





# Prevention of alcohol withdrawal syndrome in the surgical ICU: an American Association for the Surgery of Trauma Critical Care Committee Clinical Consensus Document

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## ABSTRACT

Alcohol withdrawal syndrome is a common and challenging clinical entity present in trauma and surgical intensive care unit (ICU) patients. The screening tools, assessment strategies, and pharmacological methods for preventing alcohol withdrawal have significantly changed during the past 20 years. This Clinical Consensus Document created by the American Association for the Surgery of Trauma Critical Care Committee reviews the best practices for screening, monitoring, and prophylactic treatment of alcohol withdrawal in the surgical ICU.

## INTRODUCTION

Alcohol withdrawal syndrome (AWS), characterized by the physical symptoms after cessation of alcohol in patients with alcohol use disorder (AUD), affects 8% to 40% of patients admitted to the surgical ICU and is associated with poor outcomes, including infectious complications and higher mortality.<sup>1</sup> During the past several years, the focus of management of AWS has shifted from a reactive treatment of the syndrome to proactively enacting prophylaxis. This shift has led to an abundance of literature to help guide the screening, monitoring, and empiric prophylaxis of alcohol withdrawal.

In this clinical consensus document, the American Association for the Surgery of Trauma (AAST) Critical Care Committee aims to provide practical guidance to the surgical intensivist on the best practices in screening and prophylaxis of patients at risk for AWS. These recommendations are summarized in [table 1](#).

## METHODS

The AAST Critical Care Committee chose screening, prevention, and management of AWS as a clinically relevant topic for review. A working group was formed from the committee at large to identify the most relevant questions for the bedside intensivist in the management of patients at risk for AWS. The members of this working group were then assigned specific topics to research, using peer-reviewed original literature as well as society guidelines for reference.

Literature review was performed at the authors' own discretion. Their recommendations are the result of expert consensus and do not incorporate formal processes such as GRADE methodology. The topics reviewed are not comprehensive for the topic of alcohol withdrawal but were specifically selected to be practical for the bedside intensivist. Iterative selection of studies was not performed as in a systematic review, and the methodology of literature search was at the discretion of the author. Emphasis was placed on literature published within the last 10 years, with support from existing reviews and clinical practice guidelines.

## SCREENING TOOLS

**What screening tools are available to assess patients for risk of alcohol withdrawal? During what time frame should screening be performed? Recommendation**

It is recommended that patients be screened within 6 to 24 hours of discontinuation of alcohol consumption. Blood alcohol level (BAL) can serve as an initial screen; however, subjective scoring systems (The Alcohol Use Disorders Identification Test (AUDIT), The Prediction of Alcohol Withdrawal Severity Scale (PAWSS)) have higher sensitivity and specificity for prediction of AWS.

## Discussion

AWS can develop within 6 to 24 hours after the discontinuation of alcohol consumption and symptoms may last up to 10 days.<sup>1,2</sup> In the inpatient setting, symptoms typically present within the first 2 to 3 days, but may present later.<sup>2</sup> The key to morbidity and mortality prevention is early identification and initiation of prophylaxis/treatment.<sup>1</sup>

BAL provides an objective standard for the identification of at-risk patients and is easily obtainable at the time of admission. However, the inclusion of additional variables improves screening.<sup>3</sup>

AUDIT is a 10-item survey that assesses alcohol consumption, drinking behavior, and alcohol-related problems. A score of  $\geq 8$  identifies individuals with an AUD.<sup>4</sup> Dolman *et al* found use of AUDIT in combination with elevated biomarkers including aspartate aminotransferase (AST), alanine

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**Table 1** Summary of recommendations

Problem	Recommendations
Screening tools	AUDIT PAWSS
Ancillary services to consider	Social work Addiction Medicine Psychiatry/Psychiatry Nursing
Patients to receive empiric prophylaxis (in appropriate clinical context)	History of complicated alcohol withdrawal (delirium tremens±seizures) Multiple prior episodes or long duration of alcohol use Comorbid medical or surgical illness (including TBI) Age >65 years Autonomic hyperactivity on presentation Physiologic dependence on benzodiazepines or barbiturates Elevated alcohol level, MCV, or AST:ALT ratio on presentation
Method of surveillance	mMINDS
Medications for primary prevention	Benzodiazepines Phenobarbital
Alternative medications for prevention	Clonidine Gabapentin Dexmedetomidine (adjunct to benzodiazepines) Propofol (adjunct to benzodiazepines)
ALT, alanine transaminase; AST, aspartate transaminase; AUDIT, Alcohol Use Disorders Identification Test; MCV, mean corpuscular volume; mMINDS, modified Minnesota Detoxification Scale; PAWSS, Prediction of Alcohol Withdrawal Severity Scale; TBI, traumatic brain injury.	

