Twenty per Hour: Altered Mental State Due to Ethanol Abuse and Withdrawal

Henry Z. Pitzele, MD[a,b,*], Vaishal M. Tolia, MD, MPH[c]

KEYWORDS

• Ethanol intoxication • Ethanol withdrawal
• Central nervous system • Altered mental state

Among drugs of abuse, ethanol is by far the most pervasive with nearly ubiquitous penetrance within Western civilization. Although ethanol retains a place in religious and traditional ceremonies, its properties as a social lubricant have led to its overuse, abuse, and often, toxicity and addiction. The prevalence of alcohol abuse and dependence in the United States was 8.5% in 2001, representing 17 million people.[1] In 1998, the overall economic cost in the United States, mostly secondary to lost productivity, was estimated to be 185 billion dollars.[2] The medical system represents a significant fraction of this cost, with alcohol-related complaints comprising 14.3% of health care expenditure; the total estimated cost in 1998 was $26.3 billion.[3]

No demographic group of patients is unaffected by ethanol. Although pediatric exposure and toxicity remain rare, alcohol is still the cause of appreciable numbers of calls to poison centers (>10,000/y[4,5]), as well as pediatric intensive care unit (ICU) admissions, and consultations to local municipal departments of Family and Children's Services. In addition to its constant presence in its beverage and nonbeverage forms, the blossoming popularity of alcohol (ethanol)-based hand sanitizers provides another significant source of exposure, especially for children, whose propensity for the tasting experience is high.[6]

Elderly patients are affected by ethanol similar to young adults[7] but are more likely to present to emergency departments (EDs) for treatment of the sequelae of chronic ethanol abuse, mostly gastrointestinal (GI) complaints.[8] The group most likely to

[a] Section of Emergency Medicine, Jesse Brown Veterans Affairs Medical Center, 820 South Damen Avenue, Chicago, IL 60607, USA
[b] Department of Emergency Medicine, University of Illinois at Chicago, 808 South Wood Street, Room 471, Chicago, IL 60612, USA
[c] Department of Emergency Medicine, University of California San Diego, 200 West Arbor Drive, #8676, Room 3-340, San Diego, CA 92103, USA
* Corresponding author. Section of Emergency Medicine, Jesse Brown Veterans Affairs Medical Center, 820 South Damen Avenue, Chicago, IL 60607.
E-mail address: Henry.Pitzele@va.gov

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present for acute ethanol intoxication (as well as toxicity) are adolescents and young adults.[9] This group is most likely to present for evaluation of various forms of acute trauma. The 2 are related with a disturbing coefficient of variance; up to 50% of consecutive patients suffering from trauma at a level I trauma center met the legal definition of intoxication.[10]

EDs are affected disproportionately within the health care system for the evaluation and treatment of acute ethanol intoxication.[11] In addition to alcohol-associated injuries and major trauma, patients with a primary complaint of intoxication represent a significant proportion of ED volumes and usage of resources. In a broad cross-sectional study, alcohol-related complaints accounted for approximately 2.7% of all patient visits[12] (approximately 7% of visits were between 2 AM and 4 AM).[9]

PATHOPHYSIOLOGY

Ethanol is readily absorbed through the proximal GI tract and rapidly achieves equilibrium between intra- and extracellular compartments.[13] Although up to 10% of serum ethanol can be directly excreted in the lungs, urine, and sweat,[14] the main portion of the metabolism (>90%) occurs in the liver, where alcohol dehydrogenase reduces it to acetaldehyde.[15] Although ethanol has some direct actions on the cardiovascular system, its main clinical action in acute intoxication is that of a central nervous system (CNS) depressant. These effects are mediated through 2 pathways: an increase in CNS inhibition and a decrease in CNS excitation.

The main neurotransmitter responsible for CNS inhibition is γ-aminobutyric acid (GABA). Endogenous GABA binds to $GABA_A$ receptors, allowing negatively charged chloride ions to enter the cell, thereby decreasing cellular excitability. Ethanol has a high affinity for binding to the $GABA_A$ receptor, thereby activating this inhibitory cascade, resulting clinically in sedation, motor incoordination, and cognitive dysfunction.[16] Moreover, with the chronic use of ethanol, the number of GABA receptors is upregulated, necessitating larger and larger doses to create the same level of CNS inhibition. This GABA upregulation partially explains the awakeness of some chronic ethanol users at blood alcohol concentrations (BAC) that would routinely induce coma[17] or death[18] in nontolerized individuals. Benzodiazepines work at the $GABA_A$ receptor, which explains their primary role in the treatment of alcohol withdrawal.

Excitation in the CNS is largely mediated through the neurotransmitter glutamate, which is also inhibited by ethanol. Ethanol executes this inhibition by preferentially binding to a common glutamate receptor in the CNS, the *N*-methyl-D-aspartate (NMDA) receptor.[19] To maintain wakefulness in the face of the chronic presence of alcohol, alcoholics express increased numbers of NMDA receptors as well as increased sensitivity of NMDA receptors to glutamate. Alcoholics reach a new basal level of excitatory tone, which also helps to explain the over excitation of the CNS (seizures, hallucinations) when alcohol is withdrawn.[20]

CLINICAL FEATURES OF INTOXICATION

The Diagnostic and Statistical Manual of Mental Disorders defines 4 criteria for alcohol intoxication: (1) recent ingestion of alcohol; (2) clinically significant maladaptive behavioral or psychological changes developing during or shortly after alcohol ingestion, including inappropriate sexual or aggressive behavior, mood lability, impaired judgment, and impaired social or occupational functioning; (3) clinical signs developing during or shortly after alcohol ingestion, including slurred speech, incoordination, unsteady gait, nystagmus, impairment of attention or memory, or stupor/coma; and

