

Alcoholism and critical illness: A review

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Abstract

Alcohol is the most commonly used and abused drug in the world, and alcohol use disorders pose a tremendous

burden to healthcare systems around the world. The lifetime prevalence of alcohol abuse in the United States is estimated to be around 18%, and the economic consequences of these disorders are staggering. Studies on hospitalized patients demonstrate that about one in four patients admitted to critical care units will have alcohol-related issues, and unhealthy alcohol consumption is responsible for numerous clinical problems encountered in intensive care unit (ICU) settings. Patients with alcohol use disorders are not only predisposed to developing withdrawal syndromes and other conditions that often require intensive care, they also experience a considerably higher rate of complications, longer ICU and hospital length of stay, greater resource utilization, and significantly increased mortality compared to similar critically ill patients who do not abuse alcohol. Specific disorders seen in the critical care setting that are impacted by alcohol abuse include delirium, pneumonia, acute respiratory distress syndrome, sepsis, gastrointestinal hemorrhage, trauma, and burn injuries. Despite the substantial burden of alcohol-induced disease in these settings, critical care providers often fail to identify individuals with alcohol use disorders, which can have significant implications for this vulnerable population and delay important clinical interventions.

Key words: Alcoholism; Alcohol withdrawal delirium; Alcohol-related disorders critical illness; Intensive care; Pneumonia; Sepsis; Acute respiratory distress syndrome; Delirium; Trauma

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Core tip: Alcohol abuse is a major problem among hospitalized patients, and alcoholics are predisposed to developing critical illness while also facing increased rates of complications and mortality compared to non-alcoholics. The objective of this review is to examine the literature and summarize specific disorders encountered in intensive care unit settings that are impacted by alcoholism. Since alcohol use disorders are poorly recognized in hospitalized patients, this effort aims to raise awareness for critical care practitioners who frequently manage these susceptible

patients.

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INTRODUCTION

Social, pathological, and medicinal uses of alcohol have been a component of human tradition for thousands of years. While there are obvious therapeutic properties of alcohol, its excessive consumption poses a significant burden to healthcare systems in the United States and globally. Indeed, alcohol has become the most widely used and abused drug in the world^[1]. A national survey illustrated that more than 50% of individuals above the age of 12 drink alcohol regularly on at least a social level, almost a quarter participate in binge drinking, and 7% described habitual heavy consumption, which translates into over 17 million Americans^[2]. Epidemiological data report the lifetime prevalence of alcohol use disorders in the United States to be an astounding 18%^[3]. The economic consequences of alcohol abuse have been estimated to be upwards of \$200 billion annually, of which 11% is directly attributable to healthcare costs^[4]. These figures are also likely underestimated as they fail to incorporate data from patients whose alcohol use disorders went unrecognized by their clinicians, a situation that occurs commonly in inpatient settings.

Driven by the widespread systemic effects of alcohol, multiple comorbidities, and poor nutrition, individuals with alcohol use disorders frequently require hospital admission for ailments both related and unrelated to alcoholism. Studies on hospitalized patients have suggested that between 20% to 40% of inpatients have alcohol-related conditions^[5-7]. The effect is particularly felt in medical and surgical intensive care units (ICUs), which have been overwhelmingly impacted by the burden of unhealthy alcohol use. Alcoholics are not only at an increased risk for suffering critical illness, but they also experience a greater likelihood of complications, poorer outcomes, and increased healthcare utilization compared to those patients who do not have alcohol use disorders. Despite these observations, recognition of alcohol use disorders in hospitalized patients and particularly among individuals in the ICU is inadequate. This review will focus on specific conditions encountered in the critical care setting that are impacted by the considerable burden of pathologic alcohol consumption.

