

A detailed 3D illustration of a blood vessel with a wavy, textured red wall. Inside the vessel, numerous red blood cells are depicted as biconcave discs, some in sharp focus and others blurred in the background, creating a sense of depth. The overall color palette is a range of reds, from deep maroon to bright, almost white highlights on the vessel walls.

Bleeding Disorders

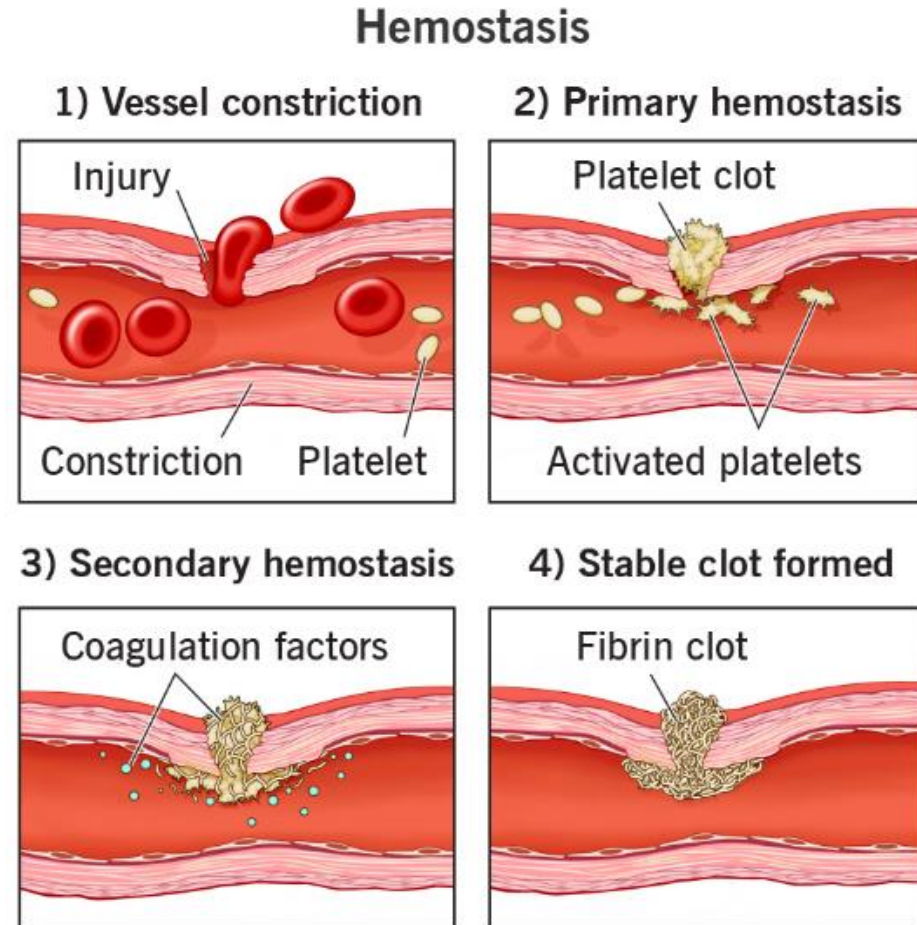
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Mechanism of hemostasis

Hemostasis phases

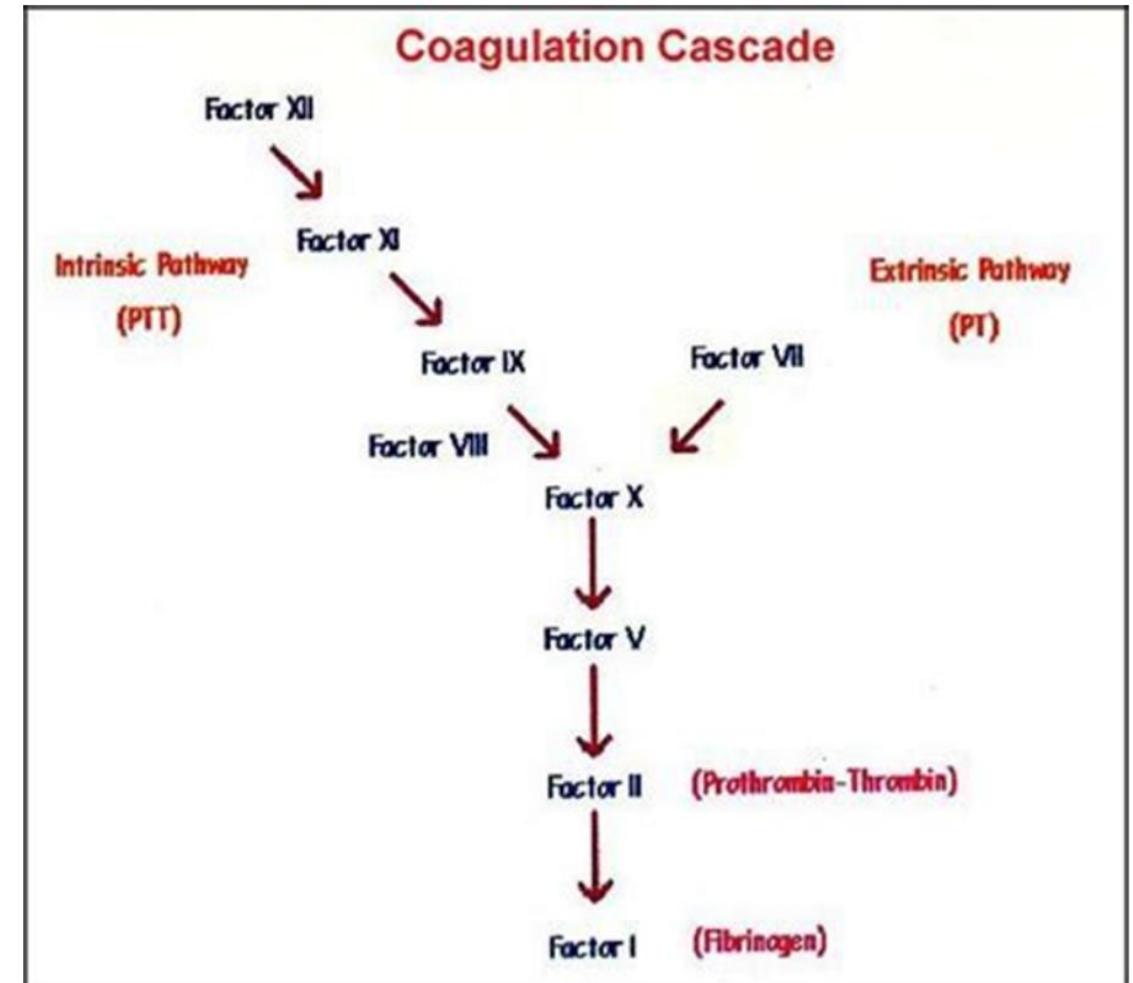
1. Vascular phase
2. Platelet phase
3. Coagulation phase
4. Fibrinolytic phase

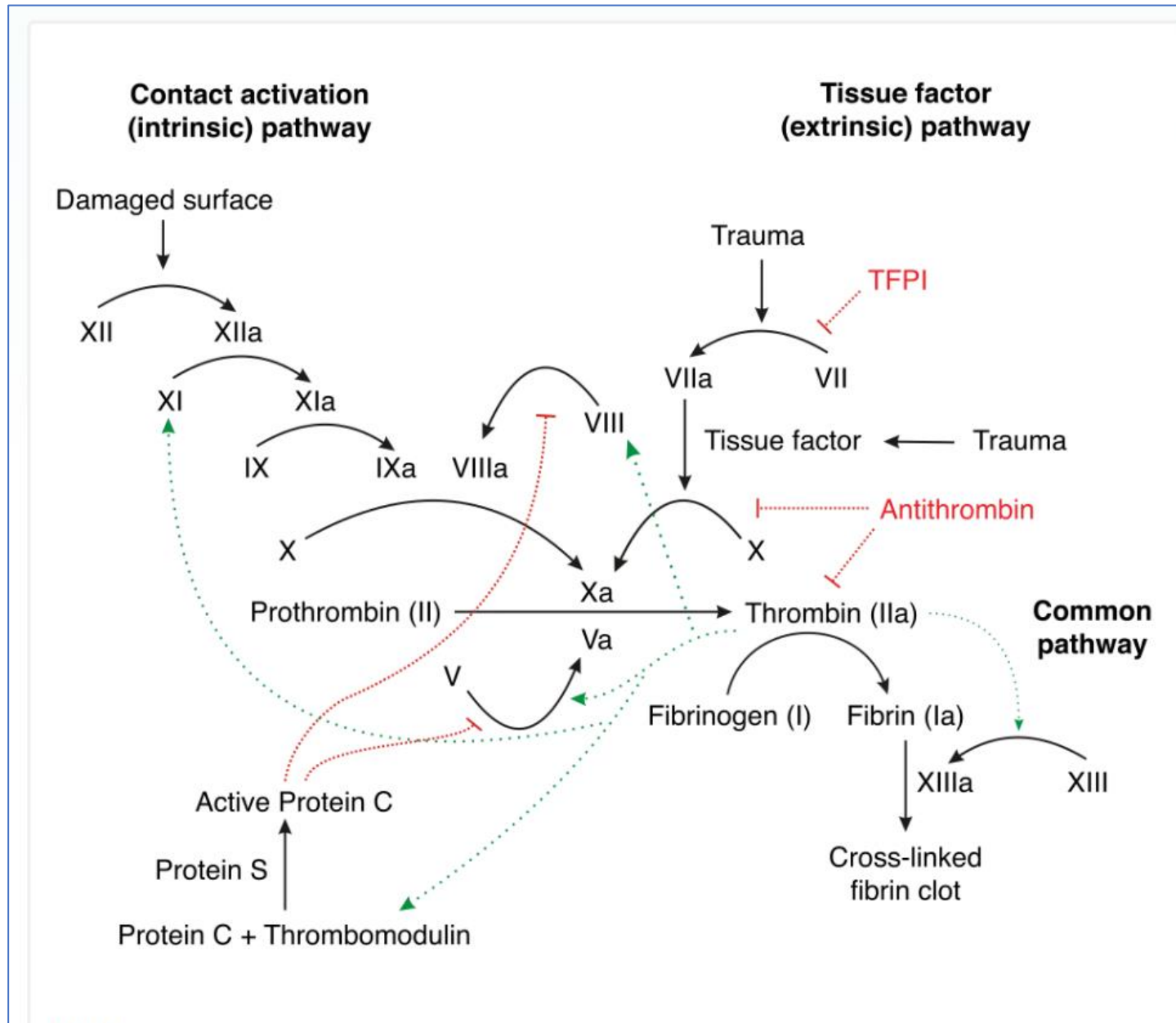


- The steps in platelet plug formation :
adhesion, activation, , secretion, aggregation
- Following injury :
 1. exposure of blood to subendothelial connective tissue (i.e., collagen) promotes initial platelet adhesion particularly in low flow areas.
 2. endothelial cells to synthesize and secrete von Willebrand factor (vWF), which promotes platelet adhesion particularly in high flow injury sites