(4) lack of a general medical condition or other mental disorder that better accounts for the signs and symptoms.[21]

The type of signs and symptoms manifested during alcohol intoxication varies with BAC (**Table 1**).[22,23] The extent of these symptoms is influenced by the rapidity of increase and decrease of the BAC. Because 80% of ethanol is absorbed in the duodenum and terminal ileum,[24] the largest determinant of the speed of alcohol absorption is the speed of gastric emptying, and therefore dependent on the presence of coingested food. Therefore, BAC increases faster with the ingestion of ethanol on an empty stomach than after a meal.[24,25] Lesser adjuvants speeding up the absorption of alcohol are female sex, lack of concurrent smoking of cigarettes,[22] the use of ranitidine, the use of carbonated alcoholic beverages, and drinks containing approximately 20% ethanol; higher and lower concentrations slow the absorption.[26]

However, in addition to the significant intraindividual differences in the rate of alcohol absorption, there are even larger interindividual differences in symptoms at a given BAC. These interindividual differences are mainly dictated by existing tolerance to ethanol; as previously mentioned, a significant ethanol history can allow a patient to be conscious, alert, cohesive, and relatively free of gross motor effects, even at BACs that would create stupor, coma, or death in nontolerized individuals. One group whose symptoms are not dose-dependent is the approximately 50% of Asians who have a deficiency in mitochondrial aldehyde dehydrogenase. Although the decreased activity of this enzyme does not clearly alter the rate of ethanol metabolism, the build up of acetaldehyde causes facial flushing and tachycardia after ingestion of trivial doses of ethanol.[27]

DIFFERENTIAL DIAGNOSIS

Unfortunately, the differential diagnosis for acute alcohol intoxication spans the entire clinical spectrum of altered mental status. Commonly, concurrent or masquerading causes of alterations in level of consciousness include trauma (especially cranial trauma), sepsis/CNS infection, metabolic derangement (including carbon dioxide narcosis and hepatic encephalopathy), seizure, and nonalcoholic toxicologic ingestion. Maintaining a broad differential, even in the face of historical data (ie, many previous visits for ethanol intoxication, emergency medical services report) or physical data (such as a perceived smell of alcohol on the patient), can obviate the need to scramble at the end of a shift, when an intoxicated patient fails the test of timely metabolism. Specifically, a low threshold for diagnostic laboratory workup and

Table 1
Effects of varying BACs

BAC (mg/dL)	Clinical Manifestations
0–50	Diminished fine motor control, relaxation, increased talkativeness
50–100	Impaired judgment and coordination
100–200	Ataxia/gait instability; slurred speech; mood, personality, and behavioral changes
200–400	Amnesia, diplopia/nystagmus, dysarthria, hypothermia, nausea/vomiting
>400	Respiratory depression, coma, death

Data from Kleinschmidt K. Ethanol. In: Shannon MW, Borron SW, Burns MJ, editors. Haddad and Winchester's clinical management of poisoning and drug overdose. 4th edition. Philadelphia: Saunders; 2007. Chapter 31, p. 591; and Charness ME, Simon RP, Greenberg DA. Ethanol and the nervous system. N Engl J Med 1989;321(7):442–54.

computed tomography (CT) of the head is useful when treating the apparently intoxicated patient with an altered mental state.

The physical finding of the scent of alcohol coming from a patient can be particularly deceptive. Fundamentally, the smell commonly attributed to ethanol is not actually the smell of ethanol but that of nonalcoholic adulterants and botanicals in the alcoholic beverage.[28] Therefore, a small amount of ingested beer causes a much more potent smell than a lethal amount of ingested grain alcohol. The smell emitted by an intoxicated patient is by no means dose-dependent[29]; the patient with an initial BAC of 400 mg/dL may have a stronger smell of alcohol after the concentration decreases to 100 mg/dL than he or she did upon presentation. This fact stands in stark contrast to the dose-dependent manner in which the actual ethanol concentration in human breath makes it reliably reflective of the BAC.[30]

A further complication in the arena of volatile components of alcohol intoxication is intoxication with nonbeverage ethanol (NBE). In addition to the accidental alcohol abusers (mostly pediatric ingestion of mouthwash, cologne, and cough medicine), there is a subsegment of chronic alcohol abusers who repeatedly present after ingestion of NBE (ie, mouthwash, cologne, cough syrup, and isopropanol). The reason that this group of patients repeatedly chooses NBE despite the broad availability of low-cost beverage ethanol is unclear. Considerations for choosing NBE are its low price and availability during times of limited beverage availability (Sundays, during hospitalization, incarceration), which can explain the 15% to 20% of patients in Veterans Affairs alcohol treatment programs who have ingested NBE.[31] The smell of the nonbeverage intoxicant can sometimes be a clue in discovering the identity of the agent (for eg, mouthwash intoxication produces a strong and pervasive minty smell within the examination room).

The danger of the nonbeverage alcohol ingestion varies with the intoxicant. Mouthwash, while predominantly containing ethanol (often approaching 30% by volume), can also contain toxic volatiles such as phenol, which have additional toxicologic concerns. Cough syrup, also heavily ethanol-based, presents with an anticholinergic toxidrome because of antihistamines, which are active therapeutic agents. Isopropanol, the most commonly abused of the toxic alcohols, has many of the same clinical features as ethanol; the predominant features are dose-dependent CNS and respiratory depression. However, isopropanol (especially in large-volume ingestions) can also cause metabolic acidosis and renal damage, occasionally necessitating emergent hemodialysis.