RECOGNITION OF ALCOHOL USE DISORDERS

The National Institute on Alcohol Abuse and Alcoholism

(NIAAA) recognizes the potential benefits of moderate alcohol consumption. According to dietary guidelines, "moderate" is considered to be an average of no more than two standard drinks per day for men and one standard drink per day in women^[8]. Research from the NIAAA shows that staying within these weekly limits as well as not exceeding more than 3 drinks in any given day for women and 4 drinks for men poses a very low risk for developing an alcohol use disorder (AUD). An AUD is an unhealthy pattern of alcohol use that causes significant clinical impairment and has been explicitly defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) to meet at least two of 11 specified criteria^[9]. The total number of criteria that are satisfied determines the severity, with two to three symptoms denoting a mild AUD, four to five signifying a moderate disorder, and six or more representing a severe problem. The DSM-V has abandoned the categorizations of "alcohol abuse" and "alcohol dependence" that were previously defined in the earlier edition, DSM-IV^[10]. While alcohol abuse and dependence represent different physiological effects of alcohol, for classification purposes these terms have been replaced with the single characterization of an alcohol use disorder.

Given that AUDs are common in critical illness and contribute significantly to morbidity and mortality, it is surprising that we are so poorly equipped to recognize the presence of these disorders in this population. Excessive alcohol use impacts one out of every four to five admissions to the ICU^[11]. One review of the literature reported this frequency to be as high as 33%^[12], and the rate of AUDs are even higher among patients admitted after traumatic injury^[13]. In parallel, studies among hospitalized patients with alcohol use disorders revealed that clinicians correctly identified the diagnosis in only 25% of cases^[14], and in critical care settings almost three quarters of surveyed ICUs used no tool to assess for alcohol use disorders and alcohol withdrawal syndromes^[15]. Several explanations may support these findings. First, individuals with alcohol use disorders may not always be forthcoming about the extent of their drinking, and worse, may not recognize that they themselves have a problem. Second, during acute illness-and especially in the ICU setting-patients may be unable to provide history or suffer from alteration in mentation that either precludes the gathering of this information or renders it significantly more challenging. Finally, practitioners may fail to elicit this history for a variety of reasons, such as a perceived lack of relevance of this information to the acute presentation. Regardless of the rationale, failure to recognize the impact of alcohol-related disease during critical illness can have significant implications for this vulnerable patient population. Precisely, it is important for critical care providers to understand that the potential for complications from acute interventions is heightened, and possible therapeutic opportunities may be delayed if alcohol use disorders are not appropriately identified.

ALCOHOL, DELIRIUM AND WITHDRAWAL SYNDROMES

Delirium is an acute state of confusion that is characterized primarily by inattentiveness. While many risk factors have been identified, medical illness commonly precipitates as well as exacerbates delirium. Thus, it occurs with high prevalence among hospitalized patients. Experts reveal that delirium occurs in about 30% of older patients at some point in time during their hospitalization, and individuals who develop delirium during their hospital stay have greater morbidity and mortality than those who do not^[16,17]. In the ICU, delirium may perhaps be the most commonly encountered diagnosis with its reported prevalence reaching as high as 70%-90% depending on the patient population and method of assessment^[18,19].

In a recent study, Mehta *et al*^[20] assessed different risk factors for the development of delirium among critically ill, mechanically ventilated patients and found that delirium was significantly more common among those with a history of alcohol use compared to those without this history. Importantly, in this same study, those individuals that developed delirium had a longer duration of mechanical ventilation, a greater likelihood of requiring tracheostomy, and an overall longer hospital stay compared to those who did not develop delirium. Alcohol abuse as a risk factor for the development of delirium was also confirmed in a recent meta-analysis^[21]. In the multivariate analysis, alcohol use had the highest odds ratio for the development of delirium after advanced age and mechanical ventilation. This key finding suggests that an assessment for alcohol use is absolutely necessary in critical care settings to identify those individuals who have a greater propensity towards experiencing delirium and ultimately poor outcomes. While many risk factors cannot be modified, it would be valuable to identify those patients with the greatest threat of developing delirium so that clinicians acknowledge and readily act upon those factors that are modifiable.

