



Porter Hospital Laboratory

115 Porter Drive
Middlebury, VT 05753

TEST CHANGE ANNOUNCEMENT

Effective September 1st, 2009

Effective September 1st, 2009 Porter Hospital Laboratory will expand its menu of Coagulation Consultation to include 5 panels available from Mayo Medical Laboratories.

- Mayo test # 550: Coagulation Consultation, Thrombosis/Hypercoagulability, Blood and Plasma
- Mayo test # 551: Coagulation Consultation, Bleeding Diathesis, Plasma
- Mayo test # 552: Coagulation Consultation, Lupus-Like Anticoagulant (LA), Plasma
- Mayo test # 553: Coagulation Consultation, Prolonged Clotting Time, Plasma
- Mayo test # 554: Coagulation Consultation, von Willebrand Disease, Plasma

These panels will not replace our current in-house coagulation tests (PT, PTT, platelet count, FAHC Lupus Panel, individual factor assays, or individual coagulation assays but are available for further evaluation of a patient who has aberrant coagulation whether abnormal or prolonged bleeding, thrombosis/ hypercoagulability or prolonged clotting.

However these tests **will** replace the current **Thrombosis Panel** and/or **Thrombosis Panel, Coumadin** which will no longer be performed.

The test information from the Mayo Medical Laboratory test dictionary has been summarized on the following pages for you convenience. If you would like to view information on these tests in their entirety the web address is: <http://www.mayomedicallaboratories.com/test-catalog>

Ordering:

- Complete the Coagulation Section of the "MayoConnect Additional Test Information Form".
- If ordering Mayo Test #550:
 - **Prior authorization from the patient's insurance company** must be obtained as genetic testing may be performed and many insurance companies do not cover genetic testing if prior approval is not obtained.
 - **The patient must sign an "Vermont State Informed Consent for Genetic Testing" a copy of this form is available in this packet.**
- Complete a Porter Laboratory Requisition using the Mayo Test Number of the Coagulation panel you wish to order.

Specimen Collection:

- An appointment should be made by calling 388-4747. Be sure all required authorizations have been completed.
- These tests require sample collection at Porter Hospital Laboratory because of special handling of the specimen for testing.

Attachments:

- Mayo test # 550: Coagulation Consultation, Thrombosis/Hypercoagulability, Blood and Plasma
- Mayo test # 551: Coagulation Consultation, Bleeding Diathesis, Plasma
- Mayo test # 552: Coagulation Consultation, Lupus-Like Anticoagulant (LA), Plasma
- Mayo test # 553: Coagulation Consultation, Prolonged Clotting Time, Plasma
- Mayo test # 554: Coagulation Consultation, von Willebrand Disease, Plasma
- MayoConnect Additional Test Information
- Vermont State Informed Consent for Genetic Testing

Coagulation Consultation, Thrombosis/Hypercoagulability, Blood and Plasma

Mayo Test Code: #550

Profile Information:

Includes screening tests of coagulation (prothrombin time [PT], activated partial thromboplastin time [APTT], dilute Russell's viper venom time [DRVVT], and thrombin time) with normal plasma mixing studies of abnormal tests and confirmatory testing, if indicated, to define presence of lupus-like anticoagulant, dysfibrinogenemia, or other causes of prolonged clotting times. Protein C, antithrombin (AT), and free protein S antigen will be determined. When the free protein S antigen level is below the normal range, testing will be performed for total protein S antigen. Coagulation assay for resistance to activated protein C will be performed along with factor V Leiden (R506Q) mutation, if indicated (e.g., heparin or warfarin effect, prolonged baseline PT or APTT). Testing for prothrombin G20210A mutation will be performed. Quantitative D-dimer will be determined to screen for intravascular coagulation and fibrinolysis. If appropriate, assays for AT antigen and protein C antigen will be performed at an additional charge. Also, if appropriate, plasminogen and coagulation factor assays will be performed at an additional charge to clarify significant abnormalities in the screening clotting times. If factor VIII result is <45%, the factor VIII inhibitor screen may be performed along with the Bethesda titrating assay, if indicated.

General Information:

Patient should not be receiving Coumadin (warfarin) or heparin. If the patient is currently on warfarin or heparin, this should be noted, as warfarin or heparin therapy can affect certain coagulation factors or assays, preclude their performance, or cause spurious results.

