### Serum acetone testing

Q We use urine ketone dipsticks for serum acetone testing on ketoacidosis patients. If the result is positive, we titer it — using doubling dilutions — and report the lowest positive dilution. This test reacts with acetoacetic acid only, not beta-hydroxybutyric acid or acetone. Many labs use Acetest tablets for testing serum acetone. This test reacts with acetoacetic acid and acetone. I found that testing serum beta-hydroxybutyrate seems to be the test of choice when monitoring the treatment of DKA. What is the best test when monitoring DKA treatment in a hospital setting?

A In diabetic ketoacidosis, lack of insulin causes a decrease in the utilization of glucose. Increased lipolysis results in the overproduction of acetoacetate, which then acts as the substrate for hepatic formation of ketone bodies. The commonly used urine dipstick tests are based on the use of a nitroprusside reaction and give a semiquantification of acetoacetate and, in most cases, will react weakly with acetone. A deficiency in this system is that urine dipsticks of this type do not detect beta-hydroxybutyrate, a reduced form of acetoacetate.

The question is whether one test is superior over another in the clinical setting of diabetic ketoacidosis. A group has prospectively measured blood beta-hydroxybutyrate levels by a reagent strip with serum ketone levels measured by the nitroprusside reaction in 19 patients with diabetic ketoacidosis. The sensitivity and specificity of measuring serum ketones by the nitroprusside reaction in diagnosing diabetic ketoacidosis were 95% and 100%. The sensitivity and specificity of beta-hydroxybutyrate testing were 90% and 100%, respectively. This group concluded that serum ketone and blood beta-hydroxybutyrate measurement are equally effective in diagnosing diabetic ketoacidosis.

When compared to urine ketone analysis, serum beta-hydroxybutyrate measurements have proven at least as — if not more — sensitive in the setting of diabetic ketoacidosis. A large study determined the serum beta-hydroxybutyrate in 60 normal controls — 50 diabetic patients and 34 patients in diabetic ketoacidosis — matched by urine ketone analysis. A significant difference was present in the positive rate of serum beta-hydroxybutyrate in diabetic ketoacidosis patients versus that of urinary ketone. Of note, the use of beta-hydroxybutyrate measurement has been found to be useful in dogs as well. One study of 116 dogs found that measurement of beta-hydroxybutyrate and urine acetoacetate measurements were both able to segregate dogs into the categories of diabetic ketoacidosis, diabetic ketosis, and normal.

In terms of monitoring diabetic ketoacidosis during treatment, the author knows of no direct comparisons between methodologies. One paper has established guidelines in which the resolution of the metabolic derangements in diabetic ketoacidosis can be followed by serum beta-hydroxybutyrate levels. The paper also suggests that the level of beta-hydroxybutyrate be used in an outpatient setting to determine the need for acute medical attention in hyperglycemic patients, giving physicians the ability to distinguish between hyperglycemia and a ketogenic state. The endpoint here, of course, is to rapidly triage patients with a metabolic derangement in the hopes of decreasing the severity of their illness and, ultimately, the duration and cost of their hospitalization. Clearly, this is a topic that requires further investigation.

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**References**


### Protocol for BNP orders

Q What is the recommended protocol for ordering BNP tests? How often should BNP’s be ordered to be clinically significant? At our hospital, some doctors are ordering BNP’s every morning for 10 to 15 days, with little change in results. From the lab viewpoint, I think this is a bit extreme. Is there a clinically significant reason to order this many BNP’s on a single patient?

A B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) are biomarkers that reflect hemodynamic stress. As with many tests in laboratory medicine, caregivers could potentially request these measurements to assist with screening, diagnosis, disease classification, risk assessment, guide management, or assess the effect of intervention. The focus of the question is how BNP and NT-proBNP should be requested and the appropriate ordering frequency for this test. The following response will assume that the testing is requested in the context of patients with suspected or established heart failure.

The American Heart Association (AHA) and American College of Cardiology (ACC) are in the process of publishing an update of practice guidelines for adult chronic heart failure patients. A summary of these guidelines is accessible on the Web at www.acc.org/clinical/guidelines/failure/summary.pdf. Clearly, a major continues on page 48.
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Tips from the clinical experts

contribution of BNP and NT-proBNP has been as an aid for the diagnosis of decompensated heart failure in the symptomatic Emergency Medicine population. Reflecting this contribution, the AHA/ACC document states that “measurement of BNP can be useful in the evaluation of patients presenting in the urgent care setting in whom the clinical diagnosis of heart failure is uncertain.” This is a Class IIa recommendation, meaning that the weight of evidence is in favor of test use; the level of evidence for utilization is rated as “A,” which is the very highest. For management of heart failure in hospitalized patients, appropriate utilization of BNP and NT-proBNP is less clear.

It is noted in the AHA/ACC guideline document that serum BNP and NT-proBNP measurements parallel the clinical severity of heart failure. However, it cannot be assumed that BNP and NT-proBNP can be used effectively for adjustment of therapy in individual patients. The AHA/ACC guidelines state that “the value of serial measurements of BNP and NT-proBNP to guide therapy for patients with heart failure is not well established.” The recommendation for use in guiding therapy is listed as Class IIb, meaning that use in these patients is less well established by evidence; the level of evidence for guiding therapy is rated “C,” which is the weakest grade and indicates that the recommendation is based only on consensus opinions of experts and case studies.

