Alcohol withdrawal syndromes in the critically ill

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Abstract
Introduction
Alcohol abuse continues to be a global problem. Here the four stages and pathogenesis of alcohol withdrawal syndrome are reviewed. The pharmacotherapy of the patient includes benzodiazepines, propofol, barbiturates, dexametomidine, beta-blockers and phenothiazines. The author’s pharmacological protocol for alcohol withdrawal syndrome is included.

Conclusion
The pharmacological strategy needs to match the severity the patient is experiencing.

Introduction
Alcohol abuse is a common problem globally, and it is estimated to result in 2.5 million deaths annually¹. Of the drugs of abuse, alcohol is the most common², with an estimated 18.3 million individuals dependent on it in the United States³. Alcohol abuse has a prevalence of 22.4% in a hospitalised population⁴. In one analysis, alcohol-related admissions accounted for 9% of admissions to a population of mixed medical intensive care unit (ICU) and surgical ICU patients; in addition these patients accounted for 13% of total ICU costs⁵. One population with a particularly high rate of alcohol abuse are trauma patients, with estimates of prevalence ranging from 31% to 70% across centres⁶,⁷.

Alcohol-related complications in the ICU affect nearly every organ system (Table 1). Alcohol abuse in patients is associated with increased length of stay⁸, outpatient pneumonia⁹,¹⁰ and an almost three times higher incidence of healthcare-associated infections¹¹. The aim of this critical review is to discuss alcohol withdrawal syndromes in the critically ill.

Discussion
The author has referenced some of its own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

Diagnosis
The gold standard for the diagnosis of alcohol withdrawal syndrome (AWS) is the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition¹². It requires that a patient's alcohol usage is heavy and prolonged, there is a cessation in alcohol intake and also that there is no other general condition that better accounts for the diagnosis. There should also be a manifestation of symptoms with two or more of the following: autonomic hyperactivity, increase in hand tremors, insomnia, nausea or vomiting, transient hallucinations, psychomotor agitation, anxiety or grand mal seizures. Finally, the symptoms should cause significant distress and interfere with important areas of functioning.

AWS has four clinical stages: (1) autonomic hyperactivity, (2) hallucinations, (3) neuronal excitation and (4) delirium tremens (Table 2)¹³. Patients generally start the withdrawal process at 5 h, with hallucinations at 24 h, and delirium at 48 h; it is rare for this to persist for more than 120 h¹⁴. While some patients may linearly progress through these stages, others may progress more rapidly. The author has seen patients in the postoperative period immediately after general anaesthesia for surgery present in delirium tremens with no manifestation of progression through the lower stages.

Pathophysiology
AWS is the result of a disruption of the delicate neurochemical balance that is controlled via inhibitory and excitatory neurotransmitters. The principal inhibitory neurotransmitter is gamma aminobutyric acid (GABA), which exerts its effect on the GABA-A neuro-receptor¹⁵. A principal excitatory transmitter is glutamate, which affects the N-methyl-D-aspartate neuro-receptor. With chronic alcohol exposure, the brain has a tolerance to the effects of the alcohol due to down-regulation of the GABA-A receptor over time¹⁶. This down-regulation may occur by modification of the GABA-A receptor in the alpha 1 subunit to make the receptor less susceptible to the effects of alcohol exposure¹⁷.

Pharmacological treatment
The severity of the symptoms of AWS should direct the appropriate pharmacotherapeutic interventions. The patient’s comorbidities, other active diagnoses as well as exposure to any other drug of abuse should also be factored into the development of their treatment plan.

Benzodiazepines
Benzodiazepines have historically been the mainstay pharmacologic intervention of AWS¹⁸; they are generally considered to be the ‘gold standard’ treatment¹⁹. It has
been shown that sedative-hypnotic agents such as benzodiazepines, in comparison with other agents, reduce mortality and control the symptoms of AWS. All benzodiazepines have the same mechanism of action on the GABA receptor. Several agents have been used for AWS including chlordiazepoxide, lorazepam, valium, oxazepam and midazolam. Lorazepam is suggested as the benzodiazepine of choice for AWS due to its intermediate half-life, which balances a smooth withdrawal, with the potential for delayed metabolism in those with impaired hepatic function such as geriatric or cirrhotic patients.

