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Diagnoses associated with an abnormal prothrombin time (PT)

Disseminated intravascular coagulation (DIC)

Overview
DIC is a consumptive thrombohemorrhagic disorder that presents with a range of hemorrhagic and thrombotic pathologies. It represents the final common pathway of many conditions that disturb the coagulation system. Tissue factor and various cytokines appear to play a central role in its initiation and continuation.

Clinical presentation
- Acute or chronic
- Bleeding and/or thrombosis; hemorrhage can be life threatening
- Symptom severity ranges from oozing after venipuncture to more systemic symptoms, such as hemoptysis or hematuria
- Skin manifestations, such as petechiae, purpuras, or ecchymoses
- Often associated with progressive organ dysfunction

Risk factors
- Underlying illness that may cause tissue damage, cell death, or production/release of tissue factor
- Common precipitators include trauma, infections, obstetric conditions such as retained dead fetus or abruptio placentae, and cancers

Important notes
- DIC is primarily a clinical diagnosis, as laboratory findings can vary with the underlying problem and are static snapshots of a fluid situation
- Usually associated with a decreased platelet count

Typical lab presentation*

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*Values may not represent those seen when confounding drugs or illnesses are present.
Factor VII (FVII) deficiency

Overview

FVII deficiency is a rare autosomal disorder that occurs in approximately 1 in 500,000 people. FVII is part of the extrinsic coagulation pathway. Patients with low FVII clotting activity may either have little to no bleeding or severe bleeding.

Clinical presentation

- Hemorrhages from the nose and gums and easy bruising
- Hematuria, gastrointestinal bleeding, splenic hematoma, pulmonary hemorrhage, bloody tears, intracranial hemorrhage, and/or subarachnoid hemorrhage
- Hemorrhages often occur prior to adulthood

Important notes

- Reduced FVII levels and clinical symptoms have no clear relation

Typical lab presentation

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References

Factor VII (FVII) inhibitors

Overview
FVII (proconvertin), part of the extrinsic coagulation pathway, is a vitamin K–dependent protein synthesized in the liver.1,2 Autoimmune antibodies can develop against FVII; however, this is so rare it is considered an anecdotal phenomenon.3

Clinical presentation3
• Bleeding complications are more severe with autoimmune FVII inhibitors compared with inherited FVII deficiency
• Bleeding in the mucous membranes
• Central nervous system bleeding, which is often fatal

Risk factors3
• Certain drugs, such as penicillin and cephalosporins
• Malignancy

Typical lab presentation3*

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References

Liver disease effect

Overview
The liver has a central role in hemostasis since it produces most of the known coagulation factors.1 Severe liver disease can lead to decreased synthesis of procoagulant factors, with the exception of FVIII, which is synthesized both inside and outside the liver.1,2 The production of abnormal fibrinogen can result from liver disease, which is referred to as acquired dysfibrinogenemia.2,3 Levels of anticoagulative factors can also be reduced in liver failure.2

Clinical presentation
• Severe bleeding and thrombotic complications can develop with advanced liver disease2
• Both the PT and aPTT can be prolonged.1 However, the PT is usually prolonged sooner and more significantly than the aPTT4

Risk factors3
• Cirrhotic complications (eg, variceal bleeding, infection) may suddenly worsen coagulation status

Important notes3
• Unlike vitamin K deficiency, liver disease will decrease levels of FV

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**Lupus anticoagulant**

**Overview**

The acquired antibody that characterizes the lupus anticoagulant is usually directed against a protein-phospholipid complex and is an in vitro anticoagulant only.\(^1\) Patients with a lupus anticoagulant are at risk for arterial and venous thromboembolism, as well as recurrent spontaneous miscarriages; however, patients may also be asymptomatic.\(^2\)

**Clinical presentation**

- **Bleeding** is not usually associated with a lupus anticoagulant.\(^3,4\) However, in rare cases when it is associated with hypoprothrombinemia and a prolonged PT, bleeding can occur.\(^3\)
- **Risk exists** for arterial and venous thromboembolism, as well as recurrent spontaneous miscarriages.\(^2\)
- **Effect on PT and aPTT** depends on the sensitivity of PT and aPTT reagents to the lupus anticoagulant. Typically results in a mild prolongation of the aPTT and not the PT; however, in some cases, the PT can be affected.\(^3,5\)

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**Typical lab presentation\(^2,3,5-7\)**

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**References**

## Typical lab presentation

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### References


### Monoclonal gammopathy

#### Overview

Monoclonal gammopathy, also known as paraproteinemia, refers to the secretion of a monoclonal immunoglobulin (Ig) or Ig fragment by plasma cells. Entities associated with monoclonal gammopathy include multiple myeloma, Waldenström macroglobulinemia, and monoclonal gammopathy of undetermined significance. Increased Ig levels in these disorders may interfere with the function of coagulation factors.

#### Clinical presentation

- Changes in coagulation factors with multiple myeloma are not usually clinically significant, but they can be associated with bruising and hemorrhages from the nose and gums
- In Waldenström macroglobulinemia, extensive bruising known as cryoglobulinemic purpura can be seen, along with hemorrhages from the nose and gums. More severe bleeding can also occur

#### Important notes

- For all paraproteinemias, the PT is more affected than the aPTT
- Monoclonal gammopathies have also been associated with the development of inhibitors to various coagulation factors
Vitamin K deficiency

Overview
Vitamin K plays a critical role in the synthesis of blood coagulation proteins FVII, FIX, FX, and prothrombin. Although diet is the primary source of vitamin K, vitamin K$_2$ synthesized by intestinal bacteria also contributes to adequate vitamin K intake.$^1$ Vitamin K deficiency can be an acquired disease$^2$; however, congenital combined deficiency of vitamin K–dependent factors has also been described. This disease is rare, having been described in fewer than 15 families, and results from defects in the vitamin K carboxylase or reductase genes.$^3$

Clinical presentation$^4$
• Varies widely for patients with vitamin K deficiency
• Possibly fatal intracranial hemorrhage in neonates
• Bleeding into joints, skin, and mucous membranes

Risk factors
• Intensive-care situations, especially when a patient has been sick for some time$^2$
• Malabsorption$^1$
• Antibiotic use, especially in patients with marginal dietary intake$^1$
• Herbal or natural product use$^5$

Important notes
• A clinical hallmark of acquired vitamin K deficiency is that the PT tends to prolong earlier than the aPTT$^2$
• For congenital deficiency of vitamin K–dependent factors, consanguinity has been described in some affected individuals$^3$
Coagulation Toolkit

Coagulation disorders

Typical lab presentation\(^3,5-7\)*

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References

Warfarin effect

Overview
Warfarin is a dicumarol derivative. It exerts an anticoagulatory effect by inhibiting the gamma carboxylation of vitamin K–dependent coagulation factors. This leads to lower levels of active coagulation factors.\(^1\) FVII is affected initially because it has the shortest half-life, while effects on FII, FIX, and FX follow later.\(^2\) As a result, early warfarin effect may present with only a prolongation of the PT/INR, while both PT and aPTT will be prolonged with longer treatment.\(^3\) Warfarin is commonly used for long-term treatment of venous and arterial thrombosis.\(^2\)

Clinical presentation\(^4\)
• Bleeding

Risk factors\(^5\)
• Age >65 years, history of stroke or gastrointestinal bleeding, atrial fibrillation, serious comorbidity (such as kidney or liver failure), and concurrent antiplatelet therapy
**Typical lab presentation**

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**References**

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**Diagnoses associated with an abnormal activated partial thromboplastin time (aPTT)**

**Acquired hemophilia**

**Overview**
Acquired hemophilia is an inhibitor of FVIII that appears spontaneously. The immune system begins producing an antibody, or inhibitor, against its own coagulation factors.1

Acquired hemophilia is both rare and dangerous1:
- Only 1-1.5 per million persons are affected yearly2
- Up to 21% mortality rate3

Prompt and accurate diagnosis is necessary to provide adequate treatment.4

**Clinical presentation**
- Intramuscular hemorrhage5
- Retroperitoneal bleeding5
- Purpura5
- Fatal bleeds may occur at any time until the inhibitor has been eliminated4

**Risk factors2**
- Associated with a wide range of conditions (eg, autoimmune and dermatologic disorders, malignancies, pregnancy); however, more than half of acquired hemophilia occurs completely on its own
- Advanced age
**Acquired von Willebrand disease (vWD)**

**Overview**

Acquired vWD, also known as acquired von Willebrand syndrome, is an uninherited vWF deficiency caused by autoimmune clearance, induced proteolysis through increased fluid shear stress, or binding to cell surfaces.¹

Patients with acquired vWD are often older than age 40 years and have no family history of bleeding diathesis.²

**Clinical presentation**

- Possible bruising³
- Mucocutaneous bleeding also occurs, while lab results match those for vWD¹
- Bleeding, possibly life threatening³

**Risk factors**

- Associated with myeloproliferative diseases (eg, essential thrombocythemia, polycythemia vera, chronic myelogenous leukemia)¹
- Monoclonal gammopathies, including monoclonal gammopathy of unknown significance and multiple myeloma³
- Associated with autoimmune disorders such as systemic lupus erythematosus²

**Important notes**²

- Associated with the therapeutic agents ciprofloxacin, valproic acid, griseofulvin, and hydroxyethyl starch
**Typical lab presentation**

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**Disseminated intravascular coagulation (DIC)**

**Overview**
DIC is a consumptive thrombohemorrhagic disorder that presents with a range of hemorrhagic and thrombotic pathologies. It represents the final common pathway of many conditions that disturb the coagulation system. Tissue factor and various cytokines appear to play a central role in its initiation and continuation.

**Clinical presentation**
- Acute or chronic
- Bleeding and/or thrombosis; hemorrhage can be life threatening
- Symptom severity ranges from oozing after venipuncture to more systemic symptoms, such as hemoptysis or hematuria
- Skin manifestations, such as petechiae, purpuras, or ecchymoses
- Often associated with progressive organ dysfunction

**Risk factors**
- Underlying illness that may cause tissue damage, cell death, or production/release of tissue factor
- Common precipitators include trauma, infections, obstetric conditions such as retained dead fetus or abruptio placentae, and cancers

**Important notes**
- DIC is primarily a clinical diagnosis, as laboratory findings can vary with the underlying problem and are static snapshots of a fluid situation
- Usually associated with a decreased platelet count
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References

Factor VIII (FVIII) deficiency

Overview
FVIII deficiency, better known as hemophilia A or classic hemophilia, is a congenital deficiency of coagulation FVIII, part of the intrinsic coagulation pathway.1-3 FVIII deficiency occurs in 1 of every 5000 live male births and accounts for approximately 4 of 5 hemophilia cases.2

Clinical presentation
- Spontaneous bleeding in the joints and muscles2
- Hematuria, intracranial hemorrhage, gastrointestinal bleeding, and/or oropharyngeal bleeding3
- Severity correlates with FVIII activity levels4
  - Mild: 6%-16%3
  - Moderate: 1%-5%3
  - Severe: <1%3

Risk factors4
- Family history of hemophilia

Important notes
- Spontaneous mutations are the cause of approximately 30% of hemophilia cases and present with no family history2
- Alloantibodies (inhibitors) to FVIII can occur in patients with hemophilia A treated with FVIII replacement. This occurs in 20%-35% of patients with a severe form of the disease2,3
Typical lab presentation1,5*

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References

Factor IX (FIX) deficiency

Overview
FIX deficiency, better known as hemophilia B or Christmas disease, is a congenital deficiency of coagulation FIX, part of the intrinsic coagulation pathway.1-3 FIX deficiency occurs in 1 of every 30,000 live male births and accounts for approximately 1 of 5 hemophilia cases.2

Clinical presentation2
• Spontaneous bleeding in the joints and muscles
• Hematuria, intracranial hemorrhage, gastrointestinal bleeding, and/or oropharyngeal bleeding

Risk factors2
• Family history of hemophilia

Important notes
• Spontaneous mutations are the cause of approximately 30% of hemophilia cases and present with no family history2
• Alloantibodies (inhibitors) to FIX can occur in patients with hemophilia B treated with FIX replacement. This occurs in 1%-4% of patients1,2
Typical lab presentation\textsuperscript{1,3,4,*}

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References

Factor IX (FIX) inhibitors

Overview
FIX, part of the intrinsic coagulation pathway, is a vitamin K–dependent protein synthesized in the liver and activated by FIII (tissue thromboplastin) and FVII.\textsuperscript{1,2} Patients without hemophilia have developed FIX inhibitors in association with systemic autoimmune disorders. Inhibitors to FIX can also develop in patients with congenital FIX deficiency who are treated with exogenous FIX.\textsuperscript{3}

Clinical presentation\textsuperscript{4}
- Bleeding varies in frequency and severity but can be fatal
- Severe bleeding into the skin, muscles, gastrointestinal sites, and genitourinary sites

Risk factors\textsuperscript{4}
- Collagen vascular diseases, the postpartum period, and malignancy

Typical lab presentation\textsuperscript{4,*}

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Key $\uparrow$ Increased $\downarrow$ Decreased $=$ No change

*Values may not represent those seen when confounding drugs or illnesses are present.
Coagulation Toolkit

Coagulation disorders

References

Factor XI (FXI) deficiency

Overview
FXI deficiency, also known as hemophilia C, is an autosomal recessive disorder that produces mild bleeding.1,2 FXI is part of the intrinsic coagulation pathway, where it activates FIX.3

Clinical presentation2
• Generally mild bleeding
  o Lack of severity may be due to normal levels of FVIII and FIX forming the tenase complex, and normal levels of FV and FX forming the prothrombinase complex

Risk factors2
• Ashkenazi Jewish descent

Important notes1
• FXI activity levels do not correlate well with bleeding risk

Typical lab presentation1-4*

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Key
↑ Increased  ↓ Decreased  = No change

*Values may not represent those seen when confounding drugs or illnesses are present.

