[هذا العمل اجتهاد شخصي لا يغني عن المصدر الأساسي للمقرر]

Hematologic disorders		
1	Anemia and sickle cell disease	
2	Transfusion problems	
3	Lymphomas and leukemias	
4	Multiple myeloma	
5	Coagulopathies and DVT	

Anemia and sickle cell disease:

1. Recognize **common presentations** of anemic patients and identify **types** of **anemia.**
2. To be able to approach anemic patient and **differentiate between Iron deficiency anemia and thalassemia** based on **iron studies** and **electrophoresis.**
3. To be able to manage **iron deficiency** anemia with **iron supplements.**
4. To understand the **pathophysiology** of hemoglobinopathy in **sickle cell disease** and **thalassemia.**
5. Approach patients with **vaso-occlusive crisis** and identify **acute chest syndrome.**
6. To identify **hemolytic** anemia.

Transfusion problems:

1. To recognize **common blood transfusion reactions.**
2. To be able to **manage** patients with **anaphylaxis.**

Lymphomas and leukemias:

1. To be able to recognize the **B-symptoms.**
2. To identify **common presentations** of patients with **lymphomas.**
3. To be able to list a workup plan to establish the **diagnosis of lymphoma.**
4. Recognize patients presenting with **leukemias** and to be able to differentiate between the **types.**

Multiple myeloma:

1. To be able to identify the **common presentation** of multiple myeloma and apply the **CRAB criteria.**

Coagulopathies and DVT:

1. To understand the **pathophysiology** in **hemophilia** and the **common presentation.**
2. To identify the **disseminated intravascular coagulation** based on **lab works and clinical presentation.**
3. Understand the **pathophysiology of Von Willebrand** disease
4. **Identify** pts presenting with **hypercoagulable states.**
5. Identify pts presenting with **acute deep vein thrombosis** & initiate **work-up** plan and **management.**

Anemia

★ A decrease in the quantity of circulating RBC, represented by a reduction in Hb concentration, Hct, or RBC count.
★ The causes of microcytic anemia can be remembered with **IRON LAST**: **IRON** deficiency, **L**ead poisoning, **A**nemia of chronic disease, **S**ideroblastic anemia, **T**halassemia.

Clinical features

(1) Pallor (mucous membranes, conjunctivae), Exertional dyspnea and fatigue, Muscle cramps.
(2) Jaundice (in hemolytic anemia), Worsening of angina pectoris, Pica (craving for ice or dirt).
(3) Features of hyperdynamic state: Bounding pulses, tachycardia/palpitations, flow murmur, pulsatile sound in ear.
(4) Features of extramedullary hematopoiesis may be present in certain severe, chronic forms of anemia (e.g., thalassemia, myelofibrosis): Hepatosplenomegaly, Paravertebral mass, Widening of diploic spaces of the skull.

Diagnostics

(1) **History**: Bleeding (recent surgery/trauma, menorrhagia, melena), Chronic disease (RA, underlying malignancy), Medication (recent isoniazid use), FHx of inherited anemias or hemophilia, Alcohol use.

(2) **CBC**[2]:

A. MCV < 80 fL = **microcytic** anemia

1. **Check iron studies** (serum iron, ferritin, TIBC, % iron saturation)
   - Low ferritin: iron deficiency anemia (IDA).
   - High/normal ferritin
     - High TIBC: IDA.
     - Low/normal TIBC: consider other Dx.
       - High CRP/ESR and/or Hx of chronic disease: anemia of chronic disease
       - Abnormal electrophoresis: thalassemia.
       - Peripheral blood smear with basophilic stippling: lead poisoning, sideroblastic anemia, thalassemias, myelodysplastic syndromes.
       - Bone marrow biopsy with ringed sideroblasts: sideroblastic anemia.[3]
   - Normal iron studies: workup for acute blood loss, hemolytic anemia, thalassemia, sideroblastic anemia.
2. **Check reticulocyte count**
   - Low (< 2%) indicates ineffective or decreased RBC production: IDA, Anemia of chronic disease, Sideroblastic anemia, Lead poisoning.
   - Normal/high: thalassemia (> 2 %).

B. MCV 80–100 fL = **normocytic** anemia

1. Check iron studies.
2. Check reticulocyte count to evaluate bone marrow response
   - Low reticulocyte count (< 2%) shows ineffective or decreased RBC production (hypoproliferative anemia): Anemia of CKD (Low EPO), Aplastic anemia (Normal/high EPO), Anemia of chronic disease, Malignancy (e.g., acute leukemia).
   - Normal/high reticulocyte count (> 2%)
     - Sign of hemolysis (↓ haptoglobin, ↑ LDH, unconjugated bilirubin, schistocytes): hemolytic anemia.
     - No sign of hemolysis: acute blood loss anemia.

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[2] MCV is the most important initial test in the diagnostic workup. Based on RBC size, further testing should be performed to determine the underlying cause.
[3] In sideroblastic anemia, the bone marrow produces ringed sideroblasts rather than erythrocytes and the body cannot incorporate iron into hemoglobin, resulting in increased serum iron and ferritin levels and increased iron saturation.

C. MCV > 100 fL = **macrocytic** anemia

1. Check peripheral blood smear:
   - Hypersegmented neutrophils (> 5 lobes) present: megaloblastic anemia.
     - Normal methylmalonic acid, ↑ homocysteine levels in serum: folic acid deficiency.
     - ↑ Methylmalonic acid, ↑ homocysteine levels in serum: vitamin B12 deficiency.
     - Orotic acid in urine: orotic aciduria.
   - No hypersegmented neutrophils present: non megaloblastic anemia:
     - Electrophoresis with ↑ HbF level: Diamond-Blackfan anemia.
     - Dysplastic RBCs and/or WBCs: myelodysplastic syndrome
     - Abnormal TSH (hypothyroidism), Alcohol use, Liver disease

Serum laboratory results in microcytic anemia

	Iron	Ferritin	% Iron saturation	Transferrin or TIBC	Reticulocyte count	RDW[4]
IDA	↓	↓	↓	↑	↓	↑
Thalassemia	Normal to ↑*	Normal to ↑*	Normal to ↑*	Normal to ↓*	Normal or ↑	Normal (occasionally ↑)
Chronic disease	↓	↑	Normal to ↓	↓	↓	Normal
Sideroblastic	↑	↑	↑	↓	↓	↑

