Alcohol Withdrawal Syndrome

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**Background**

Estimated 8-18 million Americans are Alcohol dependent

Alcohol Use Disorder (AUD) reported in 20-42% of hospitalized medical patients

Only 7% are identified by a physician

Higher in specialized populations:
- 40% presenting to Emergency Department
- 42% of hospitalized veterans
- 59-67% of trauma patients
- 44% of elderly inpatients admitted to acute geriatric units
- 60% of ICU patients

**Pathophysiology**

Increased GABA inhibition, decreased NMDA activity

Alterations in glutamate and GABA balance during AWS

Decreased synthesis of GABA and increased synthesis of glutamate in patients presenting with AWS


Diagnosis

**DM-IV Criteria for Alcohol Withdrawal**

1. Creation of or reactivation of alcohol use that has been heavy and prolonged.
2. Two (or more) of the following, developing within several hours to a few days after cessation:
   1. Autonomic hyperactivity
   2. Increased blood pressure
   3. Tremors
   4. Nausea or vomiting
   5. Transient visual, auditory, or auditory hallucinations
   6. Psychomotor agitation
   7. Agitation
   8. Generalized seizures

   a. The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder.

   b. If A is met, the patient has also met criteria for alcohol dependence.

Clinical Diagnosis

- Recent drinking, frequency, amount, time of last drink
- Past history of withdrawal, seizures, hallucinations, or Delirium Tremens (DTs)
- Prescribed medications and drug use
  
  - Identify medications that are associated with withdrawal syndromes

History provided by patient and family may be of limited value depending on social dynamics.

Alcohol Withdrawal Spectrum

**Delirium Tremens**

Global clouding of sensorium, hallucinations, disorientation, diaphoresis, agitation, autonomic symptoms (hypertension/tachycardia/seizures), hyperventilation resulting in respiratory alkalosis-subsequent reduction in cerebral blood flow.

- 5-10% of patients with AWS develop DTs
- Onset: 48-96hrs
- Time course: 1-5 days
- Historical mortality of 37%, presently estimated to be 5%

Risk factors for development of DT’s

- History of sustained drinking, previous DT’s
- Age > 30
- Concurrent illness
- Presence of significant AWS in the presence of an elevated ETIOH level

Risk factors for higher morbidity/mortality with DT’s include:

- Elderly
- Lung disease
- Hyperthermia
- Significant hepatic dysfunction

**CIWA-Ar**

Clinical Institute Withdrawal Assessment for Alcohol scale-revised

Ten symptoms assessed, maximum score 67

- Studied primarily in specialized alcohol treatment programs and medical detoxification facilities
- Has not been validated in the ED

CIWA-Ar

Pros:
- CIWA-Ar assesses whether AWS is present and quantifies severity
- CIWA-Ar is not intended to be a screening tool to determine who is most at risk
- Instead, detects withdrawal symptoms in those at known elevated risk and quantifies severity

Cons:
- Liberal use of CIWA-Ar protocols without ensuring proper diagnosis
- Leads to overuse of sedatives and complicates diagnosis and treatment of delirium from other causes
- Validated in only mild-moderate withdrawal
- Studies frequently exclude seizures (severe AWS, DT’s)
- Does not predict which patients are at risk of withdrawal
- Once positive, patient already has AWS, opportunity for prophylaxis is lost

Management

Supporative Care

Appropriate fluid resuscitation
- Increased metabolic requirements and fluid losses due to hyperthermia, hyperventilation, diaphoresis, agitation

Glucose supplementation
- Increased metabolic requirements
- Lack of glycogen stores, nutritional deficiency
- Alcoholic ketoacidosis

Thiamine supplementation to prevent thiamine deficiency syndromes
- Wernicke’s Encephalopathy Triad: encephalopathy, oculomotor dysfunction, gait ataxia
- Korsakoff’s Syndrome: selective anterograde and retrograde amnesia

Magnesium, phosphorus, calcium replacement, folate


Benzodiazepines

Current standard treatment for AWS
Most data available on older drugs
• Chlordiazepoxide
• Diazepam
• Lorazepam

Pros:
• Studies indicate using symptom triggered therapy for AWS versus fixed schedule result in shorter duration of therapy and decreased medication use
• Frequent monitoring using CIWA-Ar to determine dosing needs

Cons:
• Associated with unwanted side effects
• Addictive properties
• Relies on accurate assessment with CIWA-Ar

Inappropriate use of symptom-triggered therapy in Hospitals

Fewer than half of randomly selected patients placed on CIWA-Ar met both inclusion criteria for CIWA-Ar tool (intact verbal communication and recent alcohol use)
Postoperative patients had higher percentage of inappropriate administration of benzodiazepines

