

Alcohol withdrawal syndromes in the intensive care unit

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This article reviews the pathophysiology, diagnosis, and treatment of alcohol withdrawal syndromes in the intensive care unit as well as the literature on the optimal pharmacologic strategies for treatment of alcohol withdrawal syndromes in the critically ill. Treatment of alcohol withdrawal in the intensive care unit mirrors that of the general acute care wards and detoxification centers. In addition to adequate supportive care, benzodiazepines administered in a symptom-triggered fashion, guided by the Clinical Institute Withdrawal Assessment of Alcohol scale, revised (CIWA-Ar), still seem to be the optimal strategy in the intensive care unit.

In cases of benzodiazepine resistance, numerous options are available, including high individual doses of benzodiazepines, barbiturates, and propofol. Intensivists should be familiar with the diagnosis and treatment strategies for alcohol withdrawal syndromes in the intensive care unit. (Crit Care Med 2010; 38[Suppl.]: S494–S501)

KEY WORDS: alcohol withdrawal syndrome; Clinical Institute Withdrawal Assessment of Alcohol scale; pharmacology; intensive care unit; detoxification; benzodiazepine; barbiturates; propofol

Alcohol is the most frequently abused drug throughout the world (1). According to the National Survey on Drug Use and Health 2008, slightly more than half of Americans ≥ 12 yrs old (51.6%) reported drinking alcohol. This translates into an estimated 129.0 million people, of whom 23.3% (approximately 58 million people) of these people had participated in binge drinking at least once 30 days before the survey. Heavy drinking was reported by 6.9% of the population aged ≥ 12 yrs, or 17.3 million people (2, 3).

It is well known that alcohol and alcohol withdrawal play a significant role in traumas, burns, suicides, and visits to the emergency department. In one study, nearly 8% of all hospital admissions, 16% of postsurgical patients, and 31% of trauma patients developed alcohol withdrawal (4). The higher prevalence in trauma patients has been confirmed in other studies (5) and reflects the high association of alcohol use with numerous types of trauma. Alcohol use has been implicated in up to 86% of homicides, 37% of assaults, and 25% to 35% of non-fatal motor vehicle accidents (6). The de-

velopment of alcohol withdrawal in postsurgical and trauma patients is extremely serious and can increase the mortality in this population nearly three-fold (7, 8).

The effects of alcohol and the withdrawal from it have been noted since the early first century B.C. when Pliny the Elder wrote, in his work *Naturalis Historia*, "... drunkenness brings pallor and sagging cheeks, sore eyes, and trembling hands that spill a full cup, of which the immediate punishment is a haunted sleep and unrestful nights" (9). Treatment and understanding for this state have evolved significantly over the years. At the beginning of what is considered "modern medicine," Osler was able to keep mortality to approximately 14% by confining patients to bed without the use of restraints, withholding alcohol, and judiciously using potassium bromide, chloral hydrate, hyoscine, and possibly opium (10). Cecil (11) in 1927 wrote that it was essential to produce sleep, stimulate the neurologic and circulatory systems, and feed the patient. By the late 1930s, the mortality rate had begun to decrease significantly from nearly 50% at the turn of the century to as low as 10%. This was attributed to better nursing care and hydration, emphasizing the importance of adequate supportive care (12).

Pathophysiology of Alcohol Withdrawal Syndrome

Interestingly, despite its wide prevalence, as demonstrated by one hospital having nearly 10,000 admissions/yr for alcohol-related disorders in the early 20th

century (13), it was not until the late 1950s that it was definitively proven that the alcohol withdrawal syndrome (AWS) is a compilation of physiologic manifestations that occur on a continuum as a response to the abrupt disuse or reduction of alcohol consumption (14). These responses range from mild jitteriness to seizures and death. Over the past two decades, researchers have made significant progress in understanding the neurophysiology of alcohol addiction and withdrawal. Most notably, the gamma-aminobutyric acid type-A (GABA-A) receptors and the *N*-methyl-D-aspartate (NMDA) receptors play a critical role in the manifestations of alcohol dependence/tolerance and the alcohol withdrawal syndrome (15–17). The monoamine neurotransmitters, serotonin and dopamine, likely also play a role in the rewarding and reinforcing effects of alcohol (18).

