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Beyond the Banana Bag: Treating Nutritional Deficiencies of Alcohol Withdrawal Syndrome

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Excessive alcohol consumption can lead to a variety of health complications. With abrupt cessation or reduction in alcohol intake, individuals may experience alcohol withdrawal syndrome (AWS), with symptoms ranging from mild tremors to life-threatening seizures. To prevent well-described symptomatic nutritional deficiencies and severe electrolyte abnormalities, hospitalized patients are often placed on institutional protocols to manage both their withdrawal symptoms and concomitant nutrient deficiencies. These protocols often differ among health systems in their approach to nutrient replacement, primarily due to a lack of high-quality evidence for dosing. This review focuses on nutritional challenges seen in these individuals with AWS, with specific focus on immediate repletion strategies to prevent the neurologic and hematologic sequelae of common micronutrient deficiencies. This review also offers practical strategies to transition to outpatient repletion to minimize chronic nutritional deficiencies.

INTRODUCTION

Alcohol use disorder (AUD) is a common diagnosis encountered by health care providers both in the hospital and outpatient settings. The lifetime prevalence of AUD, as defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), has increased over the last 20 years, with estimates up to 30% of non-institutionalized United States adults, leading to higher incidences of alcohol-related health problems such as liver dysfunction and alcohol withdrawal syndrome (AWS).[1,2] While patients with AUD are often admitted to hospitals for reasons other than AWS, those at high risk for AWS are often screened with the Prediction of Alcohol Withdrawal Severity Scale (PAWSS) and monitored with the Clinical Institute Withdrawal for Alcohol (CIWA). The latter scoring system correlates symptoms to the required dose of benzodiazepines or barbiturates needed to prevent life threatening symptoms of AWS.

Individuals with AUD are known to be at high risk for nutritional deficiencies and severe electrolyte derangements. Hospital protocols often include supplementing micronutrients such as thiamine, folic acid, and a variety of minerals. To date, there are few high-quality studies investigating the optimal dosing of deficient nutrients for patients treated for AWS. This lack

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of standardized, evidenced-based dosing strategies increases the potential that patients may receive insufficient repletion, leading to progression of nutritional deficiencies and their sequelae.

Alternatively, they may receive a longer duration of supplementation than required, leading to a high pill burden without significant benefit.

Micronutrients

Individuals with AUD may be deficient in micronutrients for a variety of reasons. In addition to heavy alcohol use often being associated with a poor diet, alcohol ingestion can directly cause malabsorption as well as electrolyte disturbances through alterations in renal tubular function.[3] Providers must be aware of strategies for monitoring and replacing these micronutrients.

Thiamine

Thiamine (Vitamin B1) is a common micronutrient deficiency seen in those with AUD. It is a ubiquitous water-soluble vitamin found in whole grains, meats, and fish and is absorbed in the small intestine by both active transport and passive diffusion. Only a small percentage is stored outside of the plasma, primarily in the liver. Due to its short half-life and limited stores (~ 21 days), frequent ingestion of thiamine containing foods or supplements is required.[4]

Thiamine deficiency is uncommon in healthy individuals, as most developed countries fortify their grains and cereals with thiamine to ensure the population meets the adult recommended daily allowance (RDA) of approximately 1.1-1.2mg per day.[5] People with AUD can become thiamine deficient through a combination of decreased intake of thiamine rich foods and decreased hepatic storage. Animal models have shown direct inhibition of duodenal transport by ingested alcohol. However, the clinical relevance is unclear with several clinical studies failing to show decreased duodenal thiamine uptake with active alcohol use.[6] There are two available ways to assess thiamine status:

1. Directly measuring thiamine diphosphate serum levels
2. Measuring the function of the thiamine dependent erythrocyte transketolase enzyme.[7]

The clinical utility of either test is unclear due to a lack of experimental data showing an association between low measured thiamine and severity of clinical symptoms. Additionally, the turn-around time is too long (7-10 days) to be useful in urgent clinical decision making.