Recognition and identification of alcohol use disorders in critically ill patients is essential for a variety of other reasons as well. Specifically, chronic alcohol consumption significantly increases possibility of developing alcohol withdrawal syndromes, which include withdrawal seizures, alcoholic hallucinosis, and delirium tremens. Withdrawal syndromes, and especially delirium tremens, can be life threatening and occur in about 20% of alcoholics who stop drinking acutely^[22]. Given the prevalence of alcohol use disorders in ICUs, this represents a significant burden among critically ill patients. Further, treatment of alcohol withdrawal syndromes has been linked to greater morbidity and resource utilization particularly in the ICU^[23]. Delirium tremens carries a mortality rate between 5% and 15%^[24], and treatment guidelines underscore the importance of early identification to ensure better effectiveness of therapy in these individuals. Despite its life-threatening nature, there continues to be a relative lack of data on how best to identify, screen, and prevent

patients with a history of alcohol abuse from developing withdrawal syndromes, but the awareness of alcohol use disorders during critical illness is paramount.

ALCOHOL, PNEUMONIA, AND ASPIRATION

The connection between alcohol use and respiratory infections can be traced back over a century. William Osler in his book *Principles and Practice of Medicine* noted that a tendency towards alcohol abuse was extremely important in predisposing individuals to developing pneumonia^[25]. In the United States, pneumonia is the eighth most common cause of death overall and the leading cause of death from an infection. Given the high morbidity and mortality associated with pneumonia, it is a commonly encountered diagnosis in the ICU. Further, pneumonia not only often necessitates ICU admission, it can also occur as a complication critical illness after traumatic injury, post-operative status, and mechanical ventilation.

More recent studies have continued to uphold the finding that alcoholism is an important risk factor for the development of both "typical" pneumonias as well as more severe respiratory infections caused by more virulent and atypical organisms. In a study among patients with community-acquired pneumonia, de Roux *et al*^[26] showed that *Streptococcus pneumoniae* was seen more frequently and occurred with higher severity scores in alcoholics compared to non-alcoholics. In another prospective study among patients admitted with community acquired pneumonia, Chalmers *et al*^[27] performed multivariate regression analysis and found that a history of alcohol use was an independent risk factor for the development of complicated parapneumonic effusion and empyema, further illustrating that alcoholic subjects have a more complex disease course even with so-called typical infections^[27]. Prior to these investigations, Marik^[28] undertook a study to identify clinical, microbiological, and prognostic features of patients with septic shock from community-acquired pneumonia. He showed that patients who presented with infections secondary to *Pseudomonas* and *Acinetobacter* had a particularly high mortality greater than 80%. In his study, the only variable that identified patients who developed infections from these virulent organisms was a history of alcohol abuse. In parallel, a prospective study by Bochicchio *et al*^[29] implicated alcohol abuse in both the severity and frequency of ventilator-associated pneumonias in trauma patients admitted to the ICU.

There are several mechanisms that predispose individuals with alcohol use disorders to the development of these more severe pneumonias. First, chronic alcohol consumption alters the oropharyngeal flora such that is colonized by more gram-negative organisms^[30]. Second, states of inebriation blunt upper airway reflexes and render these individuals more susceptible to aspiration of these more virulent bacteria^[31]. Third, experimental

models have demonstrated that chronic alcohol exposure impairs normal host defense mechanisms of the airway such as mucociliary clearance^[32]. Finally, pathologic alcohol consumption impairs function of the primary innate immune cell of the lower airways—the alveolar macrophage—in both experimental models and human subjects^[33-37]. Taken together, these data highlight the significant alterations in host immunity that predispose alcoholics to the development of lower respiratory tract infections.

ALCOHOL AND SEPSIS

Sepsis is a systemic inflammatory syndrome that occurs as a result of a severe infection. It is a leading cause of death in the hospital and, as a result, is a frequently encountered diagnosis in the ICU. Studies have indicated the incidence is rising and amounts to more than a million cases annually^[38]. Importantly, the mortality from sepsis is substantial and increases across the spectrum from SIRS to septic shock, which has a mortality rate close to 50%^[39]. The role of alcoholism in increasing the risk and severity of sepsis has been shown in both experimental models and human studies. In 2013, Yoseph *et al*^[40] demonstrated that mice that were alcohol-fed for 12 wk have almost double the mortality as water-fed mice when they were subjected to the same septic insult. The authors concluded that alcohol altered intestinal integrity and host immune response, which explained the significant difference in mortality. The prior year, Barros *et al*^[41] showed similar findings in rats that were alcohol-fed for 4 wk. Interestingly, when the alcohol-fed rats were separated into two groups based on amount of alcohol consumed, they found that mortality was six fold higher on animals that received higher doses of alcohol compared to those receiving lower amounts of alcohol. In fact, those animals that consumed less alcohol had mortality rates similar to those that did not receive any alcohol at all. These findings are consistent with the idea that in moderation alcohol is not harmful, but excessive consumption is detrimental to health. These authors also demonstrated that cytokine profiles were significantly different in alcohol-fed compared to control-fed rats, indicating that chronic alcohol consumption led to a greater severity of infection. Several other experimental sepsis studies are consistent with the idea that sepsis has worse outcomes in the setting of alcohol abuse^[42-44].