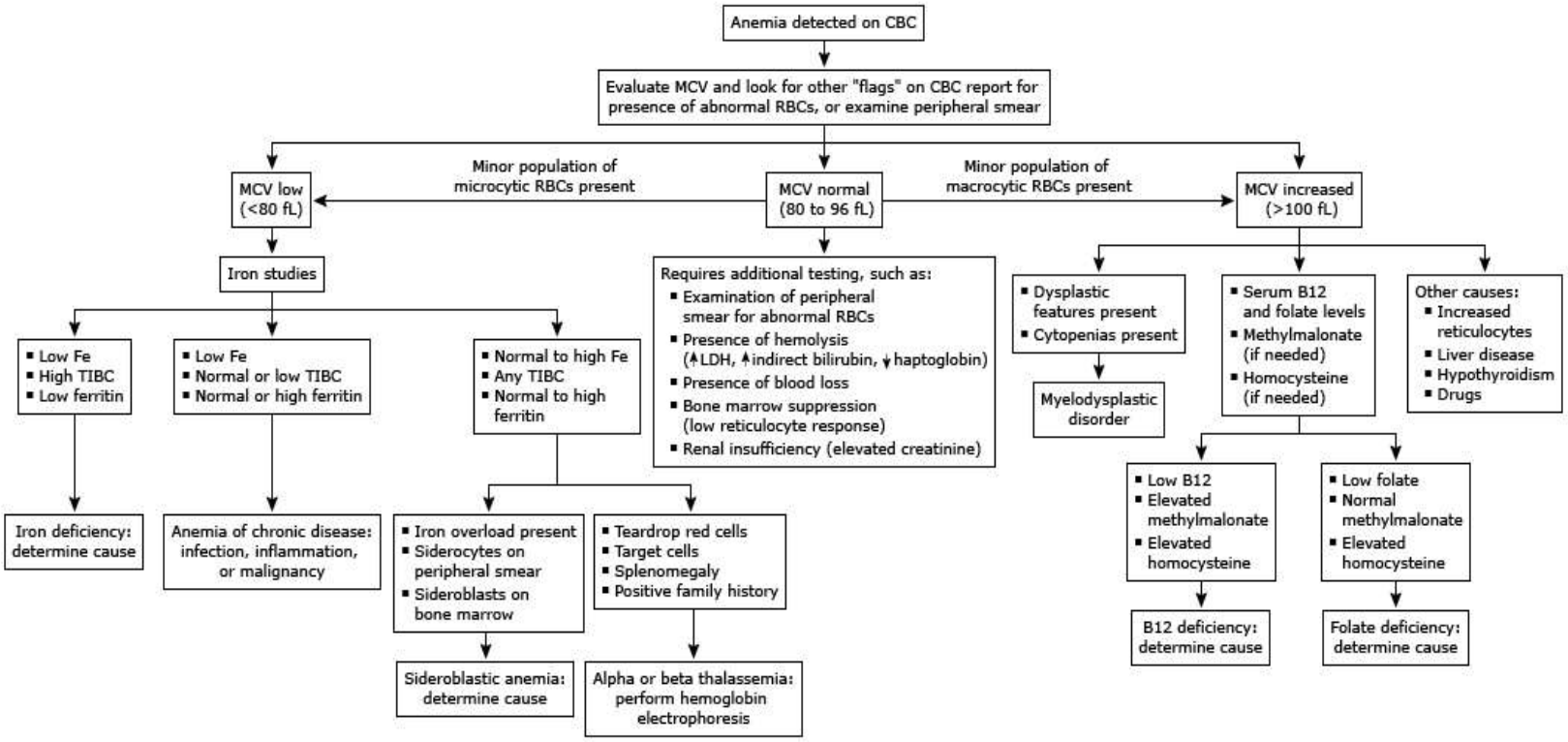
* If iron overload is present (e.g., due to multiple transfusions, ineffective erythropoiesis, ↑ GI iron absorption).

(3) Peripheral blood smear (manual examination under a microscope): May reveal classic pathologic RBC forms, which can be used to identify certain types of anemia that automated RBC indices cannot (e.g., schistocytes in hemolytic anemia).

(4) Bone marrow biopsy (manual examination of bone marrow aspirate under a microscope):

- Indications include pancytopenia and/or abnormal cells on CBC or peripheral blood smear (e.g., blasts).
- Prussian blue staining if sideroblastic anemia is suspected.
- Can be used to diagnose: Aplastic anemia, Myelodysplastic syndromes, Myeloproliferative neoplasm, Malignant invasion of the bone marrow.

[4] High RDW is a marker of anisocytosis (varying sizes of RBCs).


Anemia detected on CBC
Evaluate MCV and look for other "flags" on CBC report for presence of abnormal RBCs, or examine peripheral smear
MCV low (<80 fL)
Minor population of microcytic RBCs present
MCV normal (80 to 96 fL)
Minor population of macrocytic RBCs present
MCV increased (>100 fL)
Iron studies
Requires additional testing, such as:
Examination of peripheral smear for abnormal RBCs
Presence of hemolysis (↑LDH, ↑indirect bilirubin, ↓haptoglobin)
Presence of blood loss
Bone marrow suppression (low reticulocyte response)
Renal insufficiency (elevated creatinine)
Dysplastic features present
Cytopenias present
Myelodysplastic disorder
Serum B12 and folate levels
Methylmalonate (if needed)
Homocysteine (if needed)
Other causes:
Increased reticulocytes
Liver disease
Hypothyroidism
Drugs
Low Fe
High TIBC
Low ferritin
Iron deficiency: determine cause
Low Fe
Normal or low TIBC
Normal or high ferritin
Anemia of chronic disease: infection, inflammation, or malignancy
Normal to high Fe
Any TIBC
Normal to high ferritin
Iron overload present
Siderocytes on peripheral smear
Sideroblasts on bone marrow
Sideroblastic anemia: determine cause
Teardrop red cells
Target cells
Splenomegaly
Positive family history
Alpha or beta thalassemia: perform hemoglobin electrophoresis
Low B12
Elevated methylmalonate
Elevated homocysteine
B12 deficiency: determine cause
Low folate
Normal methylmalonate
Elevated homocysteine
Folate deficiency: determine cause

IDA (Iron Deficiency Anemia)

Clinical features

- S&Sx of anemia: Fatigue, lethargy, Pallor, Cardiac (tachycardia, angina, exertional dyspnea).
- Nail changes (thinning → flattening → then spooning "koilonychia"), hair loss, Pica.
- Angular cheilitis: inflammation and fissuring of the corners of the mouth.
- Atrophic glossitis: erythematous, edematous, painful tongue with loss of tongue papillae (smooth, bald appearance).

Diagnostics[5]

CBC	**Hb**	**MCV**	**Hct**	**MCH**	**RBC**[6]	**Reticulocyte**	**RDW**[7]
	↓	↓	↓	↓	Initially normal then ↓	Normal or ↓	↑
Iron study[8]	**Iron**	**Ferritin**[9]	**Transferrin saturation**		**Transferrin or TIBC**[10]	**Serum free erythrocyte protoporphyrin**[11]	
	↓	↓	↓		↑	↑	

- **Peripheral blood smear**: Anisocytosis and Increased zone of central pallor.
- **Bone marrow Bx**: pts w/ suspected IDA and nondiagnostic iron studies, low bone marrow iron is diagnostic.

Treatment

- **Dietary modifications**: Infants and young children → restrict cow's milk intake, use iron-fortified formula, introduce iron-rich foods (pureed form), Adults → increase consumption of iron-rich diet (meats, iron-fortified food, fresh green leafy vegetables).
- **Oral iron therapy**: Indicated in all (if tolerated). Should initially be administered for 3–6 months.[12]
- **Parenteral iron therapy**: Indicated in Nonadherence/intolerance to oral therapy, Intestinal malabsorption and Patients with Hb < 6 g/dL who decline blood transfusions.[13]
- Blood transfusion for severe anemia (Hb < 7 g/dL), Treat the underlying disease.