Clinical Information:

Thrombophilia is defined as an acquired or familial disorder that is a risk factor for thrombosis. The clinical presentations of an underlying thrombophilia include venous thromboembolism (deep vein thrombosis [DVT], pulmonary embolism, and superficial vein thrombosis), recurrent miscarriage, and complications of pregnancy (e.g., severe preeclampsia, abruptio placentae, intrauterine growth restriction, and stillbirth). Other possible clinical presentations include arterial thrombosis (especially among patients <50 years of age with no other risk factors for atherosclerotic arterial occlusive disease [diabetes mellitus, hypercholesterolemia, hypertension, or tobacco smoking]) and aseptic necrosis of bone (e.g., femoral head, mandible). Demographic or environmental exposures that compound the risk of venous thromboembolism among persons with a thrombophilia include increasing age, male gender, obesity, surgery, trauma, hospitalization for medical illness, malignant neoplasm, prolonged immobility during travel (e.g., prolonged airplane travel), oral contraceptive use, estrogen therapy (both oral and transdermal), tamoxifen and raloxifene therapy, and infertility drugs. Central venous catheters and transvenous pacemaker wires increase the risk for upper extremity DVT; this risk is unrelated to thrombophilia.

Inherited thrombophilias include:

- Deficiency due to reduced plasma protein level or dysfunctional protein of:
 - Antithrombin
 - Protein C
 - Protein S
- Dysfibrinogenemia (rare)
- Activated protein C resistance due to the factor V R506Q (Leiden) mutation
- Prothrombin G20210A mutation

Acquired thrombophilias include a lupus-like anticoagulant (antiphospholipid antibodies) and disseminated intravascular coagulation/intravascular coagulation (DIC/ICF). DIC/ICF may cause thrombotic as well as hemorrhagic events. Positive tests for DIC/ICF can also occur as consequences of thrombosis.

Acquired deficiencies of fibrinogen, protein C, protein S, and antithrombin may be found in conjunction with liver disease (they are produced by the liver) or DIC/ICF, and are of uncertain significance with respect to thrombosis risk.

Acquired deficiency of protein C and protein S are also found in patients treated with oral anticoagulants (e.g. warfarin, Coumadin) since both of these proteins are dependent upon the action of vitamin K for normal function.

Acquired protein S deficiency also occurs in thrombotic thrombocytopenic purpura (TTP), pregnancy or estrogen therapy, nephrotic syndrome, and sickle cell anemia. In acute illness the level of acute phase reactants rise (including C4b binding protein, which binds and inactivates protein S in the plasma) and the portion of bound protein S also rises, leaving a lower proportion of free protein S. The significance of acquired protein S deficiency with respect to thrombosis risk is unknown.

Useful For:

- Evaluating patients with thrombosis/hypercoagulability states
- Detecting a lupus-like anticoagulant; dysfibrinogenemia; DIC/ICF; deficiency of antithrombin, protein C, or protein S, activated protein C resistance (and the factor V R506Q [Leiden]mutation if indicated); and the prothrombin G20210A mutation

Interpretation:

Each case is individually interpreted using any clinical information from the client and test results obtained. In order to optimally interpret the results, a brief description of the coagulation concern is useful, and local coagulation test results are especially helpful, include the name and telephone number of the requesting physician so that additional consultations can occur if indicated.

Cautions:

Testing is best when performed in medically stable patients not receiving Coumadin, heparin, or fibrinolytic agents (e.g., streptokinase, tissue plasminogen activator).

Coagulation Consultation, Bleeding Diathesis, Plasma

Mayo Test Code: #551

Profile Information:

Includes assays to detect or exclude von Willebrand disease (factor VIII, von Willebrand factor antigen, and ristocetin cofactor), screening tests of coagulation (prothrombin time [PT], activated partial thromboplastin time [APTT], dilute Russell's viper venom time [DRVVT], thrombin time, fibrinogen, factor XIII screen), and screening for intravascular coagulation and fibrinolysis (D-dimer).

Mixing studies will be performed, as indicated, to define abnormalities found in screening tests. If appropriate, further coagulation factor assays will be performed at an additional charge. If factor VIII result is <45%, the factor VIII inhibitor screen may be performed along with the Bethesda titrating assay, if indicated.