Human studies have largely been consistent with the well-established findings in experimental models that chronic alcohol use both predisposes to and worsens outcomes of sepsis. Specifically, when O'Brien *et al*^[45] examined over 11000 patients admitted to the ICU of two urban hospitals over a six-year time frame, they found that alcohol dependence was independently associated with sepsis, septic shock, and mortality. Previously, Moss *et al*^[46] showed in a prospective epidemiological study of 220 critically ill

patients with septic shock that alcohol abuse was a significant risk factor for developing both pulmonary and non-pulmonary organ dysfunction. Taken together, these findings—along with an abundance of supporting experimental studies—highlight that the presence of alcohol use disorders, independent of other patient and illness characteristics, leave individuals vulnerable to infection, which occur with greater severity and more complications, compared to those who do not abuse alcohol.

ALCOHOL AND ACUTE RESPIRATORY DISTRESS SYNDROME

Acute respiratory distress syndrome (ARDS) is a form of inflammatory lung injury and hypoxemic respiratory failure with specific clinical and pathological features. It affects about 200000 individuals in the United States annually and carries a mortality risk that ranges anywhere from 20% to 50%^[47]. It is a common diagnosis in the ICU and occurs in about 15% to 20% of all patients that require mechanical ventilation. Important risk factors for the development of ARDS include sepsis, traumatic injury, pneumonia, and aspiration. As discussed earlier in this review, each of these risks is significantly increased in the alcoholic patient.

A landmark study in 1996 identified alcohol abuse as an independent risk factor the development of ARDS^[48]. In this prospective study, 351 individuals from medical and surgical intensive care were enrolled if they had a previously identified risk factor for ARDS. The incidence of ARDS for the entire population was 29%, but those with a history of alcohol use had almost twice the incidence compared to non-alcoholics (43% vs 22%). The risk was even higher among those specific patients with sepsis as their risk factor. In this group, 36% developed ARDS, but alcoholics had an incidence of 52% compared to 20% among non-alcoholics, more than doubling the risk. More importantly, mortality was also significantly higher among alcoholics who developed ARDS. In the aforementioned follow-up study by Moss *et al*^[46] performed in patients with septic shock, the risk for developing ARDS was an astounding 70% for those who had a history of alcohol abuse compared with 31% for those who did not have this history.

These initial observations in ARDS patients inspired a great deal of investigation on the mechanisms by which alcohol abuse increases susceptibility to lung injury and ARDS. Animal models have focused on the alveolar epithelium, as leakiness of this barrier system and consequent pulmonary edema is the characteristic finding in ARDS. It is worth mentioning that alcohol abuse plays a complex and compounding role in lung injury, as pneumonia, sepsis, aspiration, and traumatic injury are leading risk factors for the development of ARDS, but alcohol abuse by itself does not cause injury unless it is coupled with an additional insult. However, experimental studies have demonstrated that alcohol abuse primes

the alveolar epithelium for injury by promoting oxidative stress^[49], increasing epithelial permeability and protein leak^[50], and impairing fluid clearance through alterations in tight junction proteins within the epithelial barrier^[51]. These findings at least partially explain why alcoholics, independent of their risk for developing pneumonia and sepsis, are more likely to develop acute lung injury. While we still do not have any approved therapies aimed explicitly at reversing alcohol-induced pulmonary dysfunction, experimental investigations and early human studies show promise that specific nutritional supplements and antioxidants may one day have a role in the treatment of this phenotype^[33,52-54].

