

Management of hospitalized patients diagnosed with alcohol withdrawal syndrome

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ABSTRACT

Alcohol abuse is one of the leading health problems, with subsequent alcohol withdrawal syndrome (AWS) affecting around 50% of hospitalized patients, varying from mild to severe forms. Rapid recognition of AWS symptoms, along with prompt therapeutic management in the first 24 hours, can lead to better outcome. Improper treatment is correlated with seizure or delirium tremens, requiring specific intensive care management, and being the cause of with various complications, high mortality, and increased costs. Some studies reported possible predictive factors that may help clinicians identify patients at risk of developing severe or resistant forms.

Keywords: substance abuse, autonomic overactivity, delirium tremens, alcohol withdrawal seizures

BACKGROUND – IMPORTANCE OF THE PROBLEM

Nowadays, alcohol use disorders (AUD) are the main public health issue, with COVID-19 pandemic further aggravating this situation, through social distancing and anxiety [1-3]. Alcohol is responsible for about 10% of worldwide deaths in population aged 15-49 years, with one of five adults reporting heavy alcohol consumption at least once a month, with high risk of morbidity and disability [4-6].

Alcohol withdrawal syndrome (AWS), which develop secondary to abrupt cessation or reduction in alcohol consumption, produces around half million-hospital admissions each year [7]. It is estimated that about 50% of patients using alcohol may develop AWS symptoms during hospitalization. For severe forms, the length of stay can double, the risk of intensive care specific management may increase, and mortality can reach 5-10% of cases [8, 9]. With proper management, mortality rate is about 2.5% for the complicated forms [10].

RISK FACTORS FOR DEVELOPING ALCOHOL WITHDRAWAL SYNDROME, ESPECIALLY FOR SEVERE FORMS

Reports focused on risk factors identification in patients developing moderate to severe AWS are scarce, being a field that requires further population studies. In a retrospective research, Benedict et al. noted that patients with severe AWS are at risk of developing resistant alcohol withdrawal (RAW). Personal or familial history of AWS, personal history of psychiatric disease, thrombocytopenia, low potassium levels, male young patients, Caucasian race, high values for aspartate aminotransferase (AST) and alanine aminotransferase (ALT), cirrhosis or alcoholic hepatitis are predictive factors for AWS development in hospitalized patients [11].

A meta-analysis published by Goodson et al. revealed that thrombocytopenia and hypokalemia could predict severe form development, without being able to identify cut off values for these param-

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Article History:

Received: 23 December 2021

Accepted: 29 December 2021

ters [12]. Eyer et al. identified the same factors, along with structural brain lesion as being predictors for seizure and delirium tremens in patients with AWS [13].

Yedlapati and Stewart performed a study and showed that the main risk factors for readmission in patients with AWS are discharge against medical advice (AMA), associated with psychiatric illness, and low socioeconomic condition [14].

Regarding trauma patients, Salottolo et al. conducted a retrospective research identifying factors as older age, important head trauma, hypokalemia at admission, as being predictive for delirium appearance in this subgroup of patients [15].

CLINICAL CLASSIFICATION AND SPECIFIC MANIFESTATION

Regarding AWS clinical manifestation, there are four types of symptoms presented in Table 1, varying from mild to severe forms, being the result of autonomic overactivity or neuropsychiatric complications. They depend on the alcohol consumption habit and cessation time. Initially, first 6 to 12 hours, symptoms are mild and highly unspecific. Afterwards, up to 24 hours, the alcoholic hallucination appears, followed by the characteristic alcohol withdrawal seizures, and, after 48-72 hours, the alcohol withdrawal delirium (delirium tremens) [9,16-18]. According to published reports, there are two serious complications for patients with severe AWS: generalized tonic-clonic seizures (can develop from 2-72 hours after alcohol reduction / cessation), and delirium tremens [18-20].

TABLE 1. Main symptoms of alcohol withdrawal syndrome

dysautonomic symptoms tachycardia tachypnoea mydriasis hypertension diaphoresis hyperglycaemia low-grade fever nausea or vomiting diarrhoea	motor symptoms tremors ataxia seizure hyperreflexia visual disorders dysarthria gait disturbances
hypervigilance insomnia irritability agitation confusion disorientation	psychiatric symptoms delusions transient visual, tactile, or auditory hallucination delirium persecution anxiety dysphoria affective instability disinhibition

DMS-5 diagnostic criteria (Diagnostic and Statistical Manual of Mental Disorders) for AWS include,

in addition to cessation or reduction in alcohol consumption, the symptoms presented in Table 1 that produce important impact on normal functioning, without being induced by other medical condition or intoxication [21].

Predictive factors for refractory AWS development are high diazepam dose (> 50 mg/ first hour, or >200 mg/24 hours) in face of persistent symptoms, other drug dependences, panic disorders, the presence of different psychiatric illness [9,22].

DIFFERENTIAL DIAGNOSIS

The main differential diagnosis for patients with AWS are other intoxication / substance abuse, various neurologic or psychiatric illnesses, metabolic derangements, cerebral trauma, or infections, as presented in Table 2 [9,16,20,23,24].

