American Health Associates

Dear Valued Client:

We were notified by our ammonia reagent vendor that the claims for sample storage and stability as defined in the product instructions for use are not adequately supported (see Field Safety Notice attached). We have reviewed information from other vendors and reference laboratories and found similar limitations. The best practice is to perform this test immediately after the specimen is collected, onsite – not with a specimen transported to a remote lab. There is a high risk of false positives due to in vitro metabolism. That risk increases if samples are tested at remote labs because of (1) the time required for transport and (2) possible fluctuations in temperature. As we cannot ensure the reliability or validity of results given this guidance by the manufacturer, a decision has been made to discontinue this test immediately. Please be advised that we did not make this decision lightly. We believe it is extremely important to provide accurate results to our clients at all times.

While it is common for ammonia levels to be obtained during the evaluation of hepatic encephalopathy, the evidence does not support such use. Please see the excerpt below from JAMA; the full citation is attached.

> It is common for ammonia levels to be obtained during the evaluation of chronic liver disease. However, the evidence does not support ammonia measurement under these circumstances.[3,5,6] When patients have chronic liver disease, hepatic encephalopathy is diagnosed by the overall clinical presentation and not on ammonia levels.[7] A normal ammonia level does not exclude a diagnosis of hepatic encephalopathy, nor does an elevated ammonia level establish a diagnosis of hepatic encephalopathy.[5] In patients with chronic liver disease, the measurement of ammonia can be misleading, causing additional unnecessary testing and treatment. Even in patients with established hepatic encephalopathy, serial monitoring of ammonia is not as useful as serial bedside clinical assessment for establishing the degree of encephalopathy. Blood ammonia levels correlate poorly with the grade of hepatic encephalopathy.[6]

Thank you very much for your understanding and support. Please direct any questions or concerns you have to your AHA customer account or client service representative. At AHA we are committed to bringing excellent quality care to you and your patients.

Sincerely,

Signed by:
Dr John Cochran
32A909BA38364A6...

John D. Cochran, M.D., FCAP
American Health Associates
Laboratory Director

ThermoFisher SCIENTIFIC

The world leader in serving science

Field Safety Notice

PRODUCT: Infinity™ Ammonia Reagent for Beckman Coulter AU Chemistry Analyzers

CATALOG NO.: OSR61154

LOT NO.: All lots that are within shelf-life.

Dear Valued Customer,

Our records indicate that you have previously received Infinity Ammonia Reagent for Beckman Coulter AU Chemistry Analyzer, Catalog # OSR61154 from our company.

Following a recent internal review of product technical documentation for the Infinity Ammonia Reagent for Beckman Coulter AU Chemistry Analyzer, Catalog # OSR61154, it has been determined that all the claims for sample storage and stability as defined in the product instructions for use (IFU) are not adequately supported. Specifically, it has been identified that insufficient data exists to support the IFU statement that ammonia samples may be stored for 24 hours at -20°C. Further, while sufficient data exists to support the IFU statement that samples collected and stored in EDTA tubes are stable for 3 hours at 2-8°C, insufficient data supports the stability of plasma samples collected and stored in heparin tubes over the same period. Such samples should be tested immediately.

A risk assessment has been performed for this issue and has concluded that the probability of adverse health consequences related to this issue is remote / not likely. Prolonged storage of heparin plasma samples at 2-8°C could increase normal ammonia results to a level that may be reported as abnormal (high). Testing indicates a drop in reported ammonia concentrations upon plasma sample storage at -20°C, therefore borderline abnormal (high) ammonia concentrations could be reported as normal. However, risk is mitigated by frequency of occurrence and to date, no incidents or injuries to patients have been reported with abnormal test results. Test results should always be assessed in conjunction with the patient's medical history, clinical examination and other findings and an unexpected test result should be repeated according to the laboratory's policies.

Action Required by the Customer:

- Immediately review current ammonia sample preparation practices in your laboratory.
- If occurring, discontinue storage at -20°C of ammonia samples to be used with this product.
- Collection of samples into EDTA tubes is preferred and samples should be tested immediately. If needed, EDTA samples may be stored at 2-8°C for 3 hours or less.
- If heparin tubes are used, process and test samples immediately.
- Retain a copy of this Field Safety Notice for your laboratory records.
- If you have further distributed this product, please contact those entities, advise them of the situation and provide them with a copy of this Field Safety Notice. It is requested that you please insert your contact information and email in the acknowledgement form and request that they return it to you. Please report completed reconciliation to Fisher Diagnostics via the contact details below.

