Alcohol-Use Disorders in the Critically Ill Patient

Marjolein de Wit, Drew G. Jones, Curtis N. Sessler, Marya D. Zilberberg and Michael F. Weaver

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Alcohol-use disorders (AUDs) encompass a spectrum of disorders, including excessive use, abuse, dependence, and addiction. Abuse occurs when a patient experiences adverse socioeconomic or health consequences related to the use of the substance. Dependence is present either when the patient experiences withdrawal symptoms on discontinuation of the substance or when larger amounts are necessary to achieve the desired effect. Addiction is indicated by the patient experiencing a compulsive craving for a substance. At any one time, a patient may have more than one of these disorders simultaneously present. The National Institutes of Health have put forth guidelines that quantify excessive and unhealthy use of alcohol; a level of use above this threshold increases a patient’s risk for health problems. Men aged ≤65 years who consume more than four standard drinks in a typical day or >14 standard drinks in a typical week have excessive and unhealthy alcohol consumption. These volumes are halved for women of all ages and men aged >65 years: More than...
three standard drinks on a typical day or more than seven standard drinks in a typical week are classified as excessive and unhealthy. A standard drink has 14 g of ethanol, the equivalent in one 12-oz beer, a 5-oz glass of table wine, or a 1.5-oz glass of spirits. Thus, AUDs may be defined by either experiencing adverse events related to the use of a substance or by exceeding a minimum threshold of use.

**Medical Burden of AUDs**

An estimated 76.3 million people worldwide have AUDs, and these disorders account for 1.8 million deaths each year. AUDs have a larger impact on health in developed countries than in developing countries, where alcohol consumption is on the rise. The increased consumption in developing countries may portend a rise in the global epidemic of AUDs. The number of disability-adjusted life years caused by AUDs are the largest in the countries belonging to the former Soviet Union, Central America, and South America. Western countries and China also experience a substantial disability burden due to AUDs. An estimated 18.3 million (7.3%) Americans have dependence on or abuse of alcohol. This percentage translates into a staggering 18.3 million individuals being afflicted by these chronic health conditions. The majority of patients with AUDs (15.2 million Americans or 83%) do not have other drug use disorders, but 3.1 million patients do have other coexisting drug use disorders (such as marijuana, pain relievers, or cocaine). Tobacco users have a higher rate of alcohol consumption: 67% of smokers drink alcohol compared with 47% of nonsmokers.

AUDs are well-known risk factors for trauma and violence. Several studies from level I trauma centers reported that approximately one-half of trauma patients have detectable serum alcohol concentrations. When combining toxicology testing for both alcohol and other drugs, the prevalence of alcohol and other drug use disorders reaches 70% in select trauma centers. Further, the prevalence of these disorders is even higher among violence-induced trauma vs nonviolence-induced trauma. Trauma patients with detectable blood alcohol concentrations are also at an increased risk of future trauma-related death compared with patients without detectable alcohol. Additionally, high-risk driving and other risky behaviors are more common among persons with AUDs. This epidemic of alcohol-related trauma has led the American College of Surgeons Committee on Trauma to mandate routine screening for AUDs at level I and II trauma centers because interventions for alcohol problems can reduce subsequent alcohol-related injury and are cost-effective.

AUDs are associated with a multitude of serious medical complications and known to cause systemic disorders. They may cause liver cirrhosis, pancreatitis, bone marrow suppression with resultant pancytopenia, dilated cardiomyopathy, hypertension, atrial fibrillation, and renal dysfunction resulting in wasting of electrolytes such as potassium, magnesium, and phosphorus. Patients with AUDs experiencing GI hemorrhage have large volumes of blood loss. AUDs also have been implicated in asthma exacerbations.

The multitude of serious medical disorders attributable to AUDs results in increased risk of hospital admission. An estimated 21% to 42% of patients admitted to general hospital wards have AUDs. Further, an estimated 10% to 33% of patients admitted to the hospital ICU have AUDs. The prevalence of AUDs is even higher among patients admitted to government-owned hospitals and academic medical centers. The volume of alcohol consumption is larger in diseases typically attributed to alcohol compared with those not usually believed to be related to AUDs. The relationship of AUDs to outcomes in patients with trauma, burns, and surgery is summarized in Table 1 and discussed in the following sections.