BOX 24.2 Normal Control of Bleeding

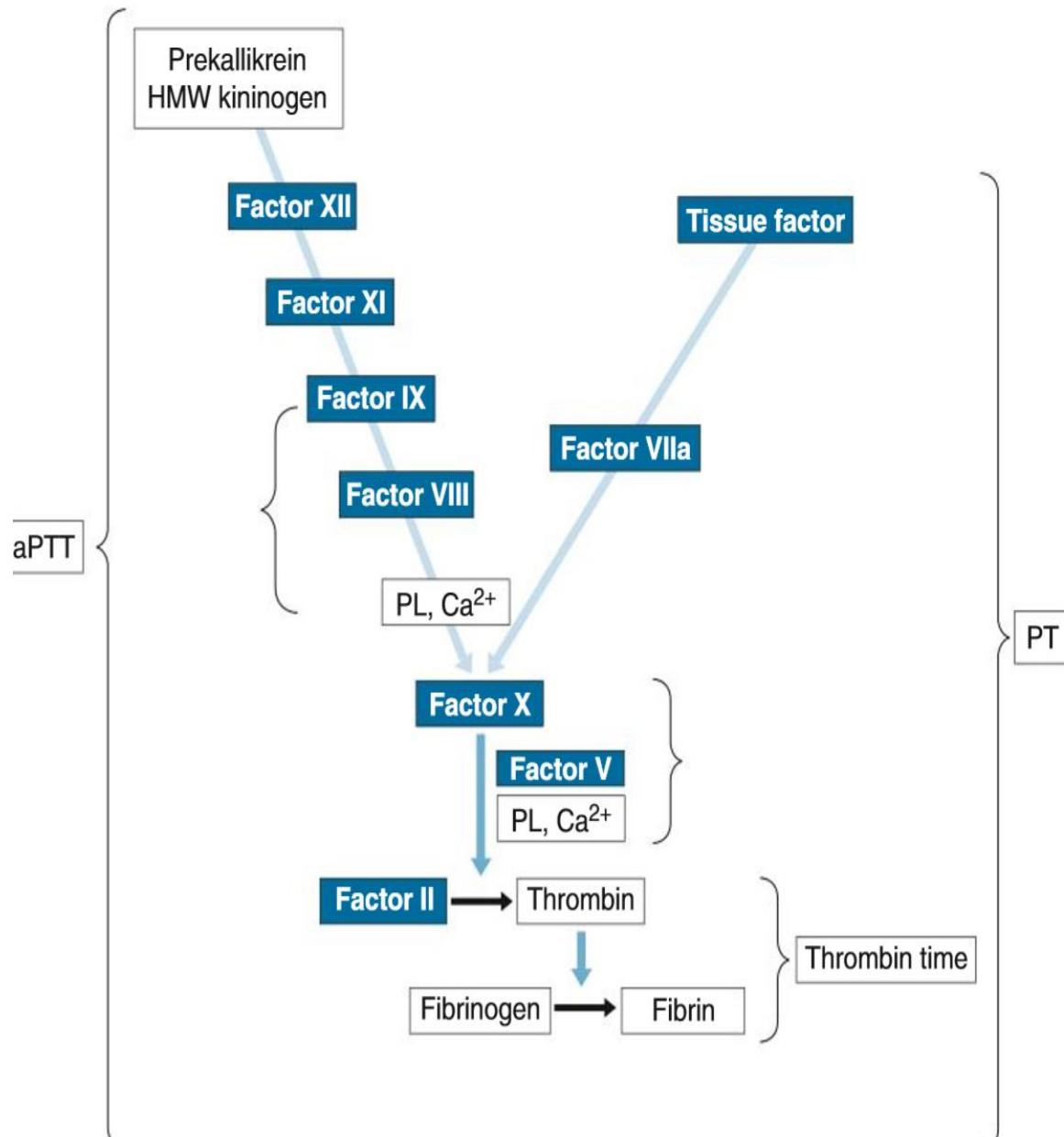
1. Vascular phase:
 - a. Vasoconstriction occurs in area of injury, and increase in extravascular pressure.
 - b. Begins immediately after injury.
2. Platelet phase:
 - a. Platelets and vessel wall become “sticky” and adhere.
 - b. Activation and aggregation of platelets results in formation of a mechanical plug and scaffold for coagulation.
 - c. Begins seconds after injury.
3. Coagulation phase:
 - a. The initiation of coagulation occurs at the site of injury via the tissue factor pathway (extrinsic pathway).
 - b. Propagation of coagulation via the tissue factor pathway then activates the intrinsic pathway which more strongly activates factor X to form thrombin.
 - c. Final coagulation to produce the fibrin clots occurs through the common pathway.
 - d. Takes place more slowly than other phases.
4. Fibrinolytic phase:
 - a. Release of plasminogen which is converted to plasmin on the clot.
 - b. Plasmin cleaves and dissolves the fibrin into fibrin degradation products.







Laboratory Tests



- intrinsic pathway measured by activated partial thromboplastin time (aPTT)
- extrinsic pathway measured by prothrombin time (PT);
- conversion of fibrinogen to fibrin measured by thrombin time (TT).
- Other proteins (prekallikrein & high-molecular-weight kininogen) participate in the contact activation phase but are not considered coagulation factors.

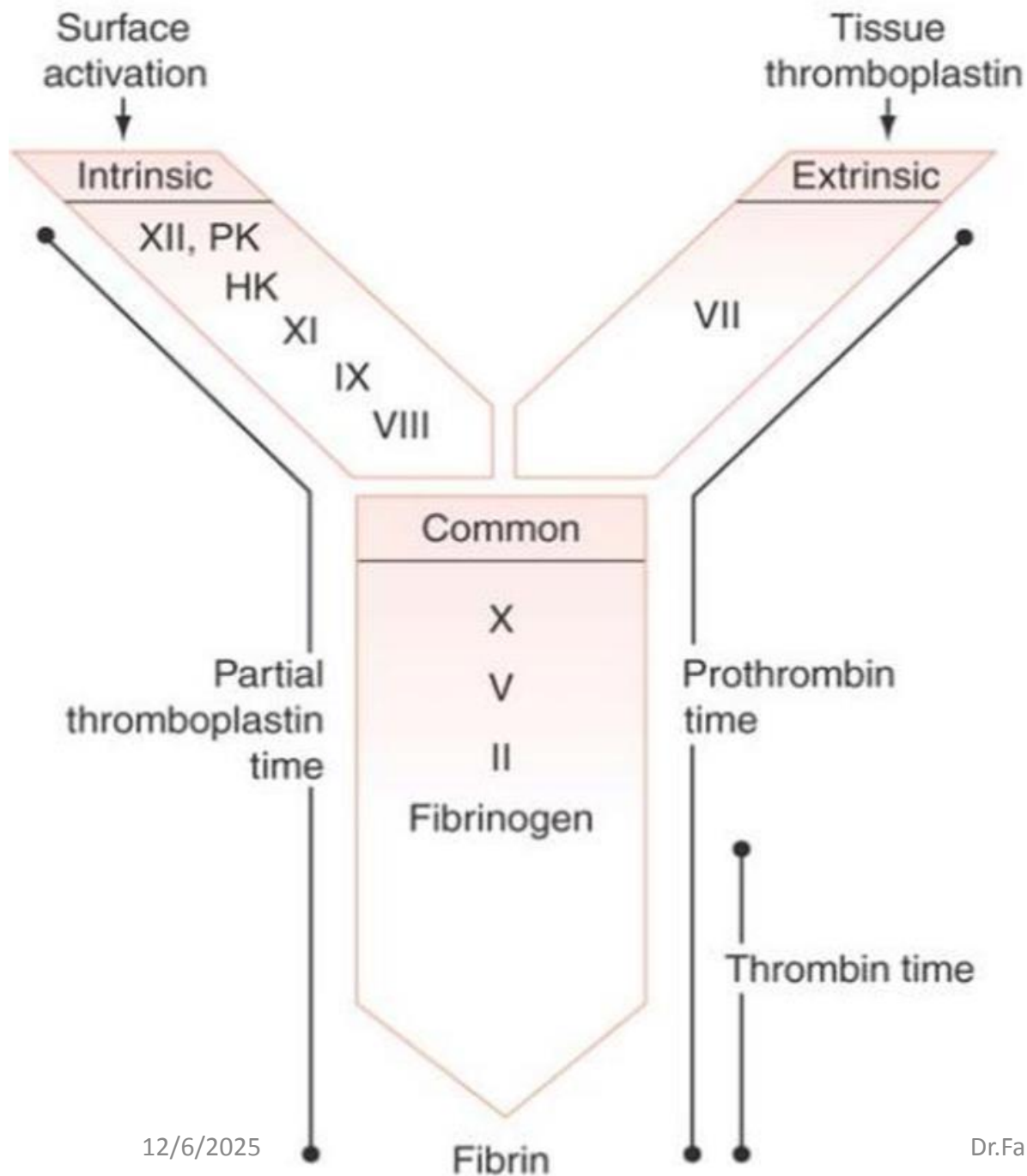


FIG. 25.4 Organization of the coagulation system based on current screening assays. The intrinsic coagulation system consists of the protein factors XII, XI, IX, and VIII; prekallikrein (PK); and high-molecular-weight kininogen (HK). The extrinsic coagulation system consists of tissue factor and factor VII. The common pathway of the coagulation system consists of factors X, V, and II and fibrinogen (I). The activated partial thromboplastin time requires the presence of every protein except tissue factor and factor VII. The prothrombin time requires tissue factor; factors VII, X, V, and II; and fibrinogen. The thrombin clotting time only tests the integrity of fibrinogen. (From McPherson RA, Pincus MR, eds. *Henry's Clinical Diagnosis and Management by Laboratory Methods*. 22nd ed. London: Saunders; 2012.)

BOX 24.6 Screening Laboratory Tests for Detection of a Potential “Bleeder”

1. PT—activated by tissue thromboplastin:
 - a. Tests extrinsic and common pathways.
 - b. Control should be run.
 - c. Normal PT is 11–15 s, depending on laboratory.
 - d. Control must be in normal range.
2. aPTT—initiated by phospholipid platelet substitute and activated by addition of contact activator (kaolin):
 - a. Tests intrinsic and common pathways.
 - b. Control should be run.
 - c. Normal aPTT is 25–35 s, depending on laboratory.
 - d. Control must be in normal range.
3. TT—activated by thrombin:
 - a. Tests ability to form initial clot from fibrinogen.
 - b. Controls should be run.
 - c. Normal TT is 9–13 s.
4. Platelet count:
 - a. Tests platelet phase for adequate number of platelets.
 - b. Normal count is 140,000–400,000/ μ L.
 - c. Clinical bleeding problem can occur if count is less than 50,000/ μ L.

aPTT, activated partial thromboplastin time; *PT*, prothrombin time; *TT*, thrombin time.