References

Factor XI (FXI) inhibitors

Overview
FXI, part of the intrinsic coagulation pathway, is synthesized in the liver and megakaryocytes and activates FIX.1 FXI inhibitors are antibodies that develop and inhibit FXI, a factor that is both procoagulant and antifibrinolytic.2

Clinical presentation
• Injury-related and surgical bleeding3
• Severe perioperative bleeding has been reported3
• Spontaneous hemorrhage is not common3

References
Risk factors

- Autoimmune disorders—primarily systemic lupus erythematosus
- Malignancies—particularly those of hematologic origin

Typical lab presentation*

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*Values may not represent those seen when confounding drugs or illnesses are present.

References


Factor XII (FXII) deficiency

Overview

FXII deficiency, also known as Hageman factor deficiency, is a congenital deficiency that does not require treatment. FXII is part of the intrinsic coagulation pathway.

Clinical presentation

- A marked prolongation of aPTT while other coagulation screening tests appear normal
- Not associated with excessive bleeding, even after trauma or surgery

Typical lab presentation*

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References

**Factor XII (FXII) inhibitors**

**Overview**

FXII, part of the intrinsic coagulation pathway, is activated by collagen, basement membranes, or activated platelets.\(^1\) FXII inhibitors are autoimmune antibodies that inhibit FXII.\(^2\) Spontaneous cases are rare.\(^3\)

**Clinical presentation**\(^2\)

- Increased risk of thrombosis or fetal loss
- Not associated with bleeding

**Risk factors**\(^1\)

- Autoimmune disorders
- Treatment with procainamide or chlorpromazine

**Typical lab presentation**\(^2\)*

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**Key**

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*Values may not represent those seen when confounding drugs or illnesses are present.

**References**


**Heparin effect**

**Overview**

Heparin is a negatively charged glycosaminoglycan obtained from animal or plant sources. It exerts its anticoagulant activity by binding to antithrombin, thrombin, and FXa, inhibiting the ability of FXa and thrombin to initiate clots.\(^1\) Heparin is given to prevent and treat venous thrombosis and for the management of arterial disease.\(^2\)

**Important notes**\(^1\)

- Since heparin can arrive in the blood from many sources, do not rely on the initial patient consult to verify possible contamination

**References**

1. References for heparin effect not provided.
Coagulation Toolkit

Coagulation disorders

Typical lab presentation

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Key: ↑ Increased, ↓ Decreased, = No change

*Heparin can cause heparin-induced thrombocytopenia type 2, an immune-mediated drug reaction that increases the risk of arterial and venous thrombosis. This disorder is associated with increased platelet activation.6

*Values may not represent those seen when confounding drugs or illnesses are present.

References

Lupus anticoagulant

Overview

The acquired antibody that characterizes the lupus anticoagulant is usually directed against a protein-phospholipid complex and is an in vitro anticoagulant only.1 Patients with a lupus anticoagulant are at risk for arterial and venous thromboembolism, as well as recurrent spontaneous miscarriages; however, patients may also be asymptomatic.2

Clinical presentation

- Bleeding is not usually associated with a lupus anticoagulant.3,4 However, in rare cases when it is associated with hypoprothrombinemia and a prolonged PT, bleeding can occur8
- Risk exists for arterial and venous thromboembolism, as well as recurrent spontaneous miscarriages2
- Effect on PT and aPTT depends on the sensitivity of PT and aPTT reagents to the lupus anticoagulant. Typically results in a mild prolongation of the aPTT and not the PT; however, in some cases, the PT can be affected6,5
Typical lab presentation\textsuperscript{2,5-7}\text{*}

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*Values may not represent those seen when confounding drugs or illnesses are present.

References


**Monoclonal gammopathy**

**Overview**

Monoclonal gammopathy, also known as paraproteinemia, refers to the secretion of a monoclonal immunoglobulin (Ig) or Ig fragment by plasma cells. Entities associated with monoclonal gammopathy include multiple myeloma, Waldenström macroglobulinemia, and monoclonal gammopathy of undetermined significance.\textsuperscript{1} Increased Ig levels in these disorders may interfere with the function of coagulation factors.\textsuperscript{2}

**Clinical presentation\textsuperscript{3}**

- Changes in coagulation factors with multiple myeloma are not usually clinically significant, but they can be associated with bruising and hemmorhages from the nose and gums
- In Waldenström macroglobulinemia, extensive bruising known as cryoglobulinemic purpura can be seen, along with hemorrhages from the nose and gums. More severe bleeding can also occur

**Important notes**

- For all paraproteinemias, the PT is more affected than the aPTT\textsuperscript{3}
- Monoclonal gammopathies have also been associated with the development of inhibitors to various coagulation factors\textsuperscript{4}
Typical lab presentation

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↑ Increased  ↓ Decreased  = No change

*Values may not represent those seen when confounding drugs or illnesses are present.

References

Platelet-type von Willebrand disease (vWD)

Overview
Platelet-type vWD, or pseudo-vWD, is a rare, autosomal dominant disorder. A gain-of-function defect in the vWF platelet receptor glycoprotein Ib causes increased binding of platelets to the vWF protein, leading to loss of vWF multimers. Platelet-type vWD shares similar clinical and laboratory features with vWD type 2B, the fundamental difference being that, in platelet-type vWD, the defect is in the platelet rather than in the vWF protein. Both disorders show abnormally enhanced low-dose, ristocetin-induced platelet aggregation (RIPA; ≤0.5 mg/dL).

- With platelet-type vWD, abnormal aggregation to low-dose RIPA persists if subject platelets are mixed with normal plasma but corrects when subject plasma is mixed with normal platelets.
- With vWD type 2B, abnormal aggregation to low-dose RIPA persists if subject plasma is mixed with normal platelets but corrects when subject platelets are mixed with normal plasma (or another source of vWF).

Clinical presentation
- Mild to moderate bleeding
- Bleeding in the mucous membranes
- Severe bleeding from the nose and gums
- Life-threatening bleeds are possible after surgery, during pregnancy, and in infection situations
- Platelet counts may be normal or mildly low

Important notes
- Distinguishing platelet-type vWD from vWD type 2B is important, because therapy used in vWD type 2B, such as FVIII/vWF preparations or desmopressin, will exacerbate platelet-type vWD.
- In addition to low-dose RIPA-based plasma/platelet mixing studies, vWD type 2B and platelet-type vWD can also be distinguished by abnormalities noted in the DNA sequencing of exon 28 of the vWF gene in vWD type 2B.
Coagulation Toolkit

Coagulation disorders

• Additional considerations for vWF testing must include:
  o vWF:Ag is an acute-phase reactant that, along with FVIII, may be elevated in clinical settings such as trauma, surgery, and clotting
  o Normal vWF:Ag levels vary by blood type

Typical lab presentation

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Key

↑ Increased  ↓ Decreased  = No change

*Platelet aggregation is normal in response to ADP, arachidonic acid, epinephrine, and collagen but increased in response to ristocetin.

*Values may not represent those seen when confounding drugs or illnesses are present.

References


Von Willebrand disease (vWD) type 1

Overview

vWD is marked by decreased quantity or quality of vWF, which plays a critical role in stabilizing FVIII. vWD is the most common of the inherited bleeding disorders. There are 3 types of vWD. Type 1 is dominantly inherited and associated with mild to moderate bleeding.

Clinical presentation

• Bleeding in types 1 and 2 is usually mild to moderate, although trauma or surgery may result in severe bleeding
• Bleeding manifestations tend to ooze or bruise; the formation of hematomas is rare

Important notes

• Considerations for vWF testing must include:
  o vWF:Ag is an acute-phase reactant that, along with FVIII, may be elevated in clinical settings such as trauma, surgery, and clotting
  o Normal vWF:Ag levels vary by blood type

CoagsUncomplicated.com
**Typical lab presentation**

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**Key**
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*Values may not represent those seen when confounding drugs or illnesses are present.

**References**

**Von Willebrand disease (vWD) type 2A**

**Overview**
VWD is marked by decreased quantity or quality of vWF, which plays a critical role in stabilizing FVIII. VWD is the most common of the inherited bleeding disorders. There are 3 major types of VWD. Type 2 is characterized by qualitative deficiencies in vWF function and occurs in 4 subtypes: 2A, 2B, 2N, and 2M. VWD type 2A is marked by the absence of intermediate- and high-molecular-weight vWF multimers. Two etiologies for the loss of multimers have been described: either defective assembly with decreased secretion, or normal secretion with increased proteolysis of multimers.

**Clinical presentation**
- Bleeding in VWD type 2A is usually mild to moderate, although trauma or surgery may result in severe bleeding
- Bleeding manifestations tend to ooze or bruise; the formation of hematomas is rare

**Important notes**
- Considerations for vWF testing must include:
  - vWF:Ag is an acute-phase reactant that, along with FVIII, may be elevated in clinical settings such as trauma, surgery, and clotting
  - Normal vWF:Ag levels vary by blood type
Typical lab presentation

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Key: ↑ Increased, ↓ Decreased, = No change

*Platelet aggregation is normal in response to all agonists except ristocetin, which is decreased in vWD type 2A.

*Values may not represent those seen when confounding drugs or illnesses are present.

References
6. Von Willebrand disease (vWD) type 2B

Overview
vWD is marked by decreased quantity or quality of vWF, which plays a critical role in stabilizing FVIII. vWD is the most common of the inherited bleeding disorders. There are 3 major types of vWD. Type 2 is characterized by qualitative deficiencies in vWF function and occurs in 4 subtypes: 2A, 2B, 2N, and 2M. In vWD type 2B, a defect in vWF causes increased binding of the vWF protein to glycoprotein Ib, the platelet vWF receptor, leading to loss of high-molecular-weight vWF multimers. VWD type 2B can be misdiagnosed for platelet-type vWD because they share similar clinical and laboratory features. The fundamental difference between the 2 disorders is that for vWD type 2B, the defect is in vWF rather than in the platelet. Both disorders show abnormally enhanced low-dose, ristocetin-induced, platelet aggregation (RIPA; ≤0.5 mg/dL). With vWD type 2B, abnormal aggregation to low-dose RIPA persists if subject plasma is mixed with normal platelets but corrects when subject platelets are mixed with normal plasma (or another source of vWF).
Coagulation Toolkit Coagulation disorders

Clinical presentation
- Bleeding in vWD type 2B is usually mild to moderate, although trauma or surgery may result in severe bleeding.
- Bleeding manifestations tend to ooze or bruise; the formation of hematomas is rare.
- Platelet counts may be normal or decreased.
- Absence of high-molecular-weight vWF multimers, but platelet-associated vWF multimers are normal.