General Information:

Patient should not be receiving Coumadin (warfarin) or heparin. If the patient is currently on warfarin or heparin, this should be noted, as warfarin or heparin therapy can affect certain coagulation factors or assays, preclude their performance, or cause spurious results.

Clinical Information:

Bleeding problems may be associated with a wide variety of coagulation abnormalities or may be due to problems not associated with coagulation (trauma and surgery as obvious examples). A partial listing of causes follows.

- Deficiency or functional abnormality (congenital or acquired) of any of the following coagulation proteins: fibrinogen (factor I), factor II (prothrombin), factor V, factor VII, factor VIII (hemophilia A), factor IX (hemophilia B), factor X, factor XI (hemophilia C; bleeding severity not always proportionate to factor level), factor XIII (fibrin-stabilizing factor), von Willebrand factor (VWF antigen and ristocetin cofactor), and alpha-2 plasmin inhibitor and plasminogen activator inhibitor (PAI-I; severe deficiency in rare cases). Neither alpha-2 plasmin inhibitor nor PAI-I are included as a routine bleeding diathesis assay component, but either can be performed if indicated or requested.
- Deficiency (thrombocytopenia) or functional abnormality of platelets such as congenital (Glanzmann's thrombasthenia, Bernard-Soulier syndrome, storage pool disorders, etc) and acquired (myeloproliferative disorders, uremia, drugs, etc) disorders.
- Platelet function abnormalities, which cannot be studied on mailed-in specimens.
- Specific factor inhibitors (most commonly directed against factor VIII) Factor inhibitors occur in 10% to 15% of the hemophilia population more commonly associated with severe deficiencies of factor VIII or IX (antigen <1%). The inhibitor appears in response to transfusion therapy with factor concentrates with no correlation of occurrence and amount of therapy. Factor VIII inhibitors may occur spontaneously in the postpartum patient, with certain malignancies, in association with autoimmune disorders (eg, rheumatoid arthritis, systemic lupus erythematosus), in the elderly, and for no apparent reason.
- Other acquired causes of increased bleeding include paraproteinemia; other factor-specific inhibitors, including those against factor V, factor XI; or virtually any of the coagulation proteins.
- Acute disseminated intravascular coagulation/intravascular coagulation and fibrinolysis (DIC/ICF), which is a fairly common cause of bleeding. Bleeding can also occur in patients with chronic ICF.

Useful For:

- Detection of the more common potential causes of abnormal bleeding (eg, factor deficiencies/hemophilia, von Willebrand disease, factor-specific inhibitors)
- As a simple screen to evaluate for an inhibitor or severe deficiency of factor XIII (rare)
- Screening for intravascular coagulation and fibrinolysis

Interpretation:

Each case is individually interpreted using any clinical information from the client and test results obtained. In order to optimally interpret the results, a brief description of the coagulation concern is useful, and local coagulation test results are especially helpful. It is important to include the name and telephone number of the requesting physician so that additional consultations can occur if indicated.

Cautions:

This test is not useful for assessing platelet function (e.g., congenital or acquired disorders such as Glanzmann's thrombasthenia, Bernard-Soulier syndrome, storage pool disease, myeloproliferative disease, associated platelet dysfunction), which requires fresh platelets.

Patient should not be receiving Coumadin or heparin. If the patient is currently on warfarin or heparin, this should be noted, as warfarin or heparin therapy can affect certain coagulation factors or assays, preclude their performance, or cause spurious results. Patient should also not be receiving fibrinolytic agents (streptokinase, urokinase, tissue plasminogen activator [tPA]).

If patient has been recently transfused, this should be noted; it is best to perform this study pretransfusion, if possible.

Coagulation Consultation, Lupus-Like Anticoagulant (LA), Plasma

Mayo Test Code: #552

Profile Information:

Initial testing includes prothrombin time (PT), activated partial thromboplastin time (APTT), and dilute Russell's viper venom time (DRVVT). If any of these results are significantly prolonged, additional testing will include thrombin time (and reptilase time), mixing studies with normal plasma if results are abnormal, and platelet neutralization procedure as indicated. If appropriate, coagulation factor assays, fibrinogen, and D-dimer will be performed at an additional charge to clarify a significant abnormality in the screening clotting times. If factor VIII result is <45%, the factor VIII inhibitor screen may be performed along with the Bethesda titrating assay, if indicated.