TABLE 2. Differential diagnosis for patients with AWS [26]

Drug intoxication or substance abuse	- methanol/isopropyl alcohol intoxication - cocaine, heroin, or opiates abuse - amphetamine or cannabis use - lithium intoxication - antidepressant overdose - atropine overdose - benzodiazepine, barbiturate, baclofen withdrawal
Neurologic disease or events	- ischemic or haemorrhagic cerebrovascular accident - post ictal state - epileptic seizure - hypertensive encephalopathy
Psychiatric disease	- dementia - psychosis
Metabolic and endocrine derangements	- hypoglycaemia - hyperuricemia - hypo – / hypernatremia - hypomagnesemia - diabetic ketoacidosis - hyperglycaemic hyperosmolar nonketotic coma (HONK) - hepatic encephalopathy - thyrotoxicosis - thiamine deficiency
Head trauma	- subdural haematoma - subarachnoid haemorrhage - diffuse axonal injury (DAI)
Infections	- septic encephalopathy - encephalitis - meningitis - brain abscess - pneumonia

DIAGNOSTIC AND THERAPEUTIC MANAGEMENT

Currently, there are some standardized assessment scales used for AWS patients' diagnosis like the Clinical Institute Withdrawal Assessment for alcohol (CIWA-A), CIWA-Ar (Revised CIWA-A) [25], CIWA-AD [26], the Alcohol Withdrawal Scale (AWS) [27], or the Prediction of Alcohol Withdrawal Severity Scale (PAWSS) [28,29]. A complete history and

clinical examination is required at admission, in order to identify the presence of alcohol abuse, the drinking habit, the time of alcohol cessation, and to predict the course of manifestations [7]. Therefore, the key of diagnosis is represented by establishing a temporal link between symptoms onset and alcohol reduction / cessation [23].

There are no specific laboratory tools for AWS diagnosis. Nevertheless, as we emphasized before, some of the laboratory tests can predict the syndrome course, therefore, a complete blood count, along with blood chemistry panel are usually performed [9]. Electroencephalogram is currently recommended for patients with pre-existing conditions, like epilepsy, brain lesions, in face of new-onset seizure with a pattern inconsistent with AWS or if the seizure pattern has changed over time [30]. Urine toxicology screen and blood alcohol level (BAL) may be helpful for some patients [31].

The main steps of the therapeutic management are presented in Table 3.

TABLE 3. Therapeutic management of patients with AWS – key points

1. Proper fluid resuscitation [31-36]
2. Adequate nutritional therapy – supplementation with [7,9,31-36]: A. thiamine – vitamin B1 (oral, intravenous) – 100 mg daily for 7-14 days B. multivitamin (B2, B6, vitamin C, nicotinamide) – for 3-5 days C. acid folic (oral, intravenous) – 1 mg daily for 7-14 days D. magnesium, calcium, potassium, sodium, phosphorus, selenium, zinc, chromium (determination and supplementation)
3. Drug therapies A. benzodiazepines (first-line) – loading-dose regimen followed by symptom-triggered therapy [7,10,33-36] · Diazepam (oral, gel, intramuscular, intravenous) – 5 mg (loading dose 10-20 mg) · Lorazepam (oral, intramuscular, intravenous) – 1 mg · Chlordiazepoxide (oral) – 25 mg · Oxazepam (oral) – 15 mg B. barbiturates – adjunct to benzodiazepine-based regimen [37] C. antipsychotic agents [33-36] · haloperidol · risperidone – 1-3 mg/day · chlorpromazine – 100-200 mg/day D. anticonvulsants – carbamazepine (600-800 mg loading dose/first day, then 200 mg/day) [20] E. therapeutic ethanol – not part of standard medical care – 2.5-5 g/hours, up to 10 g/hour [38,39] F. alpha-2 agonists [9,33-36] · clonidine, dexmedetomidine G. beta-blockers [9,33-36] · atenolol – 50-100 mg/24 hours · propranolol - 40 mg every 6 hours H. Baclofen – not routinely prescribed [40]
4. Nausea control [9,10]
5. Physical and social support – motivational enhancement and cognitive-behavioural therapies, family therapies [31,41]

Furthermore, in Table 4 we have outlined the principles of therapeutic management according to each AWS form [9,10,22,34-37].

TABLE 4. Symptom-based therapeutic management of AWS

MINOR observation for at least 36 hours supportive measures quiet environment diazepam – loading dose 20 mg (only for patients with risk factors)	MODERATE observation for at least 36-48 hours supportive measures quiet environment diazepam – symptom-triggered therapy
SEVERE observation till clinical stabilization (at least 36-48 hours) benzodiazepine – loading-dose regimen, afterwards symptom-triggered regimen	REFRACTORY observation till clinical stabilization combined pharmacological therapy → symptom-triggered benzodiazepine + antipsychotic agents, propofol, barbiturate, dexmedetomidine *e.g. haloperidol 0.5-5 mg intramuscularly every 30-60 minutes or 2-20 mg/hour + diazepam 10-20 mg every 1-2 hours *e.g. risperidone 1-5 mg/day or olanzapine 5-10 mg/day + diazepam 10-20 mg every 1-2 hours

CONCLUSIONS

Alcohol withdrawal syndrome can complicate the evolution of hospitalized patients, leading to death in face of inadequate therapeutic management. It is a serious clinical condition, requiring proper attention, and in patients at risk of developing severe to refractory forms, specific intensive care actions may be necessary. Pharmacological therapy follows some strict indication, in accordance with symptoms gravity, starting from fluid replacement and specific nutritional interventions, to benzodiazepine, barbiturates and other distinct agents use, meant to control the autonomic overactivity or neuropsychiatric complications.

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