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[5] Diagnosis of IDA requires the presence of anemia (low Hb or Hct) and evidence of low iron stores (usually determined by serum ferritin and iron levels) → Typically manifests as microcytic, hypochromic anemia with anisocytosis, low serum ferritin, and low serum iron levels.
[6] Prolonged deficiency depletes the iron stores in the body, resulting in decreased erythropoiesis and anemia.
[7] differentiates IDA from anemia of chronic disease and thalassemia trait (where the RDW is usually normal).
[8] Low ferritin and iron levels in combination with an elevated TIBC are diagnostic of iron deficiency anemia! Increased ferritin does not rule out iron deficiency anemia. It can be increased in response to simultaneous inflammation!
[9] A protein complex responsible for iron storage. Also an acute phase reactant that increases in response to systemic inflammation. Exact cutoffs vary and must be interpreted with caution in patients with an inflammatory condition (e.g., sepsis, IBD), as it may be "falsely" elevated!
[10] Transferrin transports free iron (Fe3+) in serum, It is particularly important for supplying iron to erythropoietic tissue. Transferrin saturation (indicates the amount of iron bound to transferrin) can be calculated from both transferrin and iron values. A high TfS value is an indication of iron overload and low value indicates iron deficiency.
[11] The last intermediate of the heme biosynthesis pathway. In the presence of iron, protoporphyrin is converted to heme by ferrochelatase.
[12] Adverse effects: GI discomfort, nausea, constipation, black discoloration of stool. Absorption may be enhanced by simultaneous consumption of vitamin C (e.g., with lime juice). Foods (e.g., tea, cereals) and drugs (e.g., calcium, antacids, PPIs) that decrease intestinal absorption of iron should be avoided.
[13] Available forms (ferric preparations): iron dextran, sodium ferric gluconate, and iron sucrose. Adverse effects: Thrombophlebitis, Iron dextran can cause myalgia, arthralgia, headaches, and, rarely, anaphylactic shock within 1–2 days of infusion.

Thalassemia[14]

Pathophysiology

Anemia results from a combination of inefficient erythropoiesis and increased hemolysis.

A. Inefficient erythropoiesis → anemia:

a. Beta thalassemia minor and major: faulty β-globin chain synthesis → ↓ β-chains→ ↑ γ-,δ-chains → ↑ HbF (ααγγ) and ↑ HbA2 (ααδδ).[15]

b. Alpha thalassemia major (HbH disease) and Bart disease: faulty α-globin chain synthesis → ↓ α-chains → ↑ β-, γ-chains → ↑ HbH (ββββ), ↑ Hb-Bart's (γγγγ).

c. In minor and minima forms, production of the affected chain is reduced, but enough is produced to prevent severe anemia.

B. Increased hemolysis: One of the chains (α or β) is reduced → compensatory overproduction of other chains → excess globin chains precipitate and form inclusions within RBCs → erythrocyte instability w/ hemolysis.[16]

C. Anemia → ↑ EPO → bone marrow hyperplasia and skeletal deformities.

Laboratory tests

- **Blood sample**: Microcytic hypochromic anemia[17], signs of hemolysis (↓ haptoglobin, ↑ LDH, ↑ indirect bilirubin, ↑ reticulocytes).
- **Blood smear**: target cells , teardrop cells, anisopoikilocytosis[18]
- **Bone marrow biopsy**: reactive hyperplasia.
- **Confirmatory tests**: Hb-electrophoresis[19]. DNA analysis (to test for alpha thalassemia minor and minima "< 3 alleles defective").

Imaging

- **Skeletal deformities** (e.g., high forehead, prominent zygomatic bones and maxilla, referred to as "chipmunk facies") can be seen on all imaging modalities.[20]
- **X-ray**: hair-on-end ("crew cut") sign.[21]

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[14] A group of disorders in which the normal ratio of α globin to β globin production is disrupted due to a disease-causing variant in one or more of the globin genes. This abnormal alpha- to beta-chain ratio causes the unpaired chains to precipitate and causes destruction of red blood cell precursors in the bone marrow (**ineffective erythropoiesis**) and circulation (**hemolysis**). As a result, affected individuals have variable degrees of **anemia** and **extramedullary hematopoiesis**, which in turn can cause **bone changes**, **impaired growth**, and **iron overload**.

[15] HbF protects infants up to the age of 6 months, after which HbF production declines and symptoms of anemia appear.

[16] Either in the form of removal by macrophages (generally in the spleen) or apoptosis (often already within the bone marrow).

[17] IDA usually presents with a low RBC count and a high RDW, whereas pts with thalassemia minor or thalassemia trait usually have a normal RDW and a higher RBC, and a relatively low MCV compared to IDA. IDA usually only becomes microcytic once the Hb is less than 10 g/dL.

[18] A histopathologic finding in which red blood cells appear of both varying size (anisocytosis) and varying shape (poikilocytosis).

[19] Alpha thalassemia can usually only be detected if ≥ 3 alleles are defective. Abnormal pattern depends on the exact subtype. Diagnosis of beta-thalassemia minor is confirmed by HbA2 > 3.5%.

[20] Skeletal deformities are caused by periosteal reaction to erythropoietic bone marrow hyperplasia.

[21] Lateral x-ray of the skull shows a hair-like pattern (spicules that extend perpendicular to the bone surface).

IDA as a DDX for Thalassemia

A. **Hb and MCV** – Like thalassemia minor, milder forms of IDA can cause **microcytosis** with mild anemia (eg, Hb level >10 g/dL) or a normal Hb level. However, in mild IDA, MCV is rarely below 80 fL, whereas an MCV below 75 fL is common in thalassemia minor.

B. **RBC count** – Unlike thalassemia, in which the RBC count is high, it is typically **low** in IDA.

C. **RDW** – Unlike thalassemia, in which RDW is typically low (reflecting a uniform population of small RBCs), in IDA, the RDW tends to be **large**, reflecting the considerable heterogeneity of RBC sizes.

D. **Blood smear** – Like thalassemia, in IDA, the peripheral blood smear may show **microcytosis** and, in more severe cases, **target cells**. However, the abundance of target cells tends to be greater in thalassemia than in IDA. Unlike thalassemia, in which teardrop-shaped RBCs are often seen, in IDA, teardrop cells are absent.

E. **Physical examination** – Unlike thalassemia, IDA **does not** cause splenomegaly or bony changes.

F. **Iron studies** – Unlike thalassemia, which is often associated with excess iron stores (in thalassemia major and intermedia) or normal iron stores (in thalassemia minor), in IDA the iron studies will show **low serum ferritin** and **low transferrin saturation.** Although thalassemia is more likely to be associated with iron overload than iron deficiency.

Hemolytic Anemia

A group of conditions characterized by the breakdown of RBCs. Hemolysis is caused by either

(1) abnormalities of the RBCs themselves (abnormalities in Hb, the RBC membrane or intracellular enzymes), AKA corpuscular anemia.