The acute ingestion of alcohol inhibits the excitatory (NMDA) receptors, which reduce the release of the neurotransmitter glutamate. Activation of the inhibitory GABA-A type receptor during alcohol exposure leads to anxiolytic and sedative effects, as well as impairment of motor coordination. As alcohol ingestion becomes chronic, GABA-A receptor function is decreased, and the NMDA receptors are up-regulated, leading to tolerance (15–17, 19). In the absence of alcohol, NMDA receptor function is increased and the tonic inhibition provided by GABA-A receptors is reduced. This "two-hit" phenomenon of increased excitation and loss of suppression results in the clinical manifestations of autonomic

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excitability and psychomotor agitation (17). There is some belief that the dysregulation of the dopaminergic system also plays a role in the signs and symptoms of AWS. Studies (20) documented a strong association between the A9 polymorphism in the dopamine transporter and the development of alcohol withdrawal. Furthermore, increases in dopamine may be directly related to the hallucinations observed in alcohol withdrawal (21).

Diagnosis and Clinical Manifestations

The diagnosis of alcohol withdrawal is based on history and physical findings. Although it may seem obvious to be in "withdrawal," a patient must have recently stopped ingesting alcohol or reduced consumption from that of baseline for the patient. This is the first diagnostic criteria for this syndrome in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (22). In addition, the symptoms must not be due to a general medical condition, of which there are many in the critical care population. The remainder of the criteria is outlined in Table 1. However, unlike alcohol withdrawal, delirium tremens (DTs), as defined in *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, is associated with either: 1) disturbance of consciousness (i.e., reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention, delirium, confusion, and frank psychosis; or 2) a change in cognition (such as memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not better accounted for by a preexisting, established, or evolving dementia (22).

There are four clinical states of alcohol withdrawal: 1) autonomic hyperactivity; 2) hallucinations; 3) neuronal excitation; and 4) DTs (23). These states occur along a timeline relative to time from the reduction in alcohol intake, but patients do not progress linearly from one stage to the next, often skipping one or more of them. Previous withdrawal events may play a role in the severity of symptoms experienced in alcohol withdrawal. In 1978, Ballenger and Post (24) proposed that the increase in central nervous system hyperexcitability that occurs with each successive withdrawal episode was the result of "kindling." This particularly seems to play a role in alcohol withdrawal seizures, and this may explain

Table 1. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria for alcohol withdrawal

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- A. Cessation of (or reduction in) alcohol use that has been heavy and prolonged
 - B. Two (or more) of the following, developing within several hours to a few days after criterion A
 - 1. Autonomic hyperactivity (e.g., sweating or pulse rate >100 beats/min)
 - 2. Increased hand tremor
 - 3. Insomnia
 - 4. Nausea or vomiting
 - 5. Transient visual, tactile, or auditory hallucinations or illusions
 - 6. Psychomotor agitation
 - 7. Anxiety
 - 8. Grand mal seizures
 - C. The symptoms in criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
 - D. The symptoms are not due to a general condition and are not better accounted for by another mental disorder
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the clinical observation of increasing severity of alcohol withdrawal among individual subjects, and the development of benzodiazepine-resistant alcohol withdrawal (25–27). However, although well described in laboratory studies where repeated episodes of alcohol withdrawal lead to persistent and progressive electroencephalographic abnormalities, with further episodes of withdrawal becoming increasingly resistant to benzodiazepines, it is unclear of the clinical relevance in humans (27).

Most people who go through alcohol withdrawal have minor symptoms and can be treated as an outpatient, as most alcoholics do with their "morning eye opener." This uncomplicated withdrawal syndrome can occur as early as 6 hrs from alcohol reduction/cessation and typically peaks within 24–48 hrs. Uncomplicated alcohol withdrawal is notable for patients having a clear sensorium. However, they suffer from autonomic hyperactivity and increased sympathetic outflow, causing symptoms such as diaphoresis, nausea, vomiting, anxiety, tremor, and agitation. This is secondary to increased levels of circulating catecholamines (28).

