

## ***BLEEDING DISORDER EVALUATION***

**Case history:** A 19-year-old pharmacist's wife presents with a 2-day history of epistaxis and bruising. She denies previous bleeding problems, has normal menstrual periods and no family history of bleeding abnormalities. Physical exam is normal except for many large ecchymoses on the trunk and extremities. Petechiae are absent. Stool for occult blood is negative. The CBC is normal. The platelet count is 269,000/ $\mu$ L with normal platelet function studies. Laboratory coagulation studies are listed below.

### **Clotting test results**

<b>TEST</b>	<b>RESULT</b>	<b>NORMAL</b>
aPTT	117 sec.	25 – 35 sec.
Prothrombin time	53 sec	10 – 12 sec.
Prothrombin mix	12 sec	10 – 12 sec.
Thrombin time	18 sec.	15 – 18 sec.
Factor V	100 %	50 – 100%
Factor VII	8 %	50 – 100 %
Factor IX	5 %	50 – 100 %
Factor X	7 %	50 – 100 %

A coagulation inhibitor is ruled out by the complete correction of the PT with the addition of normal plasma (Prothrombin mix or correction study). The vitamin K dependent factors (II, VII, IX and X) are decreased. It was concluded the patient had a deficiency of vitamin K and was given 10 mg subcutaneously. The PT corrected to normal in 24 hours. One week later a report was received that the patient's serum contained 9 mg/L of warfarin (warfarin levels with therapy are usually 2 –4 mg/L). This patient had surreptitious ingestion of warfarin.

The initial laboratory evaluation of clinical bleeding should include a platelet count, PT and aPTT. The table below lists the clinical conditions associated with prolongation of the PT, aPTT or both.

### **Interpretation of PT and aPTT**

<b>PT long; aPTT normal</b>	<b><u>APTT long; PT normal</u></b>	<b><u>PT and aPTT long</u></b>
Low Factor VII	Low factors XII XI VIII IX	Low factors V and X
Vitamin K deficiency	Lupus anticoagulant	Low fibrinogen, prothrombin
Warfarin (coumadin) therapy	Heparin	Vitamin K deficiency
Liver disease	Low prekallikrein/ high molecular weight kininogen	Warfarin
		Liver disease

When screening tests of hemostasis are abnormal, it is necessary to exclude the presence of a circulating anticoagulant. Heparin is the most common unsuspected anticoagulant (often due to contamination from a specimen collected from an indwelling catheter. If a repeat specimen is collected by phlebotomy rather than an indwelling line, the problem is resolved. An endogenous anticoagulant that prolongs the aPTT and may also affect the PT is the lupus anticoagulant. This antiphospholipid antibody doesn't cause bleeding, but (paradoxically) may be associated with thrombosis. Lupus like inhibitors are neutralized by the addition of excess phospholipid to plasma. A lupus-like inhibitor (lupus anticoagulant) assay is done at Rex. A second type of endogenous anticoagulant is an antibody directed against a specific clotting factor. The most common example

of this is an acquired factor VIII inhibitor. As noted above, specific factor inhibitors can often be suspected if a mixing study of the abnormal coagulation screening test fails to correct. This is done by mixing the patient's plasma with normal plasma to see if the study in question (PT, aPTT, or TCT) is corrected. Correction by the mix suggests factor deficiency, while lack of correction is characteristic of an inhibitor. Inactivation of clotting factors is time dependent, so that incubation of the patient and normal plasma for an hour may be necessary before concluding an inhibitor is not present. Antibodies to factor VIII may be quantified by the Bethesda assay.

When the PT and aPTT are both prolonged and an inhibitor is ruled out, a problem in the final common pathway of the coagulation cascade is implicated. A fibrinogen level or thrombin time (TCT), which is very sensitive to low fibrinogen, may be helpful. A normal thrombin time excludes fibrinogen deficiency and thrombin antibodies. Liver disease may cause prolonged PT and aPTT, since all coagulation factors are made in the liver except factor VIII and von Willebrand factor. Factor VIII levels are normal in liver disease.