Methanol and ethylene glycol must also be considered in the setting of altered mental status after alcohol ingestion. Ethylene glycol, a sweet-tasting alcohol, is most often ingested in the form of antifreeze and causes some inebriation, severe metabolic acidosis, oxalate crystalluria causing renal failure, and at higher doses, hypocalcemia and death.[32] Methanol, often an ingredient in paint removers and a byproduct of homemade ethanol production, also causes metabolic acidosis, multisystem organ failure, and death, but visual deficits and blindness can be added to its manifestations.[32] The toxicity of ethylene glycol and methanol are due to their metabolites, oxalic acid and formic acid, respectively. Both these metabolites are formed when the alcohol is metabolized by hepatic alcohol dehydrogenase.[33] Therefore, the mainstay of clinical therapy has been the prevention of metabolism by alcohol dehydrogenase by competitive inhibition of the enzyme, in the past using intravenous (IV) ethanol and more recently using fomepizole (4-methylpyrazole).[32]

Once ethanol use has been confirmed in an alcoholic patient with altered mental status, the patient must be considered for a concurrent secondary cause of CNS depression caused by the sequelae of drinking, specifically Wernicke encephalopathy

(WE) and hepatic encephalopathy (HE). WE is an initially reversible neuropsychiatric condition caused by low intracellular stores of vitamin B_1 (thiamine). Because thiamine is a necessary cofactor in several neuronal pathways, the lack of thiamine in brain neurons can cause the typical clinical effects of WE: oculomotor abnormalities, ataxia, and global confusion.[34] Because these symptoms overlap with the symptoms of acute intoxication, WE is often missed and many hospital protocols involve the repletion of thiamine in all intoxicated patients[35] to prevent the 15% to 20% mortality[36] in untreated patients.

HE is another potentially confounding factor in the evaluation of an acutely intoxicated chronic alcoholic patient. The prevalence of HE in patients with cirrhosis is estimated at 30% to 45%,[37] which makes it commonplace among patients in the ED. A decompensation of chronic HE can be caused by acute ethanol intoxication, as well as infection, GI bleeding, or increased dietary protein load,[38] as well as many other metabolic derangements and insults. Clinical diagnostic criteria for overt HE are (1) slow, monotonous speech pattern, (2) loss of fine motor skills, (3) extrapyramidal type movement disorders, (4) hyperreflexia, (5) asterixis, (6) hyperventilation, (7) seizures, (8) confusion/coma, and (9) decerebrate/decorticate posturing.[37] Although the venous level of ammonia does not appear in the diagnostic criteria of HE, it has been shown to correlate with the severity of HE[39] and should therefore be assayed. However, a single ammonia level is not sensitive or specific enough to establish (or rule out) the diagnosis of HE,[39] therefore the testing of serum ammonia in the ED remains an area of controversy.[40]

TREATMENT

The treatment of acute alcohol intoxication is largely supportive. The main goals of ED treatment are airway protection (which can include intubation), the diagnosis of concurrent disease processes, and the provision of a safe location in which the patient may regain their normal level of consciousness. Aspiration precautions should be taken in all such patients until a normal level of consciousness is regained. Life-threatening alcohol poisoning can be treated with hemodialysis, but active treatments for the patient acutely intoxicated with ethanol are usually constrained to intravenous fluids (IVFs), multivitamins, thiamine, and glucose.

Although IVFs are given almost ubiquitously to patients presenting with acute alcohol intoxication, the reasoning behind this treatment decision varies a great deal. A common reason for IVF administration is the treatment of perceived hypovolemia secondary to acute dehydration. The diuretic properties of ethanol in the acute state are well characterized, with one study showing the elimination of 600 to 1000 mL of urine after ingestion of 50 g of ethanol in 250 mL of water (approximately 4 drinks).[41] This diuresis is effected by the suppression of endogenous antidiuretic hormone secretion,[42] a suppression which only functions as the BAC increases,[43] as in acute intoxication. The acute loss of fluid through diuresis is compounded by losses through vomiting, diarrhea, and increased sweating. Therefore, the treatment of the nonalcoholic patient with acute intoxication, who presents with evidence of hypovolemia, remains an indication for IVF.

Chronic alcoholics, however, will not always benefit from administration of IVF. The chronic abuser may suffer the same dehydrating effects of vomiting and overall poor fluid intake as the occasional binge drinker. However, when the BAC remains steady, as it does in many alcoholics, alcohol acts as an antidiuretic, causing the retention of water and electrolytes.[44] Therefore, the chronic alcoholic patient usually presents to the ED in a state of overall isotonic over hydration.[44,45] Thus, experts recommend

that administration of IVF not be routine but rather carefully considered on a case-by-case basis, particularly in chronic alcohol abusers or those who have or are at risk for alcohol-induced cardiomyopathy.[45–47]

Multivitamins are commonly administered intravenously to intoxicated patients in the ED.[13] These vitamins are often combined in the form of a ''banana bag'', containing dextrose, thiamine, folate, and sometimes magnesium sulfate but always including the multivitamin solution that gives it the characteristic yellow color. Although many authors advocate the routine administration of vitamins to alcoholic patients,[48] citing studies that show alcoholics in the ambulatory setting to have multiple vitamin deficiencies,[15] the few studies that have been performed on intoxicated ED populations fail to show significant deficiencies in serum vitamins.[35,49] The conclusion of these studies is that the routine use of IV multivitamins in patients with acute intoxication is not warranted and once again should be carefully considered on an individualized basis.