Approximately 30% of patients will suffer from alcoholic hallucinosis. This typically occurs within 8–48 hrs after a decrease in alcohol consumption and lasts between 1–6 days (28, 29). Although all types of hallucinations have been described, visual and tactile are most common, with auditory being relatively uncommon and should suggest other causes of hallucinations. Tactile hallucinations include formication, or the sensation of ants crawling on the skin, which can result in repeated itching and excoriations. Alcoholic hallucinosis is distinguished from DTs by the presence of a clear sensorium. The presence of alcoholic hallu-

cinosis is neither a positive or negative predictor for the subsequent development of DTs (19).

Alcohol withdrawal seizures occur in up to 10% of patients, and they arise within 12–48 hrs after decreased alcohol intake. They are typically brief tonic-clonic seizures and may be single in nature, but 60% of people have multiple seizures. Sustained status epilepticus is typically not related to alcohol withdrawal but to some other organic neurologic disorder and occurs in <4% of patients diagnosed with alcohol-related seizures (30, 31). Not all seizures in patients experiencing alcohol withdrawal are alcohol withdrawal seizures. Approximately 50% of these seizures are a result of some other organic cause, such as repetitive brain trauma; thus, alcohol withdrawal seizure is still a diagnosis of exclusion (8, 32). Other signs of alcohol withdrawal, namely, autonomic hyperactivity, may not be associated with these seizures, and in chronically alcohol-dependent patients, the seizures may occur while the patient has blood alcohol levels that exceed the legal limit of intoxication (33–35). However, it should be stressed that the presence of alcohol withdrawal seizures is not predictive of the development of alcoholic hallucinosis, DTs, or even uncomplicated alcohol withdrawal.

Approximately 5% of patients will develop DTs, which typically occur 48–72 hrs after their last drink. The hallmark of this phase of withdrawal is delirium combined with autonomic hyperactivity and alcohol hallucinosis. Physiologically, this manifests as tachycardia, hypertension, and fevers with a subsequent increase in oxygen consumption, respiratory alkalosis, and decreased cerebral blood flow.

Due to the hypermetabolic state, it is not uncommon to have dehydration and electrolyte abnormalities, specifically hypomagnesemia, hypophosphatemia, and hypokalemia (36). Although basic supportive care aimed at treating dehydration has dramatically reduced the mortality in patients with isolated DTs (12), these physiologic derangements may be additive or synergistic in nature, contributing to morbidity and mortality in patients with other underlying physiologic stress, such as trauma and surgery (7, 8). In a retrospective review of >6,000 trauma patients with low injury severity scores, patients who developed AWS, compared with those who did not, had increased rates of respiratory failure, pneumonia, urinary tract infections, sepsis, tracheostomy, and percutaneous endoscopic gastrostomy tube placement. This correlated with an increase in hospital length of stay and cost (37).

Prediction and Prevention

One of the mainstays of treatment of alcohol withdrawal is to prevent its onset in high-risk populations. Multiple studies have tried to better identify those at risk for the development of alcohol withdrawal and DTs. The strongest predictor for the development of withdrawal syndromes is either a personal or family history of alcohol withdrawal or DTs (38). The strong contribution of family history suggests a genetic component toward susceptibility of development of withdrawal states. This is supported by small studies identifying polymorphisms in the dopamine A9 allele and neuropeptide Y gene in development of alcohol withdrawal (20, 39). Interestingly, race also seems to be a predictor of development of DTs. In one study, African Americans, although comprising 45% of emergency department admissions with alcohol abuse, comprised only 16% of patients admitted to the intensive care unit (ICU) with severe or benzodiazepine-resistant DTs (40).

As it is often difficult to obtain reliable history in this patient population, especially in the setting of trauma, numerous attempts have been made to develop biochemical predictors for the presence and/or severity of alcohol withdrawal. Although consistent abnormalities in readily obtained laboratory values are observed in patients with alcohol withdrawal (e.g., aminotransferases, magnesium, erythrocyte parameters), their role

in predicting the severity of alcohol withdrawal is poorly described. In addition, there is a negative association between the presence of severe alcohol withdrawal and histopathologic cirrhosis, further clouding the utility of routine liver function tests for prognostication (41). Finally, although plasma homocysteine levels have been useful in the prediction of withdrawal seizures, they have been of little value in the prediction of other withdrawal states (42).

