

ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

Section Editor: Craig M. Kessler, MD

Abnormal Partial Thromboplastin Time in Adults and Children

Rajiv K. Pruthi, MBBS
Associate Professor of Medicine
Mayo Clinic
Rochester, Minnesota

H&O What is the partial thromboplastin time (PTT) test?

RP The coagulation cascade consists of 3 pathways, an extrinsic pathway and an intrinsic pathway, which converge on a final common pathway. There are multiple clotting factors in all 3 pathways, and the PTT test measures the integrity of the intrinsic and final common pathway. It was originally developed to evaluate patients who present with hemorrhagic problems—such as spontaneous bleeding or bleeding after minor trauma or surgery—to identify deficiency of a coagulation factor. Over the years, it was recognized that inhibitors of coagulation factors would also prolong the PTT; in addition, nonspecific inhibitors like lupus anticoagulants were also recognized to prolong the PTT. The PTT test is also used to monitor anticoagulants such as unfractionated heparin and parenteral direct thrombin inhibitors. To perform the test, the patient's plasma is mixed with phospholipid calcium and an “activator,” which leads to activation of the clotting factors in the intrinsic pathway. The time that it takes to form a clot is the PTT result.

H&O What are the normal values of the PTT test?

RP The normal value for the PTT test varies with different combinations of instrumentations and reagents used in each laboratory. When a laboratory is starting to perform PTT testing, it must first establish a reference range based on samples from 20–50 healthy people. A normal range in one laboratory will not necessarily apply to another laboratory because different instruments and different reagents might be used.

H&O What types of patients should undergo a PTT test?

RP Patients who are bleeding should undergo PTT testing as part of a larger workup. Patients who are about to start anticoagulant therapy, such as unfractionated heparin or a parenteral direct thrombin inhibitor, should undergo a PTT to obtain a baseline level that can be compared with levels taken after the drug has been administered. Patients who present with venous or arterial thrombosis should undergo an initial PTT test to screen for a possible lupus anticoagulant, but more sophisticated tests are needed to confirm the diagnosis.

H&O What does an abnormal PTT indicate?

RP An abnormally prolonged PTT suggests that a patient may have a coagulation factor deficiency state or presence of an inhibitor. Both an inhibitor and a factor deficiency will prolong the PTT; the way to differentiate between them is to perform a mixing study. The patient's plasma is mixed in a 1-to-1 ratio with normal pool plasma, and the PTT test is repeated. A test result that corrects into the reference range for that laboratory suggests the presence of a clotting factor deficiency. If the test results show a factor deficiency, the next step is to identify which factors are deficient; once the deficiency is identified, it is important to investigate the etiology of the deficiency. If the patient has a prolonged PTT and a normal prothrombin time (PT), it is most likely that factors within the intrinsic pathway—namely factors VIII, IX, XI, and XII—are deficient. If both the PT and the PTT are prolonged, it suggests deficiencies in the intrinsic and extrinsic pathways or even a deficiency in the final common pathway.

A test result that does not correct—in other words, that is inhibited—suggests the presence of an inhibitor. For example, a patient has a baseline PTT of 60 seconds, which decreases to 50 seconds after the mixing study. This

small reduction occurs because the plasma is being diluted with normal plasma, but if the level does not correct into the reference range, the PTT is considered inhibited. There are 3 broad categories of inhibitors. Drugs that can act as inhibitors include heparin and direct thrombin inhibitors, such as lepirudin, argatroban, and the oral agent dabigatran. An inhibited PTT can also be due to the presence of inhibitors directed against blood clotting factors that result in bleeding disorders, most commonly factor VIII. Spontaneous development of an inhibitor against factor VIII, also called autoimmune hemophilia A, is a potentially life-threatening acquired bleeding disorder. The third category of inhibitors is called *nonspecific inhibitors*, an example of which is lupus anticoagulants. Although lupus anticoagulants are not necessarily risk factors for bleeding, they can be risk factors for thrombosis, either venous or arterial.

In some patients, the presence of one specific factor deficiency—such as factor XII deficiency—does not indicate a bleeding disorder. Factor XII is not necessarily important for clot formation. Patients might have severe deficiency of factor XII and a very long PTT, but they do not bleed. Therefore, a long PTT is not necessarily a simple problem; it could reflect a variety of underlying disorders. The PT and PTT tests should be considered screening tests rather than diagnostic tests. If the results are abnormal, further testing is needed.

H&O What additional tests should be performed in patients who present with bleeding disorders?

RP To evaluate patients for bleeding disorders, generally, the PTT is not performed on its own. In patients who present with bleeding disorders, the initial basic workup includes testing for the PT, PTT, fibrinogen, and Von Willebrand factor. In male patients, or patients with a family history of bleeding, physicians should consider testing for levels of factor VIII and factor IX. If those test results are normal—and there is no explanation for a patient's bleeding or bruising—referral to a coagulation specialist is recommended.

H&O What other factors might affect PTT?

RP It is important to remember that there are artifactual causes for prolongation of the PTT. Consider,

for example, a patient with a very high hemoglobin or hematocrit who has cyanotic congenital heart disease or a myeloproliferative disease like polycythemia vera. This patient will have a very high hematocrit, which can artifactually prolong PTT in a sample of whole blood. In this patient, it would be important to adjust the amount of anticoagulant present in the collection tube, in order to reduce the risk of an artifactual prolongation. Artifactual prolongation could also occur if a sample is collected through a central venous catheter or an arterial line that is coated with heparin; heparin contamination can result in a prolongation of the PTT.

H&O Does a prolonged PTT have different implications in children versus adults?

RP It does, because the pediatric reference range for PTT is different than in adults. Children have a longer PTT than adults do, for unclear reasons. For very young children, ages 1 or 2 years, there is no established reference range because we do not want to subject such young, healthy children to unnecessary phlebotomy. The lack of a reference range for the youngest patients is a significant limitation in pediatric coagulation.

In most children, long PTTs are due to a lupus anticoagulant. The typical scenario is a child who is scheduled for tonsillectomy for chronic recurrent tonsillitis. The ear, nose, and throat surgeon orders a routine PT and PTT prior to the surgery. Because of bacterial or viral infections, the child has developed transient lupus anticoagulants, which can prolong the PTT. Based on the abnormal PTT test result, the tonsillectomy is cancelled and more blood tests are run to identify why the PTT is prolonged.

A prolonged PTT in a child could also be due to a congenital deficiency, like hemophilia A or hemophilia B, or other factor deficiencies. It is very important to consider the result of a PTT within the context of the patient history and family bleeding history.

Suggested Reading

Kamal AH, Tefferi A, Pruthi RK. How to interpret and pursue an abnormal prothrombin time, activated partial thromboplastin time, and bleeding time in adults. *Mayo Clin Proc.* 2007;82:864-873.