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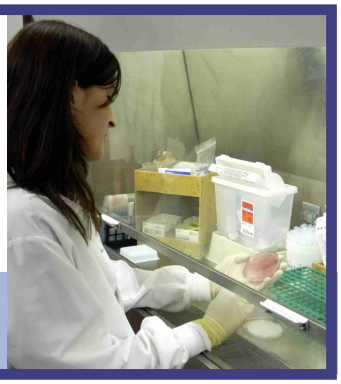

Low Molecular Weight Heparin and Heparin anti-Xa Assay

Introduction: Rex Lab uses the activated partial thromboplastin time (aPTT) for routine monitoring of unfractionated heparin (UFH). UFH produces a variable anticoagulant response in patients and requires laboratory monitoring. On the other hand, low molecular weight heparin (LMWH) has a more predictable response and laboratory monitoring is not necessary in most situations. LMWH is cleared primarily by renal excretion. With normal renal function, the elimination half-life is longer than that of unfractionated heparin and varies from two to six hours, depending on the route of administration. Adequate plasma levels are achieved by subcutaneous administration once or twice daily. The incidence of heparin-induced thrombocytopenia is lower with LMWH than with UFH. When necessary, plasma levels of UFH or LMWH may be monitored by the heparin anti-Xa assay.

Mechanism of Action of UFH and LMWH: UFH accelerates the action of antithrombin III and inhibits Factor Xa (activated factor ten) to a lesser degree. Antithrombin III activation causes a decrease in thrombin resulting in a decreased conversion of fibrinogen to fibrin and ultimately an anticoagulated state. Direct inhibition of thrombin by unfractionated heparin dramatically prolongs the thrombin clotting time (TCT). The mechanism of LMWH anticoagulation is similar but different. LMWH primarily inhibits Factor Xa instead of thrombin. LMWH does not prolong most screening coagulation tests such as the prothrombin time (PT), aPTT or TCT. This is the result of a lower inhibitory activity against thrombin compared with unfractionated heparin. The heparin anti-Xa assay is used to monitor LMWH when necessary. The reason the PT is not prolonged by unfractionated heparin or LMWH is because the reagent in the PT contains a heparin-neutralizing agent.

The Anti-Xa Assay: The level of heparin in the plasma is measur ed by its ability to inhibit exogenous Factor Xa in an anti-Xa activity assay. Patient plasma is added to a known amount of Factor Xa with excess antithrombin. If UFH or LMWH is present in the patient' s plasma, it will bind to antithrombin and inhibit Factor Xa. The amount of residual Factor Xa is inversely proportional to the amount of heparin in the plasma. The amount of residual Factor Xa is detected by adding a chromogenic substrate that resembles the natural substrate of Factor Xa. Factor Xa cleaves the chromogenic substrate, releasing a colored compound that can be detected by a spectrophotometer . Deficiencies of antithrombin in the patient do not affect the assay, because excess antithrombin is provided in the reaction.

When to Order a Heparin Anti-Xa Assay: Although it is generally accepted that LMWH does not need to be routinely monitored, there are situations where monitoring may be of value.

(continued on page 2)

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Increased Risk of Non-Therapeutic Levels with Heparin

LMWH:
1. Infants and small children
2. Obese or low body weight patients
3. Renal insufficiency or failure
4. Malignancies or hypercoagulable states
5. Pregnancy

UFH:
1. Prolonged baseline aPTT
2. Heparin resistance

Infants and small children may require a larger dose of the LMWH than adults. Studies have not yet confirmed that unit dosing is safe and effective in children, so monitoring is recommended to ensure adequate therapy. Patients who are obese or have low body weight may requir e intermittent monitoring because of possible differences in their pharmacokinetics compared with patients closer to ideal body weight. The kidney clears LMWH, so patients with renal insufficiency may benefit from periodic monitoring. Monitoring may be useful in outpatients on long-term therapy for conditions such as malignancy (Trousseau's syndrome) and thrombosis refractor y to oral anticoagulants (as in myeloproliferative disorders and antiphospholipid antibody syndrome), as well as in individuals who cannot take oral anticoagulants, such as pregnant patients. Patients receiving unfractionated heparin who have a prolonged baseline aPTT or appear resistant may be monitored with the anti-Xa assay.