In the case presentation, a single dose of vitamin K restored normal hemostasis. Blood component therapy was not required. However, surreptitious ingestion of very large doses of warfarin or long-acting vitamin K antagonists such as rat poison, may require large doses of vitamin K administered for many weeks or months to reverse the coagulopathy. Rodenticides are available over-the-counter and are much more potent inhibitors of vitamin K than warfarin. These "superwarfarins" (eg. brodifacoum) can be detected in serum samples using a specialized toxicologic assay. An assay for warfarin will not detect a rodenticide. (Assays for warfarin and brodifacoum are available from Mayo Medical Laboratories.)

*Stephen V. Chiavetta, MD*

#### *References:*

1. David Green, MD, American Society of Hematology 2001 Education Program Book, "Laboratory Evaluation of Bleeding Disorders", pages 309 – 313.
2. William L. Nichols, MD, Bleeding and Thrombosing Diseases: The Basics and Beyond, Mayo Clinic 2002 course, "Acquired Plasmatic Coagulopathies", pages 1 – 5.

### ***FOLLOW-UP RECOMMENDATIONS FOR SUBOPTIMAL PAP SMEARS***

One of the more confusing aspects of the Bethesda System classification centered on the terminology of specimen adequacy. The "Unsatisfactory" category was self-explanatory but the "satisfactory but limited by..." category was problematic, lacking standardized follow-up algorithms and resulting in unnecessary early repeat Pap tests. Recently two major steps have been taken to standardize the follow-up of patients with less than adequate Pap specimens. Bethesda 2001 eliminated the category "satisfactory but limited by..." and in 2002 The American Society for Colposcopy and Cervical Pathology (ASCCP) issued guidelines for the appropriate management of less than adequate Pap tests (1).

#### **ASCCP Guidelines for followup of Pap tests lacking an endocervical component or with partially obscuring factors:**

1. Most patients can be scheduled for a repeat Pap test in 12 months (assuming that they participate in a regular screening program).
2. Pregnant patients can be scheduled for a postpartum repeat Pap.
3. Early six-month repeat Pap testing may be helpful in high-risk patients:
  - a) history of prior abnormal Pap tests
  - b) previous Pap with an unexplained glandular abnormality
  - c) positive high-risk HPV test within the previous 12 months
  - d) HIV+ individuals

- e) inability to clearly visualize the cervix or sample the endocervical canal
- f) prior insufficient Pap tests.

### **ASCCP Guidelines for followup of Unsatisfactory Pap tests:**

1. In most situations a repeat Pap test within two to four months is recommended.
2. If the Pap test is repeatedly unsatisfactory due to obscuring blood, inflammation or necrosis, colposcopy should be considered.

At Rex we have found that the use of the SurePath® Pap Test significantly reduces unsatisfactory specimens compared to conventional Pap smears and ThinPrep® Pap Tests. The SurePath® cell enrichment process eliminates blood, mucus, inflammatory cells, necrotic debris and other extraneous factors that can pose problems with other Pap methods.

The significance of adequate endocervical/transformation zone sampling has been studied extensively. Two large recent studies each concluded that the absence of a transformation zone component in a Pap specimen is not associated with missed high-grade lesions, and thus early repeat testing of most women whose Pap tests lack an endocervical component is not warranted (2,3). Based on this data, the new ASCCP guidelines seem to represent a reasonable compromise in the quest for adequate followup of these patients.

*Keith V. Nance, MD*

### *References*

1. Davey DD, et al. ASCCP Patient Management Guidelines: Pap Test Specimen Adequacy and Quality Indicators. *J Lower Genital Tract Dis.* 2002; 6:195-199 and *Am J Clin Pathol.* 2002; 118:714-718.
2. Baer A, et al. Liquid-based Pap Smears without a Transformation Zone Component: Should Clinicians Worry? *Obstet Gynecol.* 2002; 99:1053-1059.
3. Mitchell HS. Longitudinal Analysis of Histologic High-Grade Disease after Negative Cervical Cytology According to Endocervical Status. *Cancer Cytopathology.* 2001; 93:237-240.

### ***Severe Acute Respiratory Syndrome (SARS)***

As of April 10, 2003 there have been 2,722 suspected cases worldwide, with 106 deaths. In the U.S. the CDC reports 149 suspected cases in 30 states, 6 in North Carolina of which 3 have been in Wake County.

