Coagulation Toolkit

Drugs and conditions that can affect coagulation

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Acidosis interferes with the coagulation of plasma by reducing the activity of various vitamin K-dependent factors. This markedly reduces the activity of coagulation factor complexes. Acidosis occurs when low perfusion leads to insufficient oxygen delivery to tissues.1

Reference

Bleeding history

A family history of a bleeding disorder and/or bleeding with prior surgery or trauma are suggestive of an underlying congenital bleeding disorder.1

Reference

Cardiopulmonary bypass

Most patients undergoing cardiopulmonary bypass exhibit abnormal platelet function and thrombocytopenia. Postoperatively, bleeding time may be prolonged and platelet aggregation may be abnormal, with decreased aggregation in response to ristocetin and decreased α-granule or δ-granule concentrations.1

Reference

Contraceptives

Estrogen-containing contraceptives affect clotting by increasing plasma fibrinogen, soluble fibrin, and coagulation factor activity, especially FII, FVII, FVIII, FIX, and FX.1

Reference

Dilution/consumption

In the setting of massive hemorrhage, dilution of the remaining blood by administration of IV fluids and plasma-poor red blood cells can reduce clotting factors and platelets. Consumption of coagulation factors and platelets in response to tissue factor activation can also occur. These disturbances can manifest clinically with abnormal coagulation testing and as a diffuse bleeding diathesis.1

Reference
Coagulation Toolkit

Key concomitant factors that can affect coagulation

Dysproteinemia

Dysproteinemias such as immunoglobulin A (IgA) myeloma, Waldenström macroglobulinemia, IgG myeloma, and benign monoclonal gammopathy (less common) can cause platelet dysfunction. All aspects of platelet function, including aggregation, secretion, procoagulant activity, and clot retraction, can be inhibited by myeloma proteins. The platelet function abnormalities associated with paraproteinemia are concentration dependent.1

Reference

Giant cavernous hemangioma

Giant cavernous hemangioma can be associated with thrombocytopenia due to increased platelet destruction.1 It was first described as a cause of bleeding by Kasabach and Merritt.2 Kasabach-Merritt syndrome typically occurs in a neonate or infant and is characterized by hemangioma along with widespread ecchymoses, thrombocytopenia, and a localized consumptive coagulopathy.3

References

Hypersplenism

Hypersplenism is a syndrome in which splenomegaly is accompanied by 1 or more cytopenias: thrombocytopenia, leukopenia, or anemia. Thrombocytopenia is primarily caused by increased splenic sequestration of platelets. Even though hypersplenism is characterized by splenomegaly, many patients with splenomegaly do not have hypersplenism.1

Reference

Hypothermia

Hypothermia slows the rates of all enzymatic coagulation reactions and impairs platelet function. It can occur both with exposure to the elements and from resuscitation with cold IV fluids or red blood cells.1 At core temperatures of 32°C-34°C, platelet activities, though present, are reduced. At a core temperature of 30°C, an acquired Bernard-Soulier syndrome–like platelet dysfunction may occur. This is associated with a loss of platelet secretion, aggregation, and active surfaces for the assembly of coagulation factor complexes.1

Reference

Infection

Infection can be associated with both thrombocytopenia and thrombocytosis. In the absence of DIC, thrombocytopenia (sometimes severe) may occur in septicemia associated with bacterial, fungal, or viral infections. Mild to moderate thrombocytosis is commonly associated with infection (especially chronic infections) and may also occur during recovery from infection.1

Reference
Liver disease

Both platelet number and platelet function are commonly affected by liver disease. Thrombocytopenia (typically mild to moderate) is seen in approximately one-third of patients with chronic liver disease. Platelet function may also be impaired, with abnormalities observed in platelet aggregation in response to ADP, arachidonic acid, collagen, and thrombin.1

Reference

Lupus autoimmune disease

Systemic lupus erythematosus is associated with an increased risk of developing circulating antibodies to coagulation factors, including FII, FV, FVIII, FIX, FX, and FXI.1 Lupus anticoagulant is commonly associated with an in vitro elevation of aPTT but clinically associated with an increased risk of clotting.2,3

References

Malignancy

In patients with a malignancy, the clotting system can be systemically activated, which leads to consumption of clotting factors, and then fibrinolysis. Fibrinogen and clotting factors (ie, FV, FVIII, FIX, FXI, FXII) may be either elevated or depressed, while both PT and aPTT are either shortened or prolonged.1 Plasma D-dimers may also be increased.2

Prominent thrombocytopenia may occur in several hematologic malignancies as a consequence of underlying marrow replacement or an autoimmune disorder. Myeloproliferative disorders and myelodysplastic syndrome with the 5q- chromosomal abnormality may present with prominent thrombocytosis.3