Admission ethanol levels have also been tested as a predictor for the severity of alcohol withdrawal in at-risk subjects. An ethanol level of >150 mg/dL on admission had a 100% sensitivity and a 57% specificity for the need of acute care for treatment of alcohol withdrawal (43). In a similar study, at a different treatment facility, an ethanol concentration of >150 mg/dL had an 81% positive predictive value for the need to use more than a single dose of chlordiazepoxide for the treatment of alcohol withdrawal, with a similar predictive value for development of withdrawal seizures identified (43). However, these results have not been consistently reproduced, with other studies failing to find any association between ethanol levels and development of any type of withdrawal state (34, 44). There are many potential explanations, including differences in patient population, differences in cohort size, and the potentially late onset of DTs at a time when ethanol levels would be extremely low or nonexistent (44).

Managing Alcohol Withdrawal

Supportive care

The basic principles of managing alcohol withdrawal have not changed much since the early 20th century. The goals of care are to keep the patient safe as they experience the symptoms of withdrawal: alleviate symptoms; prevent progression of symptoms; and treat underlying comorbidities. In a sense, let them “sleep it off.” Ideally, the patient should rest comfortably but be easily awakened. Adequate airway protection, intravenous access, and resuscitation must be instituted. The importance of volume resuscitation cannot be stressed enough. There is a high prevalence of intravascular volume depletion among alcoholics. In one study, of 39 deaths attributed to DTs in which volume status was recorded, all subjects were volume depleted (12). In addition, the pa-

tient must be supported nutritionally. It is well known that alcohol-dependent patients often have grossly inadequate nutritional intake at baseline and present with severe malnutrition and often dehydration (45, 46). Wernicke encephalopathy due to thiamine deficiency is commonly seen in this population and manifests as ophthalmoplegia, nystagmus, mental status changes, and unsteadiness of stance and gait. Parenteral supplementation of thiamine before the administration of glucose and carbohydrates will reverse these symptoms (47, 48). For those patients in the surgical ICU, nutrition issues are of even greater importance, because having adequate nutrition is essential to healing surgical wounds, preventing the development of new wounds, and preventing postoperative infections. Several studies (49–53) have shown that chronic alcohol consumption impairs the immune system, which is critical in wound healing.

Finally, providers must be acutely aware that delirium in the ICU may have one or more etiologies other than DTs. Sleep deprivation, history of anesthesia, and organ dysfunction are well known to induce or exacerbate delirium in the ICU. Furthermore, sepsis can cause fever, tachycardia, and delirium mimicking many of the signs and symptoms of alcohol withdrawal. This can be exacerbated by the presence of both hypercapnic and/or hypoxic respiratory failure. A similar constellation of findings are also observed in trauma patients, such as evolving brain injury or fat emboli syndrome. In addition, one must have a high index of suspicion for coexisting multiple substance abuse. A thorough substance abuse history should be obtained from the patient or family. Urine toxicology screening may be helpful to assess for the presence of other drugs of abuse at the time of admission. Cocaine intoxication, opioid, marijuana, and methamphetamine withdrawal all share common symptoms: irritability, anxiety, nausea, agitation, tachycardia, and hypertension. Treating one syndrome may mask symptoms of another that is also present, which may cause life-threatening complications.

Benzodiazepines are the primary pharmacologic agent for the treatment of AWS. Benzodiazepines act as GABA receptor agonists and function as an alcohol replacement. Their role was established in a landmark study (54) where 547 patients were randomized to one of four drugs (chlordiazepoxide, chlorpromazine, hydroxyzine, and thiamine) or placebo for the treatment

of alcohol withdrawal. Patients receiving chlordiazepoxide had the lowest incidence of both DTs and alcohol withdrawal seizures, establishing benzodiazepines as the first-line agent for treatment of alcohol withdrawal. Of note, use of the neuroleptic chlorpromazine was associated with a significant increase in seizures and nearly identical rate of delirium compared with placebo (54).

