscle mass, which is associated with adverse outcomes. How well GFR-estimating calculators that use cystatin C perform in the ICU is less well established and warrants more study.

Immune System
Many disease states common in critically ill patients (e.g., sepsis) are associated with immune system activation. It has been long established that the immune system response to critical illness is characterized by both proinflammatory and anti-inflammatory signaling cascades (23). A number of terms have been coined to describe these processes, including systemic inflammatory response syndrome, compensatory anti-inflammatory response syndrome, and mixed antagonist response syndrome. More recently, the persistent inflammation, immunosuppression, and catabolism syndrome (also commonly referred to as PICS) has been defined on the basis of clinical and laboratory criteria suggestive of a prolonged inflammatory state characterized by catabolism and weight loss and has been proposed as the biologic basis for chronic critical illness (24,25). This syndrome is different than the postintensive care syndrome, which is typically defined as a decline in physical, cognitive, or mental function among survivors of critical illness. In this article, we will use PICS to refer only to the postintensive care syndrome. In experimental animal models, crosstalk between the immune system and the kidney has been well described, with CD4+ T lymphocytes playing an important role in potentiating AKI (26). In humans, this crosstalk likely also potentiates AKI, but the precise mechanisms at play in an individual patient may vary depending on the immune system state at the time that AKI develops during critical illness.

ABCDEF Bundle Elements
We will next describe each of the ABCDEF bundle elements along with the rationale for the element (Figure 1).

A: Assess, Prevent, and Manage Pain
Pain management and alleviation of discomfort are a cornerstone of ICU care as well as ICU Liberation. Pain assessments can be particularly challenging in acutely ill, nonverbal patients. There is evidence of both undertreatment and overtreatment of pain in the ICU, which can both result in negative long-term side effects (27). Opioid therapies have long been the mainstay of ICU pain management. However, using multimodal, nonopioid techniques to treat pain can mitigate the transition to opioid dependence and complications from opioid therapy. Adjunct therapies may include acetaminophen, nonsteroidal anti-inflammatory drugs (when appropriate), neuropathic pain modulators, and local anesthetics, as well as nonpharmacologic tools such as distraction, music, and massage (28).
B: Both Spontaneous Awakening and Breathing Trials

Recommendations for SATs include stopping sedation until the patient can follow simple one-step commands, and then restarting sedation at 50% of the previous dose if necessary. These best-practice SATs are associated with fewer ventilator-dependent days and fewer ICU days (29). SBTs likewise are recommended on a daily basis. In the ABC trial, patients who received a coordinated daily SAT followed by an SBT had more days breathing without assistance over the 28-day study period and were discharged from the ICU and the hospital earlier. Although there was a small increase in the number of patients who self-exubtated in the SAT/SBT group, there was no difference in the total reintubation rate or the number who required reintubation after self-extubation. In terms of mortality benefit, the number needed to treat was 7.4 (95% confidence interval, 4.2 to 35.5) (30). The current literature supports maintaining patients “awake and alert” to minimize the side effects of deep sedation; although in some patients with acute respiratory distress syndrome (ARDS), this must be balanced with the need to maintain ventilator synchrony to avoid ventilator-induced lung injury.

C: Choice of Analgesia and Sedation

Minimization of sedatives has been recognized as an intervention that decreases ICU length of stay and ventilator-dependent days. In particular, avoidance of benzodiazepines is recommended (6). A large meta-analysis of 21 trials investigating interventions to prevent delirium suggests that dexmedetomidine reduces ICU length of stay compared with placebo (odds ratio, 0.42; 95% credible interval, 0.21 to 0.85) and likely reduces the occurrence of delirium (31). Finally, a recent multicenter, double-blind clinical trial concluded that dexmedetomidine is noninferior to propofol in terms of delirium, ventilator-free days, or death at 90 days (32).