Interpretation of Anti-Xa Activity (IU/mL): Results are reported as anticoagulant concentration in anti-Xa units/ml, such that high anti-Xa values indicate high levels of anticoagulation and low anti-Xa values indicate low levels of anticoagulation.

Optimum Range of Heparin Anti-Xa Activity (IU/ml)

Low molecular weight heparin:	
Prophylaxis for moderate risk	*0.10 to 0.25*
Prophylaxis for high risk	*0.20 to 0.50*
Therapy for deep vein thrombosis	*0.50 to 1.20*
Unfractionated heparin:	
Therapeutic levels	*0.30 to 0.70*

Laboratory Testing for Anti-Xa Assay: Beginning in January 2004, heparin anti-Xa testing will be performed on site at Rex Healthcare Laboratory. To order a "heparin anti-Xa assay" in the Hospital Information System, draw one blue top (3.2% sodium citrate) tube of whole blood 4 hours after subcutaneous injection of LMWH. The timing of the specimen collection is important, otherwise, falsely low values may occur. Hand deliver the tube to laborator y immediately (**do not tube**), otherwise falsely low values may occur due to release of platelet Factor 4 which neutralizes unfractionated heparin or LMWH Plasma should be separated from the cells as soon as possible, ideally within one hour of specimen collection. Plasma can be stored for two hours at room temperature or on ice; otherwise, store frozen. If the patient is receiving UFH and a heparin anti-Xa assay is desired, contact the Coagulation Laboratory (919) 784-2159 prior to ordering the test as different calibration curves are used in determining the final result.

Stephen V. Chiavetta, M.D.

References:
1. *Fairweather, Robert B., "When should low-molecular–weight heparin be monitored", CAP Today –Coagulation Case Study, July 1999.*
2. *Fan, Guang and Retzinger, Gregory, "Low Molecular Weight Heparin", University. of California Department of Pathology Newsletter, Volume 4, Issue 1, January/February 1998.*

Rex Pathology Associates, and the Rex Laboratory staff wish you and yours a Happy Holiday.

New Outpatient Panel for Antimicrobial Testing of Gram Negative Bacteria

In October 2003 the Rex microbiology department began using a new panel of antibiotics for susceptibility testing of gram negative bacteria isolated from outpatient specimens. After discussion with several clinicians, this revision will include more oral agents and increase the spectrum of antibiotics used for urinary tract infections. The current inpatient panel is below on the left with the new outpatient panel on the right for comparison.

Inpatient and ED antibiotic panel for susceptibility testing
Ampicillin
Ampicillin/Sulbactam
Piperacillin
Piperacillin/Tazobactam
Ticarcillin/Clav Acid
Cefazolin
Cefuroxime
Cefotetan
Ceftriaxone
Ceftazidime
Cefepime
Imipenem
Aztreonam
Ciprofloxacin
Levofloxacin
Amikacin
Gentamicin
Tobramycin
Nitrofurantoin
Trimeth/Sulfa

Outpatient panel for antimicrobial susceptibility testing
Ampicillin
Amox/Clavulanic Acid
Ticarcillin
Ticarcillin/Clav Acid
Cefazolin
Cephalothin
Cefuroxime
Cefoxitin
Cefpodoxime
Ceftriaxone
Ceftazidime
Tetracycline
Ciprofloxacin
Levofloxacin
Nalidixic Acid
Norfloxacin
Gentamicin
Tobramycin
Nitrofurantoin
Trimeth/Sulfa

Both panels contain twenty antibiotics. There is a broad overlap with the outpatient panel having the following additions and subtractions from the inpatient panel.