Important notes
- Distinguishing vWD type 2B from platelet-type vWD is important, because therapy used in vWD type 2B, such as FVIII/vWF preparations or desmopressin, will exacerbate platelet-type vWD.
- In addition to low-dose RIPA-based plasma/platelet mixing studies, vWD type 2B and platelet-type vWD can also be distinguished by abnormalities noted in the DNA sequencing of exon 28 of the vWF gene in vWD type 2B.
- Additional considerations for vWF testing must include:
  - vWF:Ag is an acute-phase reactant that, along with FVIII, may be elevated in clinical settings such as trauma, surgery, and clotting.
  - Normal vWF:Ag levels vary by blood type.

Typical lab presentation

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*Platelet aggregation is normal in response to ADP, arachidonic acid, epinephrine, and collagen but increased in response to ristocetin.

References
Von Willebrand disease (vWD) type 3

Overview

vWD is marked by decreased quantity or quality of vWF, which plays a critical role in stabilizing FVIII.1,2 vWD is the most common of the inherited bleeding disorders.1 There are 3 types of vWD. Type 3 is autosomal recessive, with patients having almost no vWF.3

Clinical presentation

• Patients with type 3 present with mucocutaneous, soft-tissue, and joint bleeding1
• Bleeding manifestations tend to ooze or bruise; the formation of hematomas is rare3

Important notes

• Considerations for vWF testing must include:
  o vWF:Ag is an acute-phase reactant that, along with FVIII, may be elevated in clinical settings such as trauma, surgery, and clotting4
  o Normal vWF:Ag levels vary by blood type5

Typical lab presentation3,4,6,7*

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References

Diagnoses associated with both an abnormal prothrombin time (PT) and an abnormal activated partial thromboplastin time (aPTT)

Disseminated intravascular coagulation (DIC)

Overview
DIC is a consumptive thrombohemorrhagic disorder that presents with a range of hemorrhagic and thrombotic pathologies. It represents the final common pathway of many conditions that disturb the coagulation system. Tissue factor and various cytokines appear to play a central role in its initiation and continuation.

Clinical presentation
- Acute or chronic
- Bleeding and/or thrombosis; hemorrhage can be life threatening
- Symptom severity ranges from oozing after venipuncture to more systemic symptoms, such as hemoptysis or hematuria
- Skin manifestations, such as petechiae, purpuras, or ecchymoses
- Often associated with progressive organ dysfunction

Risk factors
- Underlying illness that may cause tissue damage, cell death, or production/release of tissue factor
- Common precipitators include trauma, infections, obstetric conditions such as retained dead fetus or abruptio placentae, and cancers

Important notes
- DIC is primarily a clinical diagnosis, as laboratory findings can vary with the underlying problem and are static snapshots of a fluid situation
- Usually associated with a decreased platelet count

Typical lab presentation*

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References
Dysfibrinogenemia

Overview
Dysfibrinogenemia is caused by a qualitative defect in FI (fibrinogen) that can be either inherited or acquired. Inherited fibrinogen disorders can appear as defects in the amount of FI produced (ie, no FI [afibrinogenemia], not enough FI [hypofibrinogenemia]) or defects in the quality of FI (dysfibrinogenemia). Acquired dysfibrinogenemia occurs when an underlying disease (most often liver disease) alters FI, forming an abnormal protein that disrupts the normal interactions with enzymes and cofactors.

Clinical presentation
• More than 50% of cases of dysfibrinogenemia, either inherited or acquired, have no bleeding diathesis
• 20%-25% of cases have mild to moderate bleeding and/or thrombosis
• Bleeding occurs from ineffective polymerization

Risk factors
• About 60%-70% of patients with liver disease have acquired dysfibrinogenemia

Important notes
Can present with a mild to markedly prolonged diluted TT and a normal quantitative value of clottable fibrinogen. RT should be performed to evaluate cause and rule out heparin, hirudin, and antithrombins

Typical lab presentation*

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References

Factor I (FI) deficiency

Overview
FI deficiency can manifest as a complete absence of fibrinogen (afibrinogenemia) or not enough fibrinogen (hypofibrinogenemia). Fibrinogen, or FI, is a glycoprotein that is involved in the blood-clotting process. Fibrinogen is modified by thrombin to produce fibrin as part of the common coagulation pathway.

Clinical presentation
• Varies from serious life- and limb-threatening bleeds to less serious bleeds

Important notes
• Lab tests will report FI concentration instead of activity, which is usually used in factor assays
• PT, aPTT, and TT will be abnormal due to lack of fibrinogen
Typical lab presentation<sup>5,6</sup>*

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- = No change

*Platelet aggregation is typically normal with hypofibrinogenemia and abnormal with afibrinogenemia.<sup>4</sup>

*Values may not represent those seen when confounding drugs or illnesses are present.

References

**Factor II (FII) deficiency**

**Overview**
Decreased activity of FII (prothrombin), part of the common coagulation pathway, often leads to bleeding of varying severity.<sup>1,2</sup> FII deficiency is rare, occurring in <1 in 500,000 people.<sup>3</sup>

**Clinical presentation<sup>3</sup>**
- Bleeding in mucous membranes, bleeding related to surgery or trauma, joint bleeds, and intracranial hemorrhage

Typical lab presentation<sup>2,4</sup>*

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- = No change

*Values may not represent those seen when confounding drugs or illnesses are present.
Factor II/IIa (FII/IIa) inhibitors

Overview
FII (prothrombin) is part of the common coagulation pathway where it is cleaved into its active form, FIIa (thrombin). Antibodies can develop to either prothrombin or thrombin.

Clinical presentation
- With prothrombin inhibitors, bleeding is rare and thrombophilia is predominant
- With thrombin inhibitors, bleeding is of variable frequency and severity, and thrombophilia is rare

Risk factors
- Systemic lupus erythematosus is a risk factor for both types of inhibitors
- Exposure to bovine thrombin or fibrin glue during surgery is a risk factor for acquired thrombin inhibitors

Important notes
- Antiprothrombin antibodies are the most common prothrombotic inhibitors associated with a lupus anticoagulant

Typical lab presentation

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Key: ↑ Increased, ↓ Decreased, = No change

*Values may not represent those seen when confounding drugs or illnesses are present.

References
Typical lab presentation1,4,5*

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Key: ↑ Increased, ↓ Decreased, = No change

*Values may not represent those seen when confounding drugs or illnesses are present.

References

Factor V (FV) inhibitors

Overview
Activated FV serves as a key part of the prothrombinase complex that activates FII (prothrombin).1 It is unusual for specific autoantibodies that inhibit FV to develop, but an increase in the use of bovine thrombin has been associated with more of these rare autoantibodies.2

Clinical presentation
• Bleeds that are similar to those associated with congenital FV deficiency2
• Bleeding into the skin and mucous membranes1
• Bleeds in the central nervous system, joints, or muscles indicate a more serious deficiency1

Risk factors2
• Collagen vascular disease, fibrin-glue application, and malignancy

Important notes2
• The inhibitory antibody titer corresponds with the severity of the bleed

Typical lab presentation2*

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Key: ↑ Increased, ↓ Decreased, = No change

*Values may not represent those seen when confounding drugs or illnesses are present.
Factor X (FX) deficiency

Overview
Decreased activity of FX, also called Stuart-Prower factor, is an important part of both the intrinsic and extrinsic coagulation pathways and often leads to bleeding of varying severity. This condition is rare, occurring in <1 in 500,000 people.1

Clinical presentation
- Bleeding in the skin and mucous membranes, and severe menstrual bleeding
- Joint bleeds have been reported rarely
- Severity correlates with FX activity levels
  - Mild: 6%-10%
  - Moderate: 1%-5%
  - Severe: <1%

Risk factors
- A history of interfamily marriages

Typical lab presentation1,3,5

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Key: ↑ Increased, ↓ Decreased, = No change

*Values may not represent those seen when confounding drugs or illnesses are present.

References
Factor X (FX) inhibitors

Overview
FX is a vitamin K–dependent protein synthesized in the liver and activated by FVII and FIX, playing a role in both the intrinsic and extrinsic coagulation pathways. While most cases of acquired FX deficiency are associated with systemic amyloidosis, a few cases of true FX autoantibody have been reported.

Clinical presentation
• Bleeding varies in frequency and severity
• Central nervous system bleeding, which is often fatal

Risk factors
• Lupus anticoagulant, respiratory infection, gastrointestinal inflammatory disease, and malignancy
• Amyloidosis is associated with acquired FX deficiency because of increased FX clearance after binding by amyloid fibrils

Typical lab presentation

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*In amyloid.

References

Heparin effect

Overview
Heparin is a negatively charged glycosaminoglycan obtained from animal or plant sources. It exerts its anticoagulant activity by binding to antithrombin, thrombin, and FXa, inhibiting the ability of FXa and thrombin to initiate clots. Heparin is given to prevent and treat venous thrombosis and for the management of arterial disease.

Important notes
• Since heparin can arrive in the blood from many sources, do not rely on the initial patient consult to verify possible contamination
Typical lab presentation3,4**

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*Heparin can cause heparin-induced thrombocytopenia type 2, an immune-mediated drug reaction that increases the risk of arterial and venous thrombosis. This disorder is associated with increased platelet activation.6

*Values may not represent those seen when confounding drugs or illnesses are present.

References

Liver disease effect

Overview
The liver has a central role in hemostasis since it produces most of the known coagulation factors.1 Severe liver disease can lead to decreased synthesis of procoagulant factors, with the exception of FVIII, which is synthesized both inside and outside the liver.1,2 The production of abnormal fibrinogen can result from liver disease, which is referred to as acquired dysfibrinogenemia.2,3 Levels of anticoagulative factors can also be reduced in liver failure.2

Clinical presentation
• Severe bleeding and thrombotic complications can develop with advanced liver disease2
• Both the PT and aPTT can be prolonged.1 However, the PT is usually prolonged sooner and more significantly than the aPTT4

Risk factors4
• Cirrhotic complications (eg, variceal bleeding, infection) may suddenly worsen coagulation status

Important notes5
• Unlike vitamin K deficiency, liver disease will decrease levels of FV
**Coagulation Toolkit**  
**Coagulation disorders**

**Typical lab presentation**

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*Values may not represent those seen when confounding drugs or illnesses are present.

### References

**Lupus anticoagulant**

**Overview**
The acquired antibody that characterizes the lupus anticoagulant is usually directed against a protein-phospholipid complex and is an in vitro anticoagulant only. Patients with a lupus anticoagulant are at risk for arterial and venous thromboembolism, as well as recurrent spontaneous miscarriages; however, patients may also be asymptomatic.

**Clinical presentation**
- Bleeding is not usually associated with a lupus anticoagulant. However, in rare cases when it is associated with hypoprothrombinemia and a prolonged PT, bleeding can occur.
- Risk exists for arterial and venous thromboembolism, as well as recurrent spontaneous miscarriages.
- Effect on PT and aPTT depends on the sensitivity of PT and aPTT reagents to the lupus anticoagulant. Typically results in a mild prolongation of the aPTT and not the PT; however, in some cases, the PT can be affected.

CoagsUncomplicated.com
## Typical lab presentation2,5-7*

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*Values may not represent those seen when confounding drugs or illnesses are present.

## References

## Monoclonal gammopathy

### Overview
Monoclonal gammopathy, also known as paraproteinemia, refers to the secretion of a monoclonal immunoglobulin (Ig) or Ig fragment by plasma cells. Entities associated with monoclonal gammopathy include multiple myeloma, Waldenström macroglobulinemia, and monoclonal gammopathy of undetermined significance. Increased Ig levels in these disorders may interfere with the function of coagulation factors.