aminotransferase (ALT), gamma-glutamyl transferase, and red cell mean corpuscular volume (MCV) may increase the sensitivity and specificity for prediction of alcohol withdrawal.<sup>4</sup>

PAWSS, created by Maldonado *et al*, evaluates 10 factors to predict AWS: previous withdrawal, previous withdrawal seizures, history of delirium tremens (DT), history of alcohol rehabilitation, previous blackouts, concomitant use of central nervous system (CNS) depressants/illicit substances, recent alcohol intoxication, elevated BAL at admission, and evidence of increased autonomic activity. A score of  $\geq 4$  showed 100% sensitivity, specificity, positive predictive value, and negative predictive value for development of AWS.<sup>5</sup> They prospectively validated these findings where 403 patients were assessed with PAWSS and then followed with the Clinical Institute Withdrawal Assessment (CIWA) scale and daily monitoring. A PAWSS score of  $\geq 4$  again showed good sensitivity and specificity (93.1% and 99.5%, respectively).<sup>6</sup>

### What other healthcare services should be involved with screening and intervention for patients at risk for alcohol withdrawal?

#### Recommendation

Although there is no clear designation of which other services are necessary for screening and intervention for patients at risk for alcohol withdrawal, multiple services as available in individual institutions can be considered for assistance in management of AWS. Social Work, Addiction Medicine, Psychiatry, Psychiatry Nursing, or Psychology can help standardize the implementation of screening and intervention.

#### Discussion

Screening, Brief Intervention, and Referral to Treatment (SBIRT) is a process through which screening for alcohol withdrawal

is done using a validated screening tool such as AUDIT, with subsequent brief intervention at the time of the interaction and referral for ongoing treatment based on the score.<sup>7,8</sup> This has been implemented in trauma patients with improvement in AUDIT score at time of follow-up.<sup>9</sup>

The American College of Surgeons Committee on Trauma requires verified Level 1 trauma centers to have an active SBIRT program.<sup>3</sup> Zimmermann *et al* describe a multidisciplinary approach to SBIRT implementation with BAL  $>0.02$  g/dL referred to social work. They achieved higher compliance, improved screening rates (30% to 100%), and an 82% intervention and referral to treatment rate.<sup>3</sup> Although there is no clear evidence in the literature as to when consultation services are necessary for patients at risk for or undergoing alcohol withdrawal, use of these services can help standardize the implementation of screening and intervention. These consultation services vary between institutions and can include Social Work, Addiction Medicine, Psychiatry, Psychiatry Nursing, or Psychology. The use of these consultation services has been found to have decreased recidivism as evidenced by Emergency Department visits as well as increased self-reported abstinence rates at 30 days.<sup>10–12</sup>

### EMPIRIC PROPHYLAXIS

#### Is empiric prophylaxis for alcohol withdrawal beneficial?

#### Recommendation

Empiric prophylaxis for alcohol withdrawal is beneficial and has been shown to decrease complications from alcohol withdrawal for patients at risk for severe or complicated AWS.

#### Discussion

Multiple trials have demonstrated the safety and efficacy of AWS prevention protocols. The literature shows that prophylaxis rarely results in oversedation or respiratory compromise in at-risk patients.<sup>13–17</sup> When appropriately screened using validated tools such as AUDIT or PAWSS, patients who are at risk for severe or complicated alcohol withdrawal, manifested by alcohol withdrawal delirium (DTs) with or without alcohol withdrawal seizures, appear to benefit most from empiric prophylaxis.<sup>18</sup> In addition, empiric prophylaxis protocols for AWS have been proven to decrease hospital and intensive care unit length of stay, alcohol withdrawal delirium and seizures, and pulmonary complications.<sup>13–16,19</sup> Although no placebo-controlled trials exist to evaluate outcomes in trauma and critically ill patients, the significant, well-proven morbidity and mortality associated with AWS warrants empiric prophylaxis and is recommended by the American Society of Addiction Medicine (ASAM), Center for Substance Abuse Treatment, and other national and international organizations.<sup>18–20</sup>

#### Which patients being admitted to a surgical ICU should receive empiric alcohol withdrawal prophylaxis?

#### Recommendation

Current best practice is for critically ill patients admitted to a surgical ICU and deemed high risk for AWS based on objective criteria to receive empiric alcohol withdrawal prophylaxis.