In less severe cases of AWS, benzodiazepine can be administered via the oral route. However, for alcohol withdrawal severe enough to require admission to the critical care setting, the parenteral route is chosen. In some cases, it can be intermittently given as a bolus, although some patients may require a continuous infusion of the medication. With a prolonged infusion of the sedative, mechanical ventilation is necessary, which prolongs the length of stay in the ICU, and has the known complication of ventilator-associated pneumonia (VAP) and prolonged coma even with cessation of benzodiazepine. When the duration of benzodiazepine infusion in the critical care setting exceeds seven days, a benzodiazepine withdrawal syndrome has also been described.

Benzodiazepines were traditionally administered to AWS patients in a fixed dose regimen. There has now been over two decades of experience accumulated with the use of on demand or ‘symptom-triggered’ dosing of benzodiazepines for AWS treatment. This method of symptom-triggered dosing relies on the Clinical Institute Withdrawal Assessment for Alcohol [CIWA-A or CIWA-Ar (revised)]. In studies, the symptom-triggered dosing method results in both a decrease in the amount of benzodiazepines administered and a shortened duration of withdrawal symptoms. While the symptom-triggered approach has these advantages, there is quite limited experience of the use of this approach in critical care settings, and it has not shown the same benefit across all studies.

**Benzodiazepine resistance**

There are sporadic reports of AWS patients being benzodiazepine resistant and requiring extremely high doses of these agents for a prolonged time to control their symptoms. While these patients can be managed using benzodiazepine as monotherapy, it can only be done at supratherapeutic doses, which have a propensity to accumulate, and then require a significantly prolonged wean. This often precipitates unnecessary neurologic workup, including brain imaging and prolonged mechanical ventilation. Clinicians often turn to additional agents to avoid supratherapeutic benzodiazepines and the predictable sequelae.

Intravenous ethanol, while still used in some centres, is not currently favoured by many clinicians and...
offers no advantages over benzodiazepine33. It is generally reserved for use in overdoses of methanol, isopropanol or ethylene glycol34.

Barbiturates can be a reasonable agent in the setting of a severe AWS. Advantages include low cost and long half-life which can provide longer term saturation of the GABA receptors, resulting in less symptoms including agitation. A disadvantage of barbiturates is the lack of a reversal agent in case of an overdose. Pheno-barbital has been used in emergency department settings as a sole agent for mild to moderate cases of alcohol withdrawal35. In ICUs, barbiturates often get added to benzodiazepine in benzodiazepine-resistant patients with AWS. Propofol is an intravenous sedative commonly used in critical care settings for sedation via continuous infusion. Its mechanism of action is also on the GABA receptor. Propofol has the advantage of a shorter half-life and rapid wakeup when stopped; the disadvantage is propofol infusion syndrome, particularly with longer usage at higher doses. It is hypothesised that the propofol is synergistic with benzodiazepine, thereby avoiding the toxic effects of monotherapy with a high-dose benzodiazepine approach. There is limited experience to this approach37,38, although the most resistant AWS do respond to this strategy in the author’s experience. The major drawback of propofol for AWS is that it requires mechanical ventilation, so its use should be reserved for the more severe end of the spectrum.


Critical review

Table 2. Stages of alcohol withdrawal45.

| (1) Autonomic hyperactivity | Increased sympathetic outflow with an increase in circulating catecholamines with symptoms including diaphoresis, nausea, vomiting, anxiety, tremor and agitation. |
| (2) Hallucinations | Visual and tactile are common and auditory is unusual. The hallucination of ants crawling on skin is classically described. |
| (3) Neuronal excitation | Alcohol withdrawal seizures. |
| (4) Delirium tremens | Delirium that is in combination with autonomic hyperactivity and alcohol hallucinosis. |

Another agent used in case of benzodiazepine-resistant patients with AWS is propofol. It is an intravenous sedative commonly used in critical care settings for sedation via continuous infusion. Its mechanism of action is also on the GABA receptor. Propofol has the advantage of a shorter half-life and rapid wakeup when stopped; the disadvantage is propofol infusion syndrome, particularly with longer usage at higher doses. It is hypothesised that the propofol is synergistic with benzodiazepine, thereby avoiding the toxic effects of monotherapy with a high-dose benzodiazepine approach. There is limited experience to this approach37,38, although the most resistant AWS do respond to this strategy in the author’s experience. The major drawback of propofol for AWS is that it requires mechanical ventilation, so its use should be reserved for the more severe end of the spectrum.