The updated interim U.S. **SARS case definition** is as follows:

Respiratory illness of unknown etiology with onset since February 1, 2003, and the following criteria:

- Measured temperature greater than or equal to 100.5 F (>38 C) **AND**
- One or more clinical findings of respiratory illness (e.g. cough, shortness of breath, difficulty breathing, hypoxia, or radiographic findings of either pneumonia or acute respiratory distress syndrome) **AND**
- Travel within 10 days of onset of symptoms to an area with documented or suspected community transmission of SARS (excludes areas with secondary cases limited to healthcare workers or direct household contacts) **OR**
- Close contact (having cared for, having lived with, or having direct contact with respiratory secretions and/or body fluids of a patient known to be suspect SARS case) within 10 days of onset of symptoms with either a person with a respiratory illness who traveled to a SARS area or a person known to be a suspect SARS case.

**Recommended specimens for evaluation of potential cases of SARS:** (to send to the CDC, tests currently under development)

**Outpatient:**

Upper respiratory: nasopharyngeal/oropharyngeal swabs

**Inpatient:** outpatient specimens plus:

Nasopharyngeal aspirate

Blood: serum or whole blood (EDTA)  
Urine: acute illness only  
Stool

Bronchoalveolar lavage (BAL)  
Tracheal aspirate  
Pleural fluid

All of these specimens would have to be ordered as a “Reference” test in the Hospital Information System. It is *highly recommended* that you contact the Reference Desk (784-4117) or the pathologist on call if you would like specimens sent for SARS evaluation. A brief history of symptoms and exposure is necessary. These specimens are mailed directly to the CDC with specimen collection and packing instructions available in PDF format at: <http://www.cdc.gov/ncidod/sars/pdf/packingspecimens-sars.pdf>  
<http://www.cdc.gov/ncidod/sars/pdf/specimencollection-sars2.pdf>

**Laboratory workup** of the patient should also include blood cultures, sputum Gram stain and culture, and testing for viral respiratory pathogens including influenza A and B and RSV. These are ordered at Rex as Influenza A and B antigen (INFLU) and RSV direct antigen (RSV).

*Vincent C. Smith, MD*

### ***Human Chorionic Gonadotropin (hCG) Testing***

We’re having problems clarifying some outpatient physician orders for hCG testing. Some physicians are ordering “serum hCG” when they really want a pregnancy test. We also get a lot of requests for “beta hCG”, which we do not perform here at Rex. Our quantitative hCG assay measures the **intact** molecule. This assay has performed well in monitoring normal and abnormal pregnancies, but is suboptimal for monitoring of gestational trophoblastic disease or germ cell neoplasia. For the latter, we refer specimens to Mayo Medical Laboratories for Chorionic Gonadotropin, Beta Subunit, Quantitative (test 8693). The Mayo test is designed for following patients with gestational trophoblastic disease or germ cell tumors, but is not recommended for monitoring pregnancy. Clarifying which test is actually needed takes time away from your patients, your staff and our staff. We recommend that physicians and office staff adopt the following guidelines when ordering hCGs on outpatients at Rex:

- For serum pregnancy test, order “serum pregnancy test” or “**qualitative HCG**”.
- For quantitative HCG, order “quant. HCG”
- Reserve orders for “beta HCG” for patients with gestational trophoblastic disease or germ cell tumors. These tests will be sent to Mayo Medical Laboratories for the specific beta subunit assay.
- Please include the appropriate ICD-9 code as this will help our clerical staff order the correct test.

*John D. Benson, MD*

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REX Healthcare Laboratory (784-3040). Telephone extensions are: Pathologists' Direct Line (3201), Sharon Logue (Lab Director 2400), Robin Ivosic (Outreach and Microbiology Lab Manager 3053), Elaine Patterson (Core Lab Manager 3054), Jackie Okoth (Core Lab PM Manager 4248), Diane Young (Anatomic Pathology Manager 3888), Nga Moore (Customer Service Manager 3396), Diane Stephenson (Blood Bank Manager 4767), Justin Hodges (Blood Plan Manager 4750). **Client Response Center 784-6000 (phone), 784-6299 (fax)**