Adjunctive Therapies

Two types:
Manage autonomic dysfunction
• Beta-blockers, alpha agonists
Agitation control for symptoms refractory to benzodiazepines
• Barbiturates, neuroleptics, other GABA agonists
Used more frequently in severe cases
Adjunctive Therapy:

**Beta-Blockers**
- Atenolol, Metoprolol, Labetalol

**Alpha-Agonists**
- Clonidine
- Dexmedetomidine (Precedex)

**Anti-convulsants**
- Gabapentin
- Dilantin
- Carbamezapine

**Barbituates**
- Phenobarbital

**Neuroleptics**
- Haloperidol
- Olanzapine, Risperidone, other atypical antipsychotics

**Baclofen**
- Ethyl Alcohol infusions

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Phenobarbital

GABA-a receptor agonist (different mechanism than Benzo’s)
Works synergistically with Benzodiazepines
Studies in ED settings for acute management in combination with benzodiazepines

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Phenobarbital

Prospective RCT compared phenobarbital versus lorazepam in ED and at 48 hrs
Used CIWA-Ar for screening, N=44
Similar effectiveness in treatment of mild-moderate alcohol withdrawal in the ED and at 48hrs


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Phenobarbital

Single dose IV phenobarbital combined with standard Lorazepam based AWS protocol
Prospective, double blind RCT (102 patients)
51 received phenobarbital, 51 placebo
Phenobarbital group had fewer ICU admissions (8% v 25%, 95% CI 4-32)
No differences in adverse events


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Phenobarbital in the ICU

**Gabapentin**

Inpatients with severe AWS (CIWA-Ar > 15)

Oral loading protocol: 800mg initial dose, then
600mg QID (total of 3200mg in 24hr load)
600mg QID day 2
400mg TID day 3
400mg day 4


**Dexmedetomidine (Precedex)**

Adjunct treatment for AWS

Multiple studies for management of ICU delirium

Retrospective analysis of precedex in addition to benzodiazepenes

61% reduction in benzodiazepine use with Precedex (n=17, p<0.001)

21% reduction in alcohol withdrawal severity score (n=11, p<0.015)


**Baclofen**

Mechanism: GABA-B agonist

Prospective double blind RCT using CIWA-Ar

Oral Baclofen 10mg TID and lorazepam PRN versus lorazepam PRN

Need for high dose lorazepam (>20mg over 72hrs) significantly reduced in Baclofen group (6% versus 53%, P=0.004)


**Carbamazepine and Valproate**

Retrospective Cohort

Carbamazepine n=374, Valproate n=453

Higher adverse reactions with Carbamazepine 7.6% versus 2%, P < 0.001

duration of pharmacologic treatment, need for ICU, length of stay all significantly longer in Carbamazepine group

IV Ethanol

Controversial, practiced sporadically

Pros:
- Administration prevents/reduces AWS severity
- Typically reserved for severe cases

Cons:
- Narrow margin of safety
- Short duration of action
- Potential toxicity, drug interactions
- Lack of RCT data

Predictive Tools

None currently validated for ICU
None for prediction of severe AWS in hospitalized patients

- Alcohol Use Disorders Identification Test (AUDIT)
- SHOT
- AUDIT-PC

Screening Tools for Risk Stratification

Rationale:
- Most mild cases do not require pharmacologic treatment
- 5-20% of hospitalized patients with Alcohol dependence have AWS severe enough to require pharmacologic treatment

Unnecessary prophylaxis or treatment of patients with AWS can lead to:
- Excess sedation
- Falls
- Respiratory depression
- Propylene glycol toxicity (lorazepam)
- Delirium

Screening Tools for Risk Stratification

Moderate-Severe AWS implications:
- Increased morbidity/mortality
- Increased hospital stay
- Increased costs
- Worsens cognitive function

Prediction of Alcohol Withdrawal Severity Scale (PAWSS)

Potential to predict moderate – severe AWS in hospitalized patients

CIWA-Ar quantifies severity of AWS, is not a predictive tool

High sensitivity, specificity, positive and negative predictive values

10 items to assess risk of AWS

May be used to identify patients needing prophylaxis against AWS BEFORE severe AWS develops

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PAWSS
100% Sensitivity, Specificity
Limitations:
Self-reporting could conceal alcohol use
Small N (69)

Future Directions
More RCTs needed to determine risk stratification tools for AWS severity
Move toward earlier GABA replacement to complement current symptomatic treatment
Need for screening tools that incorporate patient history of currently prescribed GABA active drugs- associated risk of withdrawal