#### Discussion

Patients are at high risk for AWS if they have a previous history of complicated alcohol withdrawal (sometimes referred to as severe alcohol withdrawal), as defined above.<sup>18,21</sup> Other risk factors include multiple prior withdrawal episodes, comorbid medical or surgical illness (especially traumatic brain injury), age 65 years or older, long duration of heavy and regular alcohol

consumption, autonomic hyperactivity on presentation, and physiologic dependence on agents such as benzodiazepines and barbiturates.<sup>18</sup> Those patients with recent alcohol use (within 2 weeks of admission) with either a BAL of 0.1 g/dL or higher, elevated MCV (>90 fL), or elevated ALT to AST ratio greater than or equal to 1.5:1 are considered high risk as well.<sup>22 23</sup> Screening tools as described in previous sections can be used to identify patients who can benefit from empiric alcohol withdrawal prophylaxis as well. Current best practice is for patients deemed high risk to receive empiric prophylaxis.

### Which patients require intensive monitoring specifically for prophylaxis?

#### Recommendation

Inpatients who are at high risk for complicated alcohol withdrawal but do not otherwise meet criteria for SICU admission may be admitted to a monitored setting (SICU vs surgical step-down) with telemetry and pulse oximetry capabilities for the initiation of alcohol withdrawal prophylaxis therapy.

#### Discussion

Close monitoring during initiation of AWS prophylaxis is warranted given the potential for respiratory depression, sedation, or hemodynamic changes. We recommend that patients be monitored with continuous telemetry/pulse oximetry and frequent nursing assessments, which may necessitate an ICU setting. Patients should be monitored at least every 1 to 2 hours for the first 24 hours of alcohol withdrawal prophylaxis therapy.<sup>1 18</sup> Once stable on a prophylaxis regimen, patients may be monitored less frequently (every 4 to 8 hours).<sup>18 24</sup> Trauma patients may be at higher risk for respiratory depression if they have pulmonary risk factors including rib fractures, chest tubes, pulmonary contusions, pneumonia, or cervical collar/spinal precautions.<sup>22</sup> Patients who may be at higher risk for hemodynamic changes include those with hepatic dysfunction, liver cirrhosis, traumatic brain injury, and recent opioid, sedative, or benzodiazepine administration.<sup>22 25</sup>

## SURVEILLANCE METHODS

### What are the preferred surveillance methods for AWS in the surgical ICU?

#### Recommendation

We recommend use of the modified Minnesota Detoxification Scale (mMINDS) for ICU patients at risk for AWS.

#### Discussion

The three commonly used surveillance tools for AWS are the revised Clinical Institute Withdrawal Assessment for Alcohol (CIWA-AR), the Brief Alcohol Withdrawal Scale (BAWS), and the mMINDS. All three were designed to assist with early identification and treatment of AWS (table 2).

The CIWA-AR scale is a 10-item tool that was originally intended for voluntary detoxification centers to detect and monitor AWS.<sup>26</sup> In 2017, BAWS was developed to shorten the CIWA-AR assessment to five items: tremor, diaphoresis, agitation, confusion, and hallucinations.<sup>27 28</sup> Both the CIWA-AR and the BAWS assessments are not validated in critically ill, medically complex, or postoperative patients. In fact, 6 of the 10 items that make up the CIWA-AR scale require the patient to answer questions. In a single-center study of ICU patients, CIWA-AR was not assessed in 44% of patients, due to intubation.<sup>29</sup> Similarly, some conditions, such as traumatic brain injuries, may falsely elevate CIWA-AR scores, so the scale must be cautiously