There is little evidence to support the use of one benzodiazepine over another (36, 47, 55, 56). Therefore, other factors will dictate drug choice. Pharmacokinetics is one important factor in this decision making. Chlordiazepoxide is only available in oral forms and, thus, may not be appropriate for acute management where rapid onset of action is required or in patients unable to take *per os* medication. For patients with cirrhosis, benzodiazepines which are not hepatically metabolized into active metabolites, such as lorazepam and oxazepam, are preferred due to their more predictable pharmacokinetics. Chlordiazepoxide and diazepam have significantly longer half-lives, which may aid in a smoother course of withdrawal and may be superior in seizure and delirium management (57). Furthermore, the lipophilic nature of diazepam enables it to have a rapid onset of action as it quickly distributes into the central nervous system and then is rapidly stored in the peripheral fat. Finally, cost also may play a role in deciding on which benzodiazepine to use. Implementation of guidelines for one institution to use longer-acting agents, instead of continuous infusion of short-acting agents, demonstrated a decrease in cost from an average of \$1,000 per patient to \$60 per patient. Equivalent outcomes were obtained with similar adverse effects (58).

Although the choice of which benzodiazepine to use may not dramatically affect outcome, the method of administration does. In multiple, randomized, controlled trials, symptom-triggered therapy compared with scheduled dosing, led to a shorter duration of treatment and less benzodiazepines used. More importantly, up to 40% of patients never required treatment (59, 60). The most widely used instrument to facilitate symptom-triggered therapy and assess symptoms of alcohol withdrawal is the Clinical Institute Withdrawal Assessment of Alcohol (CIWA-A: 30 signs and symptoms) and a shortened version, CIWA-A revised (CIWA-Ar: 10 signs and symptoms) (Fig. 1). This scale has been studied

Patient: _____ Date: _____ Time: _____ (24 hour clock, midnight = 00:00)

Pulse or heart rate, taken for one minute: _____ Blood pressure: _____

NAUSEA AND VOMITING — Ask “Do you feel sick to your stomach? Have you vomited?” Observation.
 0 no nausea and no vomiting
 1 mild nausea with no vomiting
 2
 3
 4 intermittent nausea with dry heaves
 5
 6
 7 constant nausea, frequent dry heaves and vomiting

TREMOR — Arms extended and fingers spread apart. Observation.
 0 no tremor
 1 not visible, but can be felt fingertip to fingertip
 2
 3
 4 moderate, with patient’s arms extended
 5
 6
 7 severe, even with arms not extended

PAROXYSMAL SWEATS — Observation.
 0 no sweat visible
 1 barely perceptible sweating, palms moist
 2
 3
 4 beads of sweat obvious on forehead
 5
 6
 7 drenching sweats

ANXIETY — Ask “Do you feel nervous?” Observation.
 0 no anxiety, at ease
 1 mild anxious
 2
 3
 4 moderately anxious, or guarded, so anxiety is inferred
 5
 6
 7 equivalent to acute panic states as seen in severe delirium or acute schizophrenic reactions

AGITATION — Observation.
 0 normal activity
 1 somewhat more than normal activity
 2
 3
 4 moderately fidgety and restless
 5
 6
 7 paces back and forth during most of the interview, or constantly thrashes about

TACTILE DISTURBANCES — Ask “Have you any itching, pins and needles sensations, any burning, any numbness, or do you feel bugs crawling on or under your skin?” Observation.
 0 none
 1 very mild itching, pins and needles, burning or numbness
 2 mild itching, pins and needles, burning or numbness
 3 moderate itching, pins and needles, burning or numbness
 4 moderately severe hallucinations
 5 severe hallucinations
 6 extremely severe hallucinations
 7 continuous hallucinations

AUDITORY DISTURBANCES — Ask “Are you more aware of sounds around you? Are they harsh? Do they frighten you? Are you hearing anything that is disturbing to you? Are you hearing things you know are not there?” Observation.
 0 not present
 1 very mild harshness or ability to frighten
 2 mild harshness or ability to frighten
 3 moderate harshness or ability to frighten
 4 moderately severe hallucinations
 5 severe hallucinations
 6 extremely severe hallucinations
 7 continuous hallucinations

VISUAL DISTURBANCES — Ask “Does the light appear to be too bright? Is its color different? Does it hurt your eyes? Are you seeing anything that is disturbing to you? Are you seeing things you know are not there?” Observation.
 0 not present
 1 very mild sensitivity
 2 mild sensitivity
 3 moderate sensitivity
 4 moderately severe hallucinations
 5 severe hallucinations
 6 extremely severe hallucinations
 7 continuous hallucinations