ALCOHOL AND GASTROINTESTINAL ILLNESS

Chronic alcohol consumption has deleterious effects throughout the entire gastrointestinal system, including the liver, pancreas, esophagus, gastric mucosa, and malabsorption syndromes involving the small intestine. Cirrhosis of the liver is the characteristic organ dysfunction induced by longstanding unhealthy use of alcohol. According to the American Liver Foundation, in the United States alcoholism is the number one cause of cirrhosis and chronic liver disease, which combine to represent the twelfth most common cause of death in the country^[55]. In addition to morbidity and mortality associated with cirrhosis itself, it is an important comorbidity that portends a worse prognosis in critical illness as well. For instance, Watari *et al*^[56] evaluated mortality and prognostic factors in individuals admitted for community-acquired pneumonia and found that liver cirrhosis was one of three factors that was associated with 30 d mortality. Importantly, cirrhosis was the only factor that was a pre-existing condition as the other two predictors-hypotension and hypoxemia-were directly related to the severity of actual infection.

In addition to liver disease, other gastrointestinal illnesses are also affected by alcoholism. For instance, acute pancreatitis is the most common gastrointestinal cause of hospitalization in the United States, with alcohol-induced disease accounting for 30% of cases^[57,58]. This finding represents a significant disease burden and many of these cases-and especially severe forms-require ICU admission. Gastrointestinal hemorrhage is also a frequent cause of ICU admission and has a significant disease burden with an annual incidence of about 100 cases per 100000 in the United States^[59]. In this study, peptic ulcer disease, mucosal erosions, and esophageal varices made up over 80% of cases, all of which are impacted by alcohol abuse. Alcoholism has been implicated in peptic ulcer disease^[60,61], and alcohol-induced gastropathy and gastro-esophageal varices are known complications of alcoholic cirrhosis. While an alcohol abuse history is more predictive of a variceal source of gastrointestinal hemorrhage^[62], studies have clearly shown that alcoholics are significantly more likely to have complications such as rebleeding from non-variceal sources of blood loss as

well^[63,64]. Taken together, these observations illustrate the profound impact that alcohol use disorders have in gastrointestinal disease and critical illness.

ALCOHOL AND TRAUMA

Trauma is one of the leading causes of mortality worldwide, and in the United States is the leading cause of death in those under the age of 35^[65]. The Centers for Disease Control and Prevention reports that approximately 50 million individuals receive medical care for trauma annually, and traumatic injury comprises upwards of 30% of all ICU admissions^[66]. The role of alcohol use has long been recognized as a contributor to traumatic injury for both unintentional (*i.e.*, fire, fall, motor vehicle accident, drowning) and intentional (*i.e.*, suicide, homicide, assault) injuries and death. It is estimated that 50% of all alcohol-related deaths are due to injury, and alcohol is the third leading cause of preventable death in the United States^[67].

Studies examining the effects of alcohol intoxication at the time injury have produced conflicting results. Blondell *et al*^[68] evaluated over 1300 patients hospitalized after traumatic injury and found that almost a quarter of them had positive blood alcohol levels, while a similar study by Cornwell *et al*^[69] found that more than 50% screened positive for blood alcohol levels. Interestingly, Blondell *et al*^[68] found that those that were acutely intoxicated had shorter lengths of stay and lower mortality rates. Other studies have shown worse outcome for acute intoxication^[70,71], while some have shown no difference when compared to patients that are not intoxicated^[69,72]. There may be several reasons for this conflicting data. First, these studies only examine the effect of acute intoxication on patients with trauma, which may not represent those that have chronic alcohol use disorders. Second, blood alcohol concentrations at the time of presentation may not tell an accurate story of the true alcohol exposure depending on the time that elapsed between exposure and presentation. Third, studies may use different cutoffs for blood alcohol concentration in order to be categorized as "intoxicated". Similarly, in this instance the blood alcohol concentration may not be representative of actual intoxication at the time of injury, and continues to fail in identifying the extent of chronic exposure. One study by Jurkovich *et al*^[73] aimed to reconcile these differences by comparing the effect of acute intoxication against those that had an actual history of chronic alcohol abuse. Similar to Blondell's study, they found that acutely intoxicated patients had shorter lengths of stay and better outcomes, but those with behavioral and biochemical evidence of chronic alcohol abuse had a two-fold increase in complication rate. The complications seen in this study were consistent with known risk factors for alcoholics, including pneumonia and other infections. Later studies evaluating trauma and surgical patients are also consistent with findings that individuals with a chronic alcohol abuse experience worse outcomes^[74-76].