### Clinical presentation2
- Changes in coagulation factors with multiple myeloma are not usually clinically significant, but they can be associated with bruising and hemorrhages from the nose and gums
- In Waldenström macroglobulinemia, extensive bruising known as cryoglobulinemic purpura can be seen, along with hemorrhages from the nose and gums. More severe bleeding can also occur

### Important notes
- For all paraproteinemias, the PT is more affected than the aPTT3
- Monoclonal gammopathies have also been associated with the development of inhibitors to various coagulation factors4
### Typical lab presentation

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### References


### Vitamin K deficiency

#### Overview

Vitamin K plays a critical role in the synthesis of blood coagulation proteins FVII, FIX, FX, and prothrombin. Although diet is the primary source of vitamin K, vitamin K synthesized by intestinal bacteria also contributes to adequate vitamin K intake. Vitamin K deficiency can be an acquired disease; however, congenital combined deficiency of vitamin K–dependent factors has also been described. This disease is rare, having been described in fewer than 15 families, and results from defects in the vitamin K carboxylase or reductase genes.

#### Clinical presentation

- Varies widely for patients with vitamin K deficiency
- Possibly fatal intracranial hemorrhage in neonates
- Bleeding into joints, skin, and mucous membranes

#### Risk factors

- Intensive-care situations, especially when a patient has been sick for some time
- Malabsorption
- Antibiotic use, especially in patients with marginal dietary intake
- Herbal or natural product use

#### Important notes

- A clinical hallmark of acquired vitamin K deficiency is that the PT tends to prolong earlier than the aPTT
- For congenital deficiency of vitamin K–dependent factors, consanguinity has been described in some affected individuals
Typical lab presentation

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*Values may not represent those seen when confounding drugs or illnesses are present.

References

Warfarin effect

Overview
Warfarin is a dicumarol derivative. It exerts an anticoagulatory effect by inhibiting the gamma carboxylation of vitamin K–dependent coagulation factors. This leads to lower levels of active coagulation factors.1 FVII is affected initially because it has the shortest half-life, while effects on FII, FIX, and FX follow later.2 As a result, early warfarin effect may present with only a prolongation of the PT/INR, while both PT and aPTT will be prolonged with longer treatment.3 Warfarin is commonly used for long-term treatment of venous and arterial thrombosis.2

Clinical presentation2
- Bleeding

Risk factors2
- Age >65 years, history of stroke or gastrointestinal bleeding, atrial fibrillation, serious comorbidity (such as kidney or liver failure), and concurrent antiplatelet therapy
### Typical lab presentation

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*Values may not represent those seen when confounding drugs or illnesses are present.

### References

Diagnoses associated with both a normal prothrombin time (PT) and a normal activated partial thromboplastin time (aPTT)

Acquired amegakaryocytic thrombocytopenic purpura

Overview
Acquired amegakaryocytic thrombocytopenic purpura is a rare, immune-mediated disorder that presents itself with severe thrombocytopenia (<20,000 per mcL) and a decrease or absence of megakaryocytes in bone marrow.1 The process that causes this disorder is not well defined, but atypical T-cell suppression or an intrinsic colony-forming unit-megakaryocyte defect may be responsible for the decreased megakaryopoiesis. Platelet survival studies are normal, as are erythropoiesis and granulopoiesis.1,2

Clinical presentation
• Bruising and/or bleeding with the absence of splenomegaly1
• Severe thrombocytopenia1
• The clinical course is variable; some patients may follow a relapsing and remitting course, whereas others may show progression to aplastic anemia, myelodysplasia, or leukemia1,3

Risk factors
• Underlying disorders such as systemic lupus erythematosus, drug-induced nutritional B-12 deficiency, ethanol abuse, and human immunodeficiency virus-1 (HIV-1) infection1
• Predominantly seen in female and middle-aged or elderly patients4

Important notes
• Careful consideration must be taken to avoid misdiagnosing the disorder with ITP3
• Diagnosis can be differentiated from ITP using a bone marrow examination. Also, there are no antiplatelet antibodies2

Typical lab presentation2,4*

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*Values may not represent those seen when confounding drugs or illnesses are present.

References
Adenosine diphosphate (ADP) receptor defect (P2Y₁₂)

Overview
Patients with an ADP receptor defect present with normal platelet size and count but have abnormal platelet aggregation in response to ADP.¹,² This autosomal recessive disorder is most often caused by a defect on the P2Y₁₂ gene, which is the target for clopidogrel, an ADP receptor inhibitor.³,⁴ Because the P2Y₁₂ receptor amplifies and sustains platelet activation in response to ADP, the defect prevents the body from inhibiting adenylyl cyclase activity efficiently.²,⁵

Clinical presentation
• Mild bleeding following trauma or surgery⁶
• Bleeding in the mucous membranes⁷
• Minimal and rapidly reversible platelet aggregation along with reduced platelet binding to ADP even with high doses of ADP⁸

Important notes²
• Treatments can include platelet transfusions and desmopressin

Typical lab presentation²,⁸*

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*Platelet aggregation is abnormal with ADP, normal with arachidonic acid and ristocetin, and can be abnormal with epinephrine and collagen.⁶

*Values may not represent those seen when confounding drugs or illnesses are present.

References
Coagulation Toolkit
Coagulation disorders

**α2-antiplasmin deficiency**

**Overview**

α2-antiplasmin deficiency is an autosomal recessive disorder that can affect any race or sex. The gene is located on chromosome 17, and a variety of genetic defects have been reported, including additions, small deletions, and specific nucleotide substitutions. α2-antiplasmin deficiency can also be acquired. With α2-antiplasmin deficiency, a reduced inhibition of plasmin, and resultant increased fibrinolytic activity, can lead to a bleeding tendency.

**Clinical presentation**

- Bleeding from the nose and into joints, easy bruising, hematuria, and menstrual bleeding
- Bleeding after trauma or surgery may be severe and is often delayed
- Heterozygous individuals generally have hemorrhagic symptoms exclusively associated with trauma

**Risk factors**

- Patients with liver failure, amyloidosis, solid tumor, acute promyelocytic leukemia, and DIC are at increased risk of acquired α2-antiplasmin deficiency
- Patients who have received thrombolytic therapy
- Other conditions associated with a hyperfibrinolytic state

**Important notes**

- An α2-antiplasmin assay is essential for diagnosis

**Typical lab presentation**

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*Values may not represent those seen when confounding drugs or illnesses are present.

**References**


**Aplastic anemia**

**Overview**

Aplastic anemia is a disorder characterized by fatty replacement and cellular depletion of the bone marrow. This leads to bone marrow failure, with decreases in the production of erythrocytes, leukocytes, and platelets. Aplastic anemia can be either congenital (<5% of cases) or acquired (>95% of cases).

**Clinical presentation**

- Peripheral blood cytopenias or pancytopenia
- Progressive fatigue, dyspnea, and palpitations
- Bleeding and infection secondary to thrombocytopenia and leukocytopenia
- Pallor secondary to anemia
Risk factors
- The majority of cases (40%-70%) are idiopathic in nature
- Secondary causes include:
  - Chemical agents such as benzene, trinitrotoluene, arsenic, insecticides, and weed killers
  - Drugs such as the antibiotic chloramphenicol and the anti-inflammatory phenylbutazone
  - Infections such as Epstein-Barr virus and hepatitis

Important notes
- Can present in all age groups
- A complete blood count and reticulocyte count, peripheral smear, bone marrow examination, and other biochemical tests to evaluate renal and hepatic function are needed for diagnosis, in addition to cultures or serologic tests looking for infectious agents

Typical lab presentation

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References

Bernard-Soulier syndrome

Overview
A rare autosomal recessive disorder, Bernard-Soulier syndrome is caused by a defect of glycoprotein Ib/IX/V (GPIb/IX/V), a platelet receptor that binds to vWF, promotes platelet adhesion to fibrin, and regulates platelet size and shape. Bernard-Soulier syndrome is characterized by a decreased platelet count with large, irregularly shaped platelets without neutrophil inclusions. Platelet size/MPV is increased, and megakaryocytes are often normal.

Clinical presentation
- Hemorrhages are severe, often occur prior to adulthood, and decrease with age
- Hemorrhages from the nose and gums
- Purpura and ecchymoses
- Gastrointestinal bleeding
- Bleeding in the skin and mucous membranes, and severe menstrual bleeding
- Increased risk for bleeding during surgical procedures

Important notes
- Flow cytometry should be used to discover the decreased GPIb/IX/V and confirm the Bernard-Soulier syndrome diagnosis
Typical lab presentation1,5,8

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Key

- Increased
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*Platelet aggregation is normal to ADP, epinephrine, and collagen, reduced with thrombin, and absent with ristocetin.*

*Values may not represent those seen when confounding drugs or illnesses are present.

References


Chédiak-Higashi syndrome

Overview

Chédiak-Higashi syndrome is a rare, autosomal recessive, platelet storage pool disorder caused by a mutation of the lysosomal trafficking regulator (LYST) gene resulting in an abnormality of platelet α-granules.1,2 Although the platelet function abnormality in Chédiak-Higashi syndrome is due to α-granule deficiency, some patients may have a reduction or irregularities in α-granules instead of a complete absence.1 The platelet count is normal, with a prolonged bleeding time, decreased α-granules, and abnormal platelet aggregation associated with the bleeding tendency.4

Clinical presentation

- Recurrent bacterial infections, oculocutaneous albinism, and neutropenia accompanied by life-threatening infections1,5
- Mild bleeding episodes are frequently observed and progressive neurologic complications develop during childhood4
- Death often occurs during the first decade of life; patients who survive childhood will experience an accelerated phase that progresses to death5,6
Risk factors
• Epstein-Barr virus can trigger the accelerated phase of the disease

Important notes
• The diagnosis of Chédiak-Higashi syndrome is confirmed by hypopigmentation accompanied by a blood film showing giant granules within polymorphonuclear neutrophils

Typical lab presentation

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Key

↑ Increased
↓ Decreased
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*Platelet aggregation shows a decreased second wave in response to ADP and can be abnormal in response to epinephrine and collagen.

Values may not represent those seen when confounding drugs or illnesses are present.

References

Congenital thrombocytopenia with radioulnar synostosis

Overview
Congenital thrombocytopenia with radioulnar synostosis is an autosomal dominant disorder that occurs when there is a mutation of the HOXA11 gene. Much like thrombocytopenia with absent radii syndrome, it affects the hematopoietic and skeletal systems; however, congenital thrombocytopenia with radioulnar synostosis can also affect other bloodlines. It is characterized by a low platelet count with normal-sized platelets.