**Table 2** Surveillance tools for alcohol withdrawal syndrome

Tool	Components of tool
CIWA-AR	Nausea/vomiting
	Tremor
	Diaphoresis
	Anxiety
	Agitation
	Tactile disturbances
	Auditory disturbances
	Visual disturbances
	Headache
	Orientation
BAWS	Tremor
	Diaphoresis
	Agitation
	Orientation
	Hallucinations
mMINDS	Pulse
	Diastolic blood pressure
	Tremor
	Diaphoresis
	Hallucinations
	Agitation
	Orientation
	Delusions
	Seizure

BAWS, Brief Alcohol Withdrawal Scale; CIWA-AR, Clinical Institute Withdrawal Assessment for Alcohol; mMINDS, modified Minnesota Detoxification Scale.

interpreted in surgical and trauma patients.<sup>30</sup> There is limited evidence suggesting that the CIWA-AR scale may be augmented by simultaneously following the Riker Sedation Agitation Scale, a sedation scale commonly used in many ICUs, but this work has primarily been aimed at guiding treatment strategies rather than monitoring for AWS.<sup>31</sup>

The mMINDS assessment has been validated in medical ICU patients.<sup>30 32</sup> The advantage of mMINDS is that it does not require the patient to answer questions. Instead, it assesses pulse, blood pressure, and the presence of tremor, sweating, hallucinations, agitation, orientation, delusions, and seizures to analyze AWS severity. In a medical ICU, mMINDS has been shown to correlate with CIWA-AR. This correlation does diverge with worsening AWS symptoms due to the emphasis placed on subjective factors in the CIWA-AR, as the CIWA-AR may not be able to be used in more severe AWS as described above.<sup>33</sup> Additionally, in the medical ICU, a protocol based on mMINDS surveillance resulted in fewer intubations when compared with a pre-protocol period.<sup>34</sup> Taken together, mMINDS is the most objective test available and has been shown to successfully assist in the management of AWS in an ICU setting.

## MEDICATIONS

### What medications may be used for primary prevention and treatment of AWS?

In this section, we define primary prevention and treatment medications as the preferred agents for initial prophylaxis or treatment of AWS, with no recommendation as to best agent within these medications.

**Table 3** Benzodiazepine dosing and metabolism for AWS

Drug	Routes	Onset (min)	PO dosing for AWS	IV dosing for AWS	Half-life (hours)	Metabolism
Diazepam	PO, intravenous, IM, rectal	IV: 2–5	10 mg 3–4 times per day	5–10 mg every 10–15 min	43	Liver
Chlordiazepoxide	PO, intravenous, IM	PO: 30–120	50–100 mg, repeated up to 300 mg in 24 hours	NA	10	Liver
Lorazepam	PO, intravenous, IM	IV: 15–20	2–4 mg q 1 hour	1–4 mg every 5–15 min	14	Liver

AWS, alcohol withdrawal syndrome; IM, intramuscular; PO, oral.

### Benzodiazepines Recommendation

Benzodiazepines are recommended for the treatment of major symptoms of AWS, as well as prophylaxis against the worsening of mild AWS. Recommended agents are diazepam, lorazepam, and chlordiazepoxide, to be used in a standardized administration protocol.

### Discussion

Benzodiazepines have long played a prominent role in the treatment and prophylaxis of AWS and are often regarded as standard of care.<sup>21 35 36</sup> This class of medications treats the psychomotor agitation that accompanies AWS and prevents progression from minor to major symptoms. Like ethanol, benzodiazepines stimulate the gamma-aminobutyric (GABA) receptors in the brain resulting in reduced neuronal activity and sedation. Although any benzodiazepine can be used for AWS, chlordiazepoxide, lorazepam, and diazepam are preferred for their relatively long half-lives, reducing the risk of breakthrough symptoms.<sup>37</sup>

