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LITERATURE REVIEW

Serum Ammonia and Folate Levels: Opportunities for High Value Care

R. Benson Jones Jr. MD, Sean Dikdan MD, and Bracken Babula, MD

High value care encompasses a variety of principles including ordering tests with high diagnostic yield, while reducing low value practices. Two tests that are frequently ordered but rarely contribute meaningfully to the diagnosis and management of patients are serum ammonia levels and serum folate levels. The American Association for the Study of Liver Disease (AASLD) recommends against using blood ammonia levels for hepatic encephalopathy (HE), stating that the test does not add “any diagnostic, staging, or prognostic value” for patients with chronic liver disease¹. The American Society for Clinical Pathology (ASCP) in the Choosing Wisely campaign by the American Board of Internal Medicine recommended considering “folate supplementation instead of serum folate testing in patients with macrocytic anemia².” In the following discussion, we will discuss the evidence behind these claims in addition to our own argument against routinely ordering serum ammonia and serum folate levels in the assessment of hepatic encephalopathy and anemia, respectively. We will also provide a preliminary analysis of the cost related to these tests and the potential impact of changing ordering practices at our institution, a large urban academic medical system.

Serum Ammonia Levels in the Assessment of Hepatic Encephalopathy

HE is a brain dysfunction caused by liver pathology, portosystemic shunting, or both. It manifests in a wide spectrum of neurological and psychiatric abnormalities and is typically a clinical diagnosis using the West Haven Criteria (WHC) classification system¹. Because 85% of ammonia is detoxified by the liver and excreted as urea in urine (with muscle and brain tissue metabolizing the rest), it has been theorized that hyperammonemia contributes to HE³. Astrocytes synthesize more glutamine in the setting of increased ammonia, precipitating reactive oxygen species, astrocyte swelling, and enhanced gamma-aminobutyric acid (GABA) inhibition, manifesting as cerebral dysfunction. In addition, bleeding, infection, and renal failure all precipitate HE and incidentally promote hyperammonemia. With these underlying factors in mind, it would appear that ammonia levels would be helpful in the diagnosis of HE. Multiple issues with serum ammonia, however, limit its usefulness. Fist clenching, the use of a tourniquet during the process of

phlebotomy and processing time can lead to false elevations or spurious results⁴⁻⁶. The sensitivity and specificity of a venous ammonia greater than 55 $\mu\text{mol/L}$ to diagnose HE were 47.2% and 78.4%, respectively. In one study, 60% of the patients with grade 3 HE by the West Haven Criteria had a normal serum ammonia level⁷. These test characteristics underlie the AASLD recommendation to avoid checking serum ammonia in patients with chronic liver disease to diagnose or assess the severity of HE. Covert HE (i.e. Grade I HE by WHC) remains a diagnostic challenge given the lack of reproducibility of clinical findings, but trivial lack of awareness, shortened attention span, and altered sleep rhythm can raise suspicion for this diagnosis in patients with liver disease.

Institutional ordering characteristics and associated healthcare charges for serum ammonia

Between the initial date of data recording (11/25/2016) to the day the database was accessed (1/14/2020), there were a total of 7541 serum ammonia orders. Of these orders, 6206 orders occurred in the inpatient setting, with a charge of \$201 per order according to the publicly available institutional chargemaster⁸ (**Figure 1**). Note that these charges do not reflect what the patient pays; insurance companies dictate how much reimbursement the institution receives. The average dollar amount of charges per month attributable to inpatient serum ammonia orders alone is \$31,984.76, calculated by dividing the total charge amount for all serum ammonia orders over the examined time (\$1,247,406) by the number of months of data (39 months). The departments who ordered the most serum ammonia levels are Medicine (2404 orders total), Emergency Medicine in the flagship hospital (1702), and Emergency Medicine in a nearby community hospital (702) (**Figure 2**).

Serum Folate Levels in the Assessment of Anemia

Folic acid (folate) is a critical water-soluble B vitamin used in the process of DNA synthesis. Deficiency of folate manifests in newborns as neural tube defects and classically as macrocytic, megaloblastic anemia in adults. In an effort to reduce the incidence of neural tube defects, the US government began mandating supplementation of every 1 gram of grain with 140 mcg