HEADACHE, FULLNESS IN HEAD — Ask “Does your head feel different? Does it feel like there is a band around your head?” Do not rate for dizziness or lightheadedness. Otherwise, rate severity.
 0 no present
 1 very mild
 2 mild
 3 moderate
 4 moderately severe
 5 severe
 6 very severe
 7 extremely severe

ORIENTATION AND CLOUDING OF SENSORIUM — Ask “What day is this? Where are you? Who am I?”
 0 oriented and can do serial additions
 1 cannot do serial additions or is uncertain about date
 2 disoriented for date by no more than 2 calendar days
 3 disoriented for date by more than 2 calendar days
 4 disoriented for place/or person

The CIWA-Ar is not copyrighted and may be reproduced freely.
 Sullivan, J.T.; Saylor, K.; Schneidman, J.; Naranjo, C.A.; and Sellers, E.M.
 Assessment of alcohol withdrawal: The revised Clinical Institute Withdrawal
 Assessment for Alcohol scale (CIWA-Ar). *British Journal of Addiction* 84:1353-1357, 1989.

Patients scoring less than 10 do not usually need additional medication for withdrawal.

Total CIWA-Ar Score _____
 Rater’s Initials _____
 Maximum Possible Score 67

Figure 1. Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised.

by many groups and is reproducible and valid when used in detoxification centers and in patients with uncomplicated illnesses (61). Because of its ease of use, its use has often been expanded to other groups of patients not represented in the initial validation studies. This raises some potential problems and dangers. To appropriately use the CIWA-Ar scoring system, patients must have a history of recent alcohol use and must be able to communicate. A recent study reported that 48% of patients admitted to a general inpatient hospital ward for whom a CIWA-Ar-based protocol was ordered failed to meet both of these criteria. Specifically, 31% met neither, 14% were drinkers but unable to communicate, and 55% were able to communicate and were not recent drinkers. As a result, a high percentage of these patients received unnecessary treatment (62).

Although CIWA-guided symptom-triggered therapy has become the standard for treatment of alcohol withdrawal in the general hospital setting, fewer data exist as to the validity of this strategy in the ICU. This is complicated by the fact that few data exist comparing the CIWA-Ar with other standard ICU delirium and sedation scores, such as the Confusion Assessment Method for the ICU and Ramsey, which are also used to direct administration of sedatives. Furthermore, there are other indications for symptom-triggered therapy in the ICU, including pain, which can mimic many of the physiologic manifestations of alcohol withdrawal. One recent small study, however, does suggest this strategy is valid in an ICU population as well. In a study by Spies et al, symptoms of alcohol withdrawal were treated with either a continuous infusion or bolus-dosed therapy

with flunitrazepam as directed by CIWA-Ar. The infusion titrated group required a higher amount of medication, higher rate of intubation (90% vs. 65%; $p < .05$), longer ICU stay (14 vs. 8 days; $p \leq .01$), as well as higher prevalence of pneumonia (71% vs. 39%; $p \leq .01$) compared with the bolus-dosed therapy group (63). It should be noted, however, that the threshold for instituting treatment in this study was a CIWA score of 20, which is significantly higher than the threshold used in other studies (59, 60). Consequently, although the above study supports the use of CIWA in the ICU, the optimal threshold for triggering therapy remains to be determined.

Another unique challenge in the ICU is the selection bias for patients with more severe forms of alcohol withdrawal. A subgroup of patients has been identified that require very large doses of benzodiazepines for management of their alcohol withdrawal symptoms/DTs. Doses of >40 mg of diazepam in 1 hr have been suggested as the defining criteria for benzodiazepine-resistant alcohol withdrawal (64). Some subjects may have benzodiazepine requirements that exceed 2600 mg intravenous diazepam within the first 24 hrs (65). Although still a subject of debate, the mechanism for this high-level resistance is likely due to profound down-regulation of number and function of central GABA-A receptors. A recent study provided more detailed insight onto the outcome of these subjects and a strategy for treatment. Patients with benzodiazepine-resistant DTs were found to have a high rate of requiring intubation with intubated patients having a longer ICU length of stay and greater risk for nosocomial infections. Institution of a strategy of escalating doses of benzodiazepines up to 150 mg of diazepam as an individual dose and subsequent addition of phenobarbital effectively controlled symptom in this population with a mean maximal individual dose of diazepam exceeding 80 mg. In addition, phenobarbital, at doses up to 260 mg, was used to control symptoms in 58% of patients. Overall, this strategy significantly reduced the need for intubation from 47% to 22% (66). Perhaps more importantly, this study implies that the maximal dose of benzodiazepine required to achieve sedation is patient specific and probably determined by the degree of an individual's receptor dysregulation.

