Mortality rates of critically ill patients have decreased markedly in recent years thanks to advancements in care. Given the improved survival rates of critically ill patients, investigators have broadened their focus from short-term mortality to long-term mortality and morbidities that are often underrecognized by intensive care unit (ICU) practitioners. The Society of Critical Care Medicine (SCCM) has defined post–intensive care syndrome (PICS) as a new or worsening decrement in mental, cognitive, or physical health following critical illness that persists beyond the acute hospitalization. Many medication-related risk factors are associated with development of cognitive impairment in critically ill patients, including glucose dysregulation, delirium, and medications. Medications have also been associated with acute neuromuscular weakness following an ICU admission. In the past decade, the increased risk of adverse drug events (ADEs) during transitions of care has become widely known. This column focuses on how medication management strategies in the ICU, after the ICU, and after hospitalization may prevent or help manage PICS.

In the ICU
Glucose Dysregulation
Both hyperglycemia and hypoglycemia are associated with cognitive dysfunction in critically ill patients. Hyperglycemia decreases cerebral blood flow,
injures the vascular endothelium, increases permeability of the blood-brain barrier, and increases excitatory neurotransmitter release and resultant neuronal death. A retrospective study of 74 survivors of acute respiratory distress syndrome (ARDS) demonstrated that having a blood glucose value of 153.5 mg/dL (to convert to millimoles per liter, multiply by 0.0555) was associated with a 2.9 times greater chance of cognitive impairment. Additionally, a retrospective, case-control study of 37 surgical ICU patients who had experienced at least 1 episode of hypoglycemia during treatment showed that cognitive dysfunction, specifically in visuospatial skills, was higher in the hypoglycemia group than in the control group ($P < .01$).

Hyperglycemia is also a risk factor for critical illness polyneuropathy (CIP) and critical illness myopathy (CIM). Insulin has anti-inflammatory effects, protects endothelium, improves the metabolism of lipids, and is an anabolic hormone. Intensive insulin therapy (maintaining blood glucose levels between 80 and 100 mg/dL) in surgical ICU patients decreased neuropathy from 51.9% to 28.7%.

Critically ill patients (P = .02). On the basis of that study, SCCM guidelines for the use of an insulin infusion in critically ill patients suggests that patients with a blood glucose level of 150 mg/dL or greater receive an intervention to maintain blood glucose level at less than 180 mg/dL while avoiding hypoglycemia.

Pain, Agitation, and Delirium

The pain, agitation, and delirium (PAD) guidelines were published by SCCM in 2013 and summarize the best evidence available for providing physical and psychological comfort through management of PAD. A program called the ICU Liberation Collaborative has been started by SCCM to aid in the implementation of the PAD guidelines in 77 hospitals in the United States that are committed to improving outcomes for patients and their families.

**Delirium.** In 2013, a large, multicenter, prospective observational cohort study of 821 adult medical and surgical ICU patients with respiratory failure, cardiogenic shock, or septic shock, called Bringing to Light the Risk Factors and Incidence of Neuropsychological Dysfunction in ICU Survivors (BRAIN-ICU), was reported. The researchers sought to estimate the prevalence of long-term cognitive impairment following critical illness. The strongest independent predictor of cognitive impairment was ICU delirium, which was found in 50% of study patients. Three months following hospital discharge, a Repeatable Battery for Neuropsychological Status (RBANS) score similar to what has been seen in individuals with mild Alzheimer’s disease (2 standard deviations below the population mean) was found in 26% of patients, and a score similar to the scores seen in patients with moderate traumatic brain injury (1.5 standard deviations below the population mean) was found in 40% of patients.

**Pain.** Inadequate pain management has been associated with numerous complications, including nosocomial infections, increased duration of mechanical ventilation, and delirium. The treatment of pain with opiates in critically ill patients has been associated with an increased risk of delirium in some studies and a decreased risk of delirium in others. Although other medications such as gabapentin (Neurontin), nonsteroidal anti-inflammatory drugs, and acetaminophen (Tylenol) are good adjunctive therapies, opioids are the medication class of choice for treating pain in critically ill patients. The potential for the development of delirium highlights one of the many reasons why pain assessment in critically ill patients is so imperative. The PAD guidelines recommend that all adult critically ill patients be routinely assessed for pain. Self-reporting of pain is considered the reference standard for pain assessment. However, if a patient is nonverbal, the PAD guidelines recommend use of the Behavioral Pain Scale or the Critical Care Pain Observational Tool in ICU patients who are unable to self-report pain.