(2) External causes (immune-mediated or mechanical damage), which is referred to extracorpuscular anemia.

Diagnostics

(1) Labs: ↓ Haptoglobin[22], ↑ Lactate dehydrogenase (LDH), ↑ Indirect/unconjugated bilirubin[23], ↑ Reticulocytes [24]. In extreme hemolysis: ↑ free Hb (brown-colored urine "hemoglobinuria").

(2) Coombs test [25]: Direct [26]/ Indirect [27].

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[22] Hemoglobin released from broken down erythrocytes binds to haptoglobin. → ↓ free, circulating haptoglobin. Occurs mostly in intravascular hemolysis. Can be increased or normal as a reaction to an infectious process, thereby masking hemolysis.

[23] Hb released from erythrocytes is turned into indirect/unconjugated bilirubin. Increased bilirubin levels can result in icterus. Urobilinogenuria.

[24] loss of erythrocytes → reactive increase in erythropoiesis → increase in reticulocytes in the peripheral blood.

[25] This test detects antibodies and/or complement proteins on RBCs surface (direct test) or in patient's serum (indirect test). The test uses a special Coombs serum that contains anti-human globulins. A positive result in a patient with hemolysis supports the diagnosis of antibody-mediated, extracorpuscular anemia.

[26] Blood sample is purified so that only the erythrocytes remain → Coombs serum containing anti-human globulins (antigens) is added → The examiner visually analyzes the sample and looks for erythrocyte agglutination: (A) In the case of erythrocyte agglutination → positive test → confirmation of preexisting erythrocytes coated with autoantibodies. (B) In the case of absent erythrocyte agglutination → negative test.

[27] After taking a patient's blood sample, it is purified so that only the serum remains → A donor's blood sample containing erythrocytes is added → Coombs serum containing anti-human globulins (antigens) is added as well → The examiner visually analyzes the sample and looks for erythrocyte agglutination: (A) In the case of erythrocyte agglutination → positive test → confirmation of preexisting circulating, free antibodies within a patient's serum that bound to donor's RBC surfaces. (B) In the case of absent erythrocyte agglutination → negative test.

Sickle Cell Disease

- Disease of red blood cells caused by an autosomal-recessive single gene defect in the beta chain of haemoglobin, which results in sickle cell haemoglobin (HbS).[28]
- Sickle cell trait occurs when a child inherits a sickle gene from one parent and a normal gene from the other parent (heterozygous). Sickle cell disease occurs when a child inherits a sickle gene from each parent (homozygote).

Hb	Normal	Sickle cell **trait**	Sickle cell **disease**
Hb**A**	95–98%	60%	0%
Hb**S**	0%	40%	75–95%
Hb**F**	< 2%	< 2%	5–25%

Clinical features

A. Sickle cell trait "Often asymptomatic"

- Painless gross hematuria due to renal papillary necrosis: often the only symptom.
- Hyposthenuria ("low specific gravity" nocturia, enuresis), Recurrent UTIs, Renal medullary carcinoma.

B. Sickle cell disease

- Onset: manifests after 6 months of age (> 90% by age 6 y) as the production of HbF decreases and HbS levels increase.
- **Acute symptoms**: Acute hemolytic crisis "severe anemia" (Splenic sequestration crisis[29], Aplastic crisis[30], Hyperhemolysis[31]), Infection[32], Vaso-occlusive events[33].
- **Chronic symptoms**: Chronic hemolytic anemia (fatigue, weakness, pallor; usually well-tolerated), Chronic pain, Cholelithiasis (pigmented stones).

[28] Sickle cells can obstruct blood flow and break down prematurely, and associated with varying degrees of anaemia. Obstruction of small blood capillaries can cause painful crises, damage to major organs, and increased vulnerability to severe infections.
[29] Splenic vaso-occlusion → entrapment and pooling of large amounts of blood in spleen → acute LUQ pain, anemia, reticulocytosis, and signs of intravascular volume depletion (e.g., hypotension).
[30] Aplastic anemia w/ acute, severe drop in Hb and associated reticulocytopenia due to parvovirus B19 infection. Dysmorphic erythrocytes in sickle cell disease and hereditary spherocytosis are susceptible to parvovirus B19 infection, which can temporarily suppress bone marrow.
[31] intravascular and extravascular hemolysis triggered by mild oxygen deficiency "rare"
[32] Pneumonia, Meningitis, Osteomyelitis (most common: Salmonella spp., Staph A), Sepsis (most common: Strep pneumoniae).
[33] Vaso-occlusive crises (painful episodes, painful crisis): recurrent episodes of severe deep bone pain and dactylitis → most common symptoms in children and adolescents. Acute chest syndrome, Priapism, Stroke (common in children). Infarctions of virtually any organ (particularly spleen) and AVN with corresponding symptoms.

Diagnosis

- Prenatal testing - may be conducted in select cases: chorionic villus sampling and DNA analysis at 8–12 weeks of gestation. Neonatal screening.[34]
- Older children and adults
  - Liquid chromatography and isoelectric focusing to quantify hemoglobin subtypes (best tests).
  - Sickle cell test: detects sickle cells in a blood smear under anaerobic conditions.
  - Blood smear: Sickle cells (crescent-shaped RBCs), Target cells, Possibly Howell-Jolly bodies, Reticulocytosis.
  - Imaging: Skull X-ray shows hair-on-end ("crew cut") sign due to periosteal reaction to erythropoietic bone marrow hyperplasia (also present in thalassemia).

Treatment

Longterm management

A. Prevent infections[35]

B. Prevent vaso-occlusive crises and manage anemia

1. Avoid triggers[36]
2. Hydroxyurea: first-line - Indications (Frequent, acute painful episodes or other vaso-occlusive events, Severe symptomatic anemia).[37]
3. If the response to hydroxyurea alone is not adequate → Combine with EPO, Blood transfusions[38].
4. Folic acid supplementation.
5. Cholecystectomy to treat cholelithiasis.

Management of acute sickle cell crisis

A. Prompt and adequate supportive treatment: Hydration → Pain management (NSAIDs and opioids) → Thromboembolic prophylaxis (LMWH) → Nasal oxygen → Bed rest.

B. Blood transfusions[39]

C. Exchange transfusions (erythrocytapheresis): automated removal of erythrocytes containing HbS and simultaneous replacement with HbS free erythrocytes.[40]

Curative therapy: Allogeneic bone marrow transplantation → Indicated for homozygotes, < 16 y w/ severe disease.

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[34] If positive: Repeat hemoglobin electrophoresis (gold standard) confirms the diagnosis and distinguishes between heterozygotes and homozygotes and other forms of sickle cell syndrome (e.g., HbSC disease)

[35] Pneumococcal, Meningococcal vaccines. Daily penicillin prophylaxis (at least until the age of 5 years). If sepsis is suspected, treat with IV third-generation cephalosporin (e.g., ceftriaxone), If meningitis is also suspected (add vancomycin).

[36] Hypoxia, Infections, Dehydration, Acidosis, Sudden changes in temperature, Stress, Pregnancy.