The routine administration of thiamine is recommended for alcoholic patients, especially those presenting with altered mental status. The difficulty in detecting occult thiamine deficiency and early WE, combined with the significant prevalence of WE (approximately 12%[50]) and relatively high mortality, has made the cost/benefit analysis fall in favor of administering the drug; it is the timing and method of administration that are controversial. Traditionally, thiamine has been administered intravenously, usually at a dose of 100 mg.[50] Traditional literature stresses that the IV administration of thiamine should always precede the administration of dextrose, else the dextrose might precipitate an acute onset of WE in the thiamine-depleted individual. As the data suggesting this possibility are extremely limited (a single article summarizing 4 case studies, only 1 of whom was alcoholic),[51] the timing of the recommended thiamine administration to patients receiving glucose has become more relaxed. It is now recommended to be given at approximately the same time[34,52] rather than the previous insistence on before the administration of glucose.

As mentioned previously, the route of thiamine administration has also come into question. There is an increasing amount of data suggesting that oral repletion of thiamine is sufficient for routine administration,[34] decreasing the cost and risk of anaphylaxis associated with IV administration. The proponents of IV administration counter with evidence that absorption through the oral route is decreased in the intoxicated alcoholic and that sufficient blood levels are rarely achieved by single-dose administration.[53] The recommended route of administration of thiamine remains controversial, but it is clear that alcoholic patients with suspected WE should receive IV therapy, whereas most routine alcoholic patients can safely be given thiamine by mouth.[34,54]

The routine administration of glucose to the intoxicated patient presenting with altered mental status has been tempered by the usual ease of obtaining an immediate bedside fingerstick glucose level. If rapid testing is impossible, IV dextrose administration is recommended. This recommendation is even more important in cases of pediatric ethanol ingestion, who present with hypoglycemia more often than adults, even with BACs of 20 to 30 ng/dL.[55] Dextrose 5% with 0.45% sodium chloride is also the most common IV crystalloid chosen to resuscitate alcoholics because they often present with depleted glycogen stores and occasionally present with alcoholic ketoacidosis (AKA).[13]

Several drugs have been proposed for use in the management of acute alcohol intoxication, almost none of which have shown any benefit in decreasing symptom intensity or duration. The failure of caffeine,[56] naloxone,[57,58] and flumazenil[59] have been documented. IV saline, in addition to its previously mentioned indications for dehydration, is also commonly given in an attempt to hasten the drop in BAC.[46] This myth, too,

has been debunked.[46,60] There is growing experimental literature suggesting that metadoxine (an ion-pair between pyridoxine and pyrrolidone carboxylate) actually increases the speed of elimination and clinical improvement in ethanol intoxication.[61,62] The mechanism of action is unknown but is thought to enhance the metabolism of ethanol to acetaldehyde by alcohol dehydrogenase and renal clearance rates through direct action of the CNS. With a small amount of data and limited availability, this therapy (available for sale in Mexico and Asia, under the brand names Alco-liv and Viboliv, respectively[63]) requires more rigorous study before widespread use is recommended.

MEDICOLEGAL SEQUELAE: DISPOSITION OF THE INTOXICATED PATIENT

Discharging an acutely intoxicated patient in the ED is predicated on the patient's return to a nonintoxicated state. Discharge while the patient is still intoxicated opens the practitioner and the discharging hospital to theoretical liability if the patient comes to subsequent harm, whether by exposing himself to traumatic injury, later manifesting an occult life threat masked by the intoxication, or causing harm to a third party while in an intoxicated state.[64] Therefore, the most common practice is to observe the intoxicated patient in the ED until the practitioner is confident that the BAC is less than the threshold for intoxication.

One of the more difficult challenges facing emergency physicians (EP) is whether or not to obtain a BAC in an intoxicated patient. Clear indications to order a BAC assessment exist in patients who present in coma or with significant alterations in consciousness; it is unlikely for an adult patient to present in a coma as a result of ethanol alone at a blood concentration less than 300 mg/dL. However, if there is no clinical evidence of concurrent occult traumatic or metabolic/infectious cause for the patient's altered mental state and the patient does not deny imbibing ethanol, it is acceptable to observe the patient without obtaining a BAC.[65,66]

Sparse definitive literature exists on the decision to obtain a BAC. Simel and Feussner[65] published several surveys attempting to quantify consensus on standard of care and liability by examining the role of BAC assays in the context of counseling alcohol-impaired patients to avoid driving after discharge. These investigators found that 88% of the EPs surveyed preferred to avoid documentation of BAC in moderately intoxicated patients, with more than half of those opting to draw a level, doing so for legal concerns. In a subsequent study, Simel and Feussner[66] surveyed attorneys to see which physician behavior was perceived as most risky for lawsuit generation. The responding attorneys judged that the greatest risk for suit was present when a BAC was documented but no instructions against driving were given (43%). This judgment was followed in riskiness by the lack of a documented BAC in combination with proper discharge instructions forbidding driving (17%), with the least risk perceived with a documented BAC and documented instructions against driving (3.5%).[66] It is therefore wise to expend the additional effort to ensure careful documentation of the patient's fitness for discharge.