General Information:

We also recommend ordering testing for serum phospholipid (cardiolipin) antibodies. Patient should not be receiving Coumadin (warfarin) or heparin. If the patient is currently on warfarin or heparin, this should be noted, as warfarin or heparin therapy can affect certain coagulation factors or assays, preclude their performance, or cause spurious results.

Clinical Information:

Lupus-like anticoagulant (LA) is antibody to negatively charged phospholipid and interferes with coagulation tests that are phospholipid dependent. LA has been associated with arterial and venous thrombosis and fetal loss. Individuals with thrombocytopenia or factor II deficiency associated with LA may be at risk for bleeding.

LA is found in, but not limited to, patients with systemic lupus erythematosus. LA is found in other autoimmune disorders and collagen vascular diseases. It occurs in response to medications or certain infections (eg, respiratory tract infections in children) and in individuals with no obvious underlying disease.

Useful For:

- Confirming or excluding presence of LA
- Distinguishing LA from specific coagulation factor inhibitors and nonspecific inhibitors
- Investigation of a prolonged activated partial thromboplastin time (APTT), especially when combined with other coagulation studies

Interpretation:

Each case is individually interpreted using any clinical information from the client and test results obtained. In order to optimally interpret the results, a brief description of the coagulation concern is useful, and local coagulation test results are especially helpful. It is important to include the name and telephone number of the requesting physician so that additional consultations can occur if indicated.

Cautions:

This test is not useful for detecting antiphospholipid antibodies that do not affect coagulation tests. We recommend separate testing for serum phospholipid (cardiolipin) antibodies.

Patient should not be receiving Coumadin or heparin. If the patient is currently on warfarin or heparin, this should be noted, treatment with heparin causes false-positive results of in vitro coagulation testing for LA. Coumadin treatment may impair ability to detect the more subtle varieties of lupus-like anticoagulants.

Coagulation Consultation, Prolonged Clotting Time, Plasma

Mayo Test Code: #553

Profile Information:

Screening test and specific assays will be performed as required to determine presence or absence of abnormalities. This includes prothrombin time (PT), activated partial thromboplastin time (APTT), dilute Russell's viper venom time (DRVVT), fibrinogen, and thrombin time. Mixing studies with normal plasma and platelet neutralization procedure will be performed, if indicated. Quantitative D-dimer will be determined to screen for intravascular coagulation and fibrinolysis. If appropriate, coagulation factor assays will be performed at an additional charge to define abnormality. If factor VIII result is less than 45%, the factor VIII inhibitor screen may be performed along with the Bethesda titrating assay, if indicated.

Clinical Information:

When coagulation screening tests are performed to verify normal function of the coagulation system (e.g., preoperative, routine examination), they sometimes indicate an abnormality that may be unexplained (i.e. prolonged clotting times). This consultation provides validation of the prolongation and as comprehensive a work-up as needed to define the abnormality.

Possibilities for a cause of prolongation include:

- Factor deficiency(ies), congenital or acquired
- Factor inhibitors (including Coumadin therapy)
- Lupus-like anticoagulant
- Heparin contamination
- Dilution of specimen by anticoagulant if patient hematocrit is $>$ or $=$ 55%

Useful For:

- Determining cause of prolongation of prothrombin time (PT) or activated partial thromboplastin time (APTT)
- Screening for prolonged clotting times and assaying for presence of factor deficiency(ies) or inhibitor (factor-specific, lupus-like, or the presence of heparin)

Interpretation:

Each case is individually interpreted using any clinical information from the client and test results obtained. In order to optimally interpret the results, a brief description of the coagulation concern is useful, and local coagulation test results are especially helpful. It is important to include the name and telephone number of the requesting physician so that additional consultations can occur if indicated.

Cautions:

If patient hematocrit is $>$ or $=$ 55%, the volume of citrate anticoagulant should be adjusted prior to submitting the specimen for analysis to avoid dilution of plasma by anticoagulant.

Patient should not be receiving Coumadin or heparin. If the patient is currently on warfarin or heparin, this should be noted, as warfarin or heparin therapy can affect certain coagulation factors or assays, or cause spurious results.

Coagulation Consultation, von Willebrand Disease, Plasma

Mayo Test Code: #554

Profile Information:

Testing will include factor VIII activity assay, von Willebrand factor (VWF) antigen, and ristocetin cofactor assay. If appropriate, VWF multimer analysis will be performed at an additional charge to define type of von Willebrand disease. If factor VIII result is <45%, the factor VIII inhibitor screen may be performed along with the Bethesda titrating assay, if indicated.