Action being taken by Thermo Fisher Scientific

- The IFU for Infinity Ammonia Reagent for Beckman Coulter AU Chemistry Analyzer, Catalog # OSR61154 will be revised to correct the ammonia sample storage claims, the first lot to contain the revised IFU will be lot # 6615.

We apologize for any inconvenience. Thermo Fisher Scientific is committed to supplying innovative, high quality products for your laboratory's needs. If you have any technical questions or concerns, please contact our Technical Support staff at 1-800-528-0494, option #2 or email, techsupport.diagnostics.mtn@thermofisher.com.

Sincerely,

Thermo Fisher Scientific Inc., Technical Support Department

JAMA Diagnostic Test Interpretation

Serum Ammonia Level for the Evaluation of Hepatic Encephalopathy

Phillip S. Ge, MD; Bruce A. Runyon, MD

A 31-year-old Asian man with hepatitis C cirrhosis complicated by variceal hemorrhage and ascites underwent an inpatient evaluation for orthotopic liver transplantation. He was a graduate student who was doing well until he developed decompensated cirrhosis with variceal hemorrhage. When he first presented, he had hypovolemic shock from acute blood loss related to variceal hemorrhage that was treated with many blood transfusions and variceal banding procedures. When he was transferred to the liver unit on hospital day 25, his liver test abnormalities had mostly recovered and he had no further gastrointestinal bleeding. He had a serum ammonia level measured as part of the routine liver transplant evaluation. He did not have any confusion, insomnia, or decreased mental alertness. Jaundice was noted on the physical examination but he was alert and oriented with normal cognitive function. No tenderness was noted on his abdominal examination and he had mild ascites. During the inpatient liver transplant evaluation, his cognitive capacity and mental status remained stable and he had no symptoms of encephalopathy. He received oral diuretics for the management of his ascites. The Table lists results of laboratory analyses performed at admission and on hospital days 25 and 38.

HOW DO YOU INTERPRET THESE TEST RESULTS?

A. The patient has hepatic encephalopathy and should be treated.

B. The patient has subclinical hepatic encephalopathy and should be treated.

C. The patient is at high risk for developing hepatic encephalopathy and should be prophylactically treated.

D. The patient does not have hepatic encephalopathy so no treatment is necessary.

Table. Laboratory Test Results in a Patient With Hepatitis C Cirrhosis

	Day 1 (Hospital Admission)	Day 25 (Transfer to Liver Unit)	Day 38	Reference Range
White blood cell count, $\times 10^3/\mu L$	60.42	15.45	14.68	4.16-9.95
Hemoglobin, g/dL	10.9	9.9	8.1	13.5-17.1
Platelet count, $\times 10^3/\mu L$	70	319	123	143-398
Creatinine, mg/dL	1.0	1.6	0.9	0.5-1.3
Serum ammonia, µg/dL	NA	55	221	39-90
Total bilirubin, mg/dL	6.2	10.9	3.3	0.2-1.1
AST, U/L	1215	34	33	7-36
ALT, U/L	1364	28	17	4-45
Alkaline phosphatase, U/L	82	114	144	31-103
Total protein, g/dL	3.4	5.2	6.0	6.2-8.6
Serum albumin, g/dL	2.2	2.6	2.3	3.7-5.1
INR	1.9	1.2	1.2	0.8-1.2

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; INR, international normalized ratio; NA, not applicable.

Answer

D. The patient does not have hepatic encephalopathy so no treatment is necessary.

Test Characteristics

Measuring serum ammonia is useful under certain conditions. In acute liver failure, ammonia levels have prognostic significance. In one study, an arterial ammonia level of 124 µmol/L (211 µg/dL) or higher predicted mortality with 78.6% sensitivity, 76.3% specificity, and 77.5% diagnostic accuracy.[1] In another study, arterial ammonia level higher than 100 µmol/L (170 µg/dL) predicted the onset of hepatic encephalopathy and intracerebral hypertension with 59% sensitivity, 78% specificity, and 70% diagnostic accuracy. The combination of MELD score higher than 32 and ammonia level higher than 100 µmol/L (170 µg/dL) improved specificity to 94% and diagnostic accuracy to 74%.[2] An additional study demonstrated correlation between plasma ammonia levels and severity of encephalopathy.[3] The 2013 Medicare midpoint reimbursement for a serum ammonia assay is $27.07 (http://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ClinicalLabFeeSched/index.html).