Clinical presentation
• Hip dysplasia
• Proximal radioulnar synostosis along with syndactyly and clinodactyly
• Limited pronation
• Severe neonatal thrombocytopenia
  o In some children, symptomatic thrombocytopenia with bleeding
• Pancytopenia

Important notes
• Megakaryocytes in marrow aspirates will be low or absent, whereas plasma thrombopoietin levels will be high, denoting reduced platelet production
Typical lab presentation*

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References

Cyclic thrombocytopenia

Overview
Cyclic thrombocytopenia is an acquired, chronic, persistent disorder that causes fluctuations in platelet count ranging from severe thrombocytopenia to rebound thrombocytosis.1-3 The platelet count fluctuations often occur in cycles of 20-40 days, and the range of fluctuation can be extreme.1,4 The cause of cyclic thrombocytopenia is not well defined, but it is thought to be associated with the cyclic failure of megakaryopoiesis, resulting in decreased megakaryocytes.1,2

Clinical presentation
- Thrombocytopenic bleeding, usually associated with menstruation3,4
- Bruising and petechiae3
- Bleeding from the nose, gums, and mucous membranes5
- Spontaneous improvement or normalization of platelet count3
- Rebound thrombocytosis3

Risk factors2
- Occurs predominantly in women (platelet counts may fluctuate with menstrual cycles)

Important notes
- Careful consideration must be taken to avoid misdiagnosing the disorder with ITP3
- Patients should be closely monitored to observe thrombocytopenic cyclicity in order to make a differential diagnosis3
**Disseminated intravascular coagulation (DIC)**

**Overview**

DIC is a consumptive thrombohemorrhagic disorder that presents with a range of hemorrhagic and thrombotic pathologies.\(^1\) It represents the final common pathway of many conditions that disturb the coagulation system. Tissue factor and various cytokines appear to play a central role in its initiation and continuations.\(^2\)

**Clinical presentation**

- Acute or chronic\(^2\)
- Bleeding and/or thrombosis; hemorrhage can be life threatening\(^2,3\)
- Symptom severity ranges from oozing after venipuncture to more systemic symptoms, such as hemoptysis or hematuria\(^1\)
- Skin manifestations, such as petechiae, purpuras, or ecchymoses\(^1\)
- Often associated with progressive organ dysfunction\(^2\)

**Risk factors\(^5\)**

- Underlying illness that may cause tissue damage, cell death, or production/release of tissue factor
- Common precipitators include trauma, infections, obstetric conditions such as retained dead fetus or abruptio placentae, and cancers

**Important notes**

- DIC is primarily a clinical diagnosis, as laboratory findings can vary with the underlying problem and are static snapshots of a fluid situation\(^2\)
- Usually associated with a decreased platelet count\(^4\)

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**Typical lab presentation**\(^2\)\(^*\)

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**References**

## Typical lab presentation

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## References


## DiGeorge syndrome

### Overview

DiGeorge syndrome, also known as velocardiofacial syndrome (VCFS), is an autosomal dominant disorder caused by a hemizygous deletion of chromosome 22q11.2, where the gene for glycoprotein Ib β (GPIbβ) is located.\(^1\)\(^2\) These patients have a decreased density of membrane GPIb/IX/V due to their heterozygous loss of the GPIbβ gene.\(^2\) The disorder is characterized by reduced platelet count with giant platelets, normal platelet aggregation, and absence of neutrophil inclusions.\(^1\)\(^3\)

### Clinical presentation

- Cardiac abnormality, T-cell deficit, cleft palate, and hypocalcemia\(^4\)
- Facial abnormalities, learning disabilities, and psychiatric disorders\(^5\)
- The mild thrombocytopenia with DiGeorge syndrome does not cause significant bleeding, but bleeding symptoms can be comparable with Bernard-Soulier syndrome if patients inherit another mutated Bernard-Soulier syndrome allele\(^1\)\(^2\)

### Important notes

- Flow cytometry showing defective GPIb/IX/V complex can support diagnosis of DiGeorge syndrome\(^6\)
- DiGeorge syndrome can be differentiated from Bernard-Soulier syndrome by normal platelet aggregation\(^3\)
Typical lab presentation\(^1,3,7^*\)

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References


Dysfibrinogenemia

Overview

Dysfibrinogenemia is caused by a qualitative defect in FI (fibrinogen) that can be either inherited or acquired.\(^1,2\) Inherited fibrinogen disorders can appear as defects in the amount of FI produced (ie, no FI [afibrinogenemia], not enough FI [hypofibrinogenemia]) or defects in the quality of FI (dysfibrinogenemia).\(^1\) Acquired dysfibrinogenemia occurs when an underlying disease (most often liver disease) alters FI, forming an abnormal protein that disrupts the normal interactions with enzymes and cofactors.\(^2\)

Clinical presentation

- More than 50% of cases of dysfibrinogenemia, either inherited or acquired, have no bleeding diathesis\(^3\)
- 20%-25% of cases have mild to moderate bleeding and/or thrombosis\(^3\)
- Bleeding occurs from ineffective polymerization\(^2\)

Risk factors\(^4\)

- About 60%-70% of patients with liver disease have acquired dysfibrinogenemia

Important notes\(^2\)

Can present with a mild to markedly prolonged diluted TT and a normal quantitative value of clottable fibrinogen. RT should be performed to evaluate cause and rule out heparin, hirudin, and antithrombins.
Typical lab presentation

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References

Familial platelet disorder with predisposition to acute myelogenous leukemia (AML)

Overview
Familial platelet disorder is an autosomal dominant disorder characterized by a low platelet count with normal-sized platelets. The disease is caused by a defective allele of the RUNX1 gene. Affected patients have a propensity to develop hematologic malignancies; this suggests a higher tendency to develop a second mutation either in CBFA2 or another gene.

Clinical presentation
- Moderate thrombocytopenia; thrombocytopenic during the first decade of life and have an increased bleeding tendency
- May also have platelet aggregation abnormalities, particularly in response to arachidonic acid
- Myelodysplasia or AML can develop in up to 30% of patients later in life

Important notes
- Bone marrow examination shows decreased megakaryocytes

Typical lab presentation

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*Values may not represent those seen when confounding drugs or illnesses are present.
Factor XIII (FXIII) A-subunit deficiency

Overview
FXIII deficiency is a very rare autosomal recessive bleeding disorder, with severe FXIII deficiency occurring in approximately 1 in 3-5 million people. FXIII circulates as a heterotetramer (A₂B₂); the B-subunit serves as the carrier protein for the catalytic A-subunit. Lack of FXIII activity results in decreased cross-linking of fibrin strands in the blood clot, ultimately leading to reduced resistance to fibrinolysis. Although an initial clot forms and bleeding stops, patients may experience delayed bleeding as the clot breaks down. There are 2 main types: FXIII A-subunit deficiency and FXIII B-subunit deficiency. FXIII A-subunit deficiency is the more common of the 2 types, seen in approximately 95% of cases. A mutation of the gene coding for the A-subunit results in absence of the A-subunit from plasma, platelets, monocytes, and placenta.

Clinical presentation
• Patients tend to develop severe bruising, muscle hematomas, miscarriages, postnatal bleeding, intracranial hemorrhage, joint bleeds, and bleeds following surgery or trauma
• Umbilical bleeding is a typical and frequent finding. Intracranial hemorrhage is reported more frequently than with hemophilia A or B and is the main cause of death or disability
• Patients with FXIII deficiency also exhibit delayed wound healing

Risk factors
• Both sexes and all ethnicities
• Increased incidence in areas of the world with a high incidence of consanguinity

Important notes
• An abnormal urea clot lysis assay ≈1% of normal followed by quantitative tests of FXIII activity and/or antigen levels can help confirm the diagnosis

Typical lab presentation

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*Values may not represent those seen when confounding drugs or illnesses are present.
Factor XIII (FXIII) B-subunit deficiency

Overview

FXIII deficiency is a very rare autosomal recessive bleeding disorder, with severe FXIII deficiency occurring in approximately 1 in 3-5 million people.1,2 FXIII circulates as a heterotetramer (A2B2); the B-subunit serves as the carrier protein for the catalytic A-subunit.2 Lack of FXIII activity results in decreased cross-linking of fibrin strands in the blood clot, ultimately leading to reduced resistance to fibrinolysis. Although an initial clot forms and bleeding stops, patients may experience delayed bleeding as the clot breaks down.2,3 There are 2 main types: FXIII A-subunit deficiency and FXIII B-subunit deficiency. FXIII B-subunit deficiency is infrequently seen, occurring in <5% of cases. A mutation of the gene coding for the B-subunit leads to a shortened half-life of the A-subunit, causing a reduction of A-subunit antigen levels.2,4

Clinical presentation

- Patients tend to develop severe bruising, muscle hematomas, miscarriages, postnatal bleeding, intracranial hemorrhage, joint bleeds, and bleeds following surgery or trauma1
- Umbilical bleeding is a typical and frequent finding. Intracranial hemorrhage is reported more frequently than with hemophilia A or B and is the main cause of death or disability2,5
- Patients with FXIII deficiency also exhibit delayed wound healing1

Risk factors

- Both sexes and all ethnicities6
- Increased incidence in areas of the world with a high incidence of consanguinity1

Important notes7-9

- An abnormal urea clot lysis assay ≈1% of normal followed by quantitative tests of FXIII activity and/or antigen levels can help confirm the diagnosis

Typical lab presentation7,10*

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References

Glanzmann thrombasthenia

Overview
Glanzmann thrombasthenia is a rare, autosomal recessive disorder of platelet aggregation caused by an absence or deficiency of the glycoprotein IIb/IIIa (GPIIb/IIIa) complex (also known as αIIb/β3 integrin), the receptor responsible for binding fibrinogen, vWF, and fibronectin to activated platelets. The loss of platelet aggregation contributes to lifelong bleeding in the mucous membranes; however, platelet count, size, and morphology remain normal. Classification is based on GPIIb/IIIa levels: type 1: 0%-5% of normal; type 2: 6%-20% of normal; variant: 50%-100% of normal.

Clinical presentation
• Minor bruising to severe and potentially fatal hemorrhages, which is consistent within families
• Bleeding from the nose, gums, mucous membranes, continued bleeding from minor cuts, and menorrhagia. Gastrointestinal hemorrhages are not common
• Most patients present symptoms of Glanzmann thrombasthenia during childhood (aged <5 years); bleeding severity lessens with age
• Severe hemorrhagic risk with pregnancy and delivery, surgery, or trauma

Risk factors
• May cluster in ethnic populations where consanguinity is prevalent

Important notes
• Flow cytometry along with additional lab studies should be used to diagnose the disorder
• Platelet transfusions, particularly with human leukocyte antigen–matched (HLA-matched) platelets, have been a standard form of treatment. However, repeated platelet transfusions may be complicated by the development of antiplatelet antibodies or refractoriness. Therefore, localized/topical treatment may be used for minor bleeds, along with antifibrinolytics and/or other hemostatic agents with or without platelets for moderate to severe bleeds.
Typical lab presentation²,⁵-⁷*

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Key:
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*Platelet aggregation is absent except in response to ristocetin.³

*Values may not represent those seen when confounding drugs or illnesses are present.

References

Gray platelet syndrome

Overview
Gray platelet syndrome is a mild to moderate bleeding disorder characterized by a deficiency in platelet α-granules. The disorder is rare and largely autosomal recessive, although dominant inheritance has been reported.¹² The defect prevents proteins such as fibrinogen, thrombospondin, and FV from being stored in platelet α-granules. This results in large, empty platelets that are gray in appearance.²⁴ Platelet counts are low, platelet size/MPV is increased, and there are no neutrophil inclusions.⁵

Clinical presentation
• Thrombocytopenia⁶
• Mild to moderate bleeding in mucous membranes, often due to surgery or trauma³
• Nonprogressive marrow myelofibrosis may develop, likely due to the continual release of growth factors that are not packaged into α-granules from megakaryocytes within the bone marrow²
• Some patients may have splenomegaly²

Important notes
• Gray-appearing platelets on peripheral blood smear and electron microscopy revealing empty α-granules should be used to confirm diagnosis⁴
• Pale platelets, along with circulating “exhausted” platelets, can also be seen in DIC; however, patients with gray platelet syndrome have a mix of normal and pale platelets⁵
Typical lab presentation[^1][^2][^3][^4]

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Key:  
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[^1]: Platelet aggregation is normal in response to arachidonic acid, epinephrine, and ristocetin and low to variable in response to ADP and collagen. Second wave to ADP is variably decreased.[^5]

[^2]: Values may not represent those seen when confounding drugs or illnesses are present.

References

Hemolysis, Elevated Liver enzymes, and Low Platelets (HELLP)

Overview
HELLP syndrome is a disorder occurring in the latter half of pregnancy that is characterized by Hemolysis, Elevated Liver enzymes, and Low Platelets.[^1] A form of non–immune-mediated acquired thrombocytopenia, the disorder is closely related to preeclampsia; however, it may also occur independent of preeclampsia.[^2][^3] HELLP syndrome often appears at the beginning of the third trimester and deteriorates 2 to 4 days before or after delivery.[^4] It may also develop up to a week postpartum and worsen during that time, resulting in pathologic thrombosis.[^1][^5] In patients with HELLP syndrome, the delivery of the child and placenta should occur as soon as possible.[^4]

Clinical presentation
- Hemolysis, elevated liver enzymes, renal dysfunction correlated with the level of hepatic impairment, and a low platelet count[^1]
- Microangiopathic hemolytic anemia and proteinuria[^1]
- Hemorrhage or gastrointestinal bleeding[^6]
- Epigastric pain, nausea, and vomiting[^7]

Risk factors[^4][^6]
- Pregnancy, usually in older, multiparous women and during the third trimester

Important notes
- Liver function studies are helpful in the evaluation of HELLP syndrome[^1]
- Diagnosis is crucial because HELLP syndrome is associated with significant morbidity and fetal mortality[^1]
Typical lab presentation\textsuperscript{3,8,*}

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*Values may not represent those seen when confounding drugs or illnesses are present.