- PT: 11-15 s
- PTT: 25-35 s
- TT: 9-13s
- PC: 150000-400000
 - ✓ 50,000 and 100,000 (severe trauma)
 - ✓ below 50,000 (minor trauma)
 - ✓ below 20,000 (spontaneous bleeding)



Bleeding Disorders

Acquired
bleeding
disorders



Congenital
bleeding
disorders

Acquired bleeding disorders

- Vascular disorders
- Acquired Platelet disorders:
 - Qualitative
 - Quantitative
- Acquired Coagulation Disorders

BOX 24.1 Classification of Acquired Bleeding Disorders	
Vascular Disorders Palpable noninflammatory vascular purpuras Dysproteinemias Thrombotic Embolic Arthropod bites Palpable and nonpalpable inflammatory vascular purpuras Pyoderma gangrenosum Sweet syndrome Behçet disease Serum sickness Henoch—Schönlein purpura Infections Erythema multiforme Cutaneous polyarteritis nodosum Paraneoplastic vasculitis Drug-induced vasculitis Antineutrophilic cytoplasmic antibody—associated vasculitides Nonpalpable inflammatory vascular purpuras Increased transmural pressure gradient and trauma Drug reactions Coagulation disorders Decreased vessel integrity without trauma 1. Senile purpura 2. Excess glucocorticoid (Cushing syndrome, glucocorticoid treatment) 3. Scurvy—vitamin C deficiency 4. Systemic amyloidosis Waldenström hypergammaglobulinemic purpura	Drug-induced immune thrombocytopenia (quinidine, heparin, abciximab) Artificial surfaces (hemodialysis, cardiopulmonary bypass, extracorporeal membrane oxygenation) Thrombocytopenia resulting from abnormal distribution of the platelets Hypersplenism Hypothermia Massive blood transfusions Excessive fluid infusions Miscellaneous causes Cyclic thrombocytopenia, acquired pure megakaryocytic thrombocytopenia
Acquired Platelet Disorders Acquired thrombocytopenia Pseudo (spurious) thrombocytopenia Antibody-induced platelet aggregation Platelet satellitism Antiphospholipid antibodies Glycoprotein IIb/IIIa antagonists Thrombocytopenia resulting from impaired platelet production Acquired bone marrow disorders 1. Nutritional deficiencies and alcohol-induced thrombocytopenia 2. Clonal hematologic diseases (myelodysplastic syndrome, leukemias, myeloma, lymphoma, paroxysmal nocturnal hemoglobinuria) 3. Aplastic anemia 4. Marrow metastasis by solid tumors 5. Marrow infiltration by infectious agents (e.g., HIV, tuberculosis, brucellosis) 6. Hemophagocytosis 7. Immune thrombocytopenia 8. Drug-induced thrombocytopenia 9. Pregnancy-related thrombocytopenia Thrombocytopenia resulting from increased platelet destruction Immune thrombocytopenia (ITP) 1. Autoimmune thrombocytopenia (primary and secondary ITP) 2. Alloimmune thrombocytopenia Thrombotic microangiopathies (thrombotic thrombocytopenic purpura, hemolytic uremic syndrome) Disseminated intravascular coagulopathy Pregnancy-related thrombocytopenia Hemangiomas (Kasabach—Merritt phenomenon)	Acquired Qualitative Platelet Disorders Drugs that affect platelet function Aspirin and other nonsteroidal antiinflammatory drugs P2Y ₁₂ antagonists PAR1 thrombin receptor antagonist Glycoprotein IIb/IIIa receptor antagonists Drugs that increase platelet cyclic adenosine monophosphate Antibiotics Anticoagulants and fibrinolytic agents Cardiovascular drugs (nitrates and calcium antagonists [at high doses]) Volume expanders Psychotropic agents Anesthetics Oncologic drugs Hematologic disorders associated with abnormal platelet function Chronic myeloproliferative neoplasms Leukemias and myelodysplastic syndromes Dysproteinemias Acquired von Willebrand disease Systemic disorders associated with abnormal platelet function Uremia Antiplatelet antibodies Cardiopulmonary bypass Chronic liver disease Disseminated intravascular coagulation HIV infection Acquired Coagulation Disorders Anticoagulation drugs Heparin Low-molecular-weight heparins Synthetic heparin Warfarin Direct thrombin inhibitors Fibrinolytic drugs Alteplase Reteplase Tenecteplase Trauma-induced coagulopathy Liver disease Chronic renal failure Vitamin K—associated disorders Vitamin K deficiency Autoantifactor VIII inhibitor and acquired hemophilia Acquired von Willebrand disease Disseminated intravascular coagulation

Vascular Disorders

Palpable noninflammatory vascular purpuras

- Dysproteinemias
- Thrombotic
- Embolic
- Arthropod bites

Palpable and nonpalpable inflammatory vascular purpuras

- Pyoderma gangrenosum
- Sweet syndrome
- Behçet disease
- Serum sickness
- Henoch—Schönlein purpura
- Infections
- Erythema multiforme
- Cutaneous polyarteritis nodosum
- Paraneoplastic vasculitis
- Drug-induced vasculitis
- Antineutrophilic cytoplasmic antibody—associated vasculitides

Nonpalpable inflammatory vascular purpuras

- Increased transmural pressure gradient and trauma
- Drug reactions
- Coagulation disorders
- Decreased vessel integrity without trauma

1. Senile purpura
 2. Excess glucocorticoid (Cushing syndrome, glucocorticoid treatment)
 3. Scurvy—vitamin C deficiency
 4. Systemic amyloidosis
- Waldenström hypergammaglobulinemic purpura

- Scurvy :vitamin C deficiency
- Drug-induced vasculitis
- Behçet disease
- Drug-induced vasculitis
- Erythema multiforme

Acquired Platelet Disorders

Acquired thrombocytopenia

Pseudo (spurious) thrombocytopenia

Antibody-induced platelet aggregation

Platelet satellitism

Antiphospholipid antibodies

Glycoprotein IIb/IIIa antagonists

Thrombocytopenia resulting from impaired platelet production

Acquired bone marrow disorders

1. Nutritional deficiencies and alcohol-induced thrombocytopenia
2. Clonal hematologic diseases (myelodysplastic syndrome, leukemias, myeloma, lymphoma, paroxysmal nocturnal hemoglobinuria)
3. Aplastic anemia
4. Marrow metastasis by solid tumors
5. Marrow infiltration by infectious agents (e.g., HIV, tuberculosis, brucellosis)
6. Hemophagocytosis
7. Immune thrombocytopenia
8. Drug-induced thrombocytopenia
9. Pregnancy-related thrombocytopenia

Thrombocytopenia resulting from increased platelet destruction

Immune thrombocytopenia (ITP)

1. Autoimmune thrombocytopenia (primary and secondary ITP)
 2. Alloimmune thrombocytopenia
- Thrombotic microangiopathies (thrombotic thrombocytopenic purpura, hemolytic uremic syndrome)
- Disseminated intravascular coagulopathy
- Pregnancy-related thrombocytopenia
- Hemangiomas (Kasabach—Merritt phenomenon)

Drug-induced immune thrombocytopenia (quinidine, heparin, abciximab)

Artificial surfaces (hemodialysis, cardiopulmonary bypass, extracorporeal membrane oxygenation)

Thrombocytopenia resulting from abnormal distribution of the platelets

Hypersplenism

Hypothermia

Massive blood transfusions

Excessive fluid infusions

Miscellaneous causes

Cyclic thrombocytopenia, acquired pure megakaryocytic thrombocytopenia

1-Acquired thrombocytopenia

2-impaired platelet production :

Acquired bone marrow disorders

3-increased platelet destruction

4-abnormal distribution of the platelets

Acquired Qualitative Platelet Disorders

Drugs that affect platelet function

Aspirin and other nonsteroidal antiinflammatory drugs
P2Y₁₂ antagonists
PAR1 thrombin receptor antagonist
Glycoprotein IIb/IIIa receptor antagonists
Drugs that increase platelet cyclic adenosine monophosphate
Antibiotics
Anticoagulants and fibrinolytic agents
Cardiovascular drugs (nitrates and calcium antagonists [at high doses])
Volume expanders
Psychotropic agents
Anesthetics
Oncologic drugs

Hematologic disorders associated with abnormal platelet function

Chronic myeloproliferative neoplasms
Leukemias and myelodysplastic syndromes
Dysproteinemias
Acquired von Willebrand disease

Systemic disorders associated with abnormal platelet function

Uremia
Antiplatelet antibodies
Cardiopulmonary bypass
Chronic liver disease
Disseminated intravascular coagulation
HIV Infection

- Drugs
 - Aspirin ,NSAID
 - Anticoagulants ,fibrinolytics
 - Oncologic drugs
- Hematologic disorders
 - Leukemias
- Systemic disorders
 - Uremia,
 - Chronic liver disease
 - HIV Infectio

Acquired Coagulation Disorders

Anticoagulation drugs

- Heparin

- Low-molecular-weight heparins

- Synthetic heparin

- Warfarin

- Direct thrombin inhibitors

Fibrinolytic drugs

- Alteplase

- Reteplase

- Tenecteplase

- Trauma-induced coagulopathy

- Liver disease

- Chronic renal failure

- Vitamin K—associated disorders

- Vitamin K deficiency

- Autoantifactor VIII inhibitor and acquired hemophilia

- Acquired von Willebrand disease

- Disseminated intravascular coagulation

1. Anticoagulation drugs
2. Fibrinolytic drugs
3. Vitamin K deficiency
4. Liver disease

Chronic renal failure

Antiplatelet Therapy

- Platelets are an important contributor to arterial thrombi or emboli
- Antiplatelet drugs :
the primary or secondary prevention of vascular events (i.e., coronary, cerebral, or peripheral vascular events)
 - aspirin, dipyrimadole,
 - influencing platelet adhesion, aggregation, or secretion

- Aspirin is the least expensive, most widely used, and most studied antiplatelet drug.
- **irreversibly** inhibiting COX-1 in platelets(preventing synthesis of thromboxane A2) impairing platelet **secretion and aggregation**.
- Upon discontinuation aspirin's activity lasts for the life of the platelet approximately **7-10 days**

- Dipyridamoles :
inhibit activation and aggregation of platelets

1-ticlopidine, clopidogrel: Permanently inhibit P2Y₁₂

(antiplatelet effect is reversed in 5-7 days following discontinuation)