When initiating benzodiazepine therapy, consider the specific agent, route, and dosing-strategy (table 3). For severe, acute AWS, including patients with tremor, use intravenous medication initially. As symptoms abate, patients should be transitioned to oral medication as soon as possible. For patients with mild symptoms, it is appropriate to start with oral administration. Both symptom-triggered benzodiazepine therapy and “front-loading” (rapid, deeper sedation followed by tapering) strategies have been described. The approach used is primarily based on the ability of the patient to cope with mild symptoms of AWS. Patients who are less likely to tolerate any hypertension or tachycardia may benefit from more aggressive initial dosing. In patients with severe symptoms, using a front-loading approach is associated with reduced length of stay compared with symptom-based treatment only.<sup>38</sup> When using a front-loading approach, both diazepam and lorazepam may be used; however, care should be taken with lorazepam as longer onset of action may lead to frequent doses and resultant oversedation.<sup>39</sup> A symptom-triggered approach for patients uses benzodiazepines in conjunction with standardized symptom scales such as CIWA or mMINDS.<sup>21 36 37</sup> This approach decreases the total amount of medication administered and the duration of treatment when compared with fixed dosing regimens.<sup>35</sup> Fixed dosing strategies, where benzodiazepines are given at regular intervals, regardless of symptoms, are associated with increased medication administration.<sup>35 36</sup> Oral benzodiazepines are appropriate for mild symptoms using a symptom-based approach, and acceptable results have been obtained using chlordiazepoxide.

To treat AWS, best practice is for benzodiazepines to be used as part of an institutional protocol which guides physicians on appropriate use and dosing.<sup>40 41</sup> Chlordiazepoxide and diazepam have long half-lives as well as active metabolites and should be used with caution in patients with liver failure as the reduction in metabolism may lead to oversedation. In rare cases,

benzodiazepines may cause paradoxical excitation which may mimic the symptoms of AWS.<sup>42</sup> AWS refractory to benzodiazepines may be present if severe symptoms are not controlled after 50 mg of diazepam or 10 milligrams of lorazepam in the first hour of treatment, or 200 mg diazepam or 40 mg lorazepam in the first 3 hours of treatment.

### Phenobarbital Recommendation

Phenobarbital is a safe and effective pharmacologic agent for use in prevention and treatment of AWS. A fixed-dose approach is recommended due to the pharmacokinetics and long half-life of phenobarbital.

### Discussion

Benzodiazepines are the most commonly prescribed and best studied medications in the management of AWS. However, their use can result in aspiration, respiratory depression, and worsening delirium. Patients in the surgical ICU are often already at high risk for developing delirium secondary to critical illness, traumatic brain injuries, surgical interventions, and other traumatic injuries.<sup>43</sup>

Phenobarbital is an antiepileptic drug used as an alternative for the prevention of AWS. It is cross-tolerant with alcohol, upregulates GABA activity to prolong the duration of chloride channel opening, and decreases glutamate activity by binding to the 2-amino-3-hydroxy-5-methylisoxazole-4-propionic acid and kainite receptors.<sup>44 45</sup> Benefits of using phenobarbital include its availability in multiple formulations, ability to assess dosing by serum level, and long half-life (80 to 120 hours).<sup>43 46</sup> Of note, although there has been demonstration in the literature of a dose-response in regard to serum phenobarbital levels, it is unclear whether there is a universal “therapeutic” phenobarbital dose for AWS and this treatment should be individualized at this time.<sup>47</sup> Several studies have shown phenobarbital can be used safely; however, adverse events include respiratory depression, sedation, and hypotension.<sup>43–47</sup> Unlike benzodiazepines, there is no reversal agent for phenobarbital.<sup>48</sup>

Several studies have demonstrated the use of phenobarbital, as a monotherapy or in conjunction with benzodiazepines, is safe and efficacious in ICU and non-ICU settings.<sup>44 46</sup> More recent studies demonstrate its utility in ICU settings with surgical patients. Nejad *et al* implemented a phenobarbital-based protocol for patients at risk for AWS in the trauma and burn population. No patients developed AWS and no adverse side effects from phenobarbital were identified.<sup>43</sup> A study from Ammar *et al* studied a standardized phenobarbital monotherapy-based protocol in patients at medium and high risk of developing AWS, with a loading dose of 10 to 15 mg/kg administered over three doses in the first day, and a subsequent taper of 64.8 mg q12 hours for 2 days, 32.4 mg every 12 hours for 2 days, and 32.4 mg every 24 hours for 2 days. The authors found that no patients developed

severe AWS-related complications including seizure, alcoholic hallucinations, and alcoholic withdrawal delirium, and only 13% (4/31) of patients developed phenobarbital-related adverse events, which were hypotension and need for intubation.<sup>22</sup> Using a fixed-dose regimen is recommended rather than a symptom-based approach due to the long half-life and pharmacokinetics of phenobarbital. Phenobarbital has a narrow margin of safety and a symptom-based approach has not been validated.<sup>46</sup>