[37] Stimulates erythropoiesis and increases fetal Hb → sickled hemoglobin is proportionally reduced → RBC polymerization decreases → fewer vaso-occlusive episodes. Possible adverse effects: myelosuppression (beneficial in myeloproliferative disease, e.g., polycythemia vera).

[38] Not usually required to manage chronic anemia unless symptomatic and refractory to other forms of Rx, blood transfusions are indicated.

[39] Indications: **(1)** Acute, severely symptomatic anemia (e.g., aplastic crisis). **(2)** Secondary prophylaxis of acute vaso-occlusive crisis (stroke, acute chest syndrome, acute multiorgan failure). **(3)** Surgery (preoperative transfusions). **(4)** Pregnancy.

[40] **Indication**: acute vaso-occlusive crisis (stroke, acute chest syndrome, acute multiorgan failure). It allows Rapid effect! Precise control of HbS levels and iron accumulation. However it is expensive and equipment not readily available, requires experienced practitioner.

Complications Recurrent vascular occlusion and disseminated infarctions lead to progressive organ damage and loss of function.	
Spleen	**Functional asplenia**: Increased risk of infection with encapsulated bacteria (Streptococcus pneumoniae (most common), Neisseria meningitidis, H.influenzae type b, Salmonella typhi). Appearance of Howell-Jolly bodies in RBCs
Kidney	**Renal papillary necrosis**: Countercurrent microcirculation of kidney → hypoxic environment of renal medulla → RBCs sickling → vaso-occlusion → renal papillary necrosis → hematuria. Glomerulonephritis, End-stage renal failure.
Skeletal	AVN, Osteonecrosis of the femoral head, Growth impairment, Osteoporosis.
Others	**CNS** → Recurrent strokes, **Male genitals** → Priapism, **Lungs** → PHTN, Acute chest syndrome, **Heart** → Cardiomyopathy (cardiomegaly), Heart failure, MI, **Eye** → Retinal vessel occlusion.

Acute chest syndrome

★ Defined as a **new radiodensity** on chest radiograph accompanied by fever and/or respiratory symptoms (Vaso-occlusion of the pulmonary vasculature). Triggers (infection, asthma, surgery/general anesthesia).

Clinical features

- Chest pain, Rib or sternal pain, Fever.
- Respiratory distress, cough, SOB, wheezing.
- Signs of vaso-occlusive crisis (e.g., pain in arms or legs)

Diagnostics: Clinical diagnosis → Labs (anemia, leukocytosis) → CXR (new pulmonary infiltrate).[41]

Treatment: Supportive care[42], Antibiotic therapy[43], venous thromboembolic events prophylaxis (LMWH), Blood transfusion (pRBC transfusion (simple transfusion), Exchange transfusion).[44]

[41] **Diagnostic criteria —** radiographic evidence of consolidation: a new segmental (involving at least one complete segment) radiographic pulmonary infiltrate, **AND** at least one of the following: Temperature ≥38.5°C/>2 percent decrease in SpO_2/PaO2 <60 mmHg/Tachypnea (per age-adjusted normal)/Intercostal retractions, nasal flaring, or use of accessory muscles of respiration/Chest pain/Cough/Wheezing/Rales.

[42] **Pain management** (opioids), **IV fluids** (Avoid overhydration, which can lead to pulmonary edema), **Supplemental O2** (All ACS pts can be given supplemental O2 because focal hypoxemia may still be present in pts with normal saturation. goal SpO2 > 95%), **Bronchodilators** (especially in pts w/ Hx of asthma or evidence of acute bronchospasm), **Incentive spirometry** (To prevent atelectasis).

[43] Obtain blood cultures (2 sets) and sputum cultures before starting antibiotics. Start empiric antibiotics (for bacterial pneumonia → third generation cephalosporin along with a macrolide).

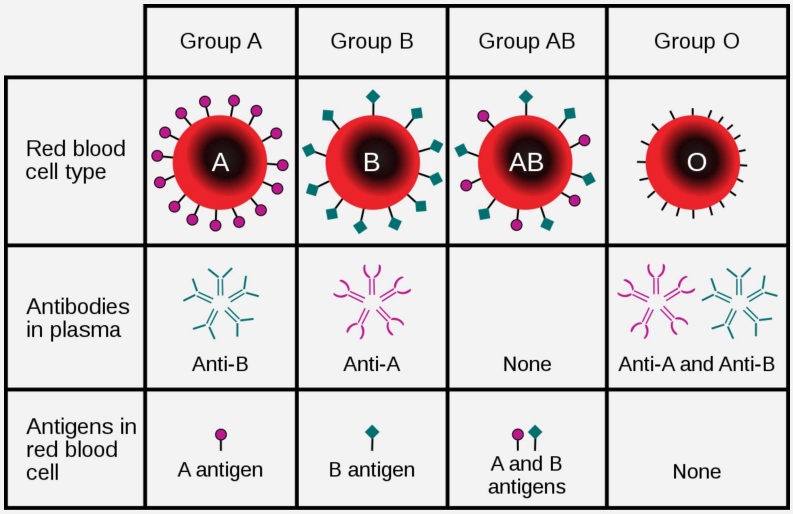
[44] Transfusions are recommended because they decrease the proportion of sickle RBCs. Transfusions are especially recommended in patients who have a history of CVS disease, low platelet count, or have multi-lobar pneumonia, as these risks have been found to be associated with an increased risk of mechanical ventilation.

Transfusion

★ Individuals with blood type O negative are “universal donors” of pRBCs! Individuals with blood type AB positive are “universal recipients” for pRBCs!

★ For FFP transfusions, individuals with blood type O are universal recipients (type O plasma contains A and B antibodies) and individuals with blood type AB are universal donors (AB plasma contains no A or B antibodies)!

★ The universal red cell donor has blood type O. The universal plasma donor has blood type AB.



Acute hemolytic transfusion reaction

Pathomechanism: ABO incompatibility results in severe destruction of donor RBCs by recipient antibodies.

Clinical features: Rapid onset during transfusion → Fever, chills, nausea, flushing, pruritus, urticaria, flank pain, dyspnea, burning pain at the IV site. Patients in a coma or under general anaesthesia may present with oozing from wounds or puncture sites. Sequelae (Renal failure, DIC, Jaundice).

Treatment:
Immediate cessation of transfusion → then **confirm** diagnosis:
(1) Test patient's blood: direct Coombs test , plasma free hemoglobin > 25 mg/dL.
(2) Repeat typing and cross-matching of the transfusion product to identify and record causative products.

Supportive care:
(1) Immediate infusion of saline to aid diuresis and manage hypotension
(2) Vasopressors may be required to maintain perfusion.
(3) Cardiac monitoring and hemodialysis if hyperkalemia secondary to severe hemolysis occurs
(4) Coagulation studies; administer FFP and platelets if DIC develops.