**Trauma Patients**

Although a high proportion of trauma patients have detectable blood alcohol levels or acute intoxication, published studies have yielded conflicting findings regarding outcomes of those with AUDs (Table 1). Fabbris and coworkers found patients with positive blood alcohol levels to be more critically ill at hospital admission; to have a higher risk of combined mortality or expected permanent disability; to require ICU care, surgery, and blood transfusions more frequently; and to have more acute medical complications. However, after adjusting for trauma severity and preexisting chronic conditions, positive blood alcohol levels were independently associated only with an increased risk of unsuspected injuries. Cunningham et al observed that among patients with traumatic brain injury, those with positive blood alcohol levels had worse injury. Most cohort studies from level I trauma centers, however, demonstrated no differences in important outcomes such as mortality and length of stay for patients with positive blood alcohol levels or acute alcohol intoxication compared with controls. In fact, Blondell et al found shorter length of stay and lower mortality rates for patients with positive blood alcohol levels. Thus, although delivery of trauma care is more complex for the patient who is acutely intoxicated, adverse effects primarily are related to injury severity or chronic illness.
It is likely that the physiologic effects of chronic alcohol abuse, rather than alcohol use at the time of trauma, influence patient outcomes. In a cohort study by Jurkovich et al., trauma patients who were acutely intoxicated had no higher risk of death or complications and had shorter hospitalizations, whereas patients with evidence of chronic alcohol abuse had a twofold higher complication rate. Several prospective studies by Spies and coinvestigators demonstrated worse outcomes for trauma patients who have evidence of chronic alcohol abuse, dependence, or both. More major complications, such as pneumonia, cardiac complications, and longer hospital ICU length of stay, were demonstrated among these patients with chronic alcohol abuse. In summary, adverse outcomes following traumatic injury are more strongly associated with chronic alcohol abuse than with acute intoxication.

**Burn Patients**

In contrast to trauma patients, patients who suffer burns and have detectable blood alcohol concentrations have worse outcomes (Table 1). McGill and colleagues detected a sixfold higher mortality rate in patients with positive levels of blood alcohol than...
those with negative levels. Silver et al demonstrated that burn patients with elevated blood alcohol concentrations have higher acuity of illness, require administration of larger volumes of fluids to achieve successful resuscitation, have longer duration of mechanical ventilation (10 additional days), and have longer hospital ICU lengths of stay (13 additional days). This increased morbidity translated into an excess cost of $95,000. Further, when controlling for injury characteristics, elevated blood alcohol concentration was associated with poorer short-term and long-term outcomes.

Surgical Patients

In contrast to the trauma and burn populations, patients who undergo elective surgery do not have a high rate of acute alcohol use or intoxication but may be at risk for adverse outcomes related to chronic alcohol abuse (Table 1). In the surgical patient population, chronic alcohol abuse is associated with more postoperative complications, including pneumonia, surgical wound infection, sepsis, poor wound healing, and cardiac complications (heart failure, ischemia, and arrhythmias). Indeed, when surgical patients experience adverse outcomes, we recommend that clinicians strongly consider carefully screening for AUDs, as the conditions may have been missed preoperatively. In our experience, patient family members have been receptive to inquiries about alcohol consumption and, on a number of occasions, relieved to discuss their concerns with clinicians.

Patients with AUDs also more frequently have serious hemorrhage, resulting in high rates of blood transfusions. These complications culminate in increased odds of repeated surgery, a long duration of mechanical ventilation, and frequent readmission to the hospital ICU. Finally, some studies have shown that surgical patients with chronic alcohol abuse have longer ICU lengths of stay and increased risk of death.

The increased risk of postoperative complications in patients with AUDs can be minimized in surgical patients undergoing elective surgery. Tønnesen et al demonstrated in a randomized controlled trial that a month-long preoperative program of alcohol abstinence, including administration of disulfiram, reduces postoperative complications in heavy drinkers (≥5 drinks/day) who had no known preexisting alcohol-related cirrhosis or organ dysfunction and were to undergo elective GI surgery. Patients who received the intervention had less intense surgical stress response; significantly fewer complications, including myocardial ischemia and arrhythmia; and better immune function. None of the patients in the intervention group developed pneumonia, but one-fourth of the control patients developed postoperative pneumonia.

Minimizing the stress response in surgical patients with AUDs has been shown to decrease postoperative morbidity. Administration of agents that decrease cortisol production (ie, administration of low-dose alcohol, morphine, and ketoconazole or propofol) is associated with significant reduction in the rate of sepsis as well as hospital ICU length of stay (discussed in more detail under the “Management of Sedation” and “Management of Withdrawal Syndromes” sections). This approach may have implications for managing other circumstances in which AUDs are associated with poor outcomes and should be investigated further.