Although it is preferable to discharge an intoxicated patient to the care of a responsible, nonintoxicated adult, it is also acceptable (if a responsible adult is not available) to discharge the patient directly if they show marked clinical improvement and are clearly no longer intoxicated. Although there is no legal consensus for an acceptable BAC suitable for discharge, the threshold commonly used in practice is approximately 100 mg/dL, in accordance with many state laws prohibiting driving above this level. Some investigators advocate a repeat BAC to document that a patient's BAC is less than 100 mg/dL before discharge; many others feel that the calculation of predicted decline in BAC is sufficient.

The rapidity of alcohol metabolism varies among individuals but has been shown in patients in the ED to be approximately 20 mg/dL/h.[67,68] In these ED studies, the speed of metabolism in individuals varied little, even across differences in sex, age, and drinking history. These ED-based studies agree with previous research, mostly performed on healthy volunteers[30] rather than on patients in the ED, that shows that at most commonly encountered BACs, the elimination of alcohol occurs according to zero-order kinetics or a fixed rate of elimination per hour, with each patient having their own rate of decrease.[30] Therefore, with 2 samples, we can calculate a patient's rate of elimination and quite accurately predict the time to elimination. However, at extremely high BACs, these kinetics seem to be much more complex.[69]

Serial examinations to document improvement in neurologic status should be performed according to an ED protocol, especially in cases when a BAC is not obtained. Failure of a patient's mental status to improve in a timely manner should provoke a more complete workup, usually including CT of the head. The length of time expected before clinical improvement depends largely on a patient's tolerance and alcohol intake. In one study involving 105 acutely intoxicated patients, the average time for normalization of mental status was 3.2 hours.[70] However, within that study population, 25% of patients failed to normalize within 7 hours, and 1 patient took 11 hours to normalize. The study concluded that any patient who does not show clinical improvement within 3 hours should be carefully evaluated for other causes of mental status depression.

One frightening theoretical scenario is of an alcohol-impaired patient walking out of an ED and into or under an automobile. Searches of US case law through the Lexis and Loislaw legal databases reveal a wealth of cases involving patients whose intoxication in the ED masked a life-threatening illness that exhibited itself after ED discharge,[71–74] but nearly none dealing with the discharge of intoxicated patients who bring traumatic harm to themselves (although such cases certainly exist[75]). There is now some precedent to support the liability of physicians to unrelated third parties who might be injured by discharged intoxicated patients.[76] The plaintiff in a seminal case of third-party liability was in an auto accident with a woman who had just received Compazine for a headache in an ED. The plaintiff sued the hospital that gave the woman the Compazine. The case was appealed to the Missouri Supreme Court and was ultimately dismissed on the grounds of statute of limitations.

Restraints are necessary for intoxicated patients who attempt to leave and for unruly patients who are endangering themselves and others in the ED. Chemical restraints are usually preferred over physical restraints,[77] but both methods are fraught with risk, clinical and medicolegal. The mainstays of chemical therapy are haloperidol and lorazepam,[78] either alone or acting synergistically together. The danger of adding further chemically induced respiratory depression to that already caused by ethanol intoxication is inherent in the use of these medications and must be weighed against the behavioral benefit achieved. The use of physical restraints has been shown to be safe and efficacious in patients in the ED[79] but is still recommended as a temporizing measure until chemical restraint takes effect. The longer-term use of physical restraints is not only dissuaded by the Centers for Medicare and Medicaid Services[80] and the Joint Commission on the Accreditation of Healthcare Organizations,[81] but has also prompted significant numbers of lawsuits for injuries sustained by restrained patients.[82]

MORBIDITY AND MORTALITY

The primary morbidity and mortality caused by alcohol intoxication is from resulting accidental and intentional trauma. Second most common are the effects of chronic alcohol abuse, such as liver failure/upper GI bleeding, alcoholic cardiomyopathy, and

electrolyte derangements. However, acute intoxication can itself prompt life-threatening sequelae, especially in the nonalcoholic individual.

Respiratory depression is a significant cause of death in lethal ethanol overdose in children and adults.[28] Several mechanisms exist by which ethanol leads to respiratory depression. The largest effect is seen from depression of the central chemoreceptors' response to hypercapnia, thereby decreasing minute ventilation.[83] At higher doses, ethanol can increase upper airway pressures, presumably through decreases in the muscular tone, which maintains airway patency.[83] In addition to direct respiratory drive depression, ethanol intoxication can often be complicated by aspiration. Moreover, chronic alcoholics are more likely to develop acute respiratory distress syndrome given a concurrent metabolic insult, such as aspiration, hypertransfusion (after a GI hemorrhage), and acute pancreatitis.[84]

AKA is a potentially life-threatening metabolic derangement that is often overlooked in the evaluation of the acutely intoxicated patient.[85] Patients with AKA are usually chronic alcoholics who present after a large ethanol binge that was terminated by nausea, vomiting, and epigastric abdominal pain.[86] This volume depletion, in combination with the alcoholic patient's low caloric intake, low glycogen stores, and relative hypoglycemia, decreases insulin levels and promotes the formation of ketone bodies, especially β-hydroxybutyrate.[86] This acidosis can become profound, and AKA has been implicated as a possible cause of sudden death in alcoholics.[87]

On presentation, patients commonly have tachycardia, hypotension, and tachypnea, with epigastric tenderness and minimal alteration in their level of consciousness.[87] Laboratory findings include an anion gap metabolic acidosis, normal or low serum glucose level, and a low or undetectable BAC because vomiting forces the cessation of intake.[87] Urine ketone levels may be low or undetectable because the ketones are predominantly β-hydroxybutyrate, and urine ketone test strips test only for acetone and acetoacetate.[88] The fundamental treatment of AKA is volume repletion with 5% dextrose solution because volume repletion with normal saline has been shown to worsen the acidosis,[89] presumably because of a chloride overload. Similar to diabetic ketoacidosis, potassium, magnesium, and phosphorus levels must be monitored and the ions repleted as necessary.