To avoid complications from sedation, one option is to avoid the use of sedatives. A 2020 study of 710 patients randomized critically ill, mechanically ventilated patients to either light sedation or no sedation. Despite having a higher average risk of in-hospital mortality on the basis of the Acute Physiology and Chronic Health Evaluation II score, the patients who received no sedation had more days free from coma or delirium and fewer thromboembolic events. There was no difference in mortality compared with patients who received light sedation, although mean agitation scores (as measured by the Richmond Agitation and Sedation Scale) were slightly higher (33).

D: Delirium: Assess, Prevent, and Manage

Delirium is defined as an acutely presenting disturbance in attention and awareness that is accompanied by a change in cognition (memory, disorientation, language, or perception). It has been well established that delirium is an independent risk factor for mortality and longer hospital length of stay (34). However, new research offers insight that the neurobiology that underlies this often-misunderstood condition may be due to a combination of hypoperfusion, changes in neurotransmitters, metabolic insufficiency, and immune response, among other factors (35).

Although the pathogenesis of delirium remains uncertain in many patients, validated tests for delirium do exist. Assessment is most often performed using the Confusion Assessment Method tool set (36). Many of the interventions in the ICU Liberation bundle are commonly used treatment and prevention modalities for delirium, including reorientation, maintaining adequate light exposure, and minimizing metabolic derangements. However, there are limited data to support the efficacy of many of these interventions, and the efficacy of many nonpharmacologic treatment methods warrants further study (37). It is important to recognize that no drug has been convincingly proven to be efficacious in the treatment of delirium (38), and several negative high-quality randomized controlled trials do not support the routine use of haloperidol or atypical antipsychotics for the prevention or reduction of the duration of delirium. There is, however, some encouraging evidence that dexmedetomidine may decrease the risk of delirium (31,39,40).

E: Early Mobility and Exercise

Early mobility has been shown to improve outcomes in multiple domains as it promotes angio- and neurogenesis, promotes the release of neurogenic peptides, and facilitates brain plasticity (41). Timely initiation of physical therapy translates to improved physical function and quality of life, increased respiratory muscle strength, and more ventilator-free days along with shorter hospital and ICU length of stays (42,43). It has been proven to be safe to participate in physical therapy despite interventions, such as vasoactive medications, mechanical ventilation, continuous KRT (CKRT) (44), and extracorporeal membrane oxygenation (45). Unfortunately, patients who are receiving support from these types of extracorporeal devices are often excluded from participating in physical therapy (46). Likewise, patients with delirium or those on continuous sedation are more likely to miss physical therapy sessions (47). Given the benefits associated with exercise, current guidelines recommend early mobility in all patients able to pass a safety screen (6).

F: Family Engagement/Empowerment

Family engagement and participation in the care of patients in the ICU yield benefits to the family, patients, and nursing staff (48). Furthermore, increased family presence was not associated with higher infection rates, delirium scores, or staff burnout (49). Even family presence during cardiopulmonary resuscitation was not associated with worse outcomes for patients or staff and yielded positive psychologic benefits for the observing family members (50). Although family visitation has recently been curtailed at many institutions because of the coronavirus disease 2019 pandemic, minimizing barriers to family connections in the ICU remains of critical importance.

(F): Food

Although not an official part of the traditional ABCDEF bundle, ensuring appropriate nutrition is of paramount importance to recovery from critical illness (51). Maintaining continuous administration of feeding is critical to avoid exacerbation of caloric deficiency and the catabolic process.
Furthermore, patients who receive early trophic feeding, even those on modest-dose vasopressors or receiving neuromuscular blockers, have lower mortality compared with those not enterally fed (52). Early enteral nutrition is similarly recommended for patients in the prone position. Similarly, the maintenance of glycemic control is an important part of supportive ICU care for all critically ill patients, although there is still ongoing debate regarding optimal glycemic control targets and how these might vary on the basis of preadmission glycemic control (53).

**Nephrologists and Intensive Care Unit Liberation**

Nephrologists, who are often consultants for the most critically ill patients in the ICU, can play an important role in facilitating the implementation of these important interventions (Figure 2).

**A: Assess Pain Medication for Metabolites in Kidney Dysfunction**

Patients with impaired kidney function, either acute or chronic, may need adjustment of their pain medications. Nephrologists should collaborate with intensivists and pharmacists to recommend dose readjustments in order to prevent toxic metabolite buildup. Common sedative and analgesic drugs to review with caution include morphine, gabapentin, and pregabalin (6). The use of baclofen and nonsteroidal anti-inflammatory drugs also needs to be evaluated closely in the setting of AKI or CKD.

**B: Both AKI and Hypervolemia Can Affect Liberation from Mechanical Ventilation**

It is essential that nephrologists and intensivists are aware of the relationship between AKI and ARDS, including the high mortality in those with both diagnoses and the negative effect of fluid overload on successful weaning from the ventilator (54). A positive fluid balance is associated with worse outcomes, including fewer ventilator-free days and longer duration of ICU care (55,56). The FACTT trial demonstrated that a conservative fluid management strategy resulted in more ventilator-free days and shorter length of stay in patients who did not have severe AKI (57).

Lung-protective ventilation with permissive hypercapnia is associated with improved mortality (58). In the setting of normal kidney function, patients with respiratory acidosis...
develop a compensatory metabolic alkalosis over 72–96 hours to maintain a relatively normal pH. The lung-protective ventilation protocol allowed for, but did not require, the use of sodium bicarbonate in those with severe acidemia (pH<7.15). Two recent review articles (59,60) address the use of alkali therapy in patients with respiratory acidosis with different conclusions. We agree with Chand et al. (60) that respiratory acidemia is usually well tolerated in ARDS, and there is limited evidence to support the routine use of sodium bicarbonate therapy. In fact, sodium bicarbonate infusions administered solely to correct pH may actually worsen hypervolemia and, ultimately, delay liberation from mechanical ventilation. In the setting of AKI, the BICAR-ICU randomized controlled trial showed in a subgroup analysis that in patients with AKI with metabolic acidosis, administration of sodium bicarbonate was associated with a lower 28-day mortality (61). Thus, bicarbonate can be considered in select patient groups in the ICU, but more research is needed to better understand where bicarbonate is of clinical benefit.

C: Consider Sedation and Medications That Are Affected by and May Affect Kidney Dysfunction

As suggested under A, nephrologists play an important role in medication adjustments on the basis of kidney function. Notably, there are many other classes of medications aside from sedatives and analgesics that warrant consideration. Choice of sedation also can affect blood pressure, which can affect kidney perfusion. For this reason, in appropriate patients, prioritizing less sedation, therefore higher blood pressure, may be a nephron-saving recommendation.

D: Decrease Delirium with Less Invasive Procedures

The use of CKRT typically requires more in-room nursing time throughout the day and night (including time for blood draws and to respond to machine alarms), and therefore, it is likely associated with more sleep disruption than intermittent hemodialysis. There are myriad reasons, clinical and cost based, that influence the clinical decision on the timing of the transition from CKRT to intermittent hemodialysis/prolonged intermittent KRT (PIKRT) and modality selection in general, but traditionally, sleep disruption has not been considered. For patients in whom CKRT remains indicated, nephrologists may consider timing laboratory studies to avoid middle of the night laboratory tests, as this has been associated with less sleep disruption (62).

E: Encourage Early Mobility Despite Kidney Replacement Therapy

Many centers limit physical therapy when patients are connected to the CKRT circuit. However, it has been shown that early rehabilitation is both safe and effective in patients receiving CKRT (44). Nephrologists can advocate for increased physical therapy sessions for patients on CKRT when clinically appropriate. Alternatively, PIKRT is associated with earlier mobilization compared with CKRT (63).

F: Feed Patients Nutritious Food and Find Family

Nutrition and nephrology are inextricably linked, with kidney function and KRTs affecting nutritional needs and nutritional intake affecting kidney recovery. In terms of calorie intake, the ICU settings often underdose calories due to patient and system factors (64). CKRT can introduce nonintentional calories from lactate, glucose, or citrate (65). These calories should be considered when calculating caloric needs for patients.