Medical Patients

AUDs have been shown to increase the need for mechanical ventilation in broad cohorts of patients admitted to a medical ICU. A large retrospective study demonstrated that among hospitalized medical patients, AUDs are significantly more common in patients requiring mechanical ventilation than those who do not. AUDs increase the need for mechanical ventilation by 49%, and a diagnosis of alcohol withdrawal syndrome is associated with longer mechanical ventilation duration. AUDs are independent risk factors for the development of sepsis, and patients with sepsis and AUDs have a higher mortality, especially in those with concurrent hepatic dysfunction. In patients with AUDs, pneumonia is the most common cause of sepsis, as AUDs may increase the risk of both bacterial and viral pneumonia, and patients with AUDs who have viral pneumonia may have an increased risk of bacterial superinfection. The severity of illness also is heightened in patients with sepsis and AUDs, increasing the need for mechanical ventilation. Severe sepsis in patients with AUDs results in a twofold higher risk of requiring mechanical ventilation and a two- to fourfold higher risk of developing ARDS.

AUDs are also independent risk factors for the development of community-acquired pneumonia. The coexistence of AUDs in patients with pneumonia or sepsis is associated with higher acuity of illness, increased need for hospitalization and ICU admission, longer hospital length of stay, and higher hospital charges. In addition, the resolution of pneumonia is delayed in patients with AUDs, resulting in protracted fevers, significantly larger area of infected lung parenchyma, and slower clearance of airspace disease on chest radiograph. Clinicians should be watchful for the development of ARDS in patients with AUDs who present with pneumonia, where
patients have rapidly deteriorating oxygenation after presentation that, in our experience, is frequently explained by the development of ARDS.

The pathogens implicated in the development of community-acquired pneumonia and AUDs are *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Legionella pneumophila*, and *Chlamydia pneumoniae*.

It is unclear whether pneumonia in patients with AUDs is associated with increased risk of bacteremia. AUDs increase the risk of pneumonia by increasing oropharyngeal colonization with gram-negative rods, decreasing mucociliary clearance, impairing alveolar macrophage function, and inducing epithelial dysfunction. Macrophage dysfunction is marked by decreased phagocytosis and impaired immune response, and epithelial cell dysfunction predisposes patients to development of ARDS.

Antibiotic administration should be targeted to the specific pathogen and source of sepsis. It is interesting to note that, even though patients with AUDs are at higher risk of developing sepsis, studies have not examined different antibiotic regimens between patient cohorts with and without AUDs.

Patients with AUDs undergoing mechanical ventilation are at increased risk of developing complications compared with patients without these disorders and are predisposed to the development of ventilator-associated pneumonia, a complication associated with twofold higher rates of death. In addition, patients who consume alcohol in excess of the limits put forth by the National Institutes of Health have an increased risk for blood stream infections and urinary tract infections.

AUDs also may lead to a higher incidence of ventilator-induced lung injury, a disorder caused by shear stresses induced through mechanical inflation of the lung.

### Immune Dysfunction

Acute and chronic alcohol ingestion are associated with alterations of both innate and adaptive immunity. Macrophages and neutrophils are affected, and leukopenia may result from depressed levels of granulocyte colony-stimulating factor. Neutrophils have abnormal chemotaxis response, and both neutrophils and macrophages have aberrant phagocytosis and impaired superoxide production. Macrophage production of tumor necrosis factor-α is impaired and may be a key to the increased risk of pneumonia seen in patients with AUDs. Macrophages also have been noted to have abnormal differentiation, increased rates of apoptosis, and abnormal lipid peroxidation. Decreased levels of glutathione have been observed in pulmonary macrophages, and glutathione repletion improves bacterial clearance. Adaptive immunity also is impaired. Proliferation of memory T cells is depressed through suppression of interleukin (IL)-23.