2-cangrelor , ticagrelor: Reversibly inhibit P2Y₁₂

(antiplatelet effect is reversed in 3-5 days following discontinuation)

Anticoagulant Therapy

1-prevention and treatment of arterial and venous thromboembolism:

- deep vein thrombosis (DVT)
- pulmonary emboli (PE)

2- prevention of stroke in patients with atrial fibrillation

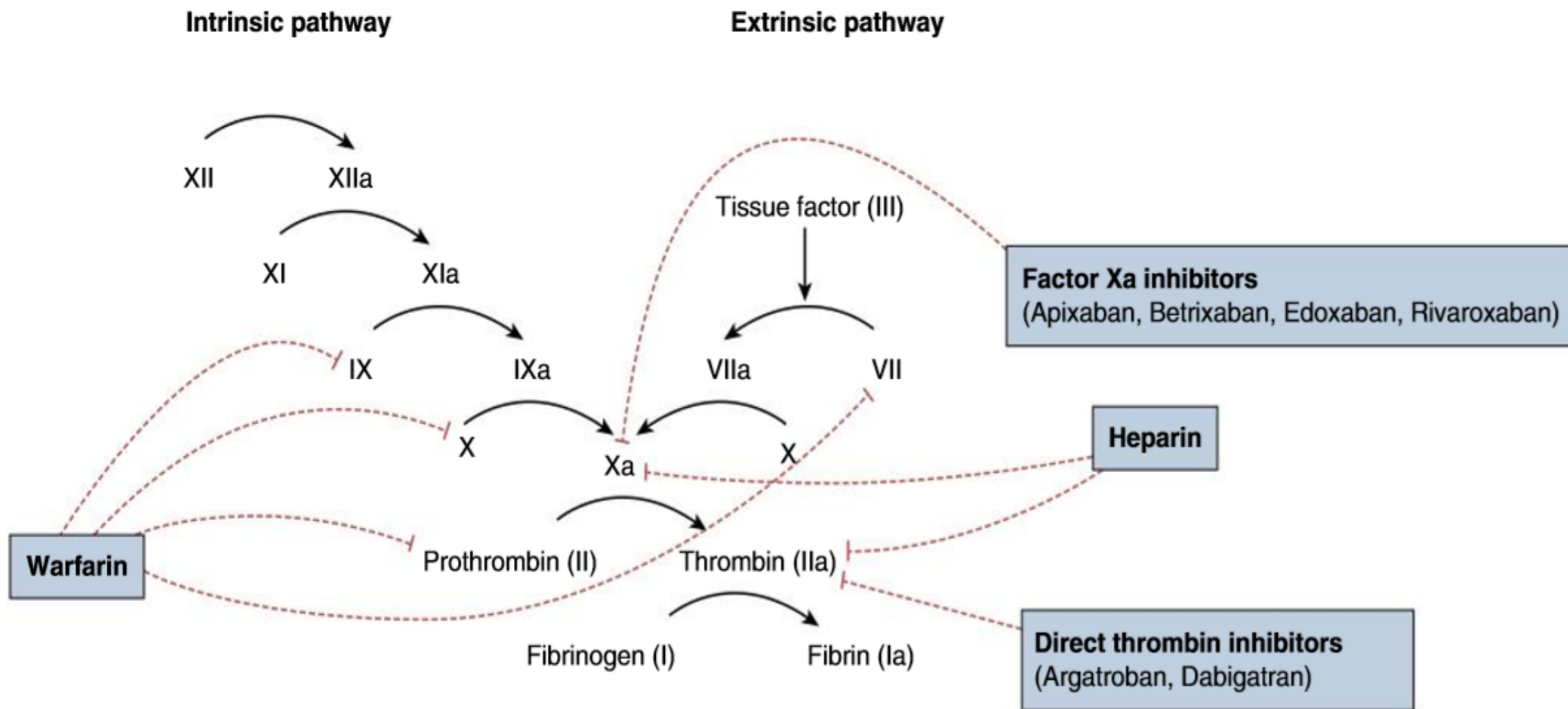
- *heparin and its derivatives,*
- *vitamin K antagonists,*
- *direct oral anti- coagulants (DOACs)*

- Heparin inhibits factor Xa and thrombin equally.
- requires monitoring with aPTT.
- Standard heparin has a half-life of 1e2 h.
- Low-molecular-weight heparin (LMWH) :longer half-life 2-4 h

- The vitamin K antagonists (i.e., warfarin) :
inhibit the biosynthesis of vitamin K dependent coagulation proteins (factors VII, IX, and X and prothrombin).
- Therapeutic anticoagulation with warfarin takes 4-5 days.
- INR is used to monitor patients on warfarin therapy.

DOACs include :

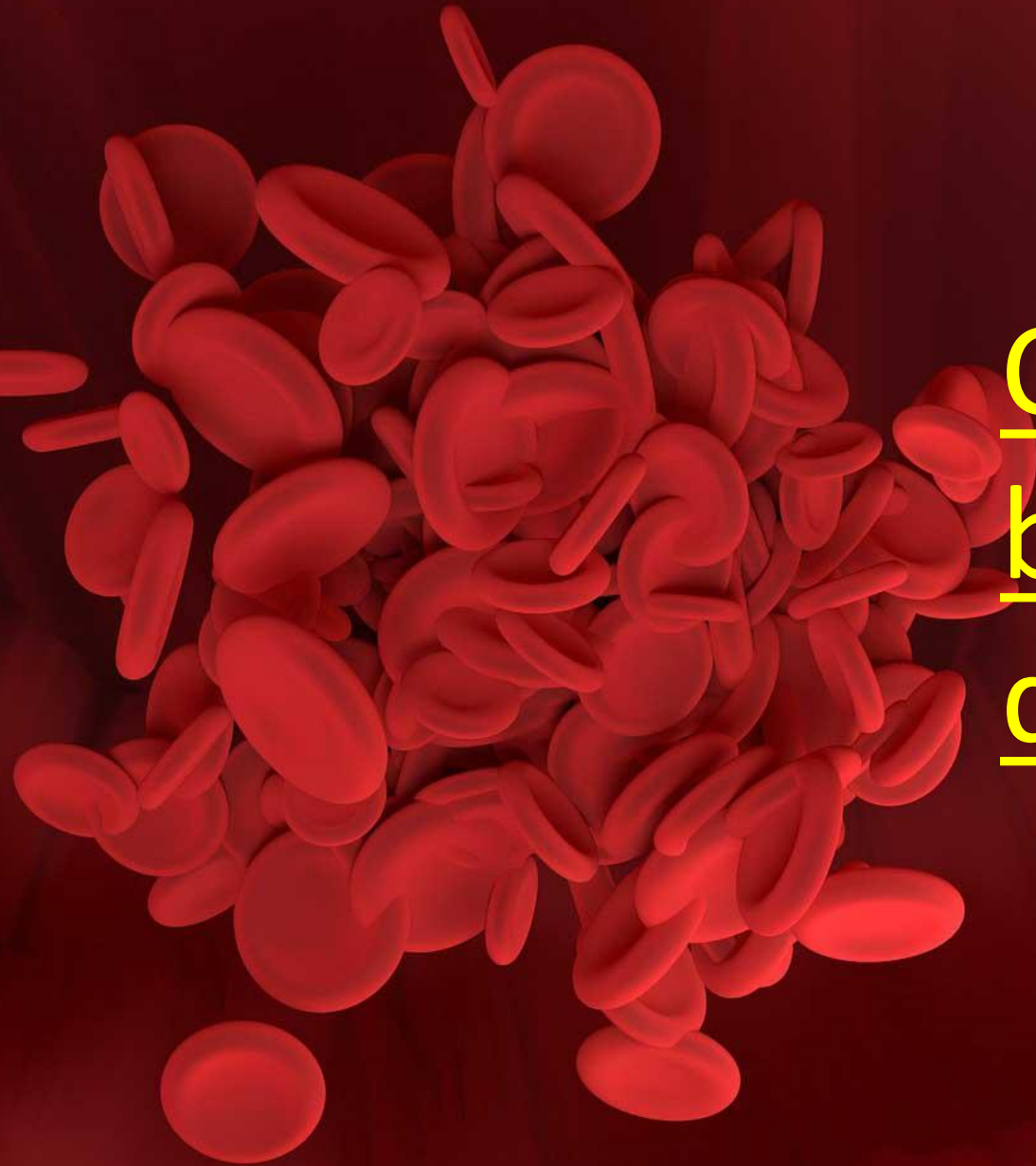
- direct thrombin inhibitors (dabigatran)
- factor Xa inhibitors
(rivaroxaban, apixaban, edoxaban, and betrixaban).



A 3D rendering of a large pile of red blood cells, depicted as biconcave discs, on a dark red background. The cells are clustered together, with some scattered around the main pile. The lighting creates soft shadows and highlights the texture of the cells.

THANK YOU

Acquired
bleeding
disorders



Congenital
bleeding
disorders

BOX 25.1 Classification of Congenital Bleeding and Thrombotic Disorders

Nonthrombocytopenic Purpuras

Vascular Wall Alterations

Hereditary hemorrhagic telangiectasia

Disorders of Platelet Function

von Willebrand disease (may have secondary factor VIII deficiency)

Bernard—Soulier disease^a

Glanzmann thrombasthenia

Others

Thrombocytopenic Purpuras

Gray platelet syndrome

May—Hegglin anomaly

Hereditary thrombocytopenia, deafness, and renal disease

Fechtner syndrome

Alport syndrome

Sebastian platelet syndrome

Others

Disorders of Coagulation

Hemophilia A (factor VIII deficiency)

Hemophilia B (factor IX deficiency)

Other coagulation factor deficiencies

Hypercoagulable States

Antithrombin III deficiency

Protein C deficiency

Protein S deficiency

Factor V Leiden mutation

Prothrombin G2021A mutation

Hyperhomocysteinemia

Congenital bleeding and thrombotic disorders

- Vascular Wall Alterations
 - Osler-Weber-Rendu syndrome
- Disorders of Platelet Function:
 - von Willebrand disease
- Thrombocytopenic Purpuras
- Disorders of Coagulation:
 - Hemophilia A (factor VIII)
 - Hemophilia B (factor IX)
- Hypercoagulable States

^aBernard—Soulier disease also has been classified as a thrombocytopenic disorder.

Hereditary Haemorrhagic Telangiectasia (Osler Weber Rendu Syndrome)



Telangiectasia



**Recurrent
Epistaxis**



Family History

Clinical presentation

- The most common objective findings in patients with genetic coagulation disorders :
 - ecchymoses,
 - hemarthrosis,
 - dissecting hematomas





FIG. 24.5 Ecchymoses on the mucosa of the hard and soft palate in a patient with chronic liver disease.