Anaphylaxis

Pathomechanism: Anti-IgA IgG in recipients with IgA deficiency bind to IgA on the surface of donor RBCs and trigger mast cell degranulation.
Clinical features: Sudden onset during the transfusion (shock, hypotension).
Treatment: Epinephrine (IM), hemodynamic stabilization, and airway management.[45]

[45] Treatment of anaphylaxis: (1) Withdrawal of offending agent if possible → (2) Airway control → (3) **Epinephrine IM** → (4) Antihistamines (H1 antihistamine “diphenhydramine” IV for urticaria, H2 antihistamine (ranitidine) IV → Methylprednisolone → O2 by facemask → If the patient is hypotensive (NS 1–2 L IV rapid bolus) → Bronchospasm and no benefit of epinephrine: nebulized albuterol (salbutamol) → Continuous monitoring of BP, HR, heart function, and pulse oximetry.

Nonhemolytic febrile transfusion reaction	**Pathomechanism**: After periods of long storage of blood products, cytokines may leak from donor RBCs and subsequently cause a mild immunologic reaction in the recipient. In addition, preformed recipient antibodies lead to lysis of the few remaining leukocytes within donor RBC concentrates, resulting in an inflammatory reaction. **Clinical features**: Onset during or within 1–6 hours after transfusion (fever, chills, malaise). **Treatment:** Cessation of transfusion until an acute hemolytic reaction is r/o. Treat with acetaminophen.
Minor allergic reactions	**Pathomechanism**: Recipient abs against plasma components in the donor blood cause allergic reaction. **Clinical features**:Onset during the transfusion. Urticaria **Treatment**: Diphenhydramine.
Transfusion related acute lung injury (TRALI)	**Pathomechanism**: Soluble factors(antibodies, certain lipids) in the donor blood lead to activation of the recipient's granulocytes. Occurs particularly following transfusion of FFP or platelets. **Clinical features** Onset (sudden): during or within 6 hours of transfusion. Symptoms and imaging results are generally the same as in ARDS: dyspnea, hypotonia, fever; CXR (diffuse infiltrates; in some cases, leukopenia). Hypotension (due to hypovolemia). **Treatment**: (1) **Discontinue transfusion**; contact blood bank. (2) **Supportive management**: Maintain sufficient ventilation/oxygen supply → Control hemodynamic parameters → Anti-inflammatory therapy with IV steroids (only in specific circumstances).
Post transfusion purpura	**Pathomechanism**: Alloantibodies against platelets result in the destruction of platelets. **Clinical features**: 5–10 days after transfusion. Mild to severe thrombocytopenia, Purpura. **Treatment**: IVIG therapy or plasmapheresis
Delayed hemolytic transfusion reaction	**Pathomechanism**: Occurs in patients who were previously sensitized to specific RBC antigens during transfusions, pregnancy, or transplantations. Re-exposure to the antigens results in a rapid increase in antibodies that bind to donor RBCs and cause extravascular hemolysis. **Clinical features:** Onset within days or weeks after transfusion (Fever, jaundice, anemia, dark urine). **Treatment**: No acute therapy required. Antibody testing to prevent future reactions.

Multiple Myeloma (**MM**)

Neoplastic proliferation of a plasma cell producing a monoclonal (same type) immunoglobulin and/or immunoglobulin fragment. The plasma cells proliferate in the bone marrow and can result in extensive skeletal destruction with osteolytic lesions, osteopenia, and/or pathologic fractures.

Pathophysiology

- Neoplastic proliferation of plasma cells
  - Bone marrow infiltration → suppression of hematopoiesis → leukopenia, thrombocytopenia, anemia.
  - Cell proliferation → osteolysis → hypercalcemia.
- Overproduction of monoclonal immunoglobulin and/or light chains
  - Non-functioning antibodies → functional antibody deficiency.
  - ↑ Serum viscosity → hyperviscosity syndrome.

Clinical features

- Often asymptomatic! Enlarged lymph nodes are not a typical finding!
- **Bone pain**- especially back pain (most common Sx), spontaneous fractures and Sx of **hypercalcemia**.
- Mild fever, night sweats, **weight loss** weakness and **anemia** (normocytic normochromic).
- Foamy urine, caused by Bence Jones proteinuria.
- Increased risk of infection[46] and petechial bleeding.

Approach "following tests are required for patients with suspected MM"

- Serum protein electrophoresis is the best initial test (monoclonal gammopathy with M protein)[47], and bone marrow biopsy[48] (is confirmatory).
- Urine protein electrophoresis (Bence Jones proteins).
- Labs (CBC and biochemistry) to assess for hypercalcemia, anemia and renal insufficiency.[49]
- Imaging to assess bone lesions.[50]

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[46] suppression of normal cell function. (strep pneumococcus, gram -ve r the most common).

[47] The term M protein originates from multiple myeloma, which characteristically peaks in the gamma-globulin zone of the electrophoresis. Synonymous terms include: M component, myeloma protein, spike protein, and paraprotein.

[48] Cytology → clusters of plasma cells. Monoclonal plasma cell infiltration in the bone marrow ≥10%.

[49] **CBC** (Anemia, thrombocytopenia, leukopenia → eventually pancytopenia, ↓ Reticulocyte count). **Labs** (Massively increased ESR, Hypercalcemia, ↑ Creatinine,Urea, Elevated total protein, ↑ β2 microglobulin).

[50] **First choice**: low-dose whole-body CT (WBLD-CT) → osteolysis and osteopenia. **Alternatives**: X-ray skeletal survey → multiple lytic lesions ("punched-out" holes), e.g. in the skull, FDG/PET scan → areas of active osteolysis, MR**I** → visualizes infiltration and replacement of bone marrow (e.g., in the spine and pelvis).

Diagnostic criteria

	Main criterion	**Plus at least 1** of the following "myeloma-defining events"
MM	≥ 10% clonal bone marrow plasma cells in biopsy.	**(A)** Organ damage (**CRAB**) (1) **Calcium**: hypercalcemia (**> 11** mg/dL). (2) Renal insufficiency: creatinine clearance **< 40** mL/min or serum creatinine **> 2** mg/dL. (3) Anemia (Hb **< 10** g/dL). (4) Bone lesions on **MRI.** **(B)** ≥ 60% clonal plasma cells of the bone marrow. **(C)** Involved/uninvolved serum free light chain ratio ≥ 100. **(D)** > 1 focal lesion on MRI.
Plasmacytoma[51]	(1) Solitary mass in the bone or soft tissue. (2) ≥ 10% clonal plasma cells confirmed in tissue biopsy. (3) No or minimal bone marrow involvement (< 10% plasma cells in bone marrow). (4) No organ damage detectable (CRAB).	

CRAB indicates organ damage: **C**alcium increased, **R**enal insufficiency, **A**nemia, and **B**one lesions!

[51] A tumor consisting of plasma cells that can grow in bone (more common) or soft tissue (extramedullary plasmacytoma). Plasmacytomas in bone occur as solitary or multiple sharply demarcated, punched-out, osteolytic lesions. The most common sites are the spine, followed by the pelvis and ribs. When plasmacytomas are present with systemic manifestations such as fever, weight loss, anemia, renal failure, and/or hypercalcemia, the condition is called multiple myeloma.