References

Hemolytic-uremic syndrome (HUS)

Overview
A form of non–immune-mediated acquired thrombocytopenia, hemolytic-uremic syndrome is characterized by hemolytic anemia, thrombocytopenia, renal failure, and increased platelet destruction.\textsuperscript{1,2} The disorder resembles HELLP syndrome and TTP, but it is more commonly seen in a younger, pediatric population.\textsuperscript{3,4} In hemolytic-uremic syndrome, inappropriate platelet aggregation predominantly involves the kidneys.\textsuperscript{5} After viral and bacterial infections, hemolytic-uremic syndrome is generally mild; however, for adults, hemolytic-uremic syndrome is associated with a higher mortality rate and a higher incidence of long-term morbidity due to renal damage.\textsuperscript{4}

Clinical presentation
- Hemolytic anemia, thrombocytopenia, and renal failure\textsuperscript{1}
- Increased serum lactate dehydrogenase (LDH)\textsuperscript{5}
- Renal failure out of proportion with elevation of liver enzyme levels\textsuperscript{5}
- Fever and hypertension\textsuperscript{4}
- Presence of hemorrhagic symptoms depends on severity of thrombocytopenia\textsuperscript{1}

Risk factors
- Commonly seen in pediatric patients\textsuperscript{4}
- Often preceded by hemorrhagic enterocolitis or bloody diarrhea due to *Escherichia coli* 0157:H7 or *Shigella*\textsuperscript{1,5,7}

Important notes
- In hemolytic-uremic syndrome, the involvement is predominantly with the kidneys, whereas in TTP, various organs, especially the central nervous system, are involved\textsuperscript{2}
- Thrombocytopenia, erythrocyte fragmentation, and increased serum LDH are usually less extreme in hemolytic-uremic syndrome compared with TTP\textsuperscript{5}
Coagulation Toolkit

**Coagulation disorders**

**Typical lab presentation**

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<td>Platelet aggregation</td>
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Key

▲ Increased ▼ Decreased ▲ = No change

*With uremia, platelet aggregation can be abnormal in response to epinephrine, collagen, and arachidonic acid and lower with the second wave in response to ADP.9*

*Values may not represent those seen when confounding drugs or illnesses are present.*

**References**


**Heparin-induced thrombocytopenia (HIT) type 1**

**Overview**

After exposure to unfractionated heparin or, to a lesser extent, LMWH, some patients will develop an acquired disorder called heparin-induced thrombocytopenia. There are 2 types of heparin-induced thrombocytopenia. Type 1 is non–immune-mediated and causes a mild decrease in platelet count as platelets are passively coated and eliminated after exposure to heparin. This type is not associated with a risk of thrombosis and resolves spontaneously after heparin discontinuation.

**Clinical presentation**

- Slight drop in platelet count (>100,000 per mcL)
- Platelet drop occurs 2-5 days after heparin initiation
- Bleeding is not usually associated with heparin-induced thrombocytopenia

**Risk factors**

- Women are more likely than men to develop heparin-induced thrombocytopenia

**Important notes**

- All heparin use should be immediately discontinued when the disorder is discovered
- Anticoagulants such as direct thrombin inhibitors should be used after heparin discontinuation to lessen the risk of thrombosis development
Heparin-induced thrombocytopenia (HIT) type 2

Overview
After exposure to unfractionated heparin or, to a lesser extent, LMWH, some patients will develop an acquired disorder called heparin-induced thrombocytopenia. There are 2 types of heparin-induced thrombocytopenia. Type 2 is an immune-mediated disorder that causes a more pronounced decrease in platelet count, compared with heparin-induced thrombocytopenia type 1, and a risk for significant thrombosis. It is an acquired disorder whereby immunoglobulin G (IgG) antibodies inhibit the complexes of heparin and platelet factor 4. Often, the platelet count will return to normal within a week after heparin discontinuation, but total recovery could take up to a month or longer. Heparin-induced thrombocytopenia type 2 with thrombosis is sometimes known as HITT.

Clinical presentation
- Moderate to severe drop in platelet count (<100,000 per mcL; range of 20,000-150,000 per mcL) or a <30% decrease from baseline
- Platelet drop occurs ≥5 days after heparin initiation but can occur sooner if heparin has been previously used
- Venous or arterial thrombosis (eg, myocardial infarction, stroke, pulmonary embolism, deep venous thrombosis)
- Limb ischemia or venous limb gangrene
- Bleeding is not usually associated with heparin-induced thrombocytopenia
- High morbidity (up to 11% of patients lose a limb) and mortality (up to 17.6% of patients die)

Risk factors
- Women are more likely than men to develop heparin-induced thrombocytopenia (1.5-fold to 3-fold increase)
- IgG antibodies may form after cardiac or orthopedic surgery

Important notes
- All heparin use should be immediately discontinued when the disorder is discovered
- Anticoagulants such as direct thrombin inhibitors should be used after heparin discontinuation to lessen the risk of thrombosis development

References
### Typical lab presentation\(^8,9\)*

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*Values may not represent those seen when confounding drugs or illnesses are present.

### Hermansky-Pudlak syndrome

**Overview**

Hermansky-Pudlak syndrome is a rare, autosomal recessive, storage pool disorder classified by oculocutaneous albinism and a platelet \(\alpha\)-granules defect.\(^1,3\) The syndrome is characterized as a mild bleeding disorder with a prolonged bleeding time and a marked absence of platelet \(\alpha\)-granules.\(^2\) The disorder has 7 known subtypes that are classified by the symptoms with which patients present; subtype 1, identified by a mutation on the Hermansky-Pudlak syndrome-1 gene, is the most severe form.\(^4\)

**Clinical presentation**\(^5\)

- Patients present with mild bleeding and hypopigmentation of the hair, skin, and eyes
- Spontaneous bruising, nosebleeds, menstrual bleeding, and prolonged bleeding after trauma or surgery
- Other symptoms are specific to subtypes of the disorder:
  - Pulmonary fibrosis and granulomatous colitis (subtypes 1 and 4)
  - Neutropenia (subtype 2)
  - In some, ceroid-lipofuscin deposits are observed in lysosomes of renal tubular cells, alveolar macrophages, and cells of the gastrointestinal tract, bone marrow, liver, spleen, lymph nodes, and heart (subtype 1)

**Risk factors**

- People with Puerto Rican backgrounds\(^5\)
  - Subtype 1 is the most common genetic disorder in Puerto Rico, affecting 1 in 1800 (1 in 22 individuals are carriers); subtype 3 is seen only in individuals of Puerto Rican ancestry
- Can also be seen in populations from southwestern Switzerland, southern Holland, and Japan, as well as some UK residents of Turkish backgrounds\(^1\)

**Important notes**\(^6\)

- Electron microscopy to identify the absence of \(\alpha\)-granules can be used in the diagnosis

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Typical lab presentation

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| Platelet aggregation| or ↓*

Key
- Increased
- Decreased
- No change

*Platelet aggregation is normal in response to arachidonic acid and ristocetin, may be decreased in response to epinephrine and collagen, and show an abnormal second wave in response to ADP.

Values may not represent those seen when confounding drugs or illnesses are present.

References

Idiopathic thrombocytopenic purpura (ITP)

Overview
ITP, or primary immune thrombocytopenia, is an immune-mediated acquired thrombocytopenia in which antibodies to surface glycoprotein cause increased destruction of platelets. While thrombocytopenia is present, the white blood cell count and hemoglobin levels remain normal with normal to increased megakaryocytes in the bone marrow. Although it is a common cause of severe isolated thrombocytopenia, there is no specific test capable of confirming a diagnosis; thus, ITP is diagnosed by the exclusion of other disorders.

Clinical presentation
- Acute bleeding symptoms and marked thrombocytopenia
- Bleeding of the mucous membranes, menstrual bleeding, nosebleeds, easy bruising, or petechiae
- ITP presents differently in children and adults:
  - In children, ITP symptoms, including low platelet counts (<20,000 per mcL), develop abruptly within 1 to 3 weeks following an acute viral illness. It is self-limiting and capable of spontaneous remission even with therapy
  - In adults, ITP commonly presents as a chronic disease that does not usually remit spontaneously. Patients are usually between age 20 and 50 years, are predominantly female, and have low platelet counts (<30,000 per mcL)

Important notes
- Careful consideration must be taken to avoid misdiagnosing the disorder with cyclic thrombocytopenia
- Peripheral blood smear will show a mixture of normal and large platelets
- Bone marrow will show adequate or increased number of megakaryocytes
Typical lab presentation

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Key: ↑ Increased, ↓ Decreased, = No change

*Values may not represent those seen when confounding drugs or illnesses are present.

References

Lupus anticoagulant

Overview
The acquired antibody that characterizes the lupus anticoagulant is usually directed against a protein-phospholipid complex and is an in vitro anticoagulant only. Patients with a lupus anticoagulant are at risk for arterial and venous thromboembolism, as well as recurrent spontaneous miscarriages; however, patients may also be asymptomatic.

Clinical presentation
- Bleeding is not usually associated with a lupus anticoagulant. However, in rare cases when it is associated with hypoprothrombinemia and a prolonged PT, bleeding can occur.
- Risk exists for arterial and venous thromboembolism, as well as recurrent spontaneous miscarriages.
- Effect on PT and aPTT depends on the sensitivity of PT and aPTT reagents to the lupus anticoagulant. Typically results in a mild prolongation of the aPTT and not the PT; however, in some cases, the PT can be affected.
Typical lab presentation^{2,5,7*}

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Key: \(\uparrow\) Increased, \(\downarrow\) Decreased, \(=\) No change

*Values may not represent those seen when confounding drugs or illnesses are present.

References


Monoclonal gammopathy

Overview

Monoclonal gammopathy, also known as paraproteinemia, refers to the secretion of a monoclonal immunoglobulin (Ig) or Ig fragment by plasma cells. Entities associated with monoclonal gammopathy include multiple myeloma, Waldenström macroglobulinemia, and monoclonal gammopathy of undetermined significance.\(^1\) Increased Ig levels in these disorders may interfere with the function of coagulation factors.\(^2\)

Clinical presentation\(^2\)

- Changes in coagulation factors with multiple myeloma are not usually clinically significant, but they can be associated with bruising and hemorrhages from the nose and gums.
- In Waldenström macroglobulinemia, extensive bruising known as cryoglobulinemic purpura can be seen, along with hemorrhages from the nose and gums. More severe bleeding can also occur.

Important notes

- For all paraproteinemias, the PT is more affected than the aPTT\(^3\)
- Monoclonal gammopathies have also been associated with the development of inhibitors to various coagulation factors\(^4\)
Montréal platelet syndrome

Overview

Montréal platelet syndrome is an autosomal dominant disorder associated with spontaneous platelet aggregation, moderate to severe thrombocytopenia, and giant platelets. The disorder is characterized by increased MPV and normal platelet membrane glycoproteins. Since the identification of the gene defect in Montréal platelet syndrome on exon 28 on the vWF gene, it has been recognized that the disorder is a variant of vWD type 2B.

Clinical presentation

- Moderate to severe thrombocytopenia with giant platelets
- Spontaneous platelet aggregation in whole blood
- Normal clot retraction
- Can be associated with mucocutaneous bleeding

Important notes

- Peripheral blood smears will show large platelets with no neutrophil inclusions
- Since patients with Montréal platelet syndrome have vWD type 2B, plasma-derived factor concentrates containing vWF activity are recommended for bleeding episodes

References

**Typical lab presentation**

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Key: ↑ Increased, ↓ Decreased, = No change

*Platelet aggregation is normal in response to ADP, collagen, arachidonic acid, and ristocetin but decreased in response to thrombin.

*Values may not represent those seen when confounding drugs or illnesses are present.

**References**


**Myeloproliferative disorders (MPD)**

**Overview**

Myeloproliferative disorders should be considered in patients who have an increased platelet count along with variable platelet sizes and morphologies. Examples of myeloproliferative disorders include essential thrombocytopenia, polycythemia vera, myelofibrosis, and chronic myelogenous leukemia. It is important to distinguish myeloproliferative disorders from reactive thrombocytopenia in the differential diagnosis because both are characterized by an increased platelet count.