Early symptoms of thiamine deficiency include short-term memory loss, weakness, and peripheral neuropathy. While thiamine deficiency induced congestive heart failure (wet beriberi) rarely occurs in developed countries, Wernicke-Korsakoff syndrome (WKS) is a common manifestation of thiamine deficiency in the United States.[8] WKS initially presents with Wernicke's Encephalopathy (WE), a reversible clinical syndrome characterized by a triad of altered mental status, gait ataxia, and nystagmus. If untreated, WE can progress to the chronic, irreversible neuronal changes of Korsakoff's Syndrome (KS), characterized by retrograde and anterograde memory loss. Different studies cite the prevalence of WKS as high as 60% in patients with AUD.[9] Alarmingly, about 80% of patients with WKS are diagnosed at autopsy, indicating that the syndrome often goes untreated.[11] It is difficult to predict which patients are most at risk for developing symptoms of thiamine deficiency due to differences in genetic susceptibilities, alcohol consumption, and diet.

Folic Acid

Folic acid (Vitamin B9) is an essential nutrient obtained from leafy vegetables, broccoli, chickpeas and fortified grains. Folic acid is an important cofactor in DNA synthesis and amino acid production. The liver accounts for 50% of the total body folic acid storage with the remaining 50% stored in the blood and bone marrow. Patients with AUD become deficient through decreased dietary intake, diminished intestinal absorption, increased renal losses, and disrupted hepatobiliary conversion to active metabolites. Fortunately, folic acid deficiency is uncommon in the United States since widespread grain fortification in 1998.[3]

The most common sign of folic acid deficiency is macrocytic anemia without the neurologic sequelae of B12 deficiency. Replacing folate may improve macrocytic anemia, but could worsen neurologic symptoms such as dementia, depression, peripheral neuropathy, or subacute combined spinal cord

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degeneration if a B12 deficiency is also present. The mechanism for neurologic worsening after folic acid replacement is poorly understood so it is important to treat concomitant B12 deficiencies prior to giving folic acid.[10,12] Common symptoms of folic acid deficiency include weakness, fatigue, shortness of breath and skin and hair changes.[13] There is also evidence that folate deficiency and the subsequent hyperhomocysteinemia can increase the risk for alcohol withdrawal seizures.[14]

Magnesium

Magnesium is a dietary nutrient found in leafy vegetables, meats, and nuts. Hypomagnesemia occurs in about 30% of patients with AUD due to inadequate dietary intake, poor absorption, and alcohol-induced urinary losses.[15] Importantly, magnesium plays a role in the homeostasis of other important electrolytes; hypomagnesemia can lead to both hypocalcemia by inhibiting parathyroid hormone and to hypokalemia through increased urinary losses[15,16] Magnesium also plays a role in thiamine homeostasis by functioning as a cofactor for the enzyme transketolase. Patients with suspected WE who fail to improve after thiamine repletion may have a more robust response after magnesium correction.[17,18] The degree of hypomagnesemia in patients presenting with AWS correlates with more severe symptoms of withdrawal and an increase in 1 year mortality.[5] Symptoms of hypomagnesemia include neuromuscular manifestations (muscular weakness, tremors, positive Trousseau's sign) and cardiac complications leading to arrhythmias and possible sudden death.[15]

Phosphorus

Phosphorus is an important micronutrient commonly found in meats, nuts and dairy products. Individuals with chronic alcohol use often have deficits in their total body stores of phosphorous due to inadequate dietary intake of foods rich in phosphate and frank malnutrition in some. These patients also have urinary losses from alcohol-induced renal tubular dysfunction.[15] A total body deficit of phosphorus often becomes apparent after correction of underlying alcoholic ketoacidosis and glucose administration, leading to phosphate shifting into cells for glucose phosphorylation and ATP production.

Other Micronutrients

A variety of other micronutrient deficiencies have been associated with AUD, including other water-soluble vitamins such as niacin, pyridoxine, cobalamin (B12), riboflavin in addition to fat-soluble vitamins and trace elements like zinc, selenium, and iron.

Initial Acute Management

When individuals with chronic heavy alcohol use present to the hospital, providers should be aware of the potential nutritional deficiencies that are likely present and aim to adequately replete these nutrients to prevent both short and long-term clinical consequences. Malnourished patients can experience refeeding syndrome when starting nutrition repletion, leading to life threatening fluid shifts and depletion in phosphorus, magnesium, and potassium. Severely malnourished patients should be closely monitored for clinical and laboratory signs of refeeding syndrome and treated timely and effectively.[19]

Approach to Thiamine Repletion

Thiamine is a universal component of vitamin repletion protocols in AWS. The goal of thiamine repletion is to replenish circulating concentrations as quickly as possible to ensure central nervous system availability and both prevent and treat Wernicke's long before it develops into Korsakoff syndrome.