References

Other drugs/foods/supplements

Other drugs1,2
- Nonsteroidal anti-inflammatory drugs
- Prostacyclin analogues: epoprostenol, iloprost, beraprost
- Phosphodiesterase inhibitors: methylxanthines (eg, theophylline), sildenafil
- Statins (eg, lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin)
- Antibiotics: β-lactam antibiotics, penicillins, nitrofurantoin, moxalactam
- Plasma expanders: dextran, hydroxyethyl starch
- Psychotropics: tricyclic antidepressants (eg, imipramine, amitriptyline, nortriptyline), phenothiazines (eg, chlorpromazine, promethazine, trifluoperazine), selective serotonin reuptake inhibitors (eg, fluoxetine, paroxetine, sertraline)
Coagulation Toolkit

Key concomitant factors that can affect coagulation

• Cardiovascular drugs: α-adrenergic receptor blockers (eg, propranolol, metoprolol, nebivolol, pindolol), calcium channel blockers (eg, verapamil, diltiazem, nifedipine), angiotensin-converting enzyme (ACE) inhibitors (eg, losartan), quinidine, diuretics (eg, furosemide), nitrates, nitroprusside
• Anesthetics: dibucaine, procaine, cocaine, halothane
• Oncologic drugs: mithramycin, daunorubicin, bis-chloroethyl nitrosourea
• Radiologic contrast agents: Renografin-76®, Renovist II, Conray® 60
• Antihistamines: diphenhydramine, chlorpheniramine
• Miscellaneous: clofibrate, hydroxychloroquine, oral α₃β₃ inhibitors, fibrinolytic agents

Foods/supplements
• Omega-3 fatty acids, fish oil, vitamin E, garlic, onion, cumin, turmeric, clove

References

Pregnancy
Numerous clotting factors are elevated during pregnancy, including FVII, FVIII, FX, and fibrinogen. Normal fibrinogen levels during pregnancy are:
• 13 to 28 weeks gravid—8.5-16.8 mcmol/L (289-571 mg/dL)
• 29 to 42 weeks gravid—9.5-19.1 mcmol/L (323-650 mg/dL)
Thrombocytopenia occurs in approximately 7%-12% of pregnancies. Women with gestational thrombocytopenia typically have platelet counts of 70,000-150,000 per mcL, are otherwise healthy, and have no history of ITP.

References

Sickle cell disease
In sickle cell disease, there is a significant activation of coagulation along with an increase in fibrinolysis. Plasma D-dimers are also elevated with increased fibrinolysis.

References

Uremia
Platelet function may be altered in patients with uremia. Abnormalities include reduced fibrinogen binding, aggregation, and secretion in response to various agonists. Prolonged bleeding time may also occur.

Reference
Anticoagulants

Heparin (unfractionated)

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.

Monitoring

Heparin effect is traditionally monitored using aPTT. However, an anti-FXa activity assay can also be used to establish a therapeutic range for heparin. A prolonged TT with a normal RT is typical of heparin effect.

Effects on lab values

Typical lab values*

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Key

↑ Increased
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= 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.

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

References

Low-molecular-weight heparin (LMWH)
(eg, tinzaparin, dalteparin, enoxaparin)¹

Overview
LMWH is a polysaccharide polymer like unfractionated heparin, but it is restricted in size to fragments ≤10,000 daltons. Since LMWH is shorter than unfractionated heparin, it only binds antithrombin and FXa, not thrombin. The primary effect is FXa inhibition.² LMWH is typically used to prevent thromboembolism and to treat acute deep venous thrombosis and pulmonary embolism.¹

Monitoring
Routine lab monitoring is not needed for most patients on LMWH because of its predictable pharmacokinetics. For patients who are pregnant, have renal failure, are of a low weight where weight-based dosing may not be accurate, or are neonates, LMWH therapy is monitored by an anti-FXa activity assay.²

Effects on lab values¹,³

Typical lab values*¹

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*Check with your lab to see if its aPTT reagents have any sensitivity to LMWH.
*Values may not represent those seen when additional drugs or confounding illnesses are present.

References
Warfarin

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.\(^2\)

Monitoring\(^4\)
Warfarin is typically monitored by the INR.

Effects on lab values\(^5,6\)

Typical lab values* 

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Key: ↑ Increased, ↓ Decreased, = No change

\(^*\)Increased with high drug dosage.