**Sedation.** Benzodiazepines have been associated with the development of delirium in
several studies. The PAD guidelines recommend using nonbenzodiazepine sedation strategies (eg, dexmedetomidine [Precedex]) in delirious patients. Three studies have demonstrated that patients are less likely to remain delirious if dexmedetomidine is used. In a double-blind, randomized, controlled trial of 106 patients receiving mechanical ventilation, The Maximizing Efficacy of Targeted Sedation and Reducing Neurological Dysfunction (MENDS) study, researchers found that the median number of days alive without delirium or coma was 7 in the dexmedetomidine group versus 3 in the lorazepam (Ativan) group (P = .01). The daily prevalence of delirium was lower in the dexmedetomidine group than in the lorazepam group (P = .004) after the day of randomization.

In a second double-blind, randomized, controlled trial of 375 medical/surgical ICU patients, the Safety and Efficacy of Dexmedetomidine Compared with Midazolam (SEDCOM) study, researchers found that the median number of days alive without delirium or coma was 7 in the dexmedetomidine group versus 3 in the lorazepam (Ativan) group (P = .01). The daily prevalence of delirium was lower in the dexmedetomidine group than in the lorazepam group (P = .004) after the day of randomization.

In a second double-blind, randomized, controlled trial of 375 medical/surgical ICU patients, the Safety and Efficacy of Dexmedetomidine Compared with Midazolam (SEDCOM) study, researchers found that 60.3% of dexmedetomidine patients and 59.3% of midazolam (Versed) patients were delirious at baseline according to the Confusion Assessment Method for the ICU. During the study period, the prevalence of delirium was 54% in the dexmedetomidine group compared with 76.6% in the midazolam group (P < .001).

A pilot, phase 3, double-blind, randomized study was conducted by Ruokonen et al in 2009 to compare dexmedetomidine with standard care (midazolam or propofol [Diprivan]). Patients with a target score of 0 to -3 on the Richmond Agitation-Sedation Scale (RASS) were more likely to be at the target RASS score with dexmedetomidine (74%) than with standard care (64%).

In a phase 3, multicenter, randomized, double-blind trial, researchers found that the composite outcome of agitation, anxiety, and delirium occurred in 27% of patients who received midazolam versus 29% of patients who received dexmedetomidine (P = .69). In a second phase 3, multicenter, randomized, double-blind trial, researchers found that the composite outcome of agitation, anxiety, and delirium occurred in 29% of patients who received propofol versus 18% of patients who received dexmedetomidine (P = .008). Overall, these studies suggest that the use of dexmedetomidine results in increased days alive without delirium and reduced daily prevalence of delirium compared with benzodiazepines.

**Management of Delirium**

Nonpharmacological management of delirium through risk factor reduction has been studied in non-ICU patients, and the results generalize to the ICU population. However, these interventions need to be investigated further in critically ill patients. An example of risk-reducing strategies that can be simplified into a simple phrase “Stop, THINK, and Medicate” is presented in Table 1.

Pharmacological interventions should be considered only after nonpharmacological strategies have been implemented and modifiable risk factors have been addressed.

<table>
<thead>
<tr>
<th>Table 1: Stop, THINK, and Medicate</th>
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<tbody>
<tr>
<td><strong>Stop</strong></td>
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<tr>
<td>Do any medications need to be stopped or lowered?</td>
</tr>
<tr>
<td>Especially consider sedatives</td>
</tr>
<tr>
<td>Is patient receiving minimal amount necessary?</td>
</tr>
<tr>
<td>Daily sedation cessation</td>
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<tr>
<td>Targeted sedation plan</td>
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<tr>
<td>Assess target daily</td>
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<tr>
<td>Do sedatives need to be changed?</td>
</tr>
<tr>
<td>Remember to assess for pain!</td>
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<tr>
<td>Electrolyte problems (eg, potassium)</td>
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Beneficial effects of haloperidol (Haldol) or atypical antipsychotics on decreasing the duration of delirium in adult ICU patients have not been definitively demonstrated (ie, no large randomized controlled trials). In a prospective pilot study, 21 18 delirious patients were randomized to receive scheduled quetiapine (Seroquel) and 18 delirious patients were randomized to receive placebo. All patients could receive intermittent haloperidol. Faster resolution of delirium was found in the quetiapine group compared with the placebo group (1 day vs 4.5 days, \( P = .001 \)) as well as a shorter duration of delirium (36 days vs 120 days, \( P = .006 \)). Additionally, less intermittent haloperidol was required in the quetiapine group (3 vs 4 days). Both groups experienced a similar amount of QT interval prolongation and extrapyramidal symptoms, but more somnolence was found in the quetiapine group (22% vs 11%, \( P = .66 \)).