There are no data to suggest that fat intake needs be altered during KRT (65); however, insufficient protein intake is directly correlated with higher rates of ICU mortality (66). It is well established that patients receiving KRT have significant protein loss (67); unfortunately, there is not a reliable clinical method to calculate these losses. Therefore, more research is needed in this field to better understand protein needs during KRT. In the interim, experts suggest that increasing the daily recommended protein intake to 1.5–2.5 g/kg per day optimizes nitrogen and amino acid balances in patients on CKRT (68).

Micronutrients are also affected by kidney function. Of patients receiving CKRT, 80% have deficiencies in one or more of the following micronutrients: ascorbic acid, copper, folate, pyridoxine, thiamine, or zinc (69). Furthermore, KRT causes more profound alterations in magnesium, potassium, phosphate, and calcium than normal kidney function (70). In particular, hypophosphatemia is common with CKRT (71) and can be mitigated by standing replacement protocols or using phosphate-containing dialysate solutions. The use of phosphate-containing dialysate solutions has been associated with more ventilator-free days in critically ill patients and shorter length of hospital stay (72).

Finally, involving family in daily ICU care is essential to mitigate the harms of critical illness and promote recovery. Although tools to predict kidney recovery remain in progress (73), frank conversations about the potential need for permanent KRT need to be included in goals of care discussions and whether this is consistent with a patient’s known wishes for care. Furthermore, in all patients, family presence decreases the risk of pharmacologic treatment of delirium and is one of the only proven treatments for this condition (74). All providers can participate in advocating for more patient-centered care with family at the bedside; for patients with kidney failure, nephrologists may have a relationship with patients and/or their families. Given the improved survival of critically ill patients, there is growing interest in PICS, and nephrologists can play a critical role in supporting these patients. Patients with new or worsening kidney failure and their caregivers will often require significant support as they adapt to these diagnoses.

Future Research

Forty-one clinical trials are currently underway to further understand the effects of PICS (ClinicalTrials.gov), many of which address the elements of the ABCDEF bundle. An area of particular growth and study has been the effect of the coronavirus disease 2019 pandemic on patients in the ICU. The pandemic created a surge of patients who required mechanical ventilation for an extended period of time. Many hospital systems severely restricted hospital
visitation, which re-emphasized the need for the ABCDEF bundle as the staff could rely less on family presence. Staffing challenges may have made the ABCDEF bundle more challenging to implement as well. More work is also needed in the area of nutrition, in particular for patients on KRT. There are further opportunities for research on how PIKRT facilitates ICU liberation, which may have the potential to significantly improve patients’ experiences in the ICU and their long-term outcomes.

Conclusions

There is excellent evidence to suggest that the daily decisions made in the ICU can affect the long-term prognosis for critical illness survivors. There is significant opportunity for new research to mitigate the long-term consequences of critical illness. However, although these new practices are being elucidated, it is imperative that hospital systems adhere to best evidence and that individual practitioners recognize their effect on the ABCDEF bundle elements. In particular, nephrologists can contribute greatly to a patient’s long-term care by monitoring medication administration for buildup of toxic metabolites, watching fluid balance closely in mechanically ventilated patients and considering bicarbonate therapy as appropriate, advocating for early and continuous calorie intake, facilitating a transition from CKRT to PIKRT/intermittent hemodialysis as early as clinically appropriate, and participating in goals of care discussions.

Disclosures

J.M. Aldrich works with SCCM on several projects related to ICU Liberation and is a past cochair of the ICU Liberation Committee, which is a nonprofit organization. K.D. Liu reports consultancy agreements with AM Pharma, Biomerieux, BOA Medical, Neumora, and Seastar Medical; holds stock in Amgen; serves or has recently served on the editorial boards of American Journal of Kidney Diseases, American Journal of Respiratory and Critical Care Medicine, and CJASN; serves on the National Kidney Foundation Scientific Advisory Board; serves an advisory or leadership role for the American Thoracic Society; and holds other interests or relationships with UpToDate. The remaining author has nothing to disclose.

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