Adjuvent agents

The alpha-2-agonist, clonidine, has traditionally been used to blunt the sympathomimetic effects of AWS39. This has been done outside critical care settings. While intravenous clonidine is available in Europe, it is not currently available for use in the United States. This has resulted in intensivists to turn to dexmedetomidine, a drug derived from clonidine. Dexmedetomidine is not FDA-approved for AWS, but rather for procedural conscious sedation and sedation for mechanical ventilation <24 h. While there have been isolated case reports of dexmedetomidine being used for AWS with good results, retrospective data has recently been published40–42. Dexmedetomidine may be used as an adjuvant agent in conjunction with benzodiazepine for AWS, and it may shorten the ICU length of stay and avoid intubation. The maximum approved infusion dose of dexmedetomidine is 0.7 mcg/kg/h, although some patients may benefit from higher doses (up to 1.4 mcg/kg/h). The patients who respond well to dexmedetomidine can be transitioned to a clonidine patch as their symptoms stabilise.

Beta-blockers

Beta-blockers have been used as an adjunctive agent in AWS. Given the sympathetic outflow associated with autonomic hyperactivity, beta-blockers are a direct antagonist. This medication can be administered either orally or intravenously, and it serves to normalise tachycardia and hypertension in non-agitated patients that are otherwise comfortable. In a randomised trial by Gottlieb, atenolol in patients with AWS served to make a more rapid resolution of their vital sign abnormalities and clinical signs such as tremor43. Beta-blockers serve an important role as part of a multimodal pharmacological plan, but they should never be used without a GABA agent.

Haloperidol

Haloperidol is a phenothiazine that is commonly prescribed in ICUs for acute agitation. It has the benefit of haemodynamic neutrality, and the possible complications of an elevation in the QTc interval and tardive dyskinesia. While haloperidol is an adjunctive agent in AWS setting, it is particularly useful for the symptoms related to delirium44.

Conclusion

AWS continues to challenge clinicians in critical care settings. Keys to good outcomes in this area include early recognition of the disorder and rapid implementation of appropriate pharmacologic treatment. The range of symptoms represents a spectrum; the pharmacologic strategy needs to match the severity that the patient is experiencing. While some patients have a good therapeutic response to a single benzodiazepine agent, more severe cases may require a multimodality therapy. The current
Table 3. Critical care treatment of alcohol withdrawal syndrome.

- Lorazepam 2 mg intravenously every 6 h
- Dexametomidine up to 1.4 mcg/kg/h intravenously titrated to RASS* = 0 (tolerate -1 to +1) (apply clonidine patch 0.1 to 0.2 mg/day before stopping infusion)
- Intubate patient and mechanical ventilation
- Lorazepam at 0.5 to 2 mg/h continuous intravenous infusion
- Propofol continuous infusion
- Phenobarbital in escalating intravenous bolus doses (65 mg, 130 mg, 260 mg)

Adjunctive agents:
- Lorazepam 2.5 mg to 5 mg every 6 h intravenously for hypertension or sinus tachycardia >120 beats/min
- Haloperidol 2.5 mg to 10 mg every 6 h intravenously, and as needed for control of agitation

*RASS, Richmond Agitation–Sedation Scale.

protocol used at our institution is presented in Table 3. With a stepwise protocol-driven plan, intubation and mechanical ventilation can be avoided except in the more severe cases, contributing to better outcomes in terms of length of stay and VAP.

Abbreviations list
AWS, alcohol withdrawal syndrome; CIWA-A, Clinical Institute Withdrawal Assessment for Alcohol; GABA, gamma aminobutyric acid; ICU, intensive care unit; VAP, ventilator-associated pneumonia.

References

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