The heterogeneity in alcohol consumption, genetic predisposition, and dietary intake makes it difficult to develop general thiamine replacement guidelines in patients presenting with AWS.[20] A Cochrane review from 2013 revealed a lack of high-quality evidence to guide clinicians in choosing the proper dose, route, and frequency of thiamine for at risk patients.[21] Currently, dosing strategies for thiamine rely on expert opinion and often differ among institutions and professional societies (Table 1*)*. The historical dose of 100mg IV thiamine daily was arbitrarily chosen in the 1950s because it represented a high dose at that time. This dose has persisted through use of the "banana bag" for AWS, which often contained 100mg IV thiamine per bag, among other vitamins and minerals.[22] This thiamine dose is likely insufficient

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Table 1. Replacement Guidelines and Recommendations for Chronic Alcohol Use and Alcohol Withdrawal Syndrome

American Society of Addiction Medicine (recommendations IV.9 and V.7) (2020)[35]	➢ Ambulatory patients with AWS -100mg oral thiamine for 3-5 days ➢ Admitted patients with AWS -100mg IV/IM for 3-5 days. ➢ Oral thiamine can also be offered.
Australian Commonwealth Department of Health Guidelines (2009)[36]	➢ Chronic alcohol use with poor dietary intake-300mg IV for 3-5 days ➢ Followed by 300mg PO for several weeks
British Association for Psychopharmacology (2012)[37]	➢ High risk for WE (malnourished, heavy alcohol use) - 250mg IV daily for 3-5 days ➢ Suspected WE - >500mg IV daily for 3-5 days
European Journal of Neurology (2010)[38]	➢ Suspected WKS-200mg IV TID until no further improvement in symptoms
National Institute for Health & Clinical Excellence (NICE) Clinical Guideline (2019)[39]	➢ IV thiamine followed by oral thiamine should be offered to high-risk alcohol drinkers ➢ Dosed at the upper end of the "British national formulary" range
Royal College of Physicians (2002)[40]	➢ WE prophylaxis - 250mg IV daily ➢ Presumptive WE - 250mg TID for 3 days. Stop if no response. If improvement, 250mg IV daily for 5 more days

in magnitude and dosing frequency for high-risk individuals. The plasma half-life of thiamine is approximately 1.5 hours, which leads some authors to suggest a required dosing interval of every 8-12 hours in patients at risk for WE.[22,23] Notably, oral preparations should be avoided in patients with AWS due to poor intestinal absorption.[24] Data from the UK National Health Service (NHS) has shown that a 5-day course of IV/IM thiamine supplementation was associated with large savings compared to shorter courses, primarily through preventing progression to Korsakoff syndrome and associated costs caring for debilitated patients in long term care facilities.[25]

While high-quality data on dosing regimens and duration are limited, potential guiding principles for clinicians to consider include (Table 2).

1. Prophylactically replacing thiamine in all patients presenting with alcohol withdrawal syndrome can prevent permanent symptoms of WKS and reduce associated healthcare costs.
2. Administering thiamine as soon as possible given evidence for developing WE after prolonged glucose administration without thiamine replacement.[26]
3. Oral bioavailability in patients with AWS is poor and initial therapy should favor IV/IM repletion. Often the intravenous therapy is continued for 2-3 days before transitioning to an oral regimen.
4. The short half-life of thiamine necessitates multiple doses per day in high-risk patients.
5. Long term oral supplementation should be considered in individuals who remain at nutritional risk with high probability of continued alcohol misuse. Higher doses than the typical RDA are likely needed to compensate for poor absorption during active alcohol consumption (typically 100mg oral thiamine/day).

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Approach to Folic Acid Repletion

The upper limit for folic acid supplementation in a healthy adult is approximately 1 mg per day.[12] The bioavailability of oral supplementation approaches 100% when consumed without food or alcohol. In cases of severe, symptomatic megaloblastic anemia when enteral access is lost or difficult to obtain, IV or IM preparations can be used. There are no high-quality studies or guidelines for how long to treat with supplemental folic acid. It is reasonable in patients with mild megaloblastic anemia to supplement 1mg by mouth daily for several months until their anemia has resolved. Higher risk patients may benefit from indefinite 1mg oral folic acid supplementation. Concomitant multivitamin with minerals supplementation should be evaluated for folic acid content to avoid dosing over the recommended daily upper limit. Typical multivitamins contain about 400mcg folic acid.