Ammonia is mostly cleared by the liver and there is some extrahepatic metabolism in muscle tissue. Hepatic encephalopathy is thought to be caused by accumulation of unmetabolized ammonia resulting in neuropsychiatric toxicity and encephalopathy. However, elevated ammonia levels also occur in urea cycle disorders, portosystemic shunting, urinary tract infection from urease-producing organisms, gastrointestinal bleeding, shock, ureterosigmoidostomy, renal disease, heavy exercise, smoking, parenteral nutrition, salicylate intoxication, medications (high-dose chemotherapy, valproic acid, bar-

biturates, narcotics, diuretics), and alcohol.[4] The accuracy of venous ammonia measurement is influenced by fist clenching, tourniquet use, and whether the sample is placed on ice.

Application of Test Result to This Patient

It is common for ammonia levels to be obtained during the evaluation of chronic liver disease. However, the evidence does not support ammonia measurement under these circumstances.[3,5,6] When patients have chronic liver disease, hepatic encephalopathy is diagnosed by the overall clinical presentation and not on ammonia levels.[7] A normal ammonia level does not exclude a diagnosis of hepatic encephalopathy, nor does an elevated ammonia level establish a diagnosis of hepatic encephalopathy.[5] In patients with chronic liver disease, the measurement of ammonia can be misleading, causing additional unnecessary testing and treatment. Even in patients with established hepatic encephalopathy, serial monitoring of ammonia is not as useful as serial bedside clinical assessment for establishing the degree of encephalopathy. Blood ammonia levels correlate poorly with the grade of hepatic encephalopathy.[6]

This patient had an elevated serum ammonia level found incidentally during his inpatient liver transplant evaluation. The patient had a normal mental status, normal cognitive function, and no evidence of overt or subclinical hepatic encephalopathy. Given the lack of objective signs of encephalopathy, measurement of serum ammonia was not necessary. The patient's elevated ammonia level was probably from diuretic use. Because there was no clinically important encephalopathy, treatment based on ammonia levels is not indicated. Given the patient's chronic liver disease, elevated serum ammonia levels do not predict any additional risk for developing hepatic encephalopathy.

What Are Alternative Diagnostic Testing Approaches?

The diagnosis of hepatic encephalopathy relies on history and physical examination, exclusion of alternative causes of altered mental status, and evaluation of precipitating causes such as gastrointestinal bleeding, infections, renal failure, hypovolemia, and metabolic disturbances. Psychometric tests including the Reitan number-connection test and the psychometric hepatic encephalopathy score allow for objective measurement of cognitive impairment and have been validated for the diagnosis and monitoring of hepatic encephalopathy.[8,9] Patients without hepatic encephalopathy should finish the timed number-connection test in the number of seconds less than or equal to their age in years.[10]

Patient Outcome

Although the patient had an elevated serum ammonia level, he demonstrated no clinical evidence of encephalopathy and was preparing his doctoral thesis without difficulty. As a result of the ammonia findings he received lactulose, which caused him considerable discomfort and frustration, without clinical benefit or improvement to his serum ammonia levels. The treatment was discontinued. Currently, 9 months following this hospitalization, the patient is waiting for a liver transplant. He is also scheduled to start non–interferon-based treatment for hepatitis C while completing his graduate studies and preparing to defend his thesis. He continues to be without hepatic encephalopathy.

Clinical Bottom Line: Serum Ammonia Level

- Measurement of serum ammonia level is not intended and not useful for the evaluation or screening of hepatic encephalopathy in patients with chronic liver disease because it can neither rule in nor rule out hepatic encephalopathy, and levels do not correlate with the degree of encephalopathy.
- Measurement of serum ammonia level is an important diagnostic step in the evaluation of acute liver failure because levels correlate with the severity of encephalopathy and elevated levels are predictive of severe encephalopathy and cerebral edema.

ARTICLE INFORMATION

Author Affiliations: Division of Digestive Diseases, David Geffen School of Medicine at UCLA, Los Angeles, California.

Corresponding Author: Bruce A. Runyon, MD, Division of Digestive Diseases/Hepatology, Santa Monica-UCLA Medical Center, 1223 16th St, Ste 3100, Santa Monica, CA 90404 (barunyon@mednet.ucla.edu).

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Additional Contributions: We thank the patient for providing permission to share his information.

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