ETHANOL WITHDRAWAL

Beyond ethanol toxicity is the complex syndrome of ethanol withdrawal. Many of the symptoms and complications of ethanol withdrawal are directly related to changes in the CNS neurotransmitters and receptor binding, leading to absence of inhibitory stimuli and the surge of excitatory pathways. This condition is caused by the response of the body to chronic ethanol exposure in an attempt to maintain a homeostatic balance. Over a half-million episodes of withdrawal from ethanol that require medication intervention for management occur each year.[90] Of the 1.2 million admissions for alcohol-related conditions, up to 5% go on to develop the most dreaded complication: delirium tremens (DTs). This complication historically had a high mortality, close to 40% in the early 20th century, with a dramatic reduction to near 5% today, presumably because of improvements in supportive and pharmacologic therapy.[91] Predicting the severity of withdrawal is not an easy task. In the mid-1950s, experiments on healthy volunteers demonstrated that prolonged use of alcohol followed by abrupt cessation led to the highest vulnerability for more severe withdrawal symptoms.[92] It is important to understand the neurochemical effects of alcohol consumption to explain the effects of withdrawal.

Pathophysiology

As mentioned previously, ethanol toxicity relies heavily on its binding to the $GABA_A$ receptor complex postsynaptically and $GABA_B$ presynaptically, with an overall effect leading to decrease in neuronal firing and increased sedation.[93] Ethanol also inhibits glutamate-modulated excitation at the NMDA receptor with a resultant upregulation of NMDA binding sites, which may be responsible for withdrawal seizures because it is a response to increase excitatory tone in chronic ethanol exposure, again to maintain a baseline arousal state.[94] This finding was demonstrated in animal models in which the hippocampus of ethanol-fed rats was analyzed and the alterations to the GABA and NMDA receptor complexes were confirmed.[95] Ethanol also has an interesting effect on opioid receptors. In vitro studies demonstrate inhibition of opioid binding to opiate receptors with chronic exposure leading to receptor upregulation and increased responsiveness. Ethanol-induced dopamine release is modulated and thus contributes to ethanol craving.[96] One of the adjunctive treatments for alcohol dependence is naltrexone, which showed efficacy in the multicenter COMBINE study of 1383 patients and showed that treatment over 16 weeks resulted in improved clinical outcomes and longer periods of abstinence.[97]

Symptoms of Ethanol Withdrawal

There is a wide range of ethanol withdrawal symptoms and most are related to the elapsed time since the last drink. Other key historical items include the duration of abuse, comorbid conditions (such as chronic liver disease from hepatitis B/C), the reason for stoppage of consumption, previous withdrawal and degree of severity, and co-ingestions. Much of the data was elucidated from early studies performed by Victor and Adams[98] who also described the 3 main features of mild, moderate, and severe ethanol withdrawal: tremulousness, convulsions, and DT, respectively. This was the first time that the time spent consuming alcohol before the cessation was correlated with the development of withdrawal symptoms and its severity.

Mild Withdrawal

Early CNS hyperactivity can lead to tremulousness, which begins only a few hours after cessation or decrease in ethanol consumption. The study by Isabell and colleagues[92] confirmed dose dependency in the development of withdrawal symptoms previously discovered by Victor and Adams.[98] The tremors can be accompanied by insomnia, anxiety, nausea, vomiting, anorexia, headache, diaphoresis, and palpitations. Some patients, who can still be managed on an outpatient basis, may also progress to have hypertension and fever. If there is no progression of symptoms, resolution usually begins within 24 to 48 hours. As symptoms progress, however, there is increased adrenergic stimulation leading to hyperthermia, hyperreflexia, tachycardia, and agitation.

Moderate Withdrawal

After 12 hours of abstinence, hallucinations in the form of altered perceptions can develop. This symptom is significantly different from DTs in that there is generally maintained sensorium. The patient usually has visual disturbances but may also have auditory and tactile hallucinations.[92] Vitals signs are usually normal in this phase of withdrawal but patient agitation and paranoia can lead them to cause harm to self and others. Thus, patients in this stage typically require hospitalization and close monitoring. The symptoms of alcoholic hallucinosis can last from 24 hours to 6 days and occur in approximately 25% of those with a history of extended ethanol abuse.[99]

Another manifestation of acute ethanol reduction or cessation in the chronic abuser is that of generalized tonic-clonic convulsions, once called rum fits. They occur in approximately 10% of alcoholic patients and can occur in patients with no previous history of seizures.[100] On further epileptic workup, patients are usually found to have a normal electroencephalogram. Recurrence or evidence of status epilepticus is rare because approximately 40% are singular and short events.[101] If status epilepticus occurs, it should lead to a more detailed workup, such as CT of the head, lumbar puncture, and analysis of cerebrospinal fluid, to exclude structural, traumatic, or infectious causes. Withdrawal seizures can occur any time from 7 to 48 hours after cessation or significant reduction in ethanol consumption but incidence peaks at 12 to 24 hours. Acute intervention usually consists of benzodiazepines and, if necessary, phenobarbital. Chronic anticonvulsant therapy is rarely required or recommended. A third of these patients will go on to develop serious withdrawal symptoms of DT.[102]