General Information:

Patient should not be receiving Coumadin (warfarin) or heparin. If the patient is currently on warfarin or heparin, this should be noted, as warfarin or heparin therapy can affect certain coagulation factors or assays, preclude their performance, or cause spurious results).

Clinical Information:

von Willebrand factor (VWF) is synthesized by the endothelial cell and megakaryocyte and is present in these cells, as well as in platelets, subendothelial tissue, and plasma.

VWF serves as an adhesive protein important in adhering platelets to subendothelial tissue at the site of vascular injury and for adhering platelets to each other (aggregation). Platelet adhesion and aggregation are essential to form a mechanical hemostatic "plug" and as the focus for interaction of clotting factors and phospholipid required for the formation of the fibrin platelet clot. VWF also stabilizes plasma factor VIII, by binding it and protecting it from proteolysis and serves as a carrier protein for that clotting factor.

Plasma VWF circulates normally in multimeric forms with molecular weights ranging from 500,000 to as much as 20,000,000. The high molecular weight (HMW) forms of VWF are the most effective components for interaction with platelets. This primary activity of plasma VWF is measured in the laboratory as VWF ristocetin cofactor activity, whereas VWF antigen testing measures the amount of VWF protein, and factor VIII coagulant activity indirectly reflects VWF interaction with factor VIII. VWF multimer analysis visualizes the distribution of VWF multimers, and is useful as a reflexive test for subtyping von Willebrand disease (VWD).

Levels of factor VIII, VWF antigen, and ristocetin cofactor activity may vary greatly within each individual over time, and also with blood type (normal type "O" individuals may have VWF lower than normals of other blood groups). VWF levels (and factor VIII) can be elevated in liver disease, pregnancy, estrogen therapy, inflammation, and after exercise (acute-phase reactant). VWF levels in hemophilia are normal.

VWD is the most common inherited bleeding disorder, affecting up to 1% of the population. It can also occur as an acquired bleeding disorder. Bleeding symptoms in all types of VWD are primarily mucosal including epistaxis, menorrhagia, gastrointestinal bleeding and ease of bruising, but surgical or posttraumatic bleeding can also occur.

Useful For:

- Detection of deficiency/abnormality of VWF and related deficiency of factor VIII coagulant activity
- Subtyping VWD as Type 1 (most common), Type 2 variants (less common), or Type 3 (rare)

Interpretation:

Each case is individually interpreted using any clinical information from the client and test results obtained. In order to optimally interpret the results, a brief description of the coagulation concern is useful, and local coagulation test results are especially helpful, as is information about recent therapy such as DDAVP (desmopressin) or transfusion with VWF concentrates or other blood products. It is important to include the name and telephone number of the requesting physician so that additional consultations can occur if indicated.

Cautions:

Testing should be performed prior to and in the absence of recent transfusion or VWF replacement, including DDAVP (desmopressin) therapy.

Low normal levels of VWF antigen or ristocetin cofactor activity do not exclude possible diagnosis of VWD (repeat testing may be indicated).

Borderline low or slightly decreased levels of VWF antigen or ristocetin cofactor activity may be observed in clinically normal individuals of blood group "O."

This test is not useful for differentiating Type 2A versus 2B VWD, or platelet-type VWD (pseudo-VWD). This differentiation requires ristocetin-induced platelet aggregation testing which must be performed using freshly drawn patient platelets and plasma.

Clinical correlation is required for differentiating acquired from congenital (hereditary) forms of VWD.

Repeat testing may be helpful for confirming or evaluating low or borderline low levels of VWF (antigen and/or ristocetin cofactor activity), especially when there is strong suspicion of VWD. The milder forms of the disease, especially Type 1 VWD, can be difficult to diagnose or exclude, reflecting the variability of baseline VWF levels.

In addition to demonstration of persistently decreased levels of VWF, clinical correlation is required for diagnosis of all VWD subtypes, especially mild Type 1 VWD.

Patient should not be receiving Coumadin (warfarin) or heparin. If the patient is currently on warfarin or heparin, this should be noted, as warfarin or heparin therapy can affect certain coagulation factors or assays, preclude their performance or cause spurious results.