Antibiotics present in outpatient panel, absent from inpatient panel
Ticaricillin
Amox/Clavulinic Acid
Cephalothin
Cefoxitin
Cefpodoxime
Tetracycline
Nalidixic Acid
Norfloxacin

Antibiotics absent from outpatient panel, present in inpatient panel
Piperacillin
Ampicillin/Sulbactam
Piperacillin/Tazobactam
Cefotetan
Cefepime
Imipenem
Aztreonam
Amikacin

These panels come as preformulated cards for the automated Vitek2 instrument used for susceptibility testing. We expect this outpatient panel will provide more relevant information for treatment of outpatient infections. Clinicians will notice that the laboratory reports do not contain all of these antibiotics. In an article to follow I will discuss the algorithms that go into reporting of susceptibilities depending on the organism isolated from culture.

Vincent S. Smith, M.D.

Susceptibility Testing of Staphylococcus Saprophyticus

The isolation of a coagulase-negative staphylococcus from the urine prompts the microbiology laboratory to differentiate the organism to the species level rather than merely report “coag negative staph”. While most coagulase-negative staphylococci are regarded as contaminants, *S. saprophyticus* is an important cause of acute urinary tract infections, predominantly in young, sexually active women. In many studies it is the second most common organism after *E. coli*. The source of *S. saprophyticus* is usually related to colonization of the rectum, urethra, urine or uterine cervix. At Rex, we have traditionally reported antimicrobial susceptibility results for this organism. However, following recent recommendations from the National Committee for Laboratory Standards (NCCLS) published in January 2003, susceptibility testing will no longer be performed on isolates of *S. saprophyticus* from urine culture. The NCCLS comment reads, “Routine testing of urine isolates of *S. saprophyticus* is not advised, because infections respond to concentrations achieved in urine of antimicrobial agents commonly used to treat acute, uncomplicated urinary tract infections (e.g., nitrofurantoin, trimethoprim +/ -sulfamethoxazole, or a fluoroquinolone).” If antimicrobial susceptibilities are desired on a particular urine isolate of *S. saprophyticus*, contact the microbiology lab at (919) 784-3051, or Dr. Smith at (919) 784-3056.

Vincent C. Smith, M.D.

Reference Range Changes for PT/PTT

New coagulation instrumentation and reagents will result in a change in the reference and therapeutic ranges of the PT (effective November 24) and PTT (effective December 15). The changes are summarized below.

Test	Normal Range Seconds	Therapeutic Range Seconds	Critical Value Seconds
Protime (PT)	Old 10.6 – 12.7s New 12.3 – 15.2s	Old INR 2.0 – 3.0 17.1 – 21.5s New INR 2.0 – 3.0 22.7 – 30.5s	Old >6.0 >31.6s New >5.0 >44.4s
PTT	Old 24 - 35s New 23.7 – 36.0s	Old 43 – 72s New 73 – 107s	Old >100s New > 120s
Thrombin Clotting Time	Old 12.9 – 18.1s New 14.4 – 18.2s		Old >90s New >120s
Fibrinogen	Old 178 – 505 mg/dl New 192 – 488 mg/dl		Old <100mg/dl New <100
Bleeding Time	Old Ivy Method	Discontinued Replaced by platelet function assay	

The normal range values are always listed with the test result. The international normalized ratio (INR) is the value used to monitor oral anticoagulant therapy and remains the same, i.e. 2.0 – 3.0. The upper range of normal of the PT is slightly longer (15.2 sec.). The therapeutic range of the PTT for unfractionated heparin is also slightly longer. The Rex Pharmacy has adjusted the heparin therapy protocol to a weight based protocol for the new PTT therapeutic range. The PTT therapeutic range of unfractionated heparin is incorporated into the heparin protocol. The laboratory critical values listed above are abnormal results that require physician notification. If a critical value is found, the technologist telephones the nursing station (inpatients) or physician's office (outpatients).

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