Although the evidence for benzodiazepine-based prophylaxis is robust, phenobarbital is not inferior to benzodiazepines, has a comparable safety profile, and is well tolerated by patients in the surgical ICU setting.<sup>22 43 48</sup>

## What medications may be used for alternative prevention and treatment of AWS?

### Recommendation

Clonidine and gabapentin are recommended for use; intravenous ethanol and non-phenobarbital antiepileptics are not currently recommended as they are not equivalent to benzodiazepines. Dexmedetomidine and propofol are recommended as benzodiazepine adjuncts.

### Discussion

Although benzodiazepines and phenobarbital are the most common agents used in the treatment of complicated AWS, alternative agents are also effective in the treatment and prevention of complicated alcohol withdrawal and may be considered for use when weighing the risks and benefits of individualized pharmacology.

#### Clonidine

Activation of the sympathetic nervous system is a key feature of AWS. Previous work has shown that the severity of AWS is positively correlated to the amount of norepinephrine (NE) released in the CNS.<sup>49</sup> Inhibition of NE release, as well as other excitatory neurotransmitters, may be accomplished via activation of the alpha-2 adrenergic receptor.<sup>50</sup> Additionally, alpha-2 adrenergic receptor agonist (AAG) medications create an anti-convulsant effect via decrease in cyclic GMP within the cerebellum.<sup>51</sup> Taken together, AAG effectively decreases excitatory neurotransmission within the CNS, creating an opportunity for treatment of AWS.

The use of clonidine in the management of AWS is supported by seven double-blind randomized controlled trials.<sup>49</sup> Subjects treated with clonidine experienced lower mean withdrawal scoring, heart rate, and blood pressure compared with benzodiazepine-treated patients.<sup>49</sup> Furthermore, there was less anxiety, better cognitive recovery, and better management of psychological symptoms reported in the clonidine groups.<sup>49</sup> Hypotension is the primary adverse effect of clonidine due to its activation of receptor subtypes A and C within the nucleus tractus solitarius.<sup>52</sup> As such, consideration should be given to use of other AWS agents in patients with shock or low baseline blood pressures.

#### Gabapentin

GABA is the principal inhibitory neurotransmitter in the mammalian CNS with target receptors GABA<sub>A</sub> and GABA<sub>B</sub>.<sup>53</sup> The acute neuroinhibitory effect induced by GABA, primarily on the GABA<sub>A</sub> receptor, is potentiated by alcohol.<sup>54</sup> Over time, neuroadaptation in the presence of chronic alcohol usage leads to a reduction of GABA<sub>A</sub> receptor populations in the CNS. Although repeated alcohol exposure produces a state of tolerance, abrupt

cessation of alcohol may produce clinical consequences consistent with neural disinhibition and excitation.<sup>54</sup>

Gabapentin's neuroinhibitory mechanisms of action include increased production of GABA, inhibition of glutamate (an excitatory neurotransmitter) synthesis, and a reduction in NE and dopamine release.<sup>49</sup> Gabapentin for the inpatient treatment of AWS is supported by two randomized trials.<sup>49</sup> Benefits of gabapentin included reduced anxiety and sedation compared with benzodiazepines, with no serious adverse events. Further advantages of gabapentin are its concomitant analgesic properties and extrahepatic metabolism, creating opportunities for its use in the injured patient population and for those with hepatic dysfunction.<sup>55</sup>

#### Intravenous ethanol

The use of intravenous ethanol has been reported in surgical and trauma ICUs to prevent AWS in patients with a history of binge drinking, multiple daily drinks, or a history of AWS. The purported benefits of IV ethanol are effective management of withdrawal symptoms without the excessive respiratory depression and sedation seen with benzodiazepine administration. Through uncontrolled case series, several groups have demonstrated the efficacy and safety of intravenous ethanol and published protocols for its use.<sup>15 56</sup> Weinberg *et al* published a randomized control trial comparing intravenous ethanol to standard benzodiazepine for AWS prophylaxis in a Trauma ICU.<sup>14</sup> They found no benefit of intravenous ethanol over diazepam overall, and patients in the intravenous ethanol group had higher rates of agitation. A randomized trial comparing ethanol and lorazepam in a cardiac ICU population showed similar results.<sup>57</sup> As intravenous ethanol does not demonstrate improved outcomes over benzodiazepines, intravenous ethanol is not recommended for prophylaxis or treatment of patients with AWS, and the ASAM guidelines do not support the use of IV ethanol for the prevention or treatment of AWS.<sup>18</sup>