Unlike thiamine, which does not seem to have adverse physiologic effects from high dosages, folic acid supplementation above the recommended daily allowance (RDA) of 1 mg by mouth daily is controversial and has been linked to increased cancer risk and neurocognitive changes in some populations.[27] To date, there are no randomized controlled trials evaluating the optimal folic acid dosing strategy for patients at risk for alcohol withdrawal seizures. In 2015, the National Toxicology Program with the US Department of Health and Human Services developed a comprehensive needs assessment for further research into optimal folic acid dosing.[28] This needs assessment should spur research into optimal folic acid dosing to help guide future patient management.

Approach to Magnesium Repletion

Serum magnesium levels are a poor representation of total body magnesium status because 99% of the body's magnesium is stored intracellularly.[29] However, serum magnesium is the most common test used to guide replacement. Clinicians should be aware that a normal serum magnesium level may mask a total body magnesium deficit. See Table 3 for dosing strategies. Patients with reduced renal function should receive approximately 25-50% of the recommended dosages.[30] Oral dosing can be split into two daily doses to avoid causing diarrhea. Serum magnesium levels should be checked at least daily in patients with AUD or more frequently in patients with symptomatic hypomagnesemia. Of note, patients receiving multiple intravenous doses of magnesium should be monitored for EKG changes. Magnesium replacement and monitoring after hospital discharge should be considered in some patients due to total body storage depletion and continued urinary losses from alcohol induced renal tubular dysfunction.[15]

Approach to Phosphorus Repletion

Patients at risk for refeeding syndrome should be treated in the hospital setting due to the need for frequent laboratory monitoring.[31] While ongoing alcohol use will place individuals at risk for ongoing

Table 2. Prophylactic Thiamine Replacement in AWS[39,41]

Moderate Risk for WKS	High Risk for WKS
• Normal dietary intake • Stable housing and employment • Existing familial support	• Poor/unknown dietary intake • Housing insecurity and unemployment • Poor social support
Dosing Strategy	**Dosing Strategy**
• High dose IV/IM thiamine daily for 3-5 days followed by oral repletion. • Counsel alcohol cessation and consider multivitamin with minerals containing thiamine at discharge	• High dose IV/IM thiamine >2 times a day for 3-5 days. • Can continue high dose IV/IM thiamine daily until no further neurologic improvement. • Encourage multidisciplinary approach to minimize risk factors of malnutrition. • Can consider thiamine 100mg PO daily at discharge

phosphorus loss, abnormalities in the excretion of urinary phosphate typically resolves after a few weeks of ongoing abstinence. Table 3 gives an approach to managing hypophosphatemia in the inpatient and ambulatory settings. Importantly, phosphorus repletion should be enteral except in

Table 3. Common Nutritional Deficiencies and Their Management in Alcohol Use Disorder and Alcohol Withdrawal Syndrome

Nutrient	Symptoms of Deficiency	Initial Replacement Strategy	Outpatient Maintenance	Comments
Thiamine (Vitamin B1)	• Wernicke's encephalopathy • Korsakoff Syndrome • Dry and wet beri-beri • Peripheral neuropathy	• Asymptomatic and low risk: 100mg oral daily • Symptomatic or moderate to high-risk: high doses multiple times daily (Table 3)	• Based on nutritional risk (Table 2)	• RDA: Male 1.2mg/day, Female 1.1mg/day (available in multivitamin)
Folic Acid (Vitamin B9)	• Macrocytic anemia • Muscle weakness	• 1mg daily (can consider IV or IM dosing if no enteral access)	• 400mcg/day(as part of a MVM*) • Consider 1 mg daily if ongoing deficiency	• RDA: 400 mcg/day • NOTE: Consider concomitant B12 deficiency
Magnesium	• Cardiovascular dysfunction • Neuromuscular irritability • Hypocalcemia, Hypoparathyroidism	• Symptomatic (serum level < 1mg/dL): aggressive IV repletion (Mg sulfate 8-12g in 1st 24 hours, 4-6g daily for following 3-7 days) • Asymptomatic (serum level >1.2mg/dL): oral Mg salts (MgOx, Mag Citrate) or IV repletion (Mg sulfate)	• Individualize oral replacement based on nutritional risk factors and serum levels	• RDA: Male 400-420mg/day, Female 310-320mg/day • NOTE: IV formulations should be infused over several hours to avoid exceeding renal threshold and further urinary loss • Oral formulations cause diarrhea, which can be reduced by dividing doses across the day
Phosphorous	• Cardiac dysfunction • Rhabdomyolysis	• Serum level 1.0-2.0mg/dL: oral replacement (level >1.5mg/dL give 1mmol/kg/day in 3-4 divided doses, level <1.5 give 1.3mmol/kg/day in 3-4 divided doses) • Serum level <1mg/dL: IV replacement up to 1.5mmol/kg/day and then transition to oral as above	• Insufficient Evidence for Ambulatory Replacement	• RDA: Male/Female 700mg/day • IV Phosphorus can chelate serum calcium causing dangerous hypocalcemia