Pathophysiology of bleeding disorders

Activation of hemostasis

A. Primary hemostasis: hemostasis achieved via platelet adhesion and aggregation at the site of endothelial injury.

1. Initiation: endothelial injury results in transient vasoconstriction → exposure of subendothelial collagen → von Willebrand factor (vWF[52]).
2. Adhesion (hemostasis): vWF and platelet GpIb receptors mediate the adhesion of platelets to the injured endothelium by forming pseudopodia; phospholipid is expressed on cellular membranes.
3. Activation: release of adenine diphosphate (ADP), thromboxane, calcium, and platelet activating factor (PAF), which assist in platelet aggregation, vasoconstriction and degranulation.
4. Aggregation (hemostasis): mediated by GpIIb/IIIa-receptor and fibrinogen → formation of a white thrombus composed of platelets and fibrin (temporary unsteady plug).

B. Secondary hemostasis: hemostasis achieved via the interaction of plasma coagulation factors (procoagulants) "coagulation cascade[53]"

1. Injury to endothelium → activation of the extrinsic pathway (hemostasis)
   - Tissue factor (F3), is present under the endothelium on fibroblasts, binds to and thus activates factor VII[54].
   - Factor VIIa and tissue factor form a complex (TF-FVIIa) that activates factor X and factor IX.
2. Additionally, activation of the intrinsic pathway (hemostasis), especially through thrombin: Thrombin activates factors XI & VIII[55] → Factor XIa activates IX[56]. Factors VIIIa and IXa form a complex that activates factor X.
   - This causes a positive feedback loop of factor X and thrombin activation via the intrinsic pathway
3. The common pathway (hemostasis) of the extrinsic and intrinsic pathways then follows:
   - Factor Xa and factor Va (activated by thrombin) form a complex that cleaves prothrombin to thrombin (= factor II).
   - Thrombin cleaves fibrinogen (factor I) into insoluble fibrin (factor Ia) monomers.
   - Cross links of the fibrin network are stabilized by factor XIIIa (activated by thrombin) → formation of a fibrin network → fibrin closely binds to the platelet plug, forming a stable fibrin clot (secondary or red thrombus).

★ The coagulation cascade requires the presence of **calcium ions** (**factor IV**)!

★ **P**rothrombin **t**ime, which measures the activity of the **ex**trinsic pathway, is increased by **war**farin therapy (**Ex-P**residen**T** went to **War**!)

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[52] A glycoprotein synthesized and stored in Weibel-Palade bodies of endothelial cells and α-granules of platelets, binds the exposed collagen.
[53] The coagulation cascade is a series of reactions, involving coagulation factor proteins, which constitutes the process by which blood changes from a liquid to a gel, forming a blood clot.
[54] Factor VII is a vitamin K dependent clotting factor produced by the liver. Functions as a serine protease in conjunction with tissue factor and initiates the extrinsic pathway coagulation cascade.
[55] Factor VIII is bound to vWF and is released during primary hemostasis.
[56] Factor IX is a circulating serine protease. The synthesis of factor IX takes place in the liver and involves vitamin K-dependent gamma-carboxylation. Factor IX is activated by factor XIa, calcium, and membrane phospholipids. Antithrombin III inactivates factor IX. Isolated factor IX deficiency is seen in patients with hemophilia B.

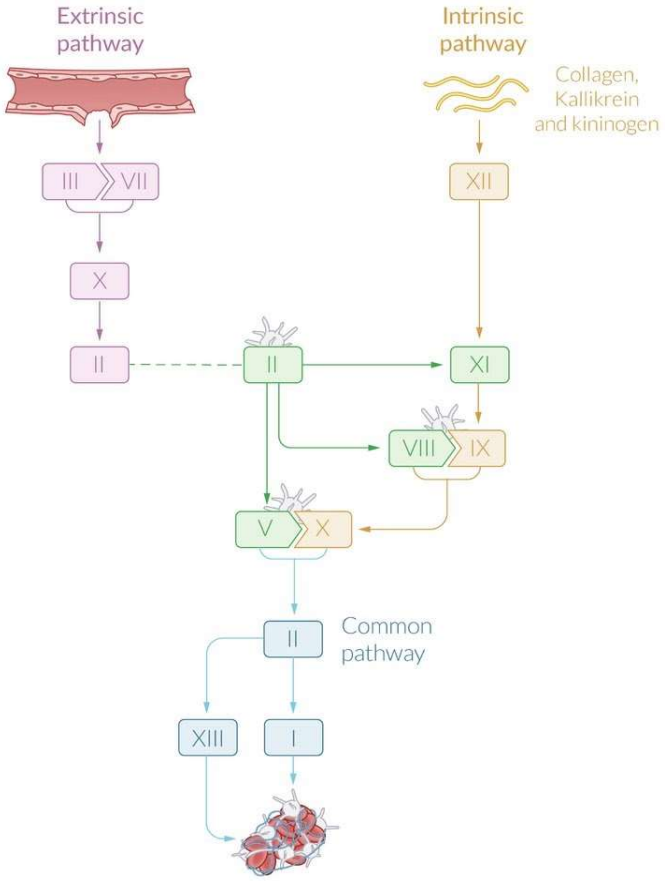
Inhibition of hemostasis

- Extrinsic pathway: tissue factor pathway inhibitor, which inhibits tissue factor
- Intrinsic pathway
  - Protein S: cofactor of protein C
  - Protein C: forms the activated protein C complex together with its cofactor protein S (APC complex) → inhibition of factors Va and VIIIa → inhibition of coagulation cascade
    - Produced in the liver; synthesis requires vitamin K.
    - Shorter half-life than the other coagulation factors dependent on vitamin K.
    - Clinical relevance: APC resistance; treatment with vitamin K antagonists.[57]
  - **Antithrombin**[58] - Clinical relevance: The efficacy of antithrombin may be affected by various factors.
- Nonspecific inhibitors of hemostasis: protease inhibitors found in plasma (e.g., α-1-antitrypsin, α-2-macroglobulin).

Diseases that affect the inhibitors of the coagulation cascade may lead to hypercoagulability!

★ A helpful way of remembering the coagulation factors of the **extrinsic** pathway is **3 + 7 = 10**.

★ A helpful way of remembering the coagulation factors of the **common** pathway is **1 x 2 x 5 = 10**. Factors Xa and Va form a complex that cleaves prothrombin (II) to thrombin (IIa). Factor IIa then cleaves fibrinogen (I) into insoluble fibrin monomers (Ia).



[57] Warfarin therapy inhibits not only factors II, VII, IX, and X, but also the production of proteins C and S. Since both of these proteins have a shorter half-life than the other factors, the first few days of warfarin therapy are characterized by a tendency towards procoagulation. To prevent thrombotic events, treatment with vitamin K antagonists requires the coadministration of heparin until the INR has reached the target range.

[58] One of the important physiological inhibitors of hemostasis. Degrades thrombin and other factors (factor IXa and Xa) and activates tPA.

Fibrinolysis

Since the fibrinolytic system continuously cleaves and degrades fibrin, hemostasis and fibrinolysis are processes that occur simultaneously in the circulatory system.[59]

Physiological fibrinolysis

- Tissue injury → release of factor XII, urokinase and tissue plasminogen activator (tPA)
  - → Breakdown of plasminogen, leading to the formation of active plasmin → breakdown of fibrin by activated plasmin.
  - → Release of degradation products, including D-dimers.
- Regulation of fibrinolysis: tPA activity is reduced if tPA binds to plasminogen activator inhibitor (PAI).

