Although we did not investigate collection tubes from various manufacturers, available evidence, including our data, indicates that these problems may be common. The more rapid coagulation process in clot-activator tubes may be associated with more extensive proteolysis in the specimen, potentially leading to greater protein fragmentation that is subsequently detected by mass spectrometry. Nonbiological changes, observed repeatedly in the low-molecular-weight serum proteome profiles, raise the question of whether serum is the specimen of choice for major protein- and/or peptide-type clinical analytes such as hormones and tumor markers (8).

In summary, clot activator-containing collection tubes may lead to preanalytical artifacts in proteomic studies. In our experience, these tubes can be effectively substituted with Li-heparin plasma tubes for chemistry analytes or plain serum tubes used for immunoassay and specimen banking.

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Equimolar Ammonia Interference in Potassium Measurement on the Osmetech OPTI CCA: A Reply

To the Editor:

We agree that the Osmetech OPTI Critical Care Analyzer (OPTI) measurement of potassium ion shows a bias with samples containing extremely high plasma ammonia concentrations, as reported by Carayannopoulos et al. (1). As a result of this report we have notified all OPTI customers of this interference at these rare high ammonia concentrations.

Hyperammonemia has an estimated incidence in newborns of 1 per 25 000–53 000 live births (2, 3). Urea cycle disorders are the usual cause (4), occasionally leading to ammonia concentrations >400 μmol/L, which would increase the potassium reported on OPTI by 0.5 mmol/L. Such a bias is greater than allowed under the US Healthcare Financing Administration/CLIA proficiency testing criteria for acceptable performance (5). In rare cases, newborns may also suffer hyperammonemia attributable to other pathologies (6), such as organic acidemias, fatty acid oxidation disorders, congenital lactic acidosis, lysinuric protein intolerance, hepatic or renal dysfunction, Reye syndrome, certain drugs (valproate, aspiraginase, fluorouracil), transient hyperammonemia in newborn, and perinatal asphyxia.

In a 10-year retrospective study of 9958 plasma ammonia measurements at a tertiary referral children’s hospital (7), 4.0% of the values were >200 μmol/L and ~1.4% were >400 μmol/L (“almost all” associated with inborn errors of metabolism). Similarly, one peer reviewer provided data from his/her tertiary care pediatric setting showing a consistent frequency of 3% of ammonia results >200 μmol/L. Both estimates are from tertiary care institutions. Lower frequencies may be seen in institutions caring for children with less severe illness. In a 1997 review of inborn errors of metabolism (8), the collective incidence of the most commonly encountered organic acidurias was estimated at 0.007%, and the collective incidence of all urea cycle defects was estimated at 0.003%. Assuming a distribution of increased ammonia concentrations consistent with that cited in Chow et al. (7), fewer than half of these acidurias and defects will lead to ammonia concentrations >400 μmol/L, and the frequency of potassium bias >0.5
mmol/L on the OPTI would thus be <1 per 20,000 (0.005%) pediatric samples submitted in a typical (non-territorial) institution.

In adults, hyperammonemia is similarly rare but typically far less severe. In 3 studies of liver failure patients, involving 129 acute and chronic cases (9,10), mean plasma ammonia concentrations were 49 to 172 μmol/L. Valproate-induced encephalopathy has led to ammonia concentrations up to 140 μmol/L (11). In 2004, in 4 unusual cases of emergency room—treated adult hyperammonemia, maximum ammonia concentrations were 103, 133, 300, and 500 μmol/L, the last in a patient under high-dose fluorouracil chemotherapy (12). Hence we expect the occurrence of OPTI potassium bias >0.5 mmol/L to be extremely rare in adult samples.

The Clinical and Laboratory Standards Institute (CLSI) Guidelines for interference testing (13) suggest a high ammonia test point of 80 μmol/L, which was measured on the OPTI during its development and revealed no offset in reported potassium. Because no significant bias was seen in potassium at ammonia concentrations <300 μmol/L, we (the developers/manufacturers) considered this method to be interference free. The OPTI has been marketed globally for 8 years, and we have received no previous complaint, query, or observation concerning ammonia interference with potassium measurement.

As part of our risk assessment, we included the possibility of incorrect clinical action based on an erroneous high potassium reported by the OPTI. We consulted an independently contracted expert (Professor Alan Plummer, Emory University School of Medicine) who believes it is possible, but extremely unlikely, that harm could come to a patient if the ammonia interference problem with the OPTI were not known by the clinicians treating the patient. In his opinion, ammonia concentrations >500 μmol/L are very rare, and if they do occur, he doubts any clinical remedy to normalize the potassium would occur before the measurement was repeated, most likely on a different analyzer. If the institution had only the OPTI analyzer, then a repeat falsely increased potassium concentration would be found, and if no other tests were obtained (e.g., electrocardiogram), it is possible the patient could receive potassium-lowering medications (e.g., insulin), which could lower potassium to clinically dangerous concentrations. Professor Plummer said he considers this scenario to be extremely unlikely because virtually all such patients would be in intensive care units and monitored very closely.

In short, we acknowledge that plasma ammonia concentrations can exceed 400 μmol/L. We thank the authors for their study, and regardless of the rarity of the extremely high ammonia concentrations that produce potassium interference, we have since included a warning statement within our Operator’s Manual and will modify our protocols to include medical opinions concerning pathological test ranges of potential interferences, above and beyond those recommended by the CLSI Guidelines.

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Preparation of Uric Acid Standard Stock Solution

To the Editor:

For measurement of uric acid in serum, calibrators of known concentration must be prepared in a suitable solvent. Uric acid is virtually insoluble in water or common organic solvents, but it can be dissolved in basic solution such as aqueous solutions of Li₂CO₃ (1), KOH (2), NaOH (3), and ammonium hydroxide (4,5). Siekmann (4) used ammonium hydroxide as the solvent for dissolving uric acid at a molar ratio of ammonium hydroxide to uric acid of ~120:1. Ellerbe et al. (5) used ammonium hydroxide as the solvent for dissolving uric acid at a ratio of ammonium hydroxide to uric acid of 1.7:1. In addition, Ellerbe et al. (5) showed that uric acid is stable in ammonium hydroxide at a molar ratio of 1.7:1.

We are working to develop a new definitive method for serum uric acid by use of HPLC-isotope dilution mass spectrometry (HPLC-ID/MS). We prepared a stock standard solution of uric acid in 1 mmol/L ammonium hydroxide at a molar ratio of 1.7:1, according to Ellerbe’s method. But uric acid was