Severe Withdrawal

Approximately 5% of ethanol abusers who undergo withdrawal develop DT and incur its 5% mortality.[91] DTs typically begin 48 to 96 hours after the last drink and can last up to 2 weeks. The symptoms are caused by a hyperactive autonomic nervous system initiated by the prolonged glutamate-induced stimulation and an increase in the available binding sites on the NMDA receptor complex. Moreover, DT is defined by disorientation, hallucinations, tachycardia, hypertension, agitation, fever, and tremulousness in the setting of profound confusion.[103] Care has to be taken to assess every patient in the ED individually because not all symptoms may be present (eg, patient is on β-blockers). Risk factors for the development of DTs include[104]

- Age above 30 years
- History of previous episodes of DTs
- Chronic heavy alcohol abuse
- Concurrent illness
- Withdrawal symptoms with a still measurable alcohol level
- Presenting to health care provider after a longer period of abstinence.

Blood flow parameters in DT reveal abnormal cardiac indices and rebound hyperventilatory respiratory alkalosis leading to a decrease in cerebral blood flow.[105] The most clinically emergent effect is on the fluid and electrolyte status. Furthermore, hyperthermia was found in more than half of the patients who died from DT in a study by Tavel and colleagues.[106] In response to the findings in this study, early recognition, adequate fluid replacement, and electrolyte repletion have helped to reduce the once significant mortality. In addition to hyperthermia, chronic alcoholics may also have hypoglycemia, hypokalemia, hypomagnesemia, and hypophosphatemia. A combination of these are responsible for the malignant arrhythmias often implicated as the cause of death in those with DT.

Hypovolemia is common, secondary to vomiting and insensible losses from diaphoresis, hyperventilation, and an increased metabolic rate. Hypoglycemia is common as a result of ethanol inhibition of gluconeogenesis (as discussed in AKA), which was first observed in animal models and could contribute to the overall state of confusion in DT. Almost all patients in the withdrawal stage, particularly those in DT, need IV glucose replacement as well as its cofactor in metabolism, thiamine. Hypokalemia results from an increase in aldosterone levels in response to hypovolemia, extrarenal losses, as well as changes in intracellular distribution of potassium through membrane effects.[107] Hypomagnesemia must be corrected along with hypokalemia because

the combination could lead to malignant ventricular arrhythmias and sudden cardiac death. Hypophosphatemia is usually a result of the malnourished state in which alcoholics present and can contribute to cardiovascular collapse, muscle breakdown, and rhabdomyolysis.[108]

Prompt recognition and treatment of ethanol withdrawal states, particularly DT, and concurrent or confounding illnesses are essential for the EP to reduce mortality and maximize chances for a good outcome.

MANAGEMENT AND DISPOSITION OF ETHANOL WITHDRAWAL STATES

The goal of management in ethanol withdrawal states is to minimize symptoms, prevent progression to entities such as seizure and DTs, and make an appropriate disposition of the patient. The importance of supportive care such as fluid replacement and electrolyte correction has already been emphasized. Thiamine and glucose are often the first interventions in the withdrawal state and can be initiated even in the prehospital setting, particularly with the ubiquitous availability of rapid blood glucose measuring tools. The mainstay of pharmacologic therapy has been benzodiazepines, which were first used in the 1950s.[109] Benzodiazepines have a favorable safety profile compared with ethanol as well as other drugs previously used, such as phenothiazines, antihistamines, and paraldehyde.[110] This drug acts at the GABA receptor complex and increases the affinity of GABA for its binding sites. Benzodiazepines have similar sedating effects as ethanol and also work as anticonvulsants without the adverse reactions of ethanol abuse.

The most commonly used benzodiazepines to treat the psychomotor agitation of mild withdrawal are diazepam, lorazepam, and chlordiazepoxide.[111] Minor withdrawal symptoms can be controlled with oral and outpatient therapy, although discharge from the ED with prescriptions for oral benzodiazepines is a controversial practice that is not supported by the literature. There is an advantage of lorazepam and oxazepam in cirrhotic patients because of their shorter half-life and prevention of over sedation. If oral medication is not sufficient and parenteral therapy is required, the IV route is superior to intramuscular because of more predictable bioavailability.

The dosing regimens for benzodiazepines are variable. chlordiazepoxide, because of its extended half-life, is a common oral agent used to manage patients on an outpatient basis. No agent in this class has been shown to be superior to another and several meta-analyses have determined that benzodiazepines reduce the risk of seizures and delirium.[110] Determining the type of therapy is often based on the planned disposition for the patient. The main quantitative instrument that is used to assist in this determination is the Clinical Institute Withdrawal Assessment for Alcohol Scale (CIWA-Ar) (**Table 2**).[112] This scale is based on the following symptoms, each of which has an assigned score and the total is the cumulative sum: nausea and vomiting, paroxysmal sweats, anxiety, agitation, tremor, headache, auditory disturbance, visual disturbance, tactile disturbance, and orientation or clouding of sensorium. Although the CIWA-Ar has been validated in the literature, its use in the ED has not[113]; this is thought to be because of the length and level of detail required to complete it.

On the CIWA-Ar, outpatient treatment may be appropriate for scores between 8 and 15, but inpatient treatment and monitoring should be considered for scores greater than 15. Outpatient therapy generally uses either chlordiazepoxide or diazepam. In addition to having a CIWA score between 8 and 15 (those <8 only need symptom-based treatment), the following represent the criteria for outpatient therapy[114]

- Able to take oral medications
- Have a reliable person to assist and monitor the patient for deterioration

- Compliance with medical regimen and appropriate follow-up
- No unstable psychiatric or medical condition or concurrent ingestions
- Not pregnant
- No history of DT or alcohol withdrawal seizures.