Currently, a multicenter, randomized, placebo-controlled, study sponsored by the National Institutes of Health called Modifying the Impact of ICU-Associated Neurological Dysfunction-USA (MIND-USA) is being conducted in delirious medical and surgical ICU patients with respiratory failure or shock to determine the effects of haloperidol versus ziprasidone versus placebo on the number of days alive without delirium or coma, mortality, and long-term cognitive function.

Medications That Cause Delirium

Medications are a common yet easily reversible cause of delirium, accounting for 12% to 39% of all cases. The American Geriatric Society recently updated the Beers criteria, listing potentially inappropriate medications to be prescribed in elderly adults. In addition, the Society also published a list of alternative medications to use instead of high-risk medications. Although narcotics and benzodiazepines have been discussed in prior sections, many other deliriogenic medications are commonly prescribed to patients in the ICU (Table 2).

Excess dopamine, decreased acetylcholine, and alterations in \( \gamma \)-aminobutyric acid are all mechanisms behind the development of delirium. \(^{22} \) Dopamine agonists used as antiparkinsonian agents can contribute to delirium. If these medications are deemed necessary, a dosage reduction or change in schedule may alleviate the problem. Quinolone antibiotics have weak dopaminergic activity. Morphine also increases the release of dopamine. \(^{24} \) Anticholinergic medications result in a cholinergic deficiency and are a modifiable risk factor for delirium. Additionally, digoxin (Lanoxin), lithium (Lithobid), and histamine, blockers demonstrate some cholinergic binding activity, although they are not traditionally classified as anticholinergic agents. \(^{22} \) The proposed mechanism behind benzodiazepine-induced delirium is alterations in \( \gamma \)-aminobutyric acid. \(^{24} \)

A prospective cohort study\(^{25} \) of 1112 critically ill patients in a 32-bed medical-surgical ICU for a total of 9867 days was conducted to determine whether anticholinergic exposure
increased the probability of a transition to delirium occurring. The transition from “awake and without delirium” to “delirium” occurred on 6% of ICU days. A 1-unit increase in the Anticholinergic Drug Scale demonstrated a nonsignificant increase in the probability of a transition to delirium occurring the following day (odds ratio, 1.05; 95% CI, 0.99-1.10). However, the authors did not evaluate whether the dose of the medication affected the transition to delirium and also did not consider patients who were already delirious and remained delirious while receiving anticholinergic medications.25

Medications can also potentiate CIP and CIM (Table 2). Neuromuscular blockers enhance microvascular permeability, stimulating denervation of the muscle in addition to having direct toxic effects on the nerve. Concomitant administration of steroids enhances the toxic effects of neuromuscular blockers on muscles. The risk of acute myopathy increases with coadministration of neuromuscular blockers and corticosteroids for longer than 24 to 48 hours.26 Additionally, hypermagnesemia, metabolic acidosis, and concomitant medications including aminoglycosides and clindamycin promote prolonged neuromuscular blockade.27 Studies on the effects of corticosteroids on CIP/CIM have yielded both positive9,10 and negative28 results. The clinical situation must be considered when determining if the use of corticosteroids is merited.

Careful review of the patient’s medication list can identify potentially deliriogenic or CIP/CIM-inducing medications. Drug/disease state interactions and drug/drug interactions resulting in delirium or CIP/CIM should be considered when dosing and choosing medications.7,24 Hepatic and renal impairment can lead to accumulation of medications, resulting in delirium and/or CIP/CIM if the medication dose is not adjusted appropriately.7,24

Transitions of Care

Although ADEs can occur at any time, it has become evident in the past decade that a significant risk for ADEs occurs during periods of transition of care.29 One of the first studies that highlighted the medication errors that occur during transitions of care demonstrated that 54% of errors were made by prescribers when ordering medications at hospital admission.30 Further, many emergency room visits and readmissions to hospitals following discharge have been associated with medications. In response to the growing amount of data demonstrating medication errors at transitions of care, The Joint Commission on Accreditation of Healthcare Organizations declared “sustaining and properly communicating correct medication information” to be a National Patient Safety Goal in 2011.