*MVM = Multivitamin/mineral

cases of extreme depletion (<1.0mg/dL) due to the risk of calcium chelation with rapid IV phosphorus administration.[31]

Other Micronutrient Deficiencies

In addition to the previously discussed micronutrients, there are multiple other important nutrient deficiencies in patients presenting with AWS that should be considered. These micronutrients can be replaced using a daily multivitamin with minerals (MVM), often continued indefinitely while actively consuming alcohol. Providers should realize that over the counter multivitamins may not include the essential minerals needed. Patients are encouraged to ask their pharmacist or health care provider for specific MVM recommendations.

Transition to Outpatient Management

After recovering from AWS with an initial period of aggressive micronutrient supplementation, the need for additional nutrient replacement depends on an individual's nutritional and social needs. Factors such as employment status, social support, food insecurity, and housing status have been shown to correlate with increased alcohol use and worsened nutritional status.[32] As an example, a meta-analysis from 2018 investigated the efficacy of nutritional interventions in homeless patients with AUD and found that several interventions (particularly providing meal services) could improve nutrition related behavior, although the data was insufficient in determining long term outcomes in nutrition status and disease progression.[33]

It is reasonable to discharge all individuals with recommendations for nutritional supplementation until they can be assessed by their outpatient provider. A complete multivitamin with minerals (MVM) is an efficient and affordable way to deliver essential micronutrients. Notably the dose of thiamine in these may be inadequate in those with ongoing heavy alcohol use.

CONCLUSION

Strategies to replete micronutrient deficiencies in patients presenting with AWS vary among institutions and individual providers due to a lack of prospective or randomized studies. Thiamine deficiency is one of the most concerning and potentially underdiagnosed nutrient deficiencies seen in this population. Thiamine replacement should be given intravenously 2-3 times a day in those who have symptoms of deficiency or are at high risk. Specific attention must be given to magnesium and phosphorous repletion based on serum levels in those at risk for refeeding syndrome. Folic acid repletion at 1 mg daily likely provides adequate treatment for deficient states. A daily MVM is a reasonable strategy to provide the remaining vitamins and minerals that are commonly deficient in this population. There are no studies examining long term benefits of outpatient nutrient replacement in patients with AUD and, hence, providers should individualize supplementation strategies based on the level of ongoing alcohol use, dietary intake, financial status and signs and symptoms of deficiency. ■

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Answers to this month's crossword puzzle:

1 E	M	2 P	T	3 Y	I	4 N	G	■	■	5 F	A	6 D	E	7 D
E	■	E	■	A	■	A	■	8 T	■	I	■	Y	■	U
9 G	A	S	T	R	O	P	A	R	E	S	I	S	■	C
■	■	T	■	D	■	■	■	A	■	S	■	10 P	11 E	T
12 D	R	I	P	■	13 P	14 U	N	C	T	U	R	E	D	■
R	■	C	■	15 D	■	N	■	E	■	R	■	16 P	I	T
17 A	C	I	D	I	F	I	E	R	■	18 E	A	S	T	■
I	■	D	■	A	■	O	■	■	■	■	■	I	■	19 N
20 N	E	E	D	S	■	21 N	I	22 P	■	23 B	L	A	D	E
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■	24 M	E	T	A	C	25 H	R	O	N	O	U	26 S	■	R
27 O	■	■	■	S	■	E	■	■	■	T	■	28 O	29 S	O
30 V	A	31 L	V	E	■	32 L	Y	33 M	34 P	H	O	M	A	S
A	■	E	■	■	■	I	■	35 A	R	■	■	36 A	P	I
37 L	E	A	K	■	38 E	X	C	R	E	T	A	■	■	S