Surgical and trauma patients with AUDs have been shown to have aberrant cytokine concentrations, resulting in an imbalance between proinflammatory cytokines and antiinflammatory cytokines. Proinflammatory cytokine production is decreased, and studies have demonstrated decreased levels of IL-1, IL-6, IL-12, tumor necrosis factor-α, and interferon-γ. Antiinflammatory cytokine concentrations of IL-10 also are decreased. Stress induced by trauma or surgery results in a production of proinflammatory cytokines and, in the normal host, is compensated by an antiinflammatory response. Depending on the balance between proinflammatory and antiinflammatory cytokines, patients with AUDs may exhibit either a proinflammatory state or an antiinflammatory state. The altered cytokine production results in a balance that favors an antiinflammatory profile when exposed to surgical stress. Cytokine abnormalities have been linked to the development of nosocomial sepsis in surgical and trauma patients.

### Management of Sedation

Patients with AUDs are significantly more likely to receive sedatives or opioids during their hospital ICU stay. Patients with AUDs are more likely to receive not only a dose of sedative or opioid but also significantly longer durations of continuous infusions, resulting in a 2.5-fold larger dose of sedative administration and a fivefold larger dose of opioid administration to achieve sedation levels similar to patients without AUDs. The administration of continuous IV infusion of sedating agents has been associated with longer duration of mechanical ventilation, but this practice has not been linked to longer mechanical ventilation duration in patients with AUDs.

Numerous studies have demonstrated that limiting the administration of sedating agents through deployment of a sedation algorithm or through the use of daily sedation interruption decreases the duration of mechanical ventilation in patients who are critically ill. However, these studies have not examined the impact of limiting sedation in a cohort of patients with AUDs. De Wit et al undertook a randomized study comparing a strategy of sedation interruption with a sedation algorithm and found that the use of a sedation algorithm was associated with shorter mechanical ventilation duration. This study was carried out in a cohort of hospital ICU patients with a high rate of AUDs (> 30%). It is possible that a sedation algorithm may be a better sedation strategy in patients with AUDs. Additionally, it is conceivable that abrupt interruption of sedation may precipitate alcohol withdrawal syndrome in patients with AUDs.
In our experience, patients with AUDs may develop signs of physical and possibly "autonomic agitation" with inadequate sedation. Inadequate sedation may lead to fever, tachycardia, and hypertension when sedation is inadequate, although evidence for these occurring in broad cohorts of patients with AUDs are lacking because diagnosis of alcohol withdrawal syndrome rests on patients self-reporting symptoms of irritability, nausea, and headache. Hospital ICU clinicians typically are unable to evaluate for these symptoms in their intubated patients.

Patients with AUDs not only experience higher levels of stress as measured by higher cortisol concentrations but also have poorer immune function. Two highly innovative studies suggested that the use of sedatives and opioids may influence the stress response and immune function.\(^48,49\) Spies et al\(^48\) demonstrated that the use of opioids may result in modulation of the stress response and result in improved outcomes. They linked the use of morphine to decreased cortisol concentrations, decreased rates of nosocomial pneumonia, and shorter hospital ICU lengths of stay in surgical patients undergoing GI surgery. In the other study by von Dossow et al\(^49\) the use of propofol as a general anesthetic, when compared with isoflurane, was associated with lower intraoperative cortisol concentrations, improved postoperative immune function, and lower rates of ICU-acquired sepsis in surgical patients with AUDs undergoing GI surgery. These data are particularly intriguing for patients undergoing emergency surgery and may provide an additional option to decrease the rate of nosocomial complications in patients with AUDs. In patients undergoing elective surgery, preoperative abstinence 1 month prior to surgery also is associated with diminished stress response and lower rates of postoperative complications.\(^47\)

Management of Withdrawal Syndromes

Despite receiving more sedation, a significant proportion (18%) of patients with AUDs in the hospital ICU setting will develop an acute withdrawal. Unfortunately, identifying patients at risk may be challenging due to altered patient sensorium, patient and family reluctance to provide accurate information on use of alcohol and other drugs, and failure of physicians to inquire about the use of alcohol. Although measurement of blood alcohol concentration is an easily obtainable test, no study to our knowledge has examined the relationship between blood alcohol concentration and the likelihood of developing alcohol withdrawal syndrome. An estimated 5% of patients with AUDs develop severe withdrawal or delirium tremens, which carries a mortality rate of 5% to 15%.\(^98,99\) Alcohol withdrawal syndrome typically manifests as agitation, but some patients present with vegetative symptoms rather than agitation. When confronted with sedated, nonverbal patients with known AUDs, clinicians would be appropriately reluctant to administer more sedating agents; however, this may be precisely what some patients require.