Clearly BNP and NT-proBNP are useful tests to assist in the diagnosis of decompensated heart failure in the urgent care setting. For use of the test in hospitalized patients, most experts state that BNP and NT-proBNP levels do not need to be drawn every day. Expert consensus is that appropriate inpatient utilization is on admission, after a major treatment effect, and when discharge is contemplated, i.e. euvolemia is achieved (BNP Consensus Panel 2004: free PDF download available at www.lejacq.com/Journal Special Supplements.cfm?CFID=32691&CF TolKEN=89747650). Other experts feel that this ordering frequency is excessive, and that BNP and NT-proBNP measurements on admission, and when discharge is contemplated, provides adequate information for patient care. Still, other heart-failure experts do not endorse drawing BNP levels at all while patients are in-house, reflecting the paucity of hard evidence expressed in the AHA/ACC guidelines.

Obiously, there is substantial controversy surrounding utilization of BNP and NT-proBNP for inpatient monitoring. Some evidence-based guidance is provided however, by the recent AHA/ACC guidelines and expert consensus. It is noteworthy that knowledge on appropriate clinical utilization of BNP and NT-proBNP is evolving rapidly, and that ongoing trials will help to better define the role of serial BNP and NT-proBNP measurements as an aid in the management of heart failure.

Quality-control criteria

Q Our lab has changed how it evaluates quality-control (QC) data over the past year. We had an interim lab manager who instituted this method. We use what is published in the CAP proficiency-testing summary as CLIA guidelines for acceptable analyte ranges. For example, an analyte such as amylase is target value ±30%, or glucose ±6.0 or 10%. The ranges are computed and set as a ±3 SD range. Our new manager questioned this method. I have not found anything to really support this kind of QC monitoring. I found a very brief mention of it on some websites by Westgard but nothing to validate this method. Do you have any insight to this kind of QC monitoring? Is it okay, and do other labs use the same method?

A Analysis of QC material is important to help ensure that random and systematic errors that can result in erroneous results are detected. Limits used to evaluate QC control are calculated from the mean and standard deviation (SD) obtained following repeated measurements of the control material by the analytical method that is to be controlled. The establishment of an accurate mean and SD is extremely important if rules used to evaluate QC results are to work as intended.

The multirule procedure developed by Westgard, et al., is commonly used to interpret results of QC data.1 This procedure consists of a set of rules designed to detect random and systematic error. The probability of the multirule procedure for error detection is much improved over the use of the Levey-Jennings chart having a ±3 SD limit for determining acceptability of QC data. Automation of the multirule procedure using computer software enables rapid evaluation of current and previous QC data.

The importance of using an SD that is appropriate to the control material being used is due to the fact that the probability of error detection is based on the statistical probability that a control value will fall within the mean and SD limits that
have been determined for the particular control. Thus, based on statistical probability, the likelihood that a measured QC value will fall outside the ±2 SD limits is calculated to be approximately one out of every 20 results, and the likelihood that it falls outside the ±3 SD limits is approximately one in every 300 QC results. These probabilities are only true, however, if the SD used in establishing the QC ranges are those that have been established following repeated measurement of the QC material. Use of artificial limits, such as the evaluation criteria established by CLIA, for use with the multirule procedure are inappropriate. For example, the evaluation limit defined for amylase by CLIA is ±30% of the peer-group mean. Applying this 30% limit to a QC material as a ±3 SD limit can result in very different QC ranges being established. As an illustration, consider the example where a QC material for amylase has a mean amylase value of 100 µL. Assuming that a ±3 SD limit is the same as a ±3 SD range results in a QC range of 70 µL to 130 µL. Multiple analyses of this same QC material over an extended time period, however, might show a mean value of 100 µL, but an actual measured SD of 5 µ/L. This corresponds to a ±3 SD range of 85 µL to 115 µL. As this example illustrates, using the CLIA evaluation limits results in a QC range that really corresponds to ±6 SD range from the mean. This would severely limit the role of QC in detecting errors. The mean and SD of QC ranges should be established by the laboratory using the material.

A variety of other techniques have also been advocated for evaluating QC data. One such method is the cumulative sum (cu-sum) control chart.2,3 The cu-sum chart is constructed by plotting the cumulative sum of the differences (on the y-axis) from the mean of successive QC observations (on the x-axis). The cu-sum technique provides better detection of systematic errors but is less sensitive to random errors when compared with the Levey-Jennings chart with ±3 SD limits.

Other techniques that may be used to control the analytical quality of laboratory test results rely on use of data that is generated from patients themselves. One example is calculation of the serum anion gap from the measured Na, Cl, and HCO3 from each patient; abnormally low or high values may indicate laboratory error. Other examples include the use of delta checks, limit checks, and monitoring of the mean value calculated from patient test results. — Sandra White, MD; Steven C. Kazmierczak, PhD, DABCC
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References

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