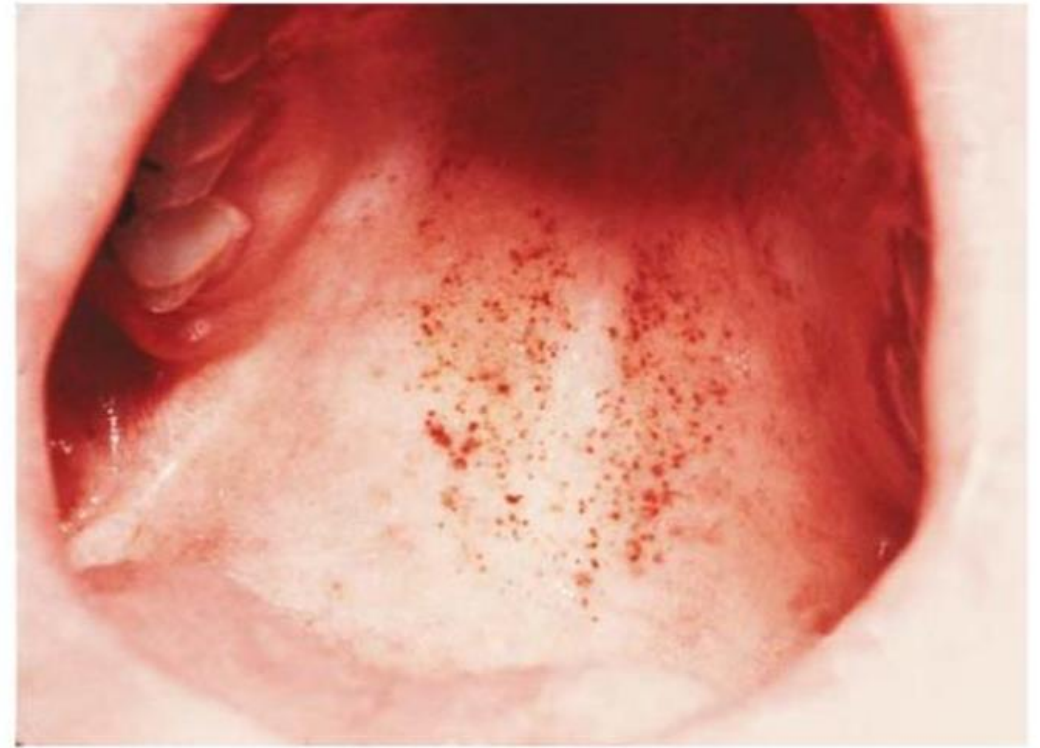
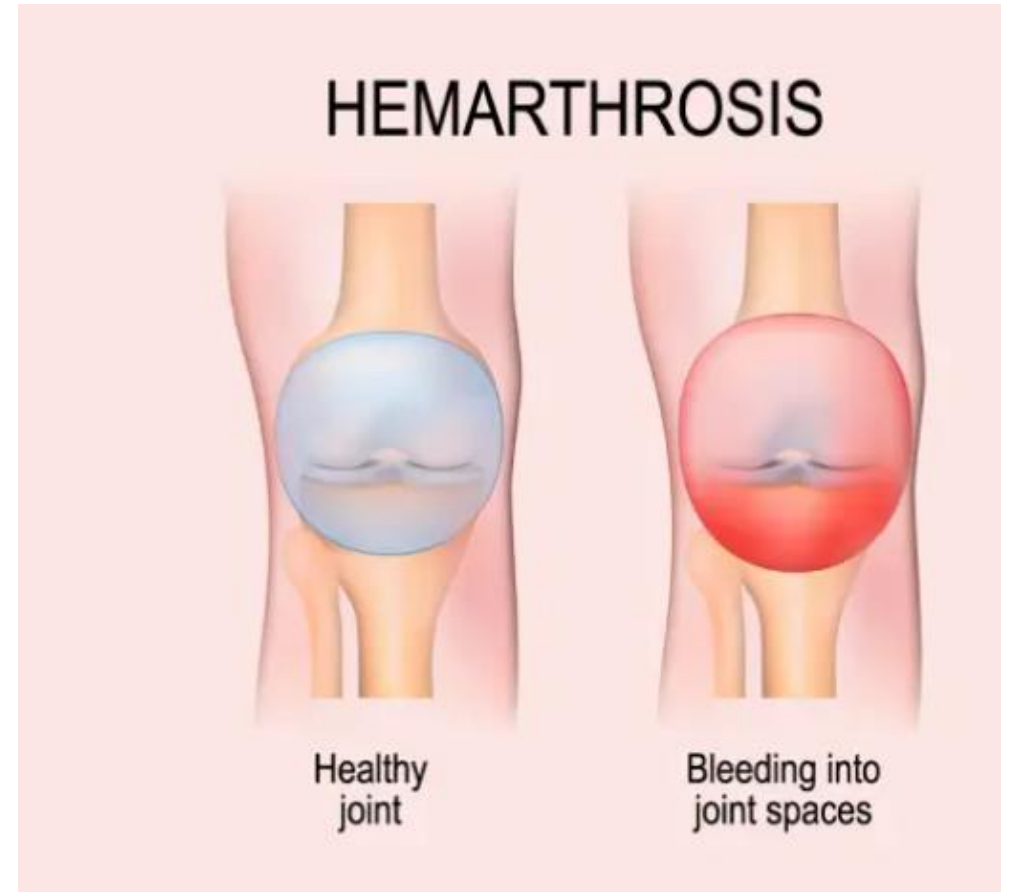
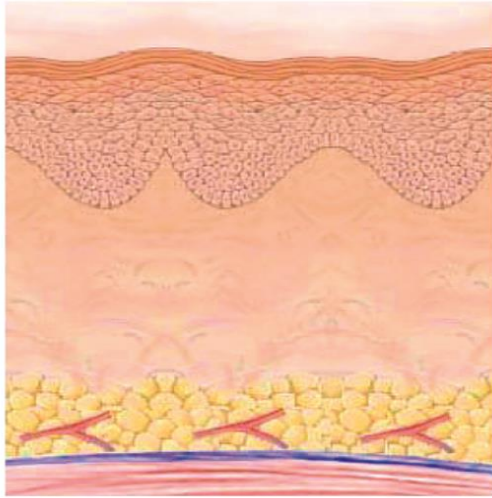


FIG. 24.4 Palatal petechiae in a patient with leukemia. (From Hoffbrand AV. *Color Atlas of Clinical Hematology*. 3rd ed. St. Louis: Mosby; 2000.)



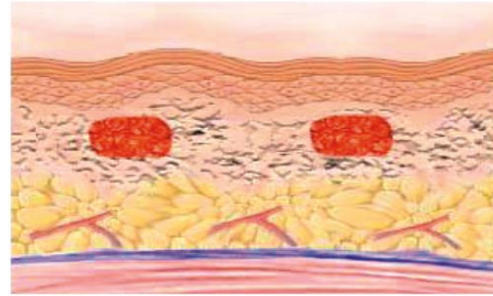
A

Normal skin



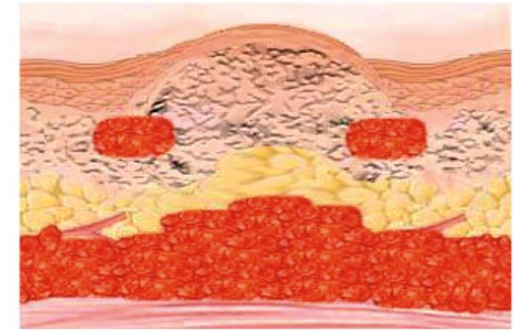
B

Dermatoporosis



C

DDH



Minimal trauma



Most common bleeding disorders

- Von Willebrand disease

The most common inherited bleeding disorder

- Hemophilia (Factor VIII deficiency)

The most common inherited coagulation disorder

- Idiopathic Thrombocytopenic Purpura (ITP)

von Willebrand disease

- von Willebrand factor (vWF):
 - ✓ attach platelets to damaged vascular wall tissues
 - ✓ carry factor VIII in circulation
- Bleeding in von Willebrand disease due to :
 - ✓ lack of platelet adhesion to endothelium
 - ✓ deficiency of factor VIII

- Type 1 is the most common form
 - accounts for about 70%-80% of cases.
 - The greater the deficiency of vWF in type 1 disease, the more likely it is that signs and symptoms of hemophilia A will be found.
- Type 2A is responsible for 15%-20% of cases.
- Type 3, which is rare, leads to severe deficiency of vWF and FVIII

Clinical Presentation Signs and Symptoms

❑ Mild variants :

- history of cutaneous and mucosal bleeding
- bleeding occurs only after surgery or trauma

❑ more severe forms (low factor VIII levels):

- hemarthroses and dissecting intramuscular hematomas.
- spontaneous epistaxis or oral mucosal bleeding
- Serious bleeding after trauma or surgical procedures

- Patients with mild forms of the disease may have a negative history for bleeding problems

Laboratory and Diagnostic Findings

❖ The diagnosis of vWD requires laboratory investigation.

□ Screening laboratory tests may show:

- prolonged aPTT,
- normal or slightly reduced platelet count,
- normal PT,
- normal TT.

Patients appropriate for testing

- physical examination.
- lifelong history of platelet- type bleeding symptoms
- positive family history of bleeding are.
- For patients thought to have an inherited disorder, testing for von Willebrand disease should be done initially
- approximately 1% of the population has the disorder.
- laboratory tests show a low platelet count, large platelets, faulty platelet adhesion, and poor aggregation with ristocetin

- **BernardeSoulier Syndrome:**

- ✓ disorder of platelet adhesion to vWF
- ✓ lack of GP Ib on platelet membrane
- ✓ platelets unable to bind to vWF thus unable to adhere to subendothelium

- **Glanzmann thrombasthenia:**

- ✓ disorder of platelet aggregation
- ✓ abnormality of complex GP IIb/IIIa on platelet membrane
- ✓ platelets adhere to the subendothelium but not to fibrinogen

BernardeSoulier Syndrome

large and defective platelets unable to interact with vWF.

- . Classic clinical findings :
- epistaxis, easy bruising, mucous membrane bleeding, perioperative bleeding, and menorrhagia.
- Ecchymosis and gingival and GI bleeding may occur.

Glanzmann thrombasthenia :

- increased incidence :
Indians, **Iranians**, Iraqi, Jews, Palestinian ,Jordanian Arabs
- The recurrent features of GT :
epistaxis, easy bruising, oral and gingival hemorrhage, GI bleeding, perioperative bleeding, hemarthrosis, and menorrhagia.
- Patients often experience bleeding from minor cuts and trauma.

Hemophilia A

❖ Deficiency or a defect of factor VIII.

- Normal homeostasis requires at least 30% factor VIII activity.
- Symptomatic patients usually have factor VIII levels below 5%.
 - 5% - 30% :mild (40% of patients with hemophilia A).
 - 1% - 5% : moderate (40% of patients),
 - less than 1% of normal activity :severe (20% of patients).
- Most affected patients are males who will demonstrate various aspects of bleeding

- The most characteristic bleeding :

hemarthrosis, which often develop without significant trauma (Fig. 25.8).

❑ Severe hemophilia :

- severe, spontaneous bleeding, with common findings including hemarthrosis, ecchymoses, soft tissue hematomas (Figs. 25.9 and 25.10), gastrointestinal and genitourinary bleeding.
- Spontaneous bleeding from the mouth, gingivae, lips, tongue, and nose

❑ Moderate hemophilia :

- moderate bleeding with minimal trauma or surgery.
- Hemarthrosis and soft tissue hematomas occur less often.

❑ mild hemophilia :

- mild bleeding after major trauma or surgery.
- Hemarthrosis and soft tissue hematomas are seldom found in these patients.
- The onset of excessive bleeding usually is delayed; at the time of surgery or injury, hemostasis appears to be normal, but bleeding of sudden onset and serious proportions may develop several hours or even several days later.

Laboratory and Diagnostic Findings

❑ Screening tests show

- prolonged aPTT,
- normal PT,
- normal platelet count (except in some cases of von Willebrand disease) indicate a problem in the intrinsic pathway.

❑ The next step is mixing tests

- Normal: then the specific missing factor is identified by specific assays.
- abnormal: tests for inhibitor activity (antibodies to the factor)

Hemophilia B In hemophilia B (Christmas disease)

- deficient or defective factor IX
- X-linked recessive trait
- Severe disease :less than 1% of normal amounts of factor IX, is less common than in hemophilia A.
- Clinical manifestations of the two disorders are identical.
- Screening laboratory test results are similar for both diseases
- Specific factor assays for factor IX establish the diagnosis.



Laboratory and Diagnostic Findings

❑ initial screening of possible acquired bleeding disorders :

- complete blood count, (CBC)
- activated partial thromboplastin time (aPTT): 25 to 35
- prothrombin time (PT): 11-15 s.
- thrombin time (TT) : 9-13 s. abnormal :more than16-18 s
- platelet count(PC)

❑ platelet count (normal range: 150,000 to 450,000/mL of blood)

- 50,000 - 100,000 :excessive bleeding only with severe trauma.
- below 50,000: bleed excessively with minor trauma.
- below 20,000:spontaneous bleeding.

The partial thromboplastin time (PTT) is the best single screening test for coagulation disorders,

- intrinsic system (factors VIII, IX, XI, and XII)
 - common pathway (factors V , X, II, fibrinogen).
-
- prothrombin time (PT) :
extrinsic pathway (factor VII)
common pathway (factors V ,X, II, fibrinogen)

A 3D rendering of a large pile of red blood cells, depicted as biconcave discs, scattered on a dark red, textured surface. The cells are rendered in a vibrant red color, matching the background. The lighting creates soft shadows, giving the cells a three-dimensional appearance. The text "THANK YOU" is centered over the pile of cells.

THANK YOU

A 3D medical illustration of a blood vessel, likely an artery, showing its internal structure and the flow of blood. The vessel is depicted with a textured, reddish-pink interior wall. Numerous red blood cells, shown as biconcave discs, are floating within the vessel lumen. The lighting is warm and focused on the center of the vessel, creating a sense of depth and highlighting the cellular details. The overall color palette is dominated by various shades of red and pink.

Suspicion of bleeding disorders

- **Bleeding occurring after the extraction** of teeth may be the first evidence of **mild coagulation disorders**
(hemophilia A, hemophilia B, vWD variants with factor VIII deficiency)
- **Spontaneous gingival bleeding and petechiae** usually are found in patients with genetic **platelet disorders** or **HHT**.
- **Hemarthrosis of the temporomandibular joint** is a rare finding in patients with genetic **coagulation disorders**

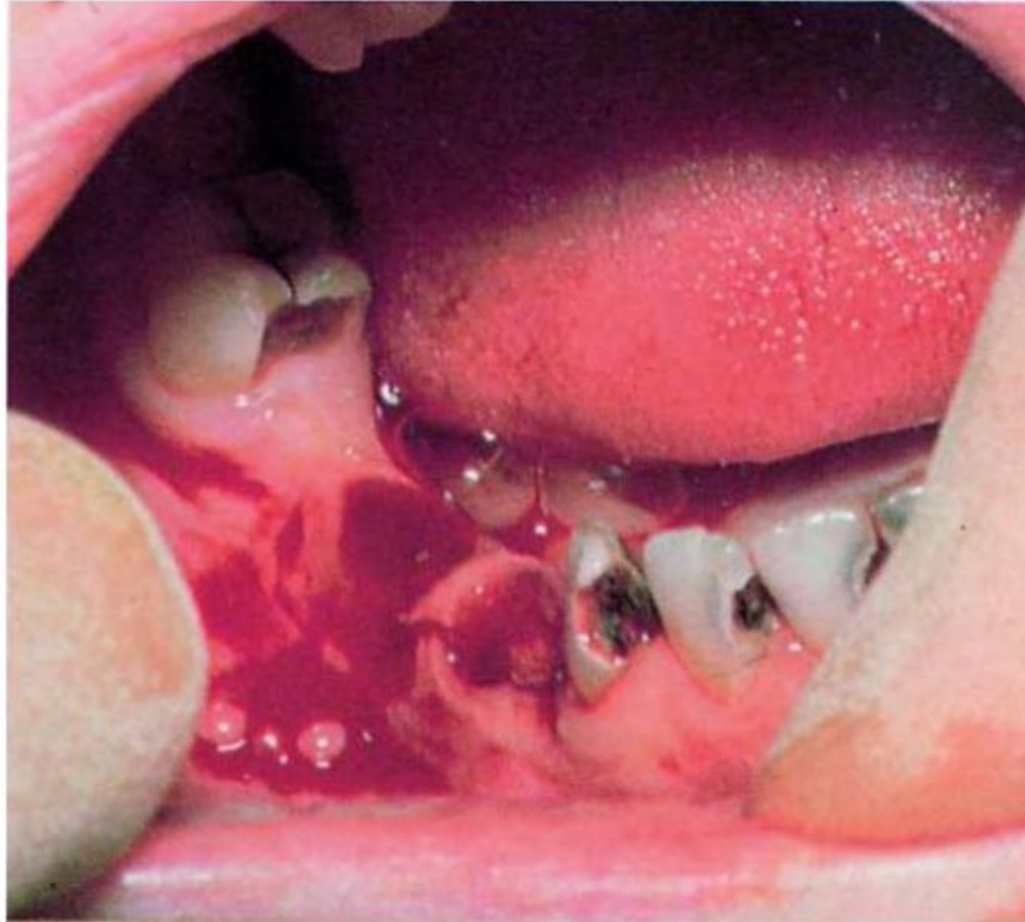


FIG. 25.12 Severe hemorrhage after dental extraction often is the first clue to more minor degrees of coagulation disorder and is a common presentation in patients with hemophilia A, hemophilia B, and von Willebrand disease. (From Forbes CD, Jackson WF. *Color Atlas and Text of Clinical Medicine*. 3rd ed. London: Mosby; 2003.)

- The dentist should use these four methods to assess risk of a potential bleeding problem.

- ☐ A thorough history
- ☐ Physical examination
- ☐ Screening clinical laboratory tests
- ☐ Observation of excessive bleeding following an invasive procedure

The history should include questions on the following topics:

1. Presence of bleeding problems in relatives
2. Excessive bleeding after operations/surgical or dental procedures.
3. Excessive bleeding after injury or trauma
4. Current use of antithrombotic drugs, or other drugs linked to bleeding
5. Past and present illness or other diseases associated with bleeding
6. Occurrence of spontaneous bleeding

Physical Examination

- The dentist should inspect the exposed skin and oral mucosa for signs:

petechiae, purpura, ecchymoses,
spider angiomas, telangiectasias,
jaundice, pallor, cyanosis

Lab tests to order

- No routine presurgical screening is needed to rule out bleeding disorders in patients with a negative history and clinical findings before low- risk dental or surgical procedures
- PC ,PT , PTT, TT
- PBS,CBC

BOX 24.5 Clinical Recognition of the Patient Who Is a “Bleeder”

1. History

- a. Bleeding problems in relatives
- b. Bleeding problems after operations and tooth extractions
- c. Bleeding problems after trauma (e.g., cuts, scrapes)
- d. Medications that may cause bleeding problems:
 - (1) Aspirin
 - (2) Anticoagulants
 - (3) Long-term antibiotic therapy
 - (4) Certain herbal preparations
- e. Presence of illnesses that may be associated with bleeding problems:
 - (1) Leukemia
 - (2) Liver disease
 - (3) Hemophilia
 - (4) Congenital heart disease
 - (5) Renal disease—uremia
- f. Spontaneous bleeding from nose, mouth, ears

2. Examination findings

- a. Jaundice, pallor
- b. Spider angiomas
- c. Ecchymoses
- d. Petechiae
- e. Oral ulcers
- f. Hyperplastic gingival tissues
- g. Hemarthrosis

3. Screening laboratory tests

- a. PT
- b. aPTT
- c. TT
- d. Platelet count

- 4. Surgical procedure—excessive bleeding after surgery may be first clue to underlying bleeding problem
aPTT, activated partial thromboplastin time; *PT*, prothrombin time; *TT*, thrombin time.



How to manage patients with bleeding disorders

TABLE 25.2 Medical Treatment of Congenital Bleeding Disorders

Condition	Defect	Medical Management
Hereditary hemorrhagic telangiectasia	Multiple telangiectasias with mechanical fragility of the abnormal vessels	Laser Surgery Estrogen Estrogen plus progesterone Thalidomide
von Willebrand disease	Deficiency or defect in vWF causing poor platelet adhesion and in some cases deficiency of factor VIII	Desmopressin Aminocaproic acid Factor VIII replacement that retains vWF
Hemophilia A	Deficiency or defect in factor VIII	Desmopressin Aminocaproic acid Factor VIII
	Some patients develop antibodies (inhibitors) to factor VIII	Porcine factor VIII, PCC, aPCC, factor VIIa, and/or steroids for patients with inhibitors
Hemophilia B	Deficiency or defect in factor IX	Desmopressin Aminocaproic acid Factor IX
	Development of antibodies (inhibitors) to factor IX is much less common than with hemophilia A	PCC, aPCC, factor VIIa, ^a and/or steroids for patients with inhibitors
Bernard—Soulier disease	Genetic defect in platelet membrane, absence of GP Ib causes disorder in platelet adhesion	Platelet transfusion Desmopressin Factor VIIa
Glanzmann thrombasthenia	Genetic defect in platelet membrane, absence of GP IIb/IIIa	Platelet transfusion Desmopressin Factor VIIa

^aFactor VIIa is activated factor VII.

aPCCs, activated prothrombin complex concentrates; GP, glycoprotein; PCCs, prothrombin complex concentrates; vWF, von Willebrand factor.



Treatment Planning Modifications

Low-risk procedures

- local anesthetic infiltrations and blocks,
- restorative, endodontic, prosthodontic procedures,
- <3 un-complicated dental extractions,
- implant placement,
- periodontal surgery,
- subgingival scaling/root planning
- biopsy procedures,

High-risk procedures

- major surgery typically performed by specialists
- complicated and multiple extractions with flaps,
- orthognathic surgery,
- oncologic resection,
- reconstructive surgery

Acquired
bleeding
disorders



Congenital
bleeding
disorders

BOX 24.7 Dental Management Considerations in Patients Taking Antithrombotic Agents^a

PREOPERATIVE RISK ASSESSMENT

- Review medical, surgical, and dental history to determine why the patient is taking antithrombotic therapy; the current dosage; history of previous bleeding events.
- Discuss relevant issues with the patient in the context of the procedure(s) planned.
- Examine the patient for signs and symptoms of bleeding disorders and obtain vital signs.
- Review recent laboratory test results (if applicable).
- Confirm patient has a primary care provider (or hematologist).
- Obtain medical consultation to discuss risk for bleeding in the context of the procedure(s) planned. Any adjustments in antithrombotic therapy should be handled by the patient's physician.
- Order preoperative laboratory tests, if applicable.
- Low risk dental procedures can be performed without special precautions.

A

Analgesics	Avoid aspirin, aspirin-containing compounds, and other NSAIDs. Acetaminophen with or without codeine is suggested for most patients.
Antibiotics	Antibiotics such as clindamycin or amoxicillin may alter normal flora altering the absorption of Vitamin K and increase warfarin levels. Other antibiotics, such as metronidazole and macrolides can interact via the cytochrome P450 system with warfarin and some DOACs causing an increase in the levels of these agents.
Anesthesia	Use of local anesthetics with vasoconstrictors to control bleeding must be used judiciously in patients with cardiac issues.

B

Bleeding	Excessive bleeding is expected for all patients taking antithrombotic agents. The risk for bleeding for patients on antiplatelet agents cannot be measured. Patients taking two or more antiplatelet agents or combination antiplatelet/anticoagulant
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agents are at a higher risk for bleeding. In patients taking warfarin, excessive bleeding after invasive dental procedures depends on the level of the patient's INR. If the INR is greater than 3.5, significant bleeding may occur after invasive dental and surgical procedures. These procedures can be performed with little risk of significant bleeding if the INR is between 2.0 and 3.5. In patients taking DOACs, the potential for bleeding is less than for warfarin.

Breathing	No issues.
Blood pressure	Elevated blood pressure complicates hemostasis.

C

Chair position	No issues.
Cardiovascular	Determine reason for antithrombotic therapy; if for cardiac reason, take appropriate management actions.

D

Devices	No issues.
Drugs	Avoid prescription of all drugs that may further increase the risk bleeding (i.e., NSAIDs), or interact to increase or reduce blood levels of antithrombotic agents. Drug interactions with antibiotics, azole antifungals, corticosteroids, cyclosporine, and carbamazepine are possible and should be checked before prescribing.

E

Equipment	Have needed armamentarium to manage hemostasis.
Emergencies	Excessive bleeding may occur after invasive dental procedures or surgery, and local measures may be required to control the bleeding (see Table 24.6).

Postoperative Care

F	
Follow-up	Patients should be contacted or examined within 24–48 h after surgical procedures to determine that excessive bleeding or infection is not occurring.

^aStrength of recommendation taxonomy (SORT) Grade: C (see Preface for further explanation).

INR, international normalized ratio [INR = (PTR)^{ISI}]; ISI, international sensitivity index (based on sensitivity of thromboplastin used in PT); PT, prothrombin time; PTR, prothrombin time ratio.



Considerations for Patients on Antithrombotic Agents

Antiplatelet Therapy

❖ patients who take single or dual-antiplatelet drugs:

- **low-risk dental procedures/surgery:**

- ✓ be maintained on their medication(s)

local hemostatic techniques

- **high-risk procedures/surgery :**

- ✓ risk assessment

- ✓ defer elective surgery until antiplatelet therapy is adjusted
or

- ✓ briefly discontinued.

Anticoagulant Therapy

- guidelines universally support the continuation of oral anticoagulation therapy (i.e., warfarin or DOACs) for minor dental/surgical procedures at low risk for causing bleeding

Warfarin

- monitoring by INR (therapeutic window INR of 2-3.5):
- minor procedures can be performed with local hemostatic measures
- preoperative INR outside of the window :
warfarin adjust by the physician
- In emergencies:
reversed with vitamin K, prothrombin complex concentrates, or fresh frozen plasma.

- drugs that can increase warfarin levels:
- reducing the intestinal absorption of vitamin K (e.g., clindamycin and amoxicillin),
- inhibiting its metabolism (i.e., metronidazole, azole antifungals, and carbamazepine).

DOAC

- Testing and monitoring parameters for the DOAC drugs have not yet been established
- Emergency reversal of DOACs may be possible following infusion of prothrombin complex concentrates

- Guidelines and expert opinion vary in terms of major surgical procedures with some advocating protocols for the discontinuation of anticoagulants, while others strictly supporting the continuation of anticoagulants irrespective of surgical complexity/risk for bleeding

Bridging

- Warfarin therapy is typically discontinued 5 days before surgery and a series of 1 mg/kg subcutaneous enoxaparin injections every 12 h (at 9 a.m. and 9 p.m.) on an outpatient basis are given, starting 3 days before the surgery
- The last enoxaparin injection is given at 9 p.m. on the evening before surgery. The INR should be checked on the morning of surgery
- Enoxaparin injections are started again on the evening after the surgery; oral warfarin therapy is also restarted that evening.
- After 3 days, the postoperative enoxaparin injections are stopped

- Patients taking warfarin who are at a lower risk for a thromboembolic event do not require bridging.
- The predictable and short half-life of DOAC agents abrogates the need for bridging,
- If DOAC is discontinued by the physician, patients are typically instructed to **discontinue the agent 12-48 h before surgery and resume the day after surgery**

Standard Heparin

- Dental emergencies in these patients during hospitalization should be treated as conservatively as possible, with avoidance of invasive procedures, if possible.
- Patients treated with hemodialysis:
 - half-life of heparin :1-2 h
 - patients can receive invasive dental treatment the day after dialysis

LMWH

- recent total hip or knee replacement , those being treated on an outpatient basis for venous thromboembolism :
- Elective **surgical procedures can be delayed** until the patient is taken off the LMWH or synthetic heparin, which, in most cases, will occur **within 3-6 months**.

LMWH

- If an invasive procedure must be performed:
half-life of the LMWHs is less than 1 day
- Thus, the physician could suggest that the:
 1. drug be stopped and the surgery be performed within 1-2 days.
 2. continue the heparin treatment, proceed with the surgery, and control bleeding with local measures.
 3. protamine may be given to reverse anticoagulation

Other Diseases

- liver disease, end-stage renal disease/renal dialysis, and acquired thrombocytopenia/qualitative platelet disorders:
- Normal PT/INR , the platelet count
 - ✓ surgery can be performed on liver disease patients with little risk of a postoperative bleeding problem
- INR > 2.5 : high risk for bleeding
 - ✓ consult with the patient's physician regarding stabilization of the patient's bleeding status before surgery

Thrombocytopenia

- minor invasive procedures
 - ✓ PC above 50,000/mL: uncomplicated extractions, can be performed.
- For more advanced surgery:
 - ✓ the platelet count should be at least 80,000-100,000/mL
 - ✓ If the platelet count is below this level, such procedures should be delayed.
 - ✓ For urgent or emergency dental needs, platelet replacement may be indicated

A detailed 3D rendering of a blood vessel's interior. The vessel wall is shown as a textured, red, fibrous structure. Numerous red blood cells, depicted as biconcave discs with a darker red center, are scattered throughout the vessel lumen. The overall color scheme is a vibrant red, emphasizing the blood's composition.

Topical Hemostatic Agents Used to Control Bleeding

❖ Excessive postoperative bleeding after extraction:

➤ local hemostatic agents in the socket

- absorbable gelatin sponges,
- gelatin-thrombin products,
- oxidized- cellulose,
- microfibrillar collagen,
- fibrin glue,
- recombinant thrombin powder

➤ ideally with primary closure

- The antifibrinolytic agents, tranexamic acid (TXA) and epsilon aminocaproic acid (EACA) block the binding of plasminogen to fibrin.
-
- Gauze used for compression soaked with TXA solution
- TXA mouthwashes (5%-10% solutions) have a beneficial effect on reducing postoperative bleeding following minor oral surgery/ dental extractions in patients taking antithrombotic agents..

Patients instruction

- extra gauze
- head elevation,
- gauze compression,
- reducing any activities that might dislodge the clot
- Vasoconstrictive agents:
 - ✓ ice or a moistened bag of black tea, which contain tannins
- Follow-up communication :within 24-48 h of the procedure

TABLE 25.6 Topical Hemostatic Agents Used to Control Bleeding

Product	Company or Manufacturer	Description	Indications and Features
Gauze	Pharmacia & Upjohn	2 × 2-inch sterile gauze pads; placed over the wound, with pressure applied by patient (by closing jaws or with fingers)	Bleeding immediately after extractions or minor surgical procedures
Gelfoam		Absorbable gelatin sponge made from purified gelatin solution; absorbs in 3–5 days	Useful for most patients taking an antithrombotic agent; helpful to place topical thrombin on Gelfoam; for extensive or invasive surgery, can be placed inside a splint
HemCon Dental Dressing	HemCon Medical Technologies	10- × 12-mm or 1- × 3-inch dressing; place on wound (best if some blood is present, helps stick dressing to the wound); made of chitosan from shellfish	Can be used on extraction sites and oral wounds; can be used in patients taking anticoagulants
Cellulose			
Surgicel Oxycel	Johnson & Johnson Becton Dickinson	Oxidized regenerated cellulose; exerts physical effect rather than physiologic; swells on contact with blood with resulting pressure adding to hemostasis; thrombin is ineffective with these agents because of inactivation as a result of pH factors	After 24–48 h, it becomes gelatinous; can be left in place or removed; useful to control bleeding when other agents ineffective

Cellulose

Surgicel Oxycel	Johnson & Johnson Becton Dickinson	Oxidized regenerated cellulose; exerts physical effect rather than physiologic; swells on contact with blood with resulting pressure adding to hemostasis; thrombin is ineffective with these agents because of inactivation as a result of pH factors	After 24–48 h, it becomes gelatinous; can be left in place or removed; useful to control bleeding when other agents ineffective
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Collagen

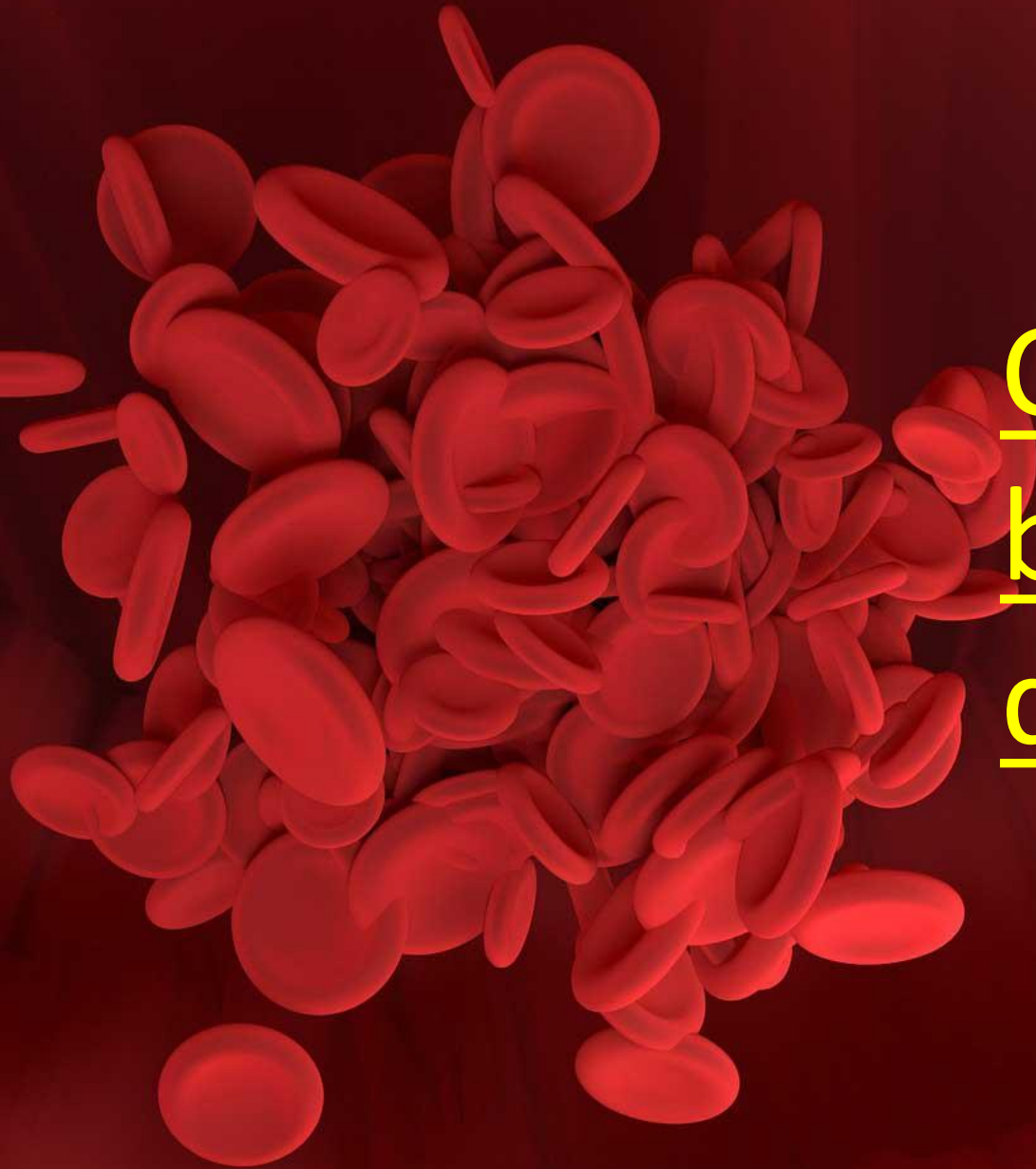
Instat	Johnson & Johnson	Absorbable collagen made from purified and lyophilized bovine dermal collagen; can be cut or shaped; adheres to bleeding surfaces when wet but does not stick to instruments, gloves, or gauze sponges	Mild to moderate bleeding usually controlled in 2–5 min; more expensive than Gelfoam
Avitene Helistat	MedChem Products Marion Merrell Dow	Microfibrillar collagen hemostat: dry, sterile, fibrous, water insoluble HCl acid salt—purified bovine corium collagen: MCH attracts platelets and triggers aggregation in fibrous mass	Thrombin ineffective with these agents because of inactivation as a result of pH factors; moderate to severe bleeding
Colla-Cote, Tape, Plug	Zimmer Dental	Absorbable collagen dressings from bovine sources; can be sutured into place, used under stents or dentures or alone; fully resorbed in 10–14 days	Shaped according to intended use: “cote” $\frac{3}{4} \times 1.5$ inch, tape 1×3 inch, plug $\frac{3}{8} \times \frac{3}{4}$ inch; all are superior hemostats for moderate to severe bleeding

Thrombin

Thrombostat	Parke-Davis	Topical thrombin—directly converts fibrinogen to fibrin; derived from bovine sources	One 5000-unit vial dissolved in 5 mL of saline can clot equal amount of blood in <1 s; useful in severe bleeding.
Thrombinar	Jones Medical		
Thrombogen	Johnson & Johnson—Merck		
Tranexamic acid		Tranexamic acid works as a competitive inhibitor of plasminogen activation; used as a mouth wash (5%), taken orally as a tablet, or given IV ϵ -Aminocaproic acid works as a competitive inhibitor of plasminogen activation; most often used as a mouth wash; can be taken orally or by IV	Useful in the short term for preventing hemorrhage after dental extractions
Lysteda (tablets)	Xanodyne		
Cyklokapron (IV)	Pfizer		
Amicar	Wyeth-Ayerst	Active ingredient is <i>N</i> -butyl 2-cyanoacrylate, serves as a glue to protect surgical wounds	Useful in the short term to prevent bleeding
Tablets (500 mg)			
Syrup (1.25 g/5 mL)			
IV (250 mg/mL)		Fibrin/tissue glue	Not available in the United States
Histocryl	B. Braun		
Beriplast	Behring Werke		



Acquired
bleeding
disorders



Congenital
bleeding
disorders

PREOPERATIVE RISK ASSESSMENT

- Evaluate and determine whether a bleeding disorder exists.
- Obtain medical consultation if undiagnosed, poorly controlled, or if uncertain. signs.
- Screen patients with bleeding history or clinical signs of a bleeding disorders with PT, aPTT, TT, and platelet count.
- Review recent laboratory test results to assess risk.

A

Analgesics	Avoid aspirin, aspirin-containing compounds, and other NSAIDs; acetaminophen with or without codeine is suggested for most patients.
Antibiotics	No issues.
Anesthesia	Avoid block anesthetic injections in patients not on desmopressin, aminocaproic acid, or factor concentrates.
Anxiety	No issues.
Allergy	Patients placed on factor VIII replacement need to be observed for signs and symptoms of allergy.

B

Bleeding	These patients are at great risk of bleeding from invasive dental procedures. Special precautions must be taken before invasive procedures. Patients with mild to moderate hemophilia can be managed using desmopressin and aminocaproic acid for many dental procedures. Factor VIII replacement is needed for patients with more severe hemophilia. Patients who are low responders for inhibitors (antibody response to factor VIII) require higher doses of factor VIII. Patients who are high responders are most difficult to manage and require activated factor VII, porcine factor VIII, steroids, or other special preparations such as prothrombin complex concentrates or activated prothrombin complex concentrations.
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Breathing No issues.
Blood pressure No issues.

C

Chair position No issues.
Cardiovascular No issues.
Consultation The patient's hematologist must be consulted before any invasive dental procedures are performed. The severity of disease must be established. The presence of inhibitors and level of response to factor VIII need to be determined. Determine if the patient can be managed with desmopressin and aminocaproic acid. Establish the type and dosage of factor replacement needed for invasive dental procedures or surgery. Determine if the patient can be managed in the dental office or will require hospitalization.

D

Devices Splints may be constructed before multiple extractions or surgical procedures in patients with severe hemophilia.
Drugs Avoid all drugs that may cause bleeding, such as aspirin and other NSAIDs, certain herbal medications, and over-the-counter drugs containing aspirin.

E

Equipment No issues.
Emergencies Excessive bleeding may occur after invasive dental procedures or surgery. Systemic and local means may be required to control the bleeding (see [Tables 25.3 and 25.6](#)).

POSTOPERATIVE CARE**F**

Follow-up Patients should be seen and examined for signs of bleeding within 24–48 h after surgical procedures.

Dr.Fahimeh Anbari

- Screen patients with positive history or clinical signs with lab tests
- Consultation
- Drugs/ Analgesics
- Anesthesia
- Devices
- Follow-up

- *mild factor VIII deficiency who lack inhibitors:*
 - ✓ often can be managed in the dental office for less invasive procedures such as scaling, soft tissue surgery, and extractions **without factor VIII replacement**;
 - ✓ desmopressin & aminocaproic acid or tranexamic acid may be used if needed.
- *moderate factor VIII deficiency without inhibitors :*
 - ✓ **may require factor VIII replacement for less invasive** dental procedures.
 - ✓ will require **factor VIII replacement for major oral surgery**
- *Patients with severe hemophilia :*
 - ✓ require **factor VIII replacement for all invasive** dental treatments

- *mild von Willebrand disease (type 1 and some type 2 variants):*
 - ✓ Surgical procedures can be performed in patients with the use of desmopressin, tranexamic acid, or aminocaproic acid
- *more severe types of von Willebrand disease:*
 - ✓ require factor VIII replacement

- Minimize Dental caries and periodontal disease
 - fluorides, fissure sealants ,dietary recommendations
 - Toothbrushing, flossing, regular dental visits
- Endodontic procedures should be performed, rather than extractions
- to control bleeding:
Intracanal injection of local anesthetic with epinephrine
- over-instrumentation and overfilling must be avoided

- Before oral surgery, the dentist can make splints
- Avoid block anesthetic injections in hemophilic patients not on desmopressin, aminocaproic acid, or factor concentrates
- Buccal approach : for surgical removal of mandibular third molars
- Wound sutures for primary healing whenever possible
- Examine for signs of bleeding within 24 -48 h after surgical procedures

The image features a dense cluster of red blood cells, depicted as biconcave discs, centered on a dark red background. The cells are rendered with a slight 3D effect, showing their characteristic shape and color. The background has a subtle, darker red pattern that resembles a microscopic view of tissue or a textured surface. The overall composition is simple and focused on the biological subject matter.

THANK YOU