Benzodiazepines are usually given according to a fixed schedule and tapered over a period of 3 to 7 days. Less severe withdrawal therapy can be given as symptoms arise.

For inpatient treatment of more moderate or severe ethanol withdrawal, symptom-driven therapy, although more cumbersome for the treating practitioner and staff, has been shown to require less overall medication and decrease the length of stay. In a 1994 study by Saitz and colleagues,[115] 101 patients were assigned to either a fixed schedule of chlordiazepoxide or a schedule based on symptom triggers. For the same outcome, approximately one-quarter (100 mg vs 425 mg) of the medication and one-eighth of the length of stay (9 hours vs 68 hours) was required in the symptom-triggered group. All end points were clinically superior, but it does force frequent reassessment by the provider, especially in the early phases of treatment. There is also some evidence for the benefit of front loading therapy in which higher doses are given initially to more quickly achieve sedation and decrease withdrawal symptoms. Some studies have shown that a significant reduction in overall medication is required compared with conventional regimens without reaching toxic levels because the initial loading dosages are titrated to the response of the individual patient.[116]

Patients with more severe withdrawal symptoms are best cared for in the ICU so that close attention can be paid to vital signs, neurologic status, fluids and electrolytes, and cardiac monitoring. Multiple comorbidities, hemodynamic/electrolyte/respiratory insufficiency, and need for high doses of sedatives or continuous infusion are some of the criteria for ICU admission.[117]

Barbiturates are another set of medications that have been used successfully to treat severe ethanol withdrawal. They also work at the GABA receptor complex by increasing the duration of chloride channel opening, as opposed to benzodiazepines, which affect the frequency. Barbiturates are especially useful when high doses of benzodiazepines are not showing reduction in autonomic symptoms.[118] Propofol can also affect the chloride channel even in the absence of GABA. Generally, because of the respiratory depression that is seen with propofol and barbiturates, airway protection by means of endotracheal intubation and mechanical ventilation is often required. Besides respiratory depression, barbiturates (and propofol) can cause hypotension, which is usually fluid responsive.[119]

Other agents such as β-blockers and clonidine are generally not recommended in acute withdrawal states because of their inability to decrease hyperactivity of the CNS, particularly seizures and DT.[120] Some patients with alcoholic hallucinosis are wrongly diagnosed with a primary psychiatric disorder and given phenothiazines or butyrophenones, which are known to lower the seizure threshold and, in rare cases, have been documented to cause malignant hyperthermia and ventricular arrythmias.[121] Anticonvulsants such as phenytoin also have no role in ethanol withdrawal states (even withdrawal-related seizures), unless the patient has an underlying seizure disorder. This situation is sometimes seen when chronic ethanol abusers suffer head trauma and have epileptogenic foci, in which case anticonvulsants may be adjunct therapy to benzodiazepines in the emergency setting.[122] There has been some evidence derived from ambulatory patients in Europe that carbamazepine is equal in efficacy to phenobarbital and oxazepam (the benzodiazepine used for comparison). There was also evidence of no significant toxicity, reduction of emotional distress, and

Table 2
Clinical Institute Withdrawal Assessment for Alcohol Scale (CIWAS-Ar)

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 heaving, and vomiting
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
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
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

Paroxysmal sweats. Observation	0 No sweat visible 1 Barely perceptible sweating 2 3 4 Beads of sweat obvious 5 6 7 Drenching sweat
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
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
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 Not present 1 Very mild 2 Mild 3 Moderate 4 Moderately severe 5 Severe 6 Very severe 7 Extremely severe

(*continued on next page*)

Table 2
(*continued*)

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
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
Total score (maximum of 67)	

From Sullivan JT, Sykora K, Schneiderman J, et al. Assessment of alcohol withdrawal: the revised Clinical Institute Withdrawal Assessment for Alcohol scale (CIWA-Ar). Br J Addict 1989;84:1353.

a faster return to work. Common side effects, however, are dizziness, nausea, and vomiting. Data from human trials are limited and it has not been evaluated for moderate or severe withdrawal states.[123]

SUMMARY

Ethanol is a common causative agent in the presentations of patients in the ED with altered mental status. The maintenance of a broad differential, especially the consideration of a concurrent brain injury, is important in the evaluation of acute alcohol intoxication. Supportive therapy is called for in the care of the acutely intoxicated individual, with the judicious use of IV fluids, thiamine repletion in the alcoholic patient, and close observation for clinical deterioration. Special consideration should be given to the sequelae of chronic alcoholic disease, especially hypoglycemia, WE, HE, and AKA. Alcoholic patients presenting after cessation or decrease of ethanol consumption should be carefully evaluated for signs of impending withdrawal, with a goal of preventing progression to life-threatening severe withdrawal and DT. The patients with the highest risk for these symptoms include those with previous episodes of life-threatening withdrawal, concurrent serious illness, and large quantities of daily alcohol intake. The patients undergoing withdrawal can be risk stratified using several systems, including the CIWA-Ar. The mainstay of prevention and treatment of these withdrawal symptoms are benzodiazepines, most often administered in the inpatient or detoxification unit settings. Patients with severe withdrawal symptoms may need monitoring in the ICU for the acute phase of their withdrawal.

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