**Clinical presentation**

- Thrombocytosis
- May be asymptomatic or have a range of symptoms, including bleeding or thrombosis
- Bleeding complications are more often observed in patients with a platelet count greater than 1,000,000 per mcL
- Bone marrow positive for myeloproliferative disorder

**Important notes**

- A complete blood count, peripheral blood smear, bone marrow evaluation, and platelet aggregation studies should be used to aid in the diagnosis
Typical lab presentation\textsuperscript{1}\textastisk

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**Key**
- ↑ Increased
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- = No change

\textsuperscript{a}Platelet aggregation abnormalities have been described with myeloproliferative disorders, but they are neither specific nor diagnostic.\textsuperscript{1}

\textsuperscript{1}Values may not represent those seen when confounding drugs or illnesses are present.

Reference

**MYH9-related disorders**

**Overview**\textsuperscript{1}

MYH9-related disorders are autosomal dominant conditions characterized by a decrease in platelet number with an increase in platelet size, along with Döhle-like inclusions in neutrophils. MYH9-related disorders include May-Hegglin anomaly, along with Sebastian, Fechtner, and Epstein syndromes, which were previously thought to be separate diseases. The disorders result from mutations in the MYH9 gene encoding the nonmuscle myosin heavy chain IIA (MHC-IIA) protein.

**Clinical presentation**\textsuperscript{1}

- Variable bleeding tendency
  - Bleeding is usually moderate but may be more severe than expected from the degree of thrombocytopenia
  - Menorrhagia and easy bruising are the most frequent manifestations
  - Life-threatening bleeding, including intracranial hemorrhage, has been reported
- Variably associated with additional defects, including sensorineural deafness, cataracts, and nephritis

**Important notes**

- It is important not to confuse this condition with ITP, which also may present with thrombocytopenia and large platelets\textsuperscript{1}
- Stained blood smear readings via electron microscopy are indispensable for diagnosis\textsuperscript{2}
- Because de novo mutations can occur, MYH9-related macrothrombocytopenia should not be ruled out if there is an absence of an inherited family history of macrothrombocytopenia\textsuperscript{1}
**Neonatal alloimmune thrombocytopenia (NAIT)**

**Overview**

A form of acquired thrombocytopenia, neonatal alloimmune thrombocytopenia results from maternal immunoglobulin G antibodies forming against specific paternal platelet antigens and crossing the placenta.\(^1,3\)

This human platelet antigen incompatibility between mother and fetus causes increased platelet destruction in the newborn.\(^2,4\) It is the most common cause of severe thrombocytopenia in newborns, occurring in 1 of every 1000 to 5000 live births.\(^1\) Common characteristics include severe thrombocytopenia, normal megakaryocytes, and normal platelet size and morphology.\(^1,5,6\) The disorder typically resolves when the maternal antibodies degrade, and platelet numbers should be normal when the newborn reaches 2 weeks of age.\(^5,7\)

**Clinical presentation**

- Associated with bleeding at or a few hours after birth\(^3\)
- Bleeding in the skin and mucous membranes\(^8\)
- Intracranial hemorrhage, resulting in death or neurological sequelae in 10%-30% of newborns\(^4\)
- Can be asymptomatic\(^7\)

**Risk factors\(^7\)**

- Severe thrombocytopenia due to neonatal alloimmune thrombocytopenia in a newborn from a previous pregnancy

**Important notes\(^7\)**

- Diagnosis should be considered if sepsis, systemic disease, skeletal anomalies, and maternal ITP have been excluded

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**Typical lab presentation\(^3,4,\)**

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**Key**  
- ↑ Increased  
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\(^4\)Platelet function is normal in May-Hegglin anomaly but can be abnormal in response to epinephrine and collagen for Epstein syndrome.\(^1\)

\(^4\)Values may not represent those seen when confounding drugs or illnesses are present.

**References**

### Coagulation disorders

#### Typical lab presentation

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**Key**

- Increased
- Decreased
- No change

*Values may not represent those seen when confounding drugs or illnesses are present.

#### References


#### Plasminogen activator inhibitor-1 (PAI-1) deficiency

**Overview**

PAI-1 deficiency is an extremely rare autosomal recessive disorder. PAI is a protein found in endothelial cells that neutralizes the activity of plasmin, plasminogen, and tissue plasminogen activator (tPA). A mutation of the PAI gene, as in PAI-1 deficiency, can lead to hyperfibrinolysis and subsequent bleeding. PAI-1 deficiency can be quantitative (absence of both PAI-1 activity and PAI-1 antigen with low tPA antigen) or qualitative (absence of PAI-1 activity, low or normal PAI-1 antigen, and low tPA antigen).

**Clinical presentation**

- Mild to moderate delayed bleeding, usually associated with injury, trauma, or surgery
- Intracranial hemorrhage, joint bleeding, and severe menstrual bleeding can occur
- Easy bruising, nosebleeds, and muscle bleeds have also been reported

**Important notes**

- A falsely low PAI-1 activity can occur when tPA levels are elevated, which can occur with a prolonged tourniquet time during blood draw. Evaluation of PAI-1 deficiency should therefore include assessment of tPA antigen or tPA–PAI-1 complex as a control.
- PAI-1 levels show a circadian variation, with the highest levels occurring in the morning.
- PAI-1 levels increase during pregnancy and decrease rapidly after delivery.

**Typical lab presentation**

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**Key**

- Increased
- Decreased
- No change

*Values may not represent those seen when confounding drugs or illnesses are present.
Platelet signal transduction disorders

Overview
Platelet signal transduction disorders are a poorly defined group of disorders that include defects of the platelet cyclooxygenase and phospholipase C pathways, as well as defective thromboxane A2 synthesis. Platelets generally exhibit decreased primary aggregation accompanied by absent secondary aggregation, and granule release is decreased even though α-granules and δ-granules are not deficient. Platelet count and morphology are usually normal.

Clinical presentation
- Mild bleeding

Typical lab presentation

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Key

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*Platelet aggregation is normal in response to ristocetin, have a normal first wave but reduced second wave in response to ADP, and can be reduced in response to arachidonic acid, epinephrine, and collagen.

*Values may not represent those seen when confounding drugs or illnesses are present.

References

Platelet-type von Willebrand disease (vWD)

Overview
- Platelet-type vWD, or pseudo-vWD, is a rare, autosomal dominant disorder. A gain-of-function defect in the vWF platelet receptor glycoprotein Ib causes increased binding of platelets to the vWF protein, leading to loss of vWF multimers. Platelet-type vWD shares similar clinical and laboratory features with vWD type 2B, the fundamental difference being that, in platelet-type vWD, the defect is in the platelet rather than in the vWF protein. Both disorders show abnormally enhanced low-dose, ristocetin-induced platelet aggregation (RIPA; ≤0.5 mg/dL). With platelet-type vWD, abnormal aggregation to low-dose RIPA persists if subject platelets are mixed with normal plasma but corrects when subject plasma is mixed with normal platelets. With vWD type 2B, abnormal aggregation to low-dose RIPA persists if subject plasma is mixed with normal platelets but corrects when subject platelets are mixed with normal plasma (or another source of vWF)
Clinical presentation
- Mild to moderate bleeding
- Bleeding in the mucous membranes
- Severe bleeding from the nose and gums
- Life-threatening bleeds are possible after surgery, during pregnancy, and in infection situations
- Platelet counts may be normal or mildly low

Important notes
- Distinguishing platelet-type vWD from vWD type 2B is important, because therapy used in vWD type 2B, such as FVIII/vWF preparations or desmopressin, will exacerbate platelet-type vWD
- In addition to low-dose RIPA-based plasma/platelet mixing studies, vWD type 2B and platelet-type vWD can also be distinguished by abnormalities noted in the DNA sequencing of exon 28 of the vWF gene in vWD type 2B
- Additional considerations for vWF testing must include:
  - vWF:Ag is an acute-phase reactant that, along with FVIII, may be elevated in clinical settings such as trauma, surgery, and clotting
  - Normal vWF:Ag levels vary by blood type

Typical lab presentation

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Key
- ↑ Increased
- ↓ Decreased
- = No change

*Values may not represent those seen when confounding drugs or illnesses are present.

References
Posttransfusion purpura

Overview
Posttransfusion purpura is an immune-mediated acquired thrombocytopenia that causes increased destruction of platelets. The disorder is likely the result of an alloantibody directed against platelet antigens, often P1A1. When a transfusion of P1A1-positive blood is transfused into a patient who is P1A1-negative, the destruction of both donor and recipient platelets occurs approximately 1 week after transfusion. However, posttransfusion purpura is self-limiting and the thrombocytopenia spontaneously resolves within a few weeks. Patients who present with posttransfusion purpura show a decreased platelet count, normal platelet size and morphology, and adequate to increased megakaryocytes.

Clinical presentation
- Severe thrombocytopenia (<10,000 per mCL)
- Purpura, bleeding into the skin, nosebleeds, gastrointestinal bleeding, postoperative bleeding, and hematuria
- Fatal intracranial hemorrhage (10% of cases)

Risk factors
- Often occurs in multiparous women aged 30-80 years with no history of transfusion
- People without P1A1 antigen may develop posttransfusion purpura

Important notes
- If transfusions are needed in patients at risk of posttransfusion purpura recurrence, P1A1-negative blood is recommended
- Patients who present with posttransfusion purpura show adequate to increased megakaryocytes on bone marrow examination

Typical lab presentation

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Key: ↑ Increased, ↓ Decreased, = No change

*Values may not represent those seen when confounding drugs or illnesses are present.

References
Quebéc platelet disorder

Overview
Quebéc platelet disorder is an extremely rare platelet storage pool disorder that is associated with a low platelet count. An autosomal dominant disorder, Quebéc platelet disorder is characterized by a defect in α-granule multimerin, causing decreased platelet FV, along with other proteins (eg, fibrinogen, vWF), in the granule. Platelets exhibit abnormal urokinase secretion within the hemostatic plug, leading to clot dissolution and delayed onset of posttrauma bleeding.

Clinical presentation
• Thrombocytopenia
• Delayed bleeding that is unresponsive to platelet transfusions
• Increased platelet size with no neutrophil inclusions

Important notes
• The presence of urokinase in patient platelet lysates detected using ELISA can help the differential diagnosis
• Quebéc platelet disorder can also be distinguished from other thrombocytopenic disorders because it displays a very abnormal platelet aggregation in response to epinephrine

Typical lab presentation

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Key: ↑ Increased, ↓ Decreased, = No change

*Platelet aggregation is very abnormal in response to epinephrine and can also be abnormal in response to collagen and ADP.

*Values may not represent those seen when confounding drugs or illnesses are present.

Reactive thrombocytosis

Overview
Reactive thrombocytosis, also known as secondary thrombocytosis, describes an increase in circulating platelets in association with an underlying condition. The increase in platelets is caused by stimulated megakaryopoiesis as a result of the growth factor interleukin-6 directly and indirectly by elevating serum thrombopoietin levels. The disorder is most common during childhood, often occurring in infants aged ≤24 months, but it can also occur in adults, usually after major surgery or trauma or resulting from chronic inflammatory disease. Reactive thrombocytosis usually resolves when the underlying disorder is treated.
**Clinical presentation**

- Increased platelet count associated with an underlying disease\(^2,4\)
- Fever\(^3\)
- Although rare, thromboembolic or hemorrhagic complications in children only after splenectomy or disease with thrombotic risk factors\(^3\)

**Risk factors**

- Major surgery, trauma, or thrombocytopenic recovery\(^3\)
- Acute blood loss, iron deficiency, or hemolytic anemia\(^4\)
- Chronic inflammation, tissue damage, and malignancy\(^5\)
- Acute and chronic bacterial or viral infections, anemia, or neoplasia during childhood\(^3\)

**Important notes**\(^5\)

- Antiplatelet therapy is not recommended since reactive thrombocytosis often resolves on its own

**Typical lab presentation**\(^6\)*

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*Values may not represent those seen when confounding drugs or illnesses are present.