#### Antiepileptics

Numerous antiepileptic drugs (AEDs), including valproic acid and carbamazepine, have been used and studied as an adjunct or alternative to benzodiazepines. AEDs have a lower potential for abuse and act at targets outside the GABA pathway. A recent systematic review and meta-analysis evaluated 26 randomized controlled trials comparing various AEDs to benzodiazepines or placebo.<sup>58</sup> The review found no difference in rate of AWS, seizure, or DTs. There was a non-statistically significant increase in the rate of mild or moderate adverse effects (dizziness, ataxia, nausea, and vomiting) with carbamazepine and valproic acid use. Although the overall quality of evidence was low as analyzed by the cited systematic review and meta-analysis, the use of AEDs is not recommended for prophylaxis or treatment of patients with AWS.<sup>58</sup>

#### Dexmedetomidine

Dexmedetomidine has anxiolytic, analgesic, and sedative properties via its actions on brain stem  $\alpha_2A$  receptors, with onset of action between 10 and 30 min, plasma half-life of 6 min, an elimination  $\frac{1}{2}$  life of 2 hours, 70% to 80% and bioavailability.<sup>49</sup> Dexmedetomidine acts via a negative feedback mechanism in regulating the release of NE.<sup>59</sup> Dexmedetomidine mitigates tachycardia, hypertension, and tremulousness by inhibiting noradrenergic hyperactivity in alcohol withdrawal.<sup>59</sup> Dexmedetomidine has shown some efficacy as an adjunct in benzodiazepine refractory DTs, with benzodiazepine and haloperidol

sparing effects.<sup>60</sup> Although dexmedetomidine is contraindicated in patients with heart block, it has been associated with more bradycardia but less hypotension than propofol.<sup>60</sup> There is some support for cognitive preservation during dexmedetomidine infusion.<sup>61–63</sup> Of note, dexmedetomidine is not an antiepileptic medication and other agents may be necessary for this indication.<sup>64</sup> With the appropriate level of monitoring, it has been used in both intubated and non-intubated patients.

Two small studies demonstrated the efficacy of dexmedetomidine in reducing benzodiazepine requirements. A prospective, double-blind, placebo-controlled trial including 24 severe alcohol withdrawal patients at a single medical ICU found that the addition of dexmedetomidine reduced 24 hour but not 7-day benzodiazepine requirements.<sup>65</sup> A single institution, randomized controlled study of 72 ICU patients with AWS found significantly reduced 24 hour diazepam requirements in those receiving adjunctive therapy with dexmedetomidine.<sup>66</sup> They also noted improved patient-nurse communication and reduced haloperidol administration in dexmedetomidine patients. A prospective study of 40 AWS patients treated with diazepam or dexmedetomidine infusion demonstrated improved hemodynamics and fewer treatment days in those receiving dexmedetomidine.<sup>67</sup> Arguably, dexmedetomidine may warrant additional consideration in geriatric patients as they are at increased risk of respiratory depression with many agents.<sup>68</sup> According to the 2020 ASAM Clinical Practice Guidelines, dexmedetomidine is recommended as an adjunct to benzodiazepine treatment, but not as monotherapy, to prevent or treat alcohol withdrawal-related delirium or seizures, and to assist with the control of autonomic hyperactivity and anxiety in inpatients.<sup>18</sup>

### Propofol

Propofol is an agonist for GABA<sub>A</sub> receptors, resulting in hyperpolarization by increasing the duration of chloride channel opening/conductance by directly activating the chloride ionophore complex.<sup>1 49 59–61 69</sup> This activation inhibits firing, thereby inducing sedation and anxiolysis.<sup>1</sup> Of note, propofol binds at a different site of the GABA<sub>A</sub> receptor than benzodiazepines, and, hence, is often used in benzodiazepine refractory cases.<sup>60 64</sup> Propofol also reduces glutamate activity, thereby preventing seizures, inhibits NMDA glutamate receptors, and is thought to inhibit other amino acids that may be upregulated in DTs.<sup>1 59 60 69</sup> Propofol acts within seconds, duration of action is approximately 10 min, and has a short elimination half-life.<sup>61 64</sup> Risks of propofol infusion include hypotension, the rare but potentially fatal propofol-related infusion syndrome, metabolic acidosis, and hypertriglyceridemia.<sup>61</sup> Of note, barbiturates and propofol have similar effects on intracranial dynamics and cerebral activity.<sup>49</sup> It is not clear if the increased duration of mechanical ventilation and hospital length of stay of patients treated with propofol is secondary to propofol itself or the severity of the withdrawal.<sup>60</sup> Two, small, single-center studies demonstrated the efficacy of propofol in alleviating DTs, with one showing no difference in ventilator days, ICU days, or hospital length of stay between patients receiving benzodiazepines versus propofol.<sup>69–71</sup> The ASAM guidelines recommend propofol in mechanically ventilated ICU patients with resistant alcohol withdrawal.<sup>18</sup> Of note, higher induction doses of propofol are required in patients with AUD, with a recommended IV loading dose of 100 to 200 mg/hour.<sup>72</sup>

## SUPPLEMENTATION

### What micronutrient supplementation should be provided to the ICU patient receiving prophylaxis or treatment for alcohol withdrawal?

#### Recommendation

Micronutrient deficiencies are common in those with chronic or severe AUD. Thiamine (vitamin B1), magnesium, phosphorus, and folic acid (vitamin B9) should be given as supplements during the acute period of critical care, even in the absence of symptoms of AWS.

#### Discussion

Significant AUD is often associated with poor nutritional intake of micronutrients, intestinal malabsorption, reduce hepatic uptake and storage, as well as alterations in renal tubular function leading to increased excretion.<sup>73</sup> The diagnosis of subtle neurologic findings associated with micronutrient deficiencies is challenging in critical environments due to the severity of illness and the concomitant use of sedatives and analgesics. As such, empiric supplementation is recommended in those with known or suspected AUD. Thiamine (vitamin B1) should be given prophylactically (100 mg po/intravenous per day for 3 to 5 days) to prevent Wernicke's encephalopathy, a reversible clinical syndrome associated with altered mental status, gait ataxia, and nystagmus. If left untreated, progression to Korsakoff's syndrome, with its permanent memory loss, can occur.<sup>74</sup> Recent guidelines recommend administering thiamine at the above dosage to all patients admitted to an ICU with AWS.<sup>18</sup> Intravenous or intramuscular dosing is preferred in those with a history of poor nutrition, malabsorption, or severe complications from withdrawal. Past guidelines recommended giving thiamine prior to intravenous glucose to optimize glucose absorption and prevent Wernicke's; however, in the absence of scientific data to support this recommendation, newer guidelines support the administration of both in any order or concurrently.<sup>18</sup>

Although often used to guide therapy, serum magnesium levels are a poor indicator of total body stores. Supplementation is recommended in those with cardiac arrhythmias, electrolyte disturbances, or a history of alcohol withdrawal seizures.<sup>18</sup> Ideal magnesium dosing in this context is not well defined. However, patients with severe magnesium deficiency in the setting of chronic AUD may require up to 1 mEq/kg of magnesium in divided dosing over the first day, while following serial magnesium levels, with 0.5 mEq/kg per day for the subsequent 3 days.<sup>75</sup>

In those with severe hypophosphatemia (serum <1 mg/dL), supplementation should be provided. Low levels of phosphate at the time of admission may be due to increased renal losses, inadequate nutrition, or because of refeeding syndrome.<sup>76</sup> Enteral repletion is preferred due to the risk of calcium chelation with rapid, intravenous administration.<sup>77</sup> Those with levels of 1 to 2 mg/dL will self-correct rapidly with an improved diet.<sup>18</sup>

Critically ill patients should have folate (vitamin B9) supplementation as hyperhomocysteinemia may increase the risk of alcohol withdrawal seizures.<sup>18</sup> Intravenous administration of 400 to 1000 µg for at least 3 days is recommended as a reliable method for improving levels.<sup>2 75</sup>

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