The revised Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) has been used successfully to monitor for acute alcohol withdrawal syndrome in hospital ICU patients.\(^91,101,102\) The CIWA-Ar was not designed originally for nonverbal patients in the hospital ICU, and it relies on autonomic signs and subjective symptoms. It is possible that the presence of other acute illnesses may contribute to increased CIWA-Ar scores unrelated to alcohol withdrawal, but to date, no study that we are aware of has evaluated confounding factors contributing to higher CIWA-Ar scores for alcohol withdrawal syndrome.\(^103\)

The key to treating withdrawal syndromes in the hospital ICU is to anticipate when they may occur and to treat vigorously to prevent new problems in patients who are critically ill.\(^100,104\) Dose of medication will depend on the patient and may vary widely among patients. Some patients may be treated with low doses of sedatives with adequate control, whereas others may need very-high-dose sedation and still continue to experience withdrawal. Benzodiazepines are the mainstay of therapy for alcohol withdrawal syndrome, but this class of medications recently has been associated with higher rates of delirium as well as longer duration of mechanical ventilation than propofol.\(^105-107\) Several studies have linked AUDs with the development of delirium in the ICU, but it is unclear whether the delirium is due to the choice of sedating medication or the underlying disorder.\(^108,109\) No specific benzodiazepine is superior to another for alcohol withdrawal syndrome treatment in the ICU, although longer-acting benzodiazepines, such as diazepam, may allow for a smoother withdrawal course.\(^110\) Either fixed-schedule therapy or symptom-triggered therapy with benzodiazepines (specifically lorazepam) is effective for treatment of alcohol withdrawal syndrome in medical inpatients outside the ICU setting, but patients receiving symptom-triggered therapy receive a lower total benzodiazepine dose.\(^108\) Compared with fixed-schedule therapy, symptom-triggered therapy with benzodiazepines is effective for alcohol withdrawal syndrome treatment in ICU patients and is associated with lower total benzodiazepine dose and reduced duration of mechanical ventilation.\(^102,111\) Severe alcohol withdrawal syndrome that is refractory to high-dose benzodiazepines has been treated successfully with the addition of phenobarbital or propofol.\(^106,112\) Weinberg et al\(^113\) have shown the use of IV alcohol infusion to be as equally effective as diazepam in the prevention of
alcohol withdrawal syndrome. However, in their study, alcohol infusion was associated with wider fluctuations in sedation level compared with diazepam administration. In addition, 19 of the 24 patients studied who received alcohol infusion never had a detectable blood alcohol concentration, suggesting that optimal dosage of alcohol infusion may be difficult to ascertain. We recommend that alcohol infusion be reserved for poisoning with methanol, isopropanol, or ethylene glycol and that it not be given for treatment of acute alcohol withdrawal syndrome due to complications such as intoxication with delirium or development of gastritis.

Asessing and medicating acute alcohol withdrawal syndrome is a necessary first step in the treatment of AUDs. After acute detoxification has begun, long-term treatment of addiction is necessary to prevent hospital readmission for continuing medical problems due to AUDs.

**CHALLENGES FACED BY ICU HEALTH-CARE PROVIDERS**

Health-care workers are victims of workplace violence more often than any other worker group, even police officers, 114,115 with AUDs, other drug use disorders, and psychiatric disorders being the most frequently implicated causes. 114-118 Violence occurs most frequently in EDs, psychiatric wards, and hospital ICUs. 116 The majority of ICUs (77%) report that nurses have experienced abuse, and 38% report that physicians have been subjected to violence. 117 Verbal abuse occurs even more frequently than physical abuse, but the majority of cases of verbal and physical abuse go unreported to the appropriate authorities. 116,117,118 Nurses who experience abuse report decreased job satisfaction, decreased productivity, and increased risk of making errors in addition to emotional distress. 116,118 ICU personnel must be vigilant while caring for patients with AUDs, particularly in volatile situations, because escalation to violence may occur rapidly.

**CONCLUSION**

AUDs are common comorbidities in patients who are critically ill and are associated with a host of complications that may result in increased resource utilization. Screening all critically ill patients for AUDs may aid clinicians in managing disease-related complications such as hemorrhage, sepsis, nosocomial pneumonia, and withdrawal. Sedation management in patients with AUDs may be particularly challenging due to the increased need for sedatives and opioids as well as the possibility of alcohol withdrawal syndrome. Diagnosis and management of alcohol withdrawal syndrome may be particularly challenging due to the nonverbal nature of many patients who are critically ill.

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