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

References
**Direct thrombin inhibitors**
*(eg, hirudin, lepirudin, argatroban, dabigatran)*

**Overview**
Direct thrombin inhibitors are a class of medicines that directly inhibit the activation of thrombin without the help of antithrombin. Thrombin normally cleaves fibrinogen to fibrin to begin the process of clot formation. The recommended clinical use for these compounds is rapidly evolving. One potential use is in patients with thrombosis who have heparin-induced thrombocytopenia.

**Monitoring**
Direct thrombin inhibitors are typically monitored by aPTT and activated clotting time.

**Effects on lab values**

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Key:
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argentroban and lepirudin may increase the normal PT 4 to 5 seconds.

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

**References**
**Factor Xa (FXa) inhibitors**
(eg, fondaparinux)

**Overview**
FXa inhibitors, such as fondaparinux, are synthetic polysaccharides that specifically inhibit FXa without having any activity against thrombin. They exert their effect by binding to antithrombin. A possible use for fondaparinux includes prevention of venous thromboembolism in high-risk patients, such as those undergoing orthopedic procedures.

**Monitoring**
Fondaparinux is typically monitored by an anti-FXa assay.

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**References**
Oral direct factor Xa (FXa) inhibitors
(eg, rivaroxaban, apixaban)

Overview
Oral direct FXa inhibitors, such as rivaroxaban and apixaban, are a newer class of medicines that are seen as an alternative to vitamin K antagonists for patients at risk for thromboembolism. Through direct targeting, these drugs inhibit the activity of both free FXa and prothrombinase-bound FXa, effectively blocking the activity of enzymes that convert prothrombin into thrombin. Rivaroxaban and apixaban are oral medicines that are eliminated by both the liver and the kidneys.

Overview
Unlike injectable direct thrombin inhibitors, oral direct FXa inhibitors don't require active laboratory monitoring. Though experience is limited, the most reliable test for assessing activity may be the anti-FXa assay.

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Key

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-a Different reagents may cause the effect of rivaroxaban on PT and aPTT to vary. The effect of apixaban on PT and aPTT is slight.
-b Effect of apixaban not studied.
-c Levels may be ≈10% lower compared with baseline with increasing doses of rivaroxaban.

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

References
Platelet antagonists

Adenosine diphosphate (ADP) receptor inhibitors
(eg, clopidogrel, ticlopidine)

Overview
ADP receptor inhibitors stop the clumping of platelets and block the binding of ADP to the P2Y₁₂ component, inhibiting ADP-induced platelet activation. This class of agents is used in the treatment of vascular diseases such as symptomatic peripheral vascular disease.¹

Effects on lab values³,⁴

Typical lab values*¹

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References

Cyclooxygenase (COX) inhibitors (eg, aspirin)¹

Overview
COX inhibitors decrease overall platelet aggregation at the site of thrombosis by blocking thromboxane A₂ production. This action permanently acetylates COX-1, which lasts for the lifetime of the platelets (7-10 days).² Aspirin has been extensively studied and is considered a fundamental part of managing arterial thrombosis.¹

Effects on lab values³,⁴

Typical lab values*¹

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*Increased with high drug dosage.
*Values may not represent those seen when additional drugs or confounding illnesses are present.

References
**Phosphodiesterase inhibitors**
*(eg, dipyridamole, cilostazol)*

**Overview**
Dipyridamole is a weak phosphodiesterase inhibitor that slows adenosine uptake by platelets, which triggers an accumulation of cyclic adenosine monophosphate (cAMP) and inhibits platelet aggregation. It does not inhibit aggregation responses to collagen, epinephrine, or ADP at usual doses. Modified-release dipyridamole can be used with low-dose aspirin.

Cilostazol exhibits antiplatelet properties, vasodilatory properties, and in vitro inhibition of vascular smooth muscle cells. It can be used for the treatment of intermittent claudication in patients who have peripheral arterial disease.

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*Values shown for dipyridamole.

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**References**
Glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors (IV use only; eg, abciximab, eptifibatide, tirofiban)\(^1\)

**Overview**

GPIIb/IIIa inhibitors act as pharmacologic antiplatelet strategies against the “final common pathway” of platelet aggregation. They inhibit the binding of fibrinogen or vWF and other adhesive proteins that connect nearby proteins.\(^2\) These drugs are used in acute coronary interventions such as percutaneous coronary intervention.\(^1\)

**Effects on lab values\(^3,4\)**

**Typical lab values**\(^*\)

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**References**

**Thrombolytics**

**Plasminogen activators**
(eg, urokinase, streptokinase)

**Overview**
Plasminogen activators comprise all of the currently used thrombolytic agents. These activators bind plasminogen with fibrin and induce plasmin action, which then degrades the fibrin into fibrin degradation products that reduce thrombus size. These agents are used to dissolve clots in a variety of clinical situations.

**Effects on lab values**

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