Figure 1

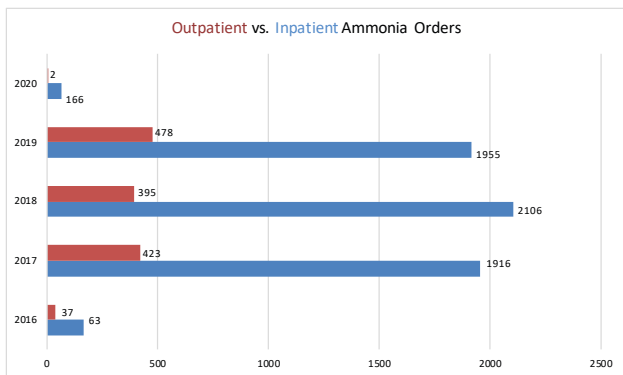


Figure 2

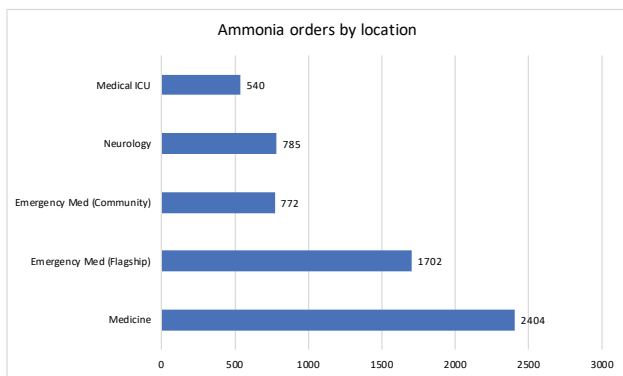
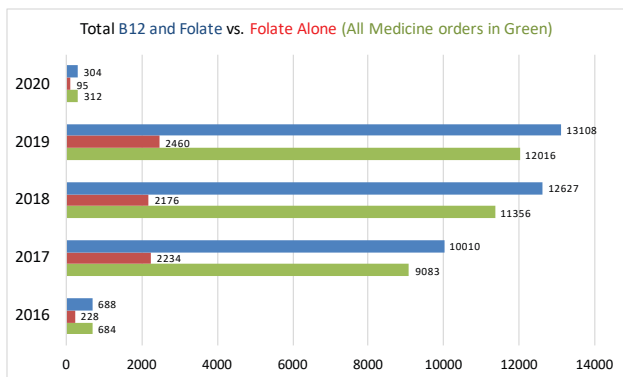


Figure 3



of folic acid in 1996, leading to a 36% reduction in the prevalence of neural tube defects in the US.⁹ This fortification has led to a significant decline in prevalence of adult folate deficiency. In an analysis of the National Health and Nutrition Examination Survey (NHANES) study group, Pfeiffer and colleagues found that "the percentage of the population with low serum folate (<3 ng/mL) declined from 21% in the period before fortification (1988--1994) to <1% of the total population in the period immediately following fortification¹⁰ (1999--2000)." Despite low prevalence of folate deficiency clinicians continue to order the assay, which

has its own innate flaws. Although the microbiologic assay for serum folate is more accurate and the gold standard, the competitive protein binding assay is more frequently used due to its relative technical ease. Unfortunately this protein binding assay has a coefficient of variance between samples from the same individuals of 21.5%¹¹. Finally, the cost of treatment of folate deficiency is orders of magnitude less expensive than the assay itself: 400 mcg folate tablets range from \$0.03 per tablet to \$0.20 cents per tablet, while the charge for the folate assay ranges from \$25 in outpatient assistance programs from commercial laboratory corporations to \$207 by the institutional chargemaster^{8, 12} (Serum folate assay pricing, LabCorp® and Quest Diagnostics Customer Service, phone call, 1/14/2020). Thus, when a macrocytic anemia and the suspicion for an isolated folate deficiency is high (malabsorptive issues, prior GI surgery, prolonged malnutrition), it is reasonable to initiate folate supplementation and to recheck a complete blood count in 4 weeks to see if the MCV and anemia has changed¹³.

Institutional ordering characteristics and associated healthcare charges for serum folate

With the same criteria as the prior analysis, there were 43,932 total serum folate and combined serum folate and vitamin B12 orders. Of these orders, 7193 were serum folate alone. The Department of Medicine ordered 33,451 (76.1%) of the total orders (**Figure 3**). The total charge per month for serum folate orders was estimated to be between \$28,161.53 and \$233,177.53 using the \$25 charge from commercial laboratory and the \$207 charge from the institutional chargemaster to generate the range. Note that the \$25 charge is a direct cost to the patient, while the \$207 is the charge submitted to insurance companies.

CONCLUSION

Serum ammonia and serum folate levels should not be routinely ordered in the diagnosis and management of hepatic encephalopathy or in the diagnosis of anemia, respectively. Chargemaster charges and simple numerical counts of orders shows a significant charge burden for tests that do not significantly impact patient care. While this analysis does not provide cost estimates to the institution as a whole as it does not incorporate assay costs and lab personnel processing time, it reveals the charges that minimal utility tests impose on the healthcare system. One proposal to reduce ordering folate levels is to replace the combined folate/B12 order with individual folate and B12 orders in physician preference lists. Future work will assess the impact of iterative changes on the reduction of these orders and strive to understand the cost of these assays to the institution.

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