Traditionally, unfractionated heparin has been used for treatment or prevention of venous or arterial clotting. Monitoring heparin therapy is necessary because each patient clears heparin at their own rate, each lot of heparin is physically different (there is now “old” and “new” heparin), and the dose response is unpredictable. Though the primary monitoring tool for unfractionated heparin (UFH) concentrations in the blood is currently the Activated Partial Thromboplastin Time (aPTT test), the recent availability of anti–factor Xa assays has caused some laboratories to reassess the use of the aPTT assay as the primary laboratory tool for monitoring heparin therapy. Anti-Xa is the only assay available for monitoring low molecular weight heparin and is sometimes ordered to monitor and adjust UFH. The anti-Xa level applies to patients who are anticoagulated with both types of heparin—unfractionated and low molecular weight heparin (LMWH), such as Lovenox®.

Low molecular weight heparin is usually not monitored, but doctors may order anti-Xa tests in some cases, such as patients who are pregnant, obese, very young, elderly, or have kidney disease or dysfunction. It is also ordered occasionally to monitor UFH therapy if the patient is not responding as expected to UFH or if the aPTT is not useful due to pre-existing conditions (e.g. lupus inhibitor, factor deficiency, etc). LMWH products are less likely to bind specifically to proteins and are eliminated by the kidneys. This results in a more predictable effect when weight based dosing is used for patient therapy.

So the underlying question seems to be: should unfractionated heparin be monitored by the aPTT, as has been done for many years, or by an anti-factor Xa method specifically calibrated using an unfractionated heparin standard?

aPTT versus Heparin Anti-Xa for Monitoring Heparin Therapy…the Debate

Traditionally, unfractionated heparin has been used for treatment or prevention of venous or arterial clotting. Monitoring heparin therapy is necessary because each patient clears heparin at their own rate, each lot of heparin is physically different (there is now “old” and “new” heparin), and the dose response is unpredictable. Though the primary monitoring tool for unfractionated heparin (UFH) concentrations in the blood is currently the Activated Partial Thromboplastin Time (aPTT test), the recent availability of anti–factor Xa assays has caused some laboratories to reassess the use of the aPTT assay as the primary laboratory tool for monitoring heparin therapy. Anti-Xa is the only assay available for monitoring low molecular weight heparin and is sometimes ordered to monitor and adjust UFH. The anti-Xa level applies to patients who are anticoagulated with both types of heparin—unfractionated and low molecular weight heparin (LMWH), such as Lovenox®.

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aPTT

The aPTT continues to be the most utilized test for monitoring low-dose IV heparin therapy and is usually used to monitor unfractionated heparin. It is widely available, inexpensive, and familiar to nurses and physicians who administer heparin to patients. However, the aPTT is influenced by coagulation factor deficiencies and circulating coagulation inhibitors (such as lupus anticoagulants). It also shows interlaboratory variation due to differing sensitivities between lots of heparin and aPTT reagents.

Laboratories using this assay to monitor heparin should optimally establish a therapeutic range for their institution by correlating aPTT results with heparin levels performed by an anti-factor Xa method.

Anti-Factor Xa

Currently, the use of UFH therapy is decreasing and being replaced with the use of LMWH as the heparin anticoagulant of choice, mainly because it has a more predictable anticoagulant response that makes routine laboratory monitoring unnecessary. The Anti-Xa assay is not susceptible to many of the preanalytical interferences affecting the aPTT. Although not currently ordered routinely, when it is used as a LMWH monitoring tool, anti-Xa is primarily ordered as a “peak” test.
It is collected when the blood level is at its highest level, about 4 hours after a LMWH dose is given. Random and “trough” levels may be ordered if the doctor suspects that the patient may not be clearing the LMWH at a normal rate. In this case, the blood would be collected just prior to the next dose.

A heparin level gives a quantitative result that can be compared to a therapeutic range (e.g. 0.3 to 0.7 units/mL) and is not affected by other conditions that prolong the aPTT.

**Principle of Anti-Factor Xa**

The activity of both UFH and LMWHs depends on binding to antithrombin. This binding induces a molecular change that dramatically accelerates its inhibitory activity. LMWHs primarily have anti-Xa activity while UFH has both anti-Xa and anti-IIa activity.

The Xa inhibitory activity of antithrombin (AT) is increased in patients receiving either LMWH or UFH. This can be measured with a clotting-based assay or more commonly, a chromogenic assay. A standard curve is constructed by adding known amounts of LMWH or UFH to plasma and a fixed amount of Xa. This results in the formation of an inactive AT-Xa complex and the residual Xa is measured using either a clotting-based assay or chromogenic assay. The residual Xa activity is inversely proportional to the concentration of heparin in the sample and may be quantitated from a calibration curve. The heparin used for preparation of the calibration curve should be the same heparin used for patient therapy at the institution, i.e., separate standard curves should be constructed for a specific UFH and a specific LMWH.
Even though some institutions continue to use the aPTT to monitor routine heparin therapy, they may decide to also offer a heparin level for some patients with clinical conditions that do one of the following: 1) prolong the baseline aPTT, 2) cause decreased sensitivity of the aPTT to heparin, or 3) show true heparin resistance (i.e., antithrombin deficiency, increased plasma binding/clearance of heparin).