Patients with cognitive impairment or those taking more than 5 medications per day (also known as polypharmacy) are 2 examples of populations of patients at higher risk for an ADE during transitions of care.29 Additionally, the number of medications a patient is receiving is an independent risk factor for delirium.31 “Deprescribing” is defined as the process of tapering or discontinuing medications to minimize polypharmacy and improve patients’ outcomes. The following 5-step protocol for deprescribing has been suggested: (1) determine that each medication has an indication; (2) consider the overall potential harm of the medications in determining how many agents should be discontinued; (3) assess each individual drug to determine if it should be discontinued; (4) prioritize the order of medications to be discontinued; and (5) initiate and monitor a drug discontinuation plan. Deprescribing can be further enhanced in the ICU by determining if medications have a current indication. For example, a patient taking an antihistamine at home for allergies and an anticholinergic agent for an overactive bladder may not need these medications when admitted to an ICU with a urinary catheter.32

A single-center study33 of 120 elderly adult ICU survivors evaluated the frequency of prescribed potentially inappropriate medications (PIMS) and actually inappropriate medications (AIMs). PIMS were defined as those medications potentially harmful to the elderly according to prior research and knowledge of pharmacological effects. PIMS could then be classified as AIMs if the benefit of the drug was outweighed by the harm after considering a patient’s clinical circumstances. Charts were reviewed and medications were identified as PIMS by using the 2003 Beers criteria and medication safety data published since 2003. In order to determine where AIMs were initiated, medications were identified at 5 distinct points during the hospital stay: admission, medical/surgical unit admission, ICU admission, ICU discharge, and hospital discharge.
The most common categories of PIMS identified at hospital discharge were the following: opioids, anticholinergic medications, antidepressants, and drugs causing orthostasis. The clinical panel, consisting of a hospitalist, geriatrician, and clinical pharmacist, determined that 36% of these PIMs were considered to be AIMs. At hospital discharge, the PIM categories with the highest positive predictive values for being AIMs included anticholinergics (55%), nonbenzodiazepine hypnotics (67%), benzodiazepines (67%), atypical antipsychotics (71%), and muscle relaxants (100%). The number of discharge PIMS was independently predicted in multivariate analysis by the number of preadmission PIMs ($P < .001$), discharge to somewhere other than home ($P = .03$), and discharge from a surgical service ($P < .001$).

Also, nearly two-thirds of AIMs were initiated in the ICU. It is likely that many of these medications initiated in the ICU or at any other time during the hospital stay may have been appropriate for temporary or short-term use depending on the patient’s clinical situation. However, the failure to discontinue these medications once no longer indicated led to inappropriate and prolonged use. This study further highlights the need to review patients’ medication lists daily and during transitions of care to determine if deprescribing is merited.

In addition to the continuation of unnecessary medications following hospital discharge, patients’ home maintenance medications may not be initiated upon hospital admission. In a large population-based Canadian cohort study of 396,380 patients aged 66 years or older, researchers looked at records of hospital and outpatient medications prescribed from at least 1 of 5 of the following groups: (1) statins, (2) antiplatelet/anticoagulant agents, (3) levothyroxine, (4) respiratory inhalers, and (5) gastric acid–suppressing drugs. Patients were divided into 3 groups: hospitalization with an ICU admission, hospitalization without ICU admission, and nonhospitalized patients (controls). Patients admitted to a hospital without an ICU stay were significantly more likely to have medications discontinued among all 5 of the medication groups compared with control patients. Also, patients admitted to a hospital with an ICU stay were significantly more likely to have medications discontinued among all 5 of the medication groups compared with control patients.

The risk of medication discontinuation was higher in all medication groups with the exception of respiratory inhalers in patients hospitalized with an ICU admission, compared with patients hospitalized without an ICU admission. The composite risk of death, hospitalization, and emergency department visits up to 1 year after hospital discharge in all study patients was significantly higher in patients in whom a statin or antiplatelet or anticoagulant was discontinued. As this study was retrospective, the clinical reasons why long-term medications were discontinued could not be delineated. However, this study highlights the importance of medication reconciliation with changes in patients’ status and transitions of care to prevent errors of omission in the patient’s discharge medication list when leaving the hospital.

**Post-ICU Clinics**

Fifty percent of patients who are readmitted within 30 days of discharge did not have a posthospitalization visit to a primary care provider. Lack of understanding of home and discharge medications was a contributing factor to readmissions. Readmissions occurred in 20% of Medicare recipients within 30 days of discharge and in 34% within 90 days of discharge in 1 study.

One method of smoothing the transition back to a primary care provider following an ICU stay is use of a post-ICU clinic. Primary care providers may not be familiar with the specific critical care issues seen in patients following critical illness and may not have the tools to assess and manage these complications. An interdisciplinary team of individuals in a post-ICU clinic can use their expertise about specific complications related to critical care to aid in the diagnosis and treatment of PICS.

Medication therapy review, reconciliation, and counseling should all be considered crucial parts of a patient’s visit to a post-ICU clinic. These functions are ideally performed by a pharmacist. The steps of the complete medication use process are listed in Table 3.

**Patient Testimonial**

Scottie Grayson is a 42-year-old man who had a 30-day hospitalization after a witnessed ventricular arrest with subsequent acute kidney injury, prolonged ventilation, and heparin-induced thrombocytopenia who was seen at the ICU Recovery Center at Vanderbilt.
Table 3: The Complete Medication Use Process

1. Before clinic visit: review of patient’s chart for medical history, hospital course, and medications
2. Medication reconciliation: compare and reconcile medication lists before, during, and after hospitalization
3. Medication therapy review: ensure that each medication has an appropriate indication
4. Patient interview: identify adverse drug events, identify any untreated problems
5. Patient counseling: review medication indication, directions, potential adverse effects, and monitoring
6. Assessment: review barriers to obtaining medications, promote medication regimen adherence, and order any needed laboratory tests
7. Conclusion of visit: discuss medication changes and patient’s follow-up plan

University Medical Center. The following is Mr Grayson’s testimonial regarding how targeted medication interventions affected his post-ICU recovery:

Recently I suffered a cardiac arrest and spent 30 days in Vanderbilt Medical Center. When I returned home I was shocked to learn that I was bringing home 11 prescriptions for a total of 24 pills a day. For someone who was taking zero prescriptions previously, it was very overwhelming. I repeatedly had to ask my wife what all these pills were for and if I really needed them. Although the staff had gone over all these medications with my wife, I was in the dark. During my first few weeks home, I was in a fog. I don’t know how much of it was the medication and how much of it was my body still healing from the trauma. I believe I would have been less anxious and overwhelmed if I personally would have had a better understanding of what all the medications had been for. The complete medication review by the pharmacist at the ICU Recovery Center at Vanderbilt helped me to feel better about my medications. During his visit at the ICU Recovery Center at Vanderbilt, Mr Grayson was provided a pill caddy to help organize his medications. Additionally, 3 medications, omeprazole, sodium bicarbonate, and quetiapine, started for acute needs in the hospital, were discontinued.

Conclusion

Medication management strategies in the ICU, upon transition to the medical/surgical unit, and after hospitalization are critical to preventing and treating PICS. Glucose management strategies, delirium prevention and treatment, and avoidance or proper dosage adjustment of deliriogenic or neuromuscular weakness–inducing medications are all strategies to prevent PICS.

REFERENCES


**CE Test Instructions**

This article has been designated for CE contact hour(s). The evaluation tests your knowledge of the following objectives:

1. Describe medication related risk factors associated with cognitive impairment that develop in critically ill patients.

2. Discuss medications associated with acute neuromuscular weakness following an intensive care unit stay.

3. Evaluate the role of a post–intensive care unit clinic in providing a comprehensive medication review for easing the transition from the critical care setting to home.

**Contact hour: 1.0**

Pharmacology contact hour: 1.0

Synergy CERP Category: A

To complete evaluation for CE contact hour(s) for test #ACC632, visit www.aacnacconline.org and click the “CE Articles” button. No CE test fee for AACN members. This test expires on April 1, 2019.

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