Alternative agents

The above study highlights the importance of adjuvants, in addition to benzodiazepines, for management. Phenobarbital has been used in some of the initial trials of pharmacotherapy for alcohol withdrawal and, in some studies, has been found to be superior to diazepam (56, 67). Mechanistically, it is synergistic with benzodiazepines for GABA-A activation and in animals is capable of weakly inhibiting stimulatory NMDA receptors providing another potential benefit (68, 69). The onset of action of a dose of phenobarbital is 20–30 mins; therefore, caution must be used in dosing administration to avoid redosing before the peak effects have been achieved from the initial dose (67, 70). Furthermore, its narrow therapeutic window, in regard to respiratory depression compared with benzodiazepines, suggests that this should not be a primary agent but should be used only in closely monitored settings.

Propofol is another attractive alternative agent for benzodiazepine-resistant alcohol withdrawal. Numerous case series (66, 71) have documented the effectiveness of propofol both in intubated and even in nonintubated subjects for treatment of resistant alcohol withdrawal. Mechanistically, propofol is capable of both activating GABA-A receptor and blocking stimulatory NMDA receptors (72–74). The potent NMDA-blocking properties of propofol, combined with its short half-life and predictable metabolism, make it an attractive choice for ICU patients with benzodiazepine resistance. However, there are no randomized controlled data, and concerns still exist that long-term use at high doses can lead to hypertriglyceridemia and propofol-related infusion syndrome (71, 75, 76).

Perhaps the most controversial alternative agent is ethanol. As far back as the early 1900s, medical textbooks recommended giving alcohol to a person in alcohol withdrawal as a means of treating the withdrawal symptoms. Alcoholics are known to self-medicate by drinking alcohol when they feel the symptoms of withdrawal beginning. Consequently, most hospitals still carry ethanol on their formularies with many protocols describing the use of either intravenous or oral ethanol (beer) for prevention or even treatment of alcohol withdrawal (77). This is more likely to happen on surgical specialty services and is presumably to keep the patient stable through the acute illness, at the same time maintaining the

level of alertness of the patient (78). There are few studies to support this form of treatment, and the efficacy, complications, and optimum delivery strategies have not been well delineated for ethanol administration for alcohol withdrawal. In one study, a retrospective chart review performed on 124 patients treated with intravenous or oral alcohol was compared with a prospective cohort of 76 patients who were given a 5% alcohol drip at 0.8 mL/kg/hr, and blood alcohol content was monitored at 6, 24, and 72 hrs. The rate of alcohol infusion was titrated based on clinical symptoms and blood alcohol content. The mean duration of the treatment was 3 days. Outcomes between the two groups were similar with only one patient in the intravenous ethanol group being diagnosed with asymptomatic hyponatremia (78). In a separate set of studies, intravenous ethanol failed to prevent the onset of severe alcohol withdrawal in nearly 35% of at-risk postoperative surgical patients with 10% of treated subjects having symptoms of congestive heart failure in a related study by the same group (compared with 0% for benzodiazepine-containing regimens) (79, 80). Again, serum ethanol levels were not predictive of failure (80).

Finally, it should be acknowledged that, although there may be a significant placebo effect to holding a beer, there are many potential adverse effects to ethanol compared with other available agents. Abstinence from alcohol up to 1 month preoperatively is associated with improved postoperative outcomes, such as myocardial ischemia, arrhythmias, and hypoxemia. Infectious complications were also noted with persistent alcohol use, including wound infections in almost half the subjects, superficial and deep abscesses, pneumonia, urinary tract infections, and bacteremia. All patients required therapeutic intervention (50). The mechanism of this is not fully elucidated, but alcohol has well-described toxic effects on endothelial cells, macrophages, and neutrophils (49, 81). However, what remains unclear is how long one must remain abstinent to start obtaining these benefits. In animals, alcohol-induced endothelial damage reverses almost immediately after withdrawal, suggesting some of these effects could be immediate (81). Consequently, the above-mentioned immunosuppressive effects and other organ dysfunction related to alcohol ingestion, need for monitoring of blood alcohol concentrations, and the unpredictable metabolism make safe ad-

ministration of alcohol as a primary treatment difficult.