While the effect of acute intoxication on trauma

outcomes in general may show conflicting results, the effect on burn injury is much more convincing. Specifically, the results of large review on the topic by Howland and Hingson^[77] demonstrated that 50% of all people who died in a fire were legally intoxicated. A later study by McGill *et al*^[78] compared alcohol users, drug users, and control subjects. They found that both alcohol users and drug users suffered significantly more severe burn injuries compared to control subjects. Mortality among alcohol users was twice that of drug users and six times that of control subjects. This study was interesting in that alcohol users, despite a similar injury pattern, had worse outcomes when compared to other substance abusers. In this study, it may not be completely unbiased to compare outcomes between the alcohol group and the control group since the extent of injury was more severe among the alcoholics. However, a more recent case-control study by Silver *et al*^[79] matched burn-injured patients with a positive blood alcohol concentration to those without alcohol exposure. Due to the matching design, these researchers were able to match the control group by age, gender, and extent of injury (*i.e.*, total body surface area involved, inhalation injury, *etc.*). Despite a similar injuries and mechanism, those burn victims with positive blood alcohol concentration had significantly worse short-term and long-term outcomes with higher severity of illness scores, greater fluid requirements, worse acidemia, more than three-fold longer duration of mechanical ventilation, and more than double the ICU length of stay compared to matched controls. Taken together, these studies demonstrate the significant detrimental effects of alcohol exposure on burn injury outcomes.

OTHER CONSIDERATIONS

A history of alcohol abuse also has implications for critically ill patients undergoing surgery^[75,80-83]. The accumulated data from these studies suggest that patients with alcohol use disorders who undergo surgery have greater risks for complications, including delayed wound healing, pneumonia, and infection. They also have longer ICU lengths of stay and increased mortality. These observations are analogous to the conclusions derived from studies on non-surgical alcoholic patients and suggest that surgeons may need to be judicious about considering major elective surgery in these susceptible patients.

While the focus of this review has been on known complications of alcoholism during critical illness, there is a potential for alcohol use disorders to play a role in previously unstudied associations. For instance, critical illness polyneuropathy (CIP) and myopathy (CIM) are significant complications of critical illness. Sepsis, systemic inflammatory response syndrome, multiple organ failure, and prolonged critical illness are crucial risks for developing CIP and CIM^[84,85], and intriguingly these same factors are known threats that alcoholics face. Further, alcoholics are clinically prone to both myopathies and neuropathies^[86,87]. While the risk for CIP and CIM with alcohol abuse has not been

formally established, this may have specific implications for management. Experimental studies show that oxidative stress plays a role in alcoholic myopathy, and reversing this oxidant stress is able to attenuate the myopathy^[88-90].

CONCLUSION

Alcohol use and abuse are commonplace in society and present a major burden for our healthcare system. Alcohol use disorders not only predispose individuals to develop critical illness, but also leave these vulnerable patients with longer ICU stays, more complications, and ultimately greater mortality. Despite the pervasiveness of alcohol use disorders in hospitalized patients, and especially among those admitted to the ICU, recognition of these disorders remains poor and no guidelines exist on the best way to screen for alcohol dependence and risk for withdrawal syndromes. While there may be several explanations for why alcohol use disorders are not consistently identified in the ICU setting, critical care providers should employ any and all methods to better evaluate their patients for these conditions and their potential implications. While there are currently limited therapeutic options aimed directly at combating the alcohol-induced organ dysfunction experienced by critically ill patients, earlier identification will allow for more timely intervention and an opportunity to assist these individuals to confront their addiction. Hopefully, this approach will lead to improved outcomes as we await newer treatments to benefit this susceptible patient population.

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