**References**


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**Scott syndrome**

**Overview**

Scott syndrome is a disorder of platelet dysfunction that occurs despite normal platelet secretion and aggregation.\(^1,2\) This rare autosomal recessive disorder is characterized by an abnormality in platelet procoagulant activity.\(^2\) Due to a mutation in ANO6 encoding TMEM16F, platelets cannot translocate phosphatidylserine, leading to the failure of the FVa/Xa complex and causing decreased thrombin and fibrin generation.\(^2,3\)

**Clinical presentation**

- Bleeding with invasive procedures (e.g., dental extractions, surgeries, trauma)\(^2\)
- Bleeding in the mucous membranes\(^4\)
- Severe postpartum bleeding is possible\(^2\)

**Important notes**\(^1,4,5\)

- Flow cytometry is used to confirm the gene mutation by noting the absence of annexin V (a protein with a high affinity for phosphatidylserine) to active platelets
Typical lab presentation

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References

Thrombocytopenia with absent radii (TAR) syndrome

Overview
Unlike the majority of thrombocytopenias, thrombocytopenia with absent radii syndrome is an autosomal recessive disorder.¹ Neonates with this rare congenital disorder present with severe thrombocytopenia and shortened or absent forearms due to bilateral radial aplasia.¹,² Although thrombocytopenia with absent radii syndrome affects the hematopoietic and skeletal systems, hands and fingers are unaffected.²,³ Thrombocytopenia with absent radii syndrome is marked by a low platelet count of normal-sized platelets.⁴

Clinical presentation
- Severe neonatal thrombocytopenia with purpura²
  - Platelet numbers increase through adolescence and can be near normal by adulthood
- Intracranial hemorrhage in neonates²
- Bilateral radial aplasia²
- Renal and cardiac defects³
- Skeletal abnormalities in the lower limbs can occur³
- Bone marrow shows increased thrombopoietin levels and reduced megakaryocytes⁵

Important notes²,³
- Differential diagnosis of thrombocytopenia with absent radii syndrome should include Fanconi anemia and DiGeorge syndrome
Typical lab presentation\(^3,5\)\(^*\)

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References

**Thromboxane A\(_2\) receptor defect**

**Overview**
Thromboxane A\(_2\) receptor defect is an autosomal dominant disorder that causes problems in the interaction between platelets and agonists.\(^1,2\) Normally, thromboxane A\(_2\) is a product of platelet activation and a powerful platelet agonist that causes platelet aggregation. Thromboxane A\(_2\) is then synthesized by activated platelets from arachidonic acid through the cyclooxygenase pathway and diffuses across the membrane to activate other platelets.\(^3\) With a defect in the thromboxane A\(_2\) receptor, although platelet count and size are normal, there is impaired platelet aggregation in response to arachidonic acid.\(^1,4\)

**Clinical presentation**
- Mild bleeding\(^1\)
- Normal platelet count and size\(^3\)

Typical lab presentation\(^3,5\)\(^*\)

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\(^*\)Platelet aggregation is abnormal in response to arachidonic acid and variable in response to other agonists. The response to ristocetin is preserved.\(^6\)

\(^*\)Values may not represent those seen when confounding drugs or illnesses are present.
Thrombotic thrombocytopenic purpura (TTP)

Overview
A form of non–immune-mediated acquired thrombocytopenia, TTP is a disorder characterized by an increased destruction of platelets. TTP is caused by an abnormality of ADAMTS-13, a plasma metalloproteinase that cleaves vWF, and can be due to congenital deficiency or an acquired defect. In TTP, inappropriate platelet aggregation is systemic, extensive, and generally involves the central nervous system. Patients who present with TTP show a decreased platelet count, normal platelet size and morphology, and adequate to increased megakaryocytes.

Clinical presentation
- Severe thrombocytopenia and hemolytic anemia, plus neurologic signs and symptoms, represent the classic clinical presentation of TTP.
- Increased serum lactate dehydrogenase (LDH)
- Fever and/or renal dysfunction in a minority of patients
- Malaise, weakness, fatigue, and abdominal pain
- Presence of hemorrhagic symptoms depends on severity of thrombocytopenia
- Peripheral blood smear will show red cell schistocytes, reticulocytosis, and nucleated red blood cells

Risk factors
- Women are more affected than men
- Peak incidence occurs at age 20-40 years
- Pregnancy
- Usage of certain medications (eg, ticlopidine)
- Patients with viral infections or autoimmune disorders

Important notes
- Diagnosis requires only the presence of microangiopathic hemolytic anemia and thrombocytopenia, absent another apparent cause
- In TTP, the microvascular thromboses and resulting ischemia involve various organs, mostly in the central nervous system; in hemolytic-uremic syndrome, the involvement is predominantly with the kidneys
- Thrombocytopenia, erythrocyte fragmentation, and increased serum LDH are usually more severe in TTP compared with hemolytic-uremic syndrome

Typical lab presentation

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*Values may not represent those seen when confounding drugs or illnesses are present.
References

Von Willebrand disease (vWD) type 1

Overview
vWD is marked by decreased quantity or quality of vWF, which plays a critical role in stabilizing FVIII.1-2 vWD is the most common of the inherited bleeding disorders. There are 3 types of vWD. Type 1 is dominantly inherited and associated with mild to moderate bleeding.1

Clinical presentation1
• Bleeding in types 1 and 2 is usually mild to moderate, although trauma or surgery may result in severe bleeding
• Bleeding manifestations tend to ooze or bruise; the formation of hematomas is rare

Important notes
• Considerations for vWF testing must include:
  o vWF:Ag is an acute-phase reactant that, along with FVIII, may be elevated in clinical settings such as trauma, surgery, and clotting4
  o Normal vWF:Ag levels vary by blood type5

Typical lab presentation1,4,6

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*Values may not represent those seen when confounding drugs or illnesses are present.
Von Willebrand disease (vWD) type 2A

Overview

vWD is marked by decreased quantity or quality of vWF, which plays a critical role in stabilizing FVIII. vWD is the most common of the inherited bleeding disorders. There are 3 major types of vWD. Type 2 is characterized by qualitative deficiencies in vWF function and occurs in 4 subtypes: 2A, 2B, 2N, and 2M. vWD type 2A is marked by the absence of intermediate- and high-molecular-weight vWF multimers. Two etiologies for the loss of multimers have been described: either defective assembly with decreased secretion, or normal secretion with increased proteolysis of multimers.

Clinical presentation

- Bleeding in vWD type 2A is usually mild to moderate, although trauma or surgery may result in severe bleeding
- Bleeding manifestations tend to ooze or bruise; the formation of hematomas is rare

Important notes

- Considerations for vWF testing must include:
  - vWF:Ag is an acute-phase reactant that, along with FVIII, may be elevated in clinical settings such as trauma, surgery, and clotting.
  - Normal vWF:Ag levels vary by blood type

Typical lab presentation

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*Platelet aggregation is normal in response to all agonists except ristocetin, which is decreased in vWD type 2A.
*Values may not represent those seen when confounding drugs or illnesses are present.
Von Willebrand disease (vWD) type 2B

Overview
vWD is marked by decreased quantity or quality of vWF, which plays a critical role in stabilizing FVIII. vWD is the most common of the inherited bleeding disorders. There are 3 major types of vWD. Type 2 is characterized by qualitative deficiencies in vWF function and occurs in 4 subtypes: 2A, 2B, 2N, and 2M. In vWD type 2B, a defect in vWF causes increased binding of the vWF protein to glycoprotein Ib, the platelet vWF receptor, leading to loss of high-molecular-weight vWF multimers. vWD type 2B can be misdiagnosed for platelet-type vWD because they share similar clinical and laboratory features. The fundamental difference between the 2 disorders is that for vWD type 2B, the defect is in vWF rather than in the platelet. Both disorders show abnormally enhanced low-dose, ristocetin-induced, platelet aggregation (RIPA; ≤0.5 mg/dL).

Clinical presentation
• Bleeding in vWD type 2B is usually mild to moderate, although trauma or surgery may result in severe bleeding
• Bleeding manifestations tend to ooze or bruise; the formation of hematomas is rare
• Platelet counts may be normal or decreased
• Absence of high-molecular-weight vWF multimers, but platelet-associated vWF multimers are normal

Important notes
• Distinguishing vWD type 2B from platelet-type vWD is important, because therapy used in vWD type 2B, such as FVIII/vWF preparations or desmopressin, will exacerbate platelet-type vWD
• In addition to low-dose RIPA-based plasma/platelet mixing studies, vWD type 2B and platelet-type vWD can also be distinguished by abnormalities noted in the DNA sequencing of exon 28 of the vWF gene in vWD type 2B
• Additional considerations for vWF testing must include:
  o vWF:Ag is an acute-phase reactant that, along with FVIII, may be elevated in clinical settings such as trauma, surgery, and clotting
  o Normal vWF:Ag levels vary by blood type
**Typical lab presentation**

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**Key**
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*Platelet aggregation is normal in response to ADP, arachidonic acid, epinephrine, and collagen but increased in response to ristocetin.*

*Values may not represent those seen when confounding drugs or illnesses are present.

**References**


**Von Willebrand disease (vWD) type 3**

**Overview**

vWD is marked by decreased quantity or quality of vWF, which plays a critical role in stabilizing FVIII. vWD is the most common of the inherited bleeding disorders. There are 3 types of vWD. Type 3 is autosomal recessive, with patients having almost no vWF.

**Clinical presentation**

- Patients with type 3 present with mucocutaneous, soft-tissue, and joint bleeding
- Bleeding manifestations tend to ooze or bruise; the formation of hematomas is rare
Important notes

• Considerations for vWF testing must include:
  o vWF:Ag is an acute-phase reactant that, along with FVIII, may be elevated in clinical settings such as trauma, surgery, and clotting.
  o Normal vWF:Ag levels vary by blood type.

Typical lab presentation

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References


Wiskott-Aldrich syndrome protein (WASP) defect

Overview

Wiskott-Aldrich syndrome protein defect is the name given to 2 inherited disorders caused by a defect in the Wiskott-Aldrich syndrome protein gene: x-linked thrombocytopenia and Wiskott-Aldrich syndrome. Both disorders display decreased or absent Wiskott-Aldrich syndrome protein production. Platelet count is decreased, and platelets are small with reduced α-granules and δ-granules indicative of a storage pool defect. With x-linked thrombocytopenia, platelet decreases are moderate; the decreases are more severe in Wiskott-Aldrich syndrome.

Clinical presentation

• Petechiae, bruising, and bloody diarrhea possible at birth
• Acute hemorrhage may occur
• Often seen with mild to severe eczema and immunodeficiency
• Associated with autoimmune disorders such as hemolytic anemia

Important notes

• Increased risk of lymphoma, especially in adults
Typical lab presentation\textsuperscript{1,2,4,5*}

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*Platelet aggregation is usually abnormal for Wiskott-Aldrich syndrome, especially in response to ADP, epinephrine, and collagen.\textsuperscript{1}

*Values may not represent those seen when confounding drugs or illnesses are present.

References

X-linked amegakaryocytic thrombocytopenia (XLAT)

Overview
X-linked amegakaryocytic thrombocytopenia is an autosomal recessive disorder characterized by a decreased platelet count with normal-sized platelets.\textsuperscript{1,2} What distinguishes it from other congenital thrombocytopenia disorders is the near absence of megakaryocytes on bone marrow examination. A defect in the C-Mpl gene leads to dysfunction of the thrombopoietin receptor, decreasing megakaryocyte proliferation.\textsuperscript{3}

Clinical presentation
• Easy bruising and bleeding\textsuperscript{4}
• Severe thrombocytopenia with bleeding symptoms, typically in the neonatal period\textsuperscript{5}
• Severe thrombocytopenia presenting at birth can develop into pancytopenia and severe aplastic anemia\textsuperscript{6}
• Orthopedic or neurological abnormalities in 10%-30% of affected patients\textsuperscript{3}

Important notes\textsuperscript{1}
• Flow cytometry can detect the defective C-Mpl on the platelet surface
### Typical lab presentation

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### References