The β -blockers and α -agonists, such as clonidine, have been studied extensively in regard to their autonomic symptom control in alcohol withdrawal and are part of many ICU-based protocols (82–85). In patients with underlying heart disease, controlling blood pressure and tachycardia helps to prevent further cardiac compromise. These agents do not, however, treat the underlying pathophysiologic mechanism of alcohol withdrawal and, therefore, must be used in conjunction with benzodiazepines. Failure to do so may lead to masking of the severity of the withdrawal syndrome and subsequent undermedication. In addition, at least one study of propranolol in AWS showed an increase in the occurrence of delirium (84). Similar results were observed with the clonidine analog, lofexidine (86). Finally, dexmedetomidine, a centrally acting α -agonist used for sedation, has been documented in case reports to aid in management of withdrawal symptoms (87, 88). Currently, a randomized controlled trial is planned to evaluate the effectiveness of this drug as an adjunct to benzodiazepines.

Neuroleptic agents, in particular phenothiazines and haloperidol, are widely used for reducing symptoms of alcohol withdrawal but have only rarely been studied independently of benzodiazepines with no head-to-head trials between haloperidol and benzodiazepines (85). Some concern exists with their use, especially in isolation. First, these drugs are well known to decrease the seizure threshold. In humans, chlorpromazine was associated with an increase in withdrawal seizures (12%) compared with placebo (7%) or chlordiazepoxide (1%) (54). Haloperidol decreases the seizure threshold in animals and humans with one trial showing increased delirium and mortality in patients treated with haloperidol compared with the GABA agonist chlormethiazole (89). This is of even greater concern, given the inferiority and propensity toward nosocomial pneumonia with chlormethiazole compared with benzodiazepines for treatment of alcohol withdrawal in the ICU (85). In addition, care must be taken in using this class of agents in high doses due to their well-described side effects of hypotension and QT prolongation. These effects, specifically electrocardiographic abnormalities, can be further exacerbated by the reported high prevalence of QT prolongation in subjects with alcohol withdrawal and alcoholic

liver disease (90, 91). For all of these reasons, neuroleptics should only be considered as adjuncts to benzodiazepines.

Anticonvulsants, such as carbamazepine, have been studied in numerous trials of therapy for mild AWS as both inpatient and outpatient. In animal studies, carbamazepine has been shown to prevent alcohol withdrawal seizures by raising the seizure threshold, and it potentially inhibits the kindling phenomenon seen (92). In humans, studies (93–95) showed that it is superior to placebo and equal in efficacy to benzodiazepines for mild-to-moderate AWS. Similar data (96) have been obtained with valproic acid, which has a benzodiazepine-sparing effect in mild withdrawal. In contrast, in a randomized placebo-controlled study (97) of the newer anticonvulsant, oxcarbazepine, no difference between this agent and placebo in inpatient detoxification was observed. It should also be stressed that phenytoin is ineffective for the treatment of alcohol withdrawal seizures and is not indicated for this condition. In multiple trials, phenytoin was ineffective in preventing alcohol withdrawal seizure recurrence (98–100). Consequently, although this class of drugs may be reasonably recommended as adjuncts, they should not be used as monotherapy for treatment of established alcohol withdrawal and DTs.

In conclusion, AWS is a common disorder in the ICU and especially in a trauma population. It has a wide range of clinical manifestations from mild tremulousness to delirium, none of which are specific to alcohol withdrawal, and practitioners must always have a high index of suspicion for other disorders. In the setting of surgical patients, benzodiazepines continue to be the cornerstone of pharmacologic therapy for alcohol withdrawal delirium. Delivery of these medications in a symptom-triggered, CIWA-guided fashion must be done with close monitoring and careful titration due to the cumulative sedating effects of other postsurgical medications.

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