References:
5. Laboratory Monitoring of Heparin Therapy: Partial Thromboplastin Time or Anti-Xa Assay?, LabMedicine, Volume 40, Number 1, January 2009
6. PowerPoint Presentation: Laboratory Monitoring of Unfractionated and Low Molecular Weight Heparin, Carol Lee Shearer CLS(NCA), MT(ASCP), Hemostasis Application Consultant – Region I, Siemens Healthcare Diagnostics

(Continued from page 3)

Conclusions
Even though it is difficult to establish and maintain a validated therapeutic range with each reagent lot or instrument change, the aPTT continues to be the test most often utilized by laboratories for monitoring IV heparin therapy. New challenges are arising in laboratories as LMWH and other new anticoagulants not requiring routine laboratory monitoring replace UFH. However, it is doubtful that UFH therapy will totally vanish anytime soon since there is a role for an anticoagulant whose effects can be rapidly reversed in the event of bleeding.

The decision of whether to use the aPTT or a heparin level to monitor unfractionated heparin is probably best left to each institution, since it depends on patient population, local medical practices, and laboratory resources. Laboratories changing from using the aPTT to a heparin level for monitoring UFH will need to work closely with their clinicians, pharmacists, and nurses to implement dosing algorithms that incorporate heparin levels. Also, heparin protocols for individual patients based on sex, age, height and weight should include monitoring the platelet count for heparin-induced thrombocytopenia/thrombosis, whether the aPTT or heparin level is used.

Test Your CLIA Knowledge

1. How long does CLIA require the laboratory to retain test requisitions and authorizations?
   a. 1 year  b. 2 years  c. 3 years  d. Indefinitely

2. Which of the following activities is NOT included as part of the General Laboratory Systems?
   a. Patient confidentiality  b. Specimen identification and integrity  c. Specimen submission  d. Proficiency testing performance

3. What is the minimum quality control frequency for performing prothrombin times on an automated test system?
   a. 2 levels of control each day of patient testing  b. 2 levels of control each day of patient testing and each time the reagent changes  c. 2 levels of control every 8 hours  d. 2 levels of control every 8 hours and each time the reagent is changed

4. For unmodified FDA-cleared or approved, non-waived test system the laboratory must perform which of the following verification of performance steps before reporting patient test results?
   a. Accuracy and precision  b. Accuracy, precision, reportable range, and reference range  c. Accuracy, precision, reportable range, sensitivity, specificity, reportable range, and reference range  d. None, just plug it in and away you go

5. Which of the following test systems require calibration verification to be performed at a minimum of every 6 months?
   a. A chemistry analyzer that performs a daily 2 point calibration  b. An automated cell counter with a minimum of 2 levels of control materials performed each day of patient testing  c. A chemistry analyzer that performs a monthly 3 point calibration  d. Both A and B

6. Which subpart of the CLIA regulations are the Personnel Requirements found in?

7. What is the minimum frequency for performing gram stain quality controls?

8. Which of the following is considered a non-regulated proficiency testing analyte?
   a. Rubella  b. Uric Acid  c. TSH  d. PSA

9. Which of the following does NOT have to be included on a test report?
   a. Patient name and unique identifier  b. Identity of the testing personnel  c. Laboratory name and location  d. Date when test results are reported as final

10. A CLIA inspection could be conducted at a laboratory that has been issued a certificate of waiver or a certificate of provider-performed procedures under which of the following situations?
    a. To determine if the laboratory is performing tests in a manner that does not constitute an imminent and serious risk to public health.
    b. To evaluate a complaint from the public.
    c. To determine whether the laboratory is performing tests beyond the scope of the certificate held by the certificate held by the laboratory.
    d. To collect information regarding the appropriateness of tests specified as waived tests or provider-performed microscopy procedures.

   e. All of the above.

Trivia Game Answers: 1, B, 2, C, 3, D, 4, B, 5, A, 6, 7, D, 8, B, 9, B, 10, E
ADA Now Recommends HgbA1c to Diagnose and Screen for Diabetes

Each year the American Diabetic Association (ADA) updates its Standard of Care Recommendations. One significant change in the 2010 guidelines is the use of the Hemoglobin A1c (HgbA1c) assay to diagnose and screen for diabetes. While the ADA had previously recommended HbA1c only for monitoring of known diabetics, the ADA now endorses HgbA1c as one of the options to diagnose diabetes. Other recommended diagnostic tests include the fasting blood glucose, random blood glucose, and oral glucose tolerance tests.

HgbA1c, which estimates average glucose levels over the past 3 months, is used to evaluate diabetic control over time. Previously, the ADA did not recommend the HgbA1c due to lack of assay standardization. They now believe that the test is well-monitored and reproducible in any chemistry platform certified by the National Glycohemoglobin Standardization Program (NGSP). Some Point of Care (POC) testing systems are not certified, however, so the lab should use caution when selecting testing equipment.

The ADA recommends the following HgbA1c range guidelines:
1) Values near 5% indicate absence of diabetes,
2) A range of 5.7% to 6.4% identifies increased risk for future diabetes,
3) > 6.5% diagnosis of diabetes

The HgbA1c test does not require an overnight fast and while the test may not be as sensitive as the fasting blood glucose, the ease of testing may facilitate increased screening for diabetes. Hopefully this will encourage those in the prediabetic range to make positive lifestyle changes to ward off diabetes. For a complete review of the new Recommendations, see http://care.diabetesjournals.org/content/33/Supplement_1S11.full.

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References: