Hemostasis and bleeding disorders

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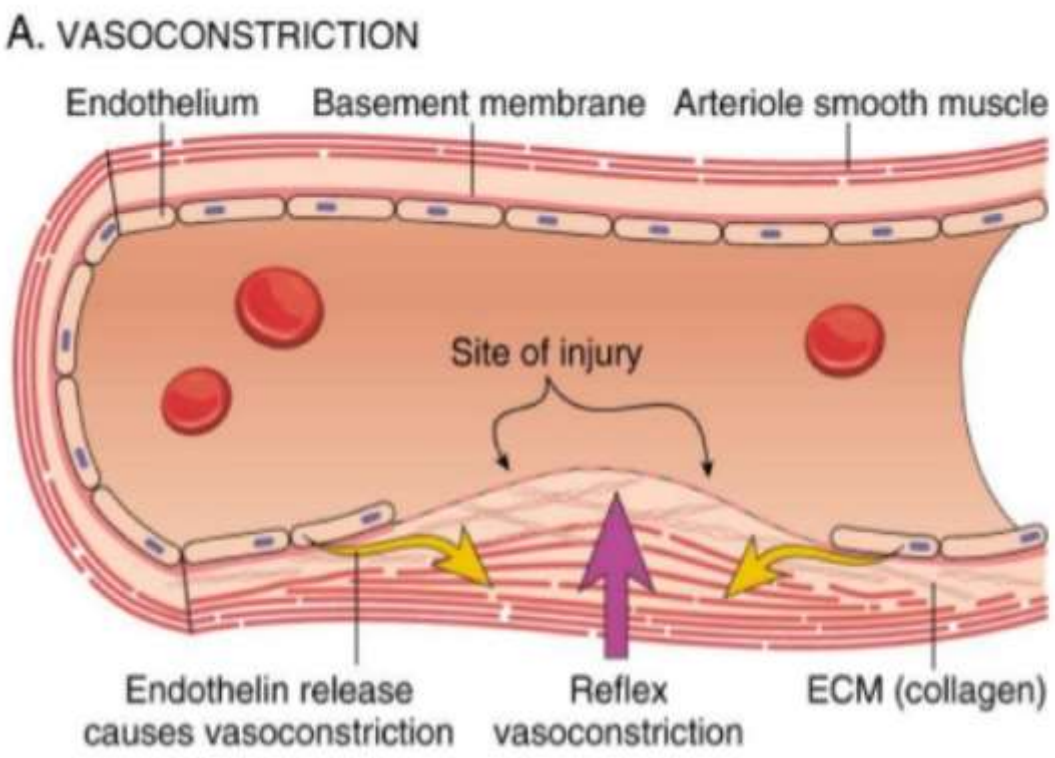
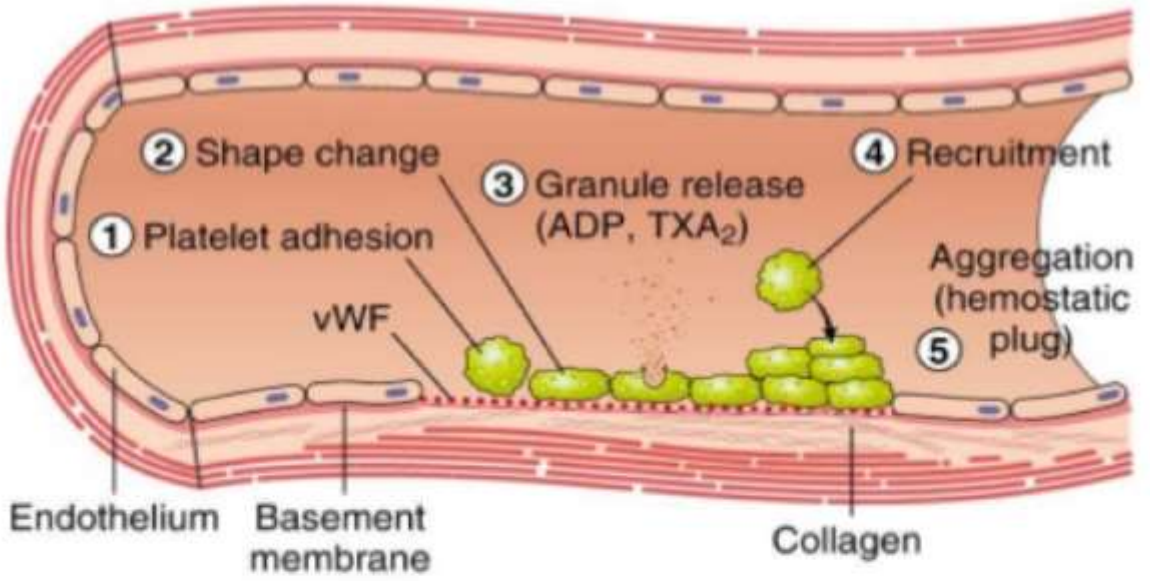
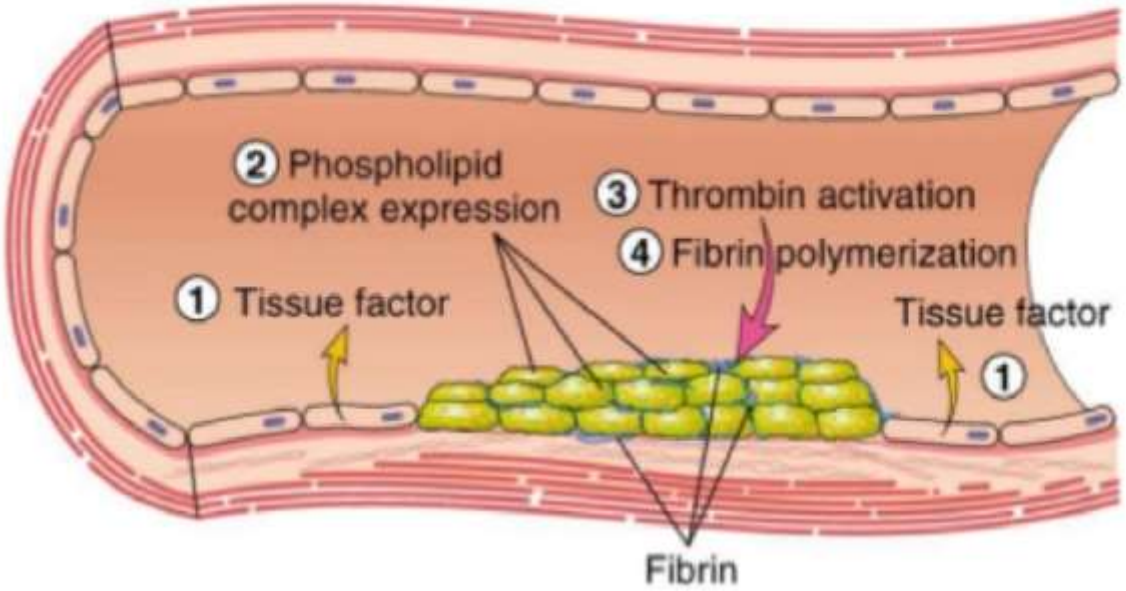
Hemostasis

- The dynamic process of coagulation as it occurs in areas of vascular injury.
- The main components : platelets, vascular wall, procoagulant and anticoagulant proteins, and fibrinolytic system.
- Hemostasis stages:
  1. vascular spasm, or vasoconstriction, a brief and intense contraction of blood vessels;
  2. formation of a platelet plug; stops bleeding within 3-7 minutes
  3. blood clotting or coagulation, which reinforces the platelet plug with fibrin mesh that acts as a glue to hold the clot together. Once blood flow has ceased, tissue repair can begin.

Hemostasis stages







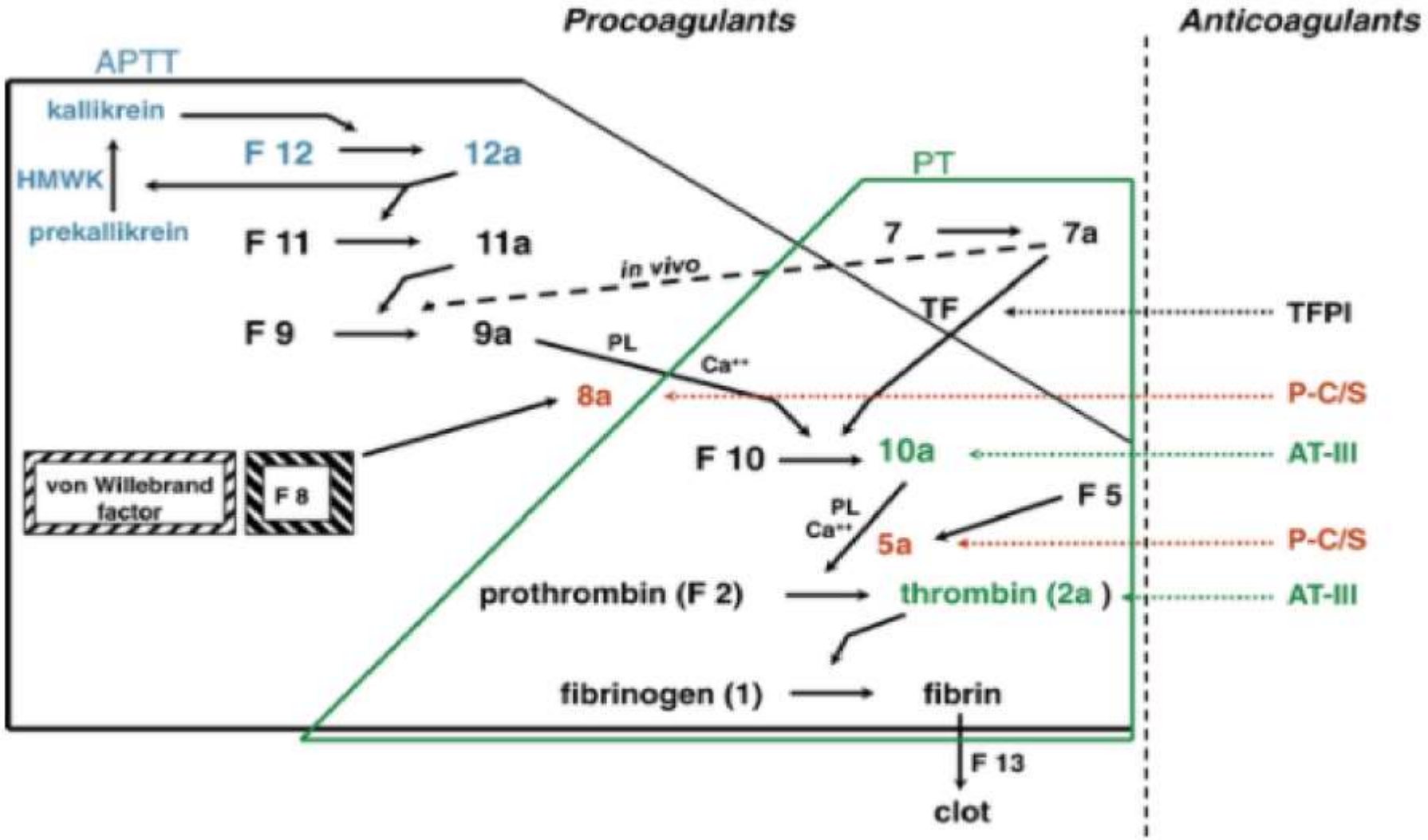
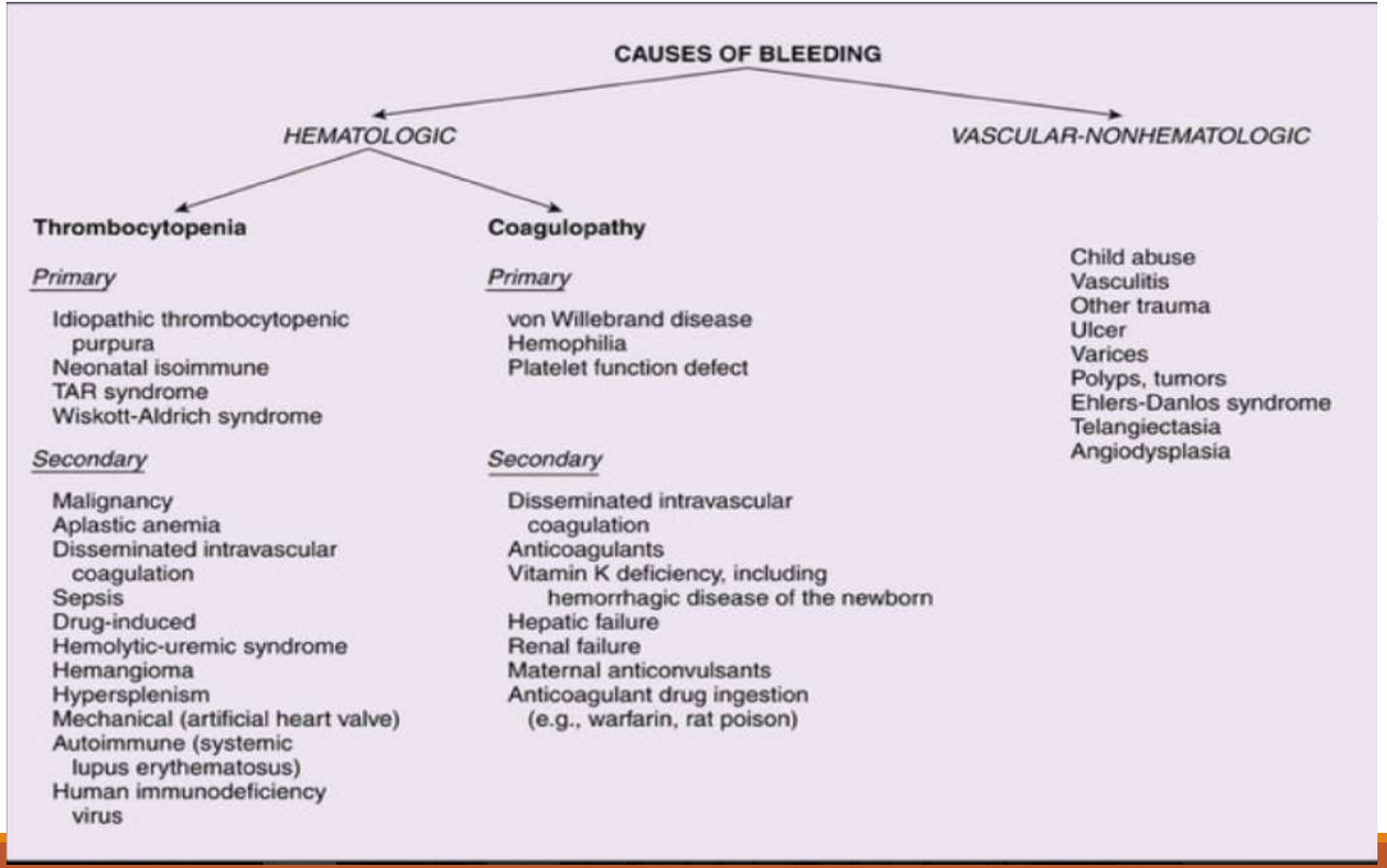


FIGURE 151-2 Simplified pathways of blood coagulation.
The area inside the solid black line is the intrinsic pathway measured by the activated partial thromboplastin time (APTT). The area inside the green line is the extrinsic pathway, measured by the prothrombin time (PT). The area encompassed by both lines is the common pathway. *AT-III*, Antithrombin III; *F*, factor; *HMWK*, high-molecular-weight kininogen; *P-C/S*, protein C/S; *PL*, phospholipid; *TFPI*, tissue factor pathway inhibitor

Clotting factor number	Clotting factor name	Function	Plasma half-life (h)	Plasma concentration (mg/L)
I	Fibrinogen	Clot formation	90	3000
II	Prothrombin	Activation of I, V, VII, VIII, XI, XIII, protein C, platelets	65	100
III	TF	Co factor of VIIa	-	-
IV	Calcium	Facilitates coagulation factor binding to phospholipids	-	-
V	Proacclerin, labile factor	Co-factor of X-prothrombinase complex	15	10
VI	Unassigned			
VII	Stable factor, proconvertin	Activates factors IX, X	5	0.5
VIII	Antihaemophilic factor A	Co-factor of IX-tenase complex	10	0.1
IX	Antihaemophilic factor B or Christmas factor	Activates X: Forms tenase complex with factor VIII	25	5
X	Stuart-Prower factor	Prothrombinase complex with factor V: Activates factor II	40	10
XI	Plasma thromboplastin antecedent	Activates factor IX	45	5
XII	Hageman factor	Activates factor XI, VII and prekallikrein		-
XIII	Fibrin-stabilising factor	Crosslinks fibrin	200	30
XIV	Prekallikerin (F Fletcher)	Serine protease zymogen	35	
XV	HMWK- (F Fitzgerald)	Co factor	150	
XVI	vWf	Binds to VIII, mediates platelet adhesion	12	10 µg/mL
XVII	Antithrombin III	Inhibits IIa, Xa, and other proteases	72	0.15-0.2 mg/mL
XVIII	Heparin cofactor II	Inhibits IIa	60	-
XIX	Protein C	Inactivates Va and VIIIa	0.4	-
XX	Protein S	Cofactor for activated protein C		-

HMWK – High molecular weight kininogen; vWf – Von Willebrand factor; TF – Tissue factor


CAUSES OF BLEEDING
HEMATOLOGIC
VASCULAR-NONHEMATOLOGIC
Thrombocytopenia
Primary
Idiopathic thrombocytopenic purpura
Neonatal isoimmune
TAR syndrome
Wiskott-Aldrich syndrome
Secondary
Malignancy
Aplastic anemia
Disseminated intravascular coagulation
Sepsis
Drug-induced
Hemolytic-uremic syndrome
Hemangioma
Hypersplenism
Mechanical (artificial heart valve)
Autoimmune (systemic lupus erythematosus)
Human immunodeficiency virus
Coagulopathy
Primary
von Willebrand disease
Hemophilia
Platelet function defect
Secondary
Disseminated intravascular coagulation
Anticoagulants
Vitamin K deficiency, including hemorrhagic disease of the newborn
Hepatic failure
Renal failure
Maternal anticonvulsants
Anticoagulant drug ingestion (e.g., warfarin, rat poison)
Child abuse
Vasculitis
Other trauma
Ulcer
Varices
Polyps, tumors
Ehlers-Danlos syndrome
Telangiectasia
Angiodysplasia

Hemostatic disorders

Clinical history inquiry should include:

- A detailed **family history** of bleeding and thrombotic disorders
- Age at onset of bleeding indicates whether the problem is congenital or acquired
- The **sites of bleeding** (mucocutaneous or deep) and **degree of trauma** (spontaneous or significant)
- Medication history

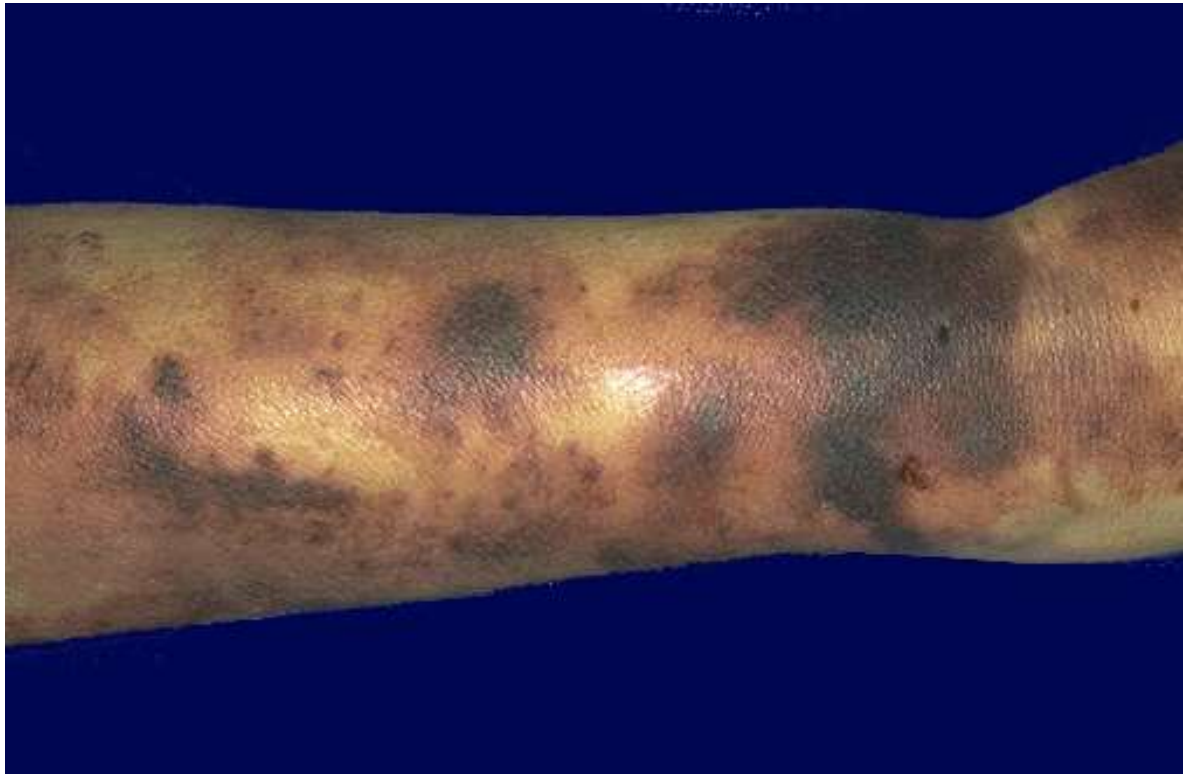
physical examination:

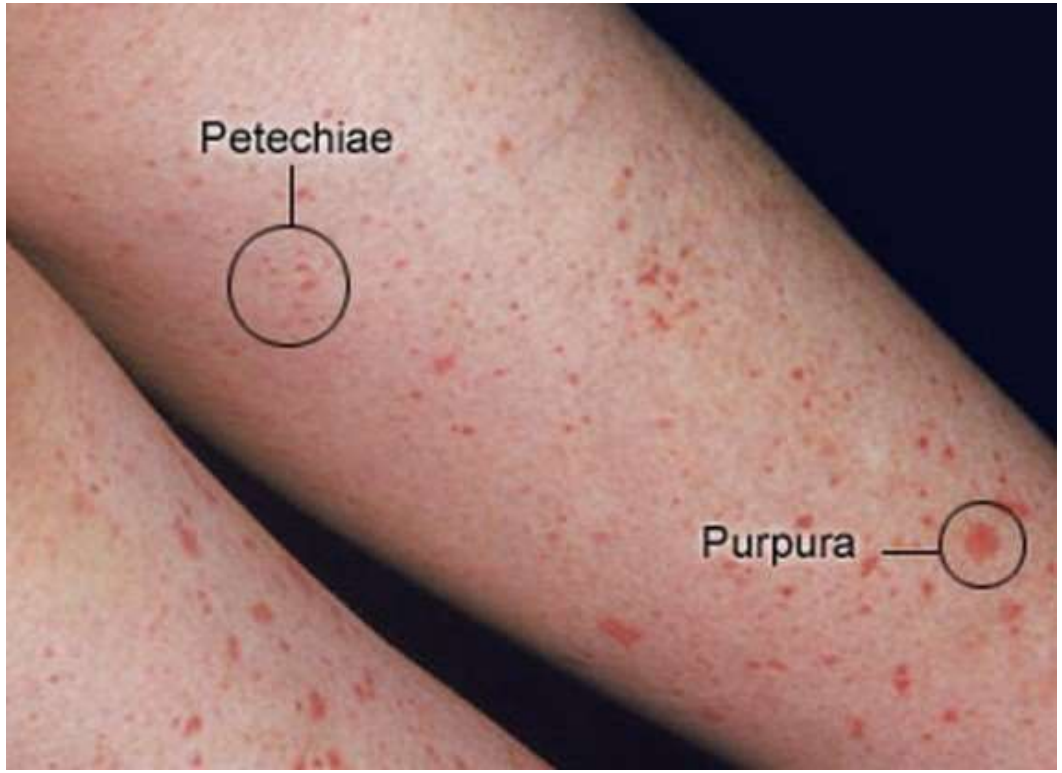
- Presence of superficial bleeding (skin or mucous membrane), or deeper bleeding (muscle, joints or internal organs)
- **Petechia**: non-blanching lesion <2 mm. **Purpura** is a group of adjoining petechiae, **ecchymoses** (bruises) are isolated lesions larger than petechiae, and **hematomas** are raised, palpable ecchymoses.
- manifestations of an underlying disease, lymphadenopathy, hepatosplenomegaly.
- Manifestations of thrombosis or arterial clot

Clinical manifestations of bleeding disorders

Bleeding symptoms	Bleeding disorder	
	Platelet defects (qualitative or quantitative)	Clotting factor deficiencies (eg, factor VIII or factor IX deficiencies)
Overview of bleeding events	**Mucocutaneous bleeding (oral cavity, nasal, gastrointestinal, and genitourinary sites)**	**Deep tissue bleeding (including joints and muscles)**
Excessive bleeding after minor cuts	Yes	Not usually
Petechiae	Common	Uncommon
Ecchymoses	Generally small and superficial; may be significant, depending upon the defect or degree of thrombocytopenia	May develop large subcutaneous and soft tissue hematomas
Hemarthroses, muscle hematomas	Uncommon	Common in severe deficiency states or in association with injury in those with mild to moderate deficiency states
Bleeding with invasive procedures, including surgery	Often immediate, with degree of bleeding dependent upon the severity of the defect, ranging from none (eg, mild degrees of thrombocytopenia or mild platelet function defect) to mild to severe (eg, Glanzmann thrombasthenia)	May be associated either with procedural bleeding or delayed bleeding, depending upon the type and severity of the defect

Non-blanching rashes
Ecchymoses, petechiae and purpura

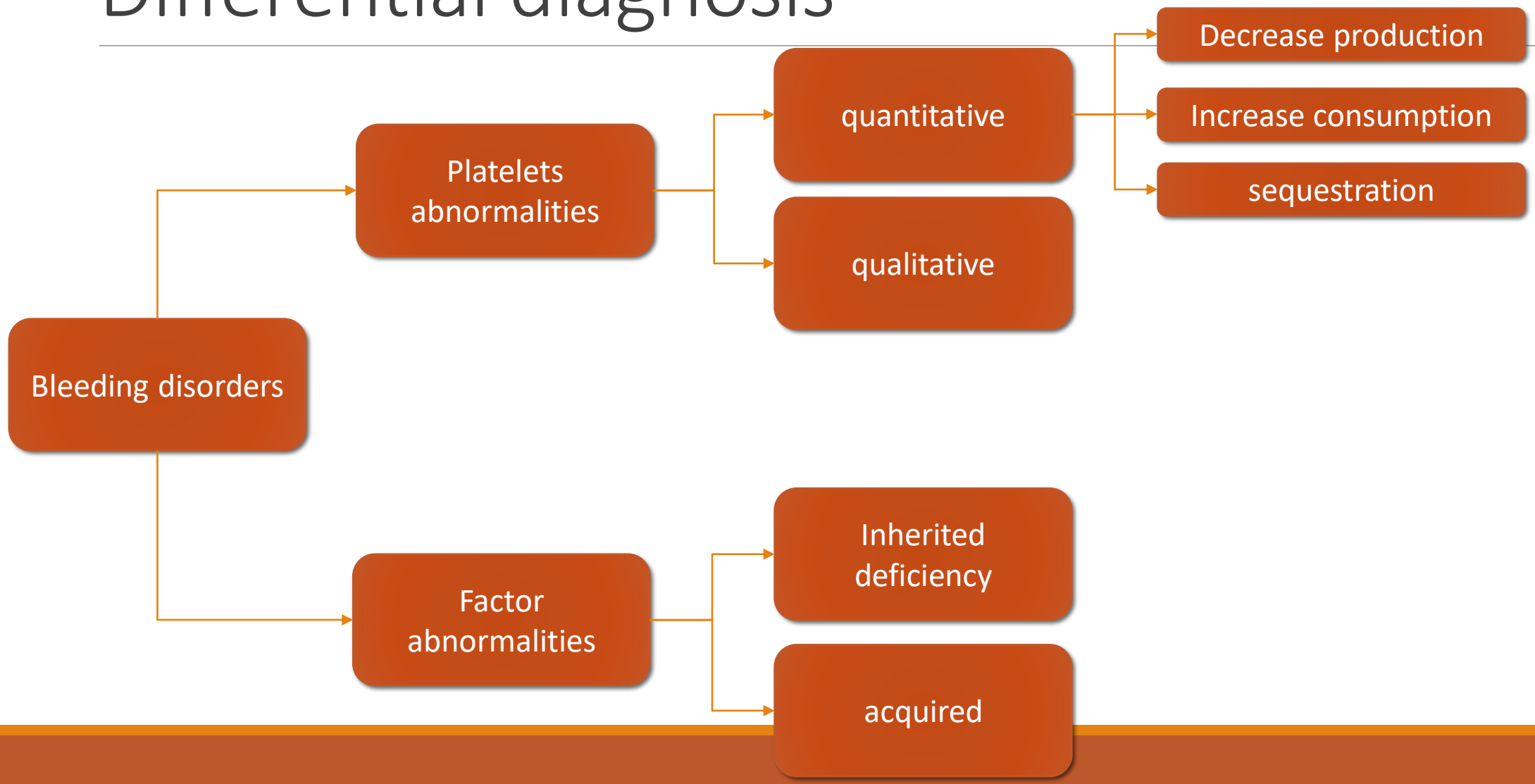




Initial laboratory tests

TEST	MECHANISM TESTED	NORMAL VALUES	DISORDER
Prothrombin time	Extrinsic and common pathway	<12 sec beyond neonate; 12–18 sec in term neonate	Defect in vitamin K–dependent factors; hemorrhagic disease of newborn, malabsorption, liver disease, DIC, oral anticoagulants, ingestion of rat poison
Activated partial thromboplastin time	Intrinsic and common pathway	25–40 sec beyond neonate; 70 sec in term neonate	Hemophilia; von Willebrand disease, heparin; DIC; deficient factors 12 and 11; lupus anticoagulant
Thrombin time	Fibrinogen to fibrin conversion	10–15 sec beyond neonate; 12–17 sec in term neonate	Fibrin split products, DIC, hypofibrinogenemia, heparin, uremia
Bleeding time	Hemostasis, capillary and platelet function	3–7 min beyond neonate	Platelet dysfunction, thrombocytopenia, von Willebrand disease, aspirin
Platelet count	Platelet number	150,000–450,000/mL	Thrombocytopenia differential diagnosis
PFA	Closure time		
Blood smear	Platelet number and size; RBC morphology	–	Large platelets suggest peripheral destruction; fragmented, bizarre RBC morphology suggests microangiopathic process (e.g., hemolytic uremic syndrome, hemangioma, DIC)

Differential diagnosis



Disorders of platelets

Thrombocytopenia: platelets less than 150,000/mm^3

Mucocutaneous bleeding is the hallmark of platelet disorders

platelet counts less than 20,000/mm^3 carries risk for spontaneous bleeding

Etiology:

- 1- decreased production on either a congenital or an acquired
- 2- sequestration of the platelets within an enlarged spleen or other organ,
- 3- increased destruction of normally synthesized platelets on either an immune or a nonimmune basis

Differential diagnosis of childhood thrombocytopenic syndromes

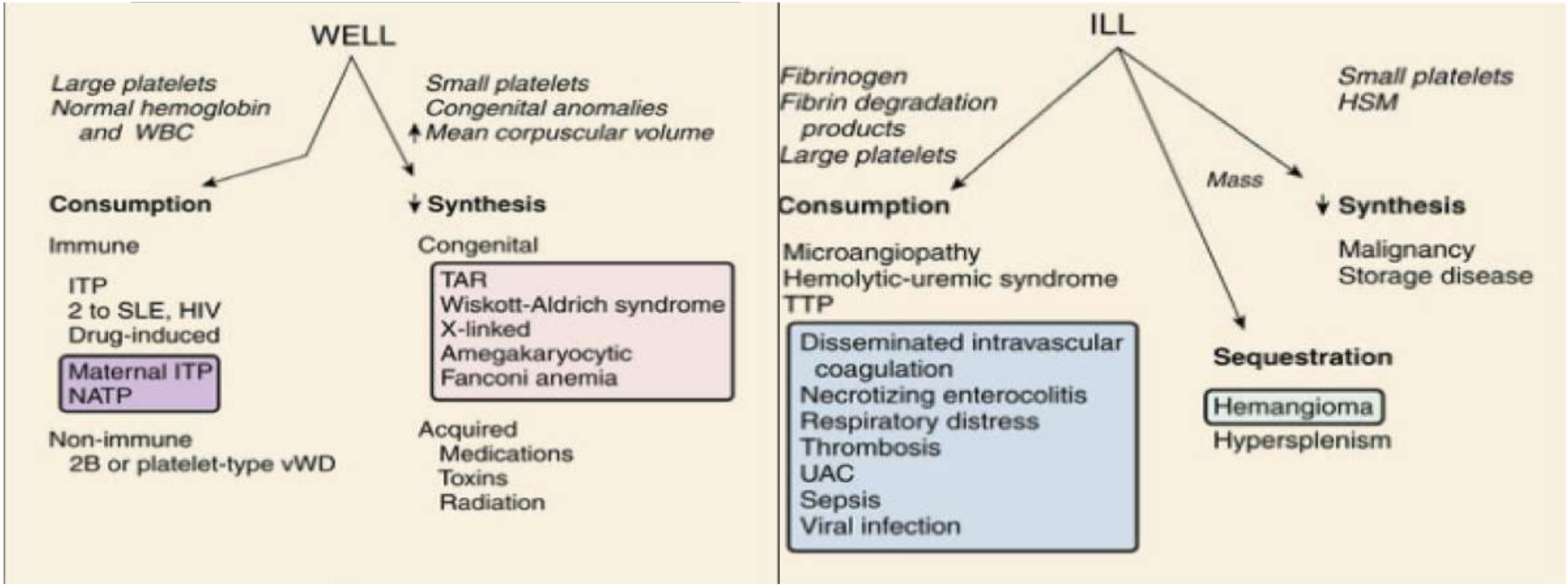


Table 484-1 Differential Diagnosis of Thrombocytopenia in Children and Adolescents

DESTRUCTIVE THROMBOCYTOPENIAS

Primary Platelet Consumption Syndromes

Immune thrombocytopenias
- Acute and chronic ITP
- Autoimmune diseases with chronic ITP as a manifestation
  - Cyclic thrombocytopenia
  - Autoimmune lymphoproliferative syndrome and its variants
  - Systemic lupus erythematosus
  - Evans syndrome
  - Antiphospholipid antibody syndrome
  - Neoplasia-associated immune thrombocytopenia
- Thrombocytopenia associated with HIV
- Neonatal immune thrombocytopenia
  - Alloimmune
  - Autoimmune (e.g., maternal ITP)
- Drug-induced immune thrombocytopenia (including heparin-induced thrombocytopenia)
- Posttransfusion purpura
- Allergy and anaphylaxis
- Posttransplant thrombocytopenia

Nonimmune thrombocytopenias
- Thrombocytopenia of infection
  - Bacteremia or fungemia
  - Viral infection
  - Protozoan
- Thrombotic microangiopathic disorders
  - Hemolytic-uremic syndrome
  - Eclampsia, HELLP syndrome
  - Thrombotic thrombocytopenic purpura
  - Bone marrow transplantation-associated microangiopathy
  - Drug-induced
- Platelets in contact with foreign material
- Congenital heart disease
- Drug-induced via direct platelet effects (ristocetin, protamine)
- Type 2B VWD or platelet-type VWD

Combined Platelet and Fibrinogen Consumption Syndromes
- Disseminated intravascular coagulation
- Kasabach-Merritt syndrome
- Virus-associated hemophagocytic syndrome

IMPAIRED PLATELET PRODUCTION
- Hereditary disorders
- Acquired disorders
  - Aplastic anemia
  - Myelodysplastic syndrome
  - Marrow infiltrative process—neoplasia
  - Osteopetrosis
  - Nutritional deficiency states (iron, folate, vitamin B_{12}, anorexia nervosa)
  - Drug- or radiation-induced thrombocytopenia
  - Neonatal hypoxia or placental insufficiency

SEQUESTRATION
- Hypersplenism
- Hypothermia
- Burns

HELLP, hemolysis, elevated liver enzymes, and low platelets; HIV, human immunodeficiency virus; ITP, immune thrombocytopenic purpura; VWD, von Willebrand disease.

From Wilson DB: Acquired platelet defects. In Orkin SH, Nathan DG, Ginsburg D, et al, editors: Nathan and Oski's hematology of infancy and childhood, *ed 7, Philadelphia, 2009, WB Saunders, p. 1555, Box 33-1.*

Autoimmune thrombocytopenic purpura of childhood (childhood ITP)

- The most common cause of acute onset of thrombocytopenia in otherwise healthy child
- Incidence in Males=females
- Peak incidence between 1 – 4 years of age
- Follows acute viral infection
  - Most common viruses have been described in association with ITP, including Epstein-Barr virus and HIV .
  - Epstein-Barr virus-related ITP is usually of short duration and follows the course of infectious mononucleosis.
  - HIV-associated ITP is usually chronic (lasts more than 6 months).
- abrupt onset of petechial, purpura, and epistaxis. Other physical exam findings are normal
- normal red blood cell (RBC) and white blood cell (WBC) counts.

ITP

- usually 1 to 4 weeks after an acute viral infection (commonest cause)
- antibody (IgG or IgM) that binds to the platelet membrane.
- splenic destruction of antibody-coated platelets leading to sever thrombocytopenia < 10.000 platelets/mm3
- Diagnosis is based on clinical presentation and the platelet count.
- bone marrow examination is not necessary, unless indicated.

Treatment

- Therapy is seldom indicated for platelet counts greater than 20,000/mm^3
- Therapy for moderate and severe clinical bleeding with severe thrombocytopenia (platelet count <10,000/mm3):
  - **prednisone** , 2 to 4 mg/kg/24 hours for 2 weeks
  - IVIG, 1 g/kg/24 hours for 1 to 2 days
  - Splenectomy is indicated in acute ITP only for life-threatening bleeding.
- Repeated treatments with IVIG, IV anti-D, or high-dose pulse steroids are effective in delaying the need for splenectomy
- Platelet transfusion in ITP is usually contraindicated unless life-threatening bleeding is present

prognosis

Intracranial bleeding, occurs in fewer than 1% of patients with ITP

Therapy does not affect the long-term outcome of ITP

Approximately 80% of children have a spontaneous resolution within 6 months after diagnosis.

Chronic ITP : lasts >6 months, Secondary causes of chronic ITP, especially SLE and HIV infection

Splenectomy induces a remission in 70% to 80% of childhood chronic ITP cases.

Other disorders associated with low platelets

Wiskott-Aldrich syndrome

- X-linked disorder characterized by hypogammaglobinemia, eczema, and thrombocytopenia
- Plateles are small
- Hematopoietic stem cell transplantation cures the immunodeficiency and thrombocytopenia

Thrombotic microangiopathy

- thrombocytopenia, anemia secondary to intravascular RBC destruction

Disseminated intravascular coagulation (DIC)

- wide-ranging hemostatic disorder with activation and clearance of platelets

thrombotic thrombocytopenic purpura

- platelet consumption, precipitated by a congenital or acquired deficiency of a metalloproteinase that cleaves von Willebrand factor.

Platelets function disorders

- Congenital :
  - Glanzmann thrombasthenia .
  - Bernard-Soulier syndrome .
- Acquired :
  - systemic illnesses, e.g., liver disease, kidney disease (uremia).
  - drugs, e.g., acetylsalicylic acid (aspirin).
  - Other nonsteroidal anti-inflammatory drugs, valproic acid, and high-dose penicillin.

Bernard-Soulier syndrome

a severe congenital platelet function disorder, is caused by absence or severe deficiency of the VWF receptor (GPIb complex) on the platelet membrane.

characterized by thrombocytopenia, with giant platelets and markedly prolonged bleeding time (>20 min) .

inherited as an autosomal recessive disorder.

Glanzmann thrombasthenia

Is a congenital disorder associated with severe platelet dysfunction (aggregation dysfunction) that yields prolonged bleeding time and a normal platelet count.

Platelets have normal size and morphologic features on the peripheral blood smear.

Is inherited in an autosomal recessive manner.

For both Bernard-Soulier syndrome and Glanzmann thrombasthenia, the diagnosis is confirmed by flow cytometric analysis of the patient's platelet glycoproteins

Hereditary Clotting Factor Deficiencies (Bleeding Disorders)

Factor 8 and factor 9 deficiencies (Hemophilias) are the most common severe inherited bleeding disorders.

von Willebrand disease is the most common congenital bleeding disorder.

Procoagulant proteins:

Deficiency contact factors (prekallikrein, kininogen, and factor 12) cause a prolonged activated partial thromboplastin time (APTT) but are not associated with a predisposition to bleeding.

Hemophilia

Hemophilia A (factor 8 deficiency) occurs in 1 in 5000 males.

Hemophilia B (factor 9 deficiency), also called Christmas disease, occurs in approximately 1 in 25,000

Clinically the two disorders are indistinguishable

The severity of the disorder is determined by the degree of clotting factor deficiency:

- Severe hemophilia: less than 1% factor 8 or factor 9
- Moderate hemophilia: 1% to 5% factor 8 or factor
- Mild hemophilia: >5% factor 8 or factor 9

Clinical features

Neither factor VIII nor factor IX crosses the placenta; bleeding symptoms may be present from birth or may occur in the fetus.

Only 2% of neonates with hemophilia sustain intracranial hemorrhages .

30% of male infants with hemophilia bleed with circumcision.

Obvious symptoms such as easy bruising, intramuscular hematomas, and hemarthroses begin when the child begins to cruise.

The hallmark of hemophilic bleeding is **hemarthroses** which may be induced by minor trauma or occur spontaneously .

spontaneous bleeding in sever hemophilia < 1 %

Life-threatening bleeding in the patient with hemophilia is caused by bleeding into vital structures (central nervous system, upper airway

labs

- prolonged aPTT.
- Results of the other screening tests of the hemostatic mechanism (platelet count, bleeding time, prothrombin time, and thrombin time) are normal.
- The specific assay for factors VIII and IX will confirm the diagnosis of hemophilia.

Treatment

Early, appropriate **replacement therapy** is the hallmark of excellent hemophilia care

Prophylactic therapy starting in infancy has greatly diminished the likelihood of chronic arthropathy in children with hemophilia.

Recombinant factor VIII (FVIII) or recombinant factor IX (FIX)

Desmopressin acetate increase factor 8 level in patient with mild or moderate hemophilia A.


Hemophilia

complications

Long-term complications of hemophilia A and B include :

Chronic arthropathy, development of an inhibitor to either factor VIII or factor IX,

Risk of transfusion-transmitted infectious diseases (not with recombinant factors)

Von Willebrand Disease

von Willebrand disease (VWD) is the most common inherited bleeding disorder, with an estimated prevalence cited at 1 : 100 to 1 : 10,000 .

VWF has several functions in coagulation. First, VWF serves to tether platelets to injured subendothelium via binding sites for platelets and for collagen. Second, VWF serves as a carrier protein for factor VIII (FVIII),

VWD typically presents with mucosal bleeding, similar to that seen with other platelet defects.

Epistaxis, easy bruising, and menorrhagia in women are common complaints.

Symptoms, however, are variable, and do not necessarily correlate well with VWF levels.

Surgical bleeding, particularly with dental extractions or adenotonsillectomy, is another common presentation.

Severe type 3 VWD may present with joint bleeds.

Most patients will have a family history of bleeding. Women are more likely to be diagnosed with VWD because of the potential for symptoms with menorrhagia.

CLASSIFICATION

Table 1. Classification of von Willebrand Disease

Type	Description
1	Partial quantitative deficiency of VWF
2	Qualitative VWF defects
2A	Decreased VWF-dependent platelet adhesion with deficiency of HMW multimers
2B	Increased affinity for platelet GPIbα
2M	Decreased VWF-dependent platelet adhesion with a normal multimer distribution
2N	Decreased VWF binding affinity for FVIII
3	Virtually complete deficiency of VWF

FVIII, factor VIII; HMW, high-molecular-weight; VWF, von Willebrand factor.

treatment

Table 477-3	VWD Treatment		
TREATMENT	**VWD TYPES**	**ADMINISTRATION**	**DOSING**
Desmopressin*	Type 1 VWD Some type 2 VWD (use with caution)	IV or IN	0.3 µg/kg IV† 1 spray IN (<50 kg) 2 sprays IN (>50 kg)
von Willebrand factor concentrates‡	Type 3 VWD Type 2 VWD Severe type 1 VWD (or type 1 clearance defects)	IV	40-60 ristocetin cofactor activity units/kg (adjust dose depending on baseline VWF level and desired peak VWF level)

FEATURE	HEMOPHILIA A	HEMOPHILIA B	VON WILLEBRAND DISEASE
Inheritance	X-linked	X-linked	Autosomal dominant
Factor deficiency	Factor 8	Factor 9	vWF, factor 8
Bleeding site(s)	Muscle, joint, surgical	Muscle, joint, surgical	Mucous membranes, skin, surgical, menstrual
Prothrombin time	Normal	Normal	Normal
Activated partial thromboplastin time	Prolonged	Prolonged	Prolonged or normal
Bleeding time/PFA-100	Normal	Normal	Prolonged or normal
Factor 8 coagulant activity	Low	Normal	Low or normal
von Willebrand factor antigen	Normal	Normal	Low
von Willebrand factor activity	Normal	Normal	Low
Factor 9	Normal	Low	Normal
Ristocetin-induced platelet agglutination	Normal	Normal	Normal, low, or increased at low-dose ristocetin
Platelet aggregation	Normal	Normal	Normal
Treatment	DDAVP* or recombinant factor 8	Recombinant factor 9	DDAVP* or vWF concentrate

Thank you