Fibrinolytic therapy

- Fibrin-specific agents
  - Tissue plasminogen activator: Alteplase
  - Recombinant plasminogen activator (rtPA): produced by recombinant biotechnology techniques (Reteplase, Tenecteplase).
- Non-fibrin-specific agents: Streptokinase[60], Urokinase.
- Mechanism of action: directly or indirectly increase the conversion of plasminogen to plasmin
- Indications: Early STEMI (< 12 hours), Early ischemic stroke (< 3 hours), Massive PE.
- Effects: ↑ PT, ↑ PTT, No change in platelet count.
- Contraindications to fibrinolytic therapy: Prior intracranial hemorrhage, Recent surgery, Severe HTN, Active bleeding.
- Adverse effect: bleeding
- Reversal of adverse effects
  - Antifibrinolytics: Tranexamic acid, Aminocaproic acid.[61]
  - FFP or cryoprecipitate (Cryoprecipitate is obtained from frozen blood plasma via centrifuge and contains more factor VIII and fibrinogen than FFP).

Alteplase is a synthetic tissue plasminogen activator that converts plasminogen to plasmin and is used in the treatment of STEMI, massive PE, and ischemic stroke.

[59] Fibrinolysis is also stimulated when endothelial injury occurs, but is then inhibited by thrombin (during the various coagulation pathways). As the vessel heals, stimuli for thrombin formation decrease and fibrinolysis predominates again.

[60] a protein, produced by group A streptococci, that catalyzes the. conversion of plasminogen to plasmin, which is responsible for clot breakdown

[61] Tranexamic acid: a synthetic lysine analog and inhibitor of plasminogen with antifibrinolytic action. Aminocaproic acid: a lysine derivative and inhibitor of the plasminogen-plasmin cascade with antifibrinolytic action

Hemophilia

A hereditary recessive X-linked “males” (inherited or spontaneous mutation) or antibody production against clotting factors) clotting disorders. **Types** → A (F8), B (F9), C (F11).[62]

Clinical features

- Spontaneous or delayed bleeding (joints, muscular & soft tissue, mucosa) in response to different degrees of trauma:
  - Ecchymosis (recurrent hematoma formation or bruising), hemarthrosis (repeated and can lead to joint destruction), epistaxis, muscle/soft tissue hematomas, CNS (stroke, neck stiffness, headache), GI (hematemesis, melena), GU (hematuria).
  - Oral mucosa bleeding, epistaxis, excessive bleeding following small procedures (e.g., dentist procedures).

Petechial bleeding is a common sign of platelet disorders, NOT coagulation disorders such as hemophilia!

Diagnostics

- Hx, FHx, Genetic testing.
- CBC (normal, to r/o thrombocytopenia). AST/ALT (liver dysfunction can contribute to prolongation of PT and aPTT).
- Screening: PT (normal), Platelet count (normal), aPTT (usually prolonged).[63] If aPTT prolonged → mixing study[64].
- If mixing study is positive (or if Hx/FHx are strongly positive) → quantitative assessment of factor activity levels.

Rx:

- Clotting factors? when needed (surgery/trauma) for mild/moderate. And prophylactic for severe.
- Desmopressin[65]? for mild hemophilia A.
- Antifibrinolytic therapy[66] (tranexamic acid)? In addition to factor substitution (eg. oral cavity surgery).
- *Extra: plasminogen (by tPA) → plasmin → degrades fibrin/fibrinolytic (clot)*

Von Willebrand disease

A disorder of primary hemostasis characterized by either a deficiency or disorder of vWF (most common congenital hemostatic disorder).

- **Clinical findings** - Mostly asymptomatic but if symptomatic:
  - Ecchymosis (esp. mucosal hemorrhages) → from reduced half-life of factor VIII.
  - Petechial hemorrhages, hematomas/hemarthrosis in severe cases → caused by impaired platelet aggregation.
  - Other: epistaxis, gingival bleeding, menorrhagia, GI bleeding, and excessive bleeding during surgery.
- **Dx**
  - Prolonged bleeding time and sometimes prolonged aPTT. ↓ Factor VIII levels.[67]
  - vWF-specific measurements: by vWF antigen assay (↓ factor levels).

Platelet aggregation inhibitors are contraindicated in vW disease because of the increased risk of bleeding!

- **Rx**: only if symptoms occur
  - Recombinant von Willebrand factor (rVWF) concentrate. Desmopressin → Stimulates vWF release from endothelial cells.
  - Other treatment options: factor VIII concentrates ; OCPs in cases with menorrhagia; antifibrinolytic drugs (i.e., aminocaproic acid, tranexamic acid). Avoid aspirin, NSAIDS, and IM injections.

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[62] All types result in impaired secondary hemostasis (plasmatic coagulation) that manifests as increased aPTT.

[63] Platelets, PT and aPTT → (normal platelets and PT, prolonged aPTT). If positive → Do mixing study, +ve/Strong family history → quantitative assessment of factor activity level. PT → extrinsic & common (7, 10, 5, 2, 1). PTT → intrinsic & common (7, 11, 9, 8, 10, 5, 2, 1)

[64] Mix a patient's plasma with external plasma that’s known to contain sufficient clotting factors & measure the resulting aPTT → will be corrected.

[65] Synthetic vasopressin → triggers the release of factor VIII from endothelial cells.

[66] Antifibrinolytic therapy is contraindicated in pts with hematuria (usually macroscopic) due to the formation of blood clots in the urinary tract.

[67] Factor VIII levels are a good assessment for vWD because this factor is found bound to vWF in blood, in which state it is protected from rapid breakdown.

DIC (Disseminated Intravascular Coagulation)

Systemic activation of the clotting cascade with microthrombi formation, platelet consumption, and subsequent exhaustion of all clotting factors.[68]

Causes: DIC does not occur in isolation. A number of underlying conditions are responsible for initiating and propagating the process - common causes:
Sepsis (bacterial, fungal, viral, and parasitic) - **Trauma**, especially to CNS - **Malignancy**, especially acute promyelocytic leukemia, mucinous tumors (eg, pancreatic, gastric, ovarian), and brain tumors - **Obstetrical complications**, including preeclampsia, retained dead fetus, amniotic fluid embolism, abruptio placenta, acute fatty liver of pregnancy - **Intravascular hemolysis**, often due to acute hemolytic transfusion reaction (AHTR) in the setting of ABO incompatible transfusion, but also in other forms of hemolysis such as in severe malaria.

🧠 **Etiology** → "**STOP** Making **T**rouble!" **S** - **Sepsis/Snakebites**, **T** - **Trauma** (acute traumatic coagulopathy), **O** - **Obstetric complications**,[69] **P** - **Pancreatitis**, **M** - **Malignancy**, **T** - **Transfusion**.

Compensatory changes [70] → lead us to classify DIC to 2 types, acute (decompensated)[71] & chronic (compensated)[72].

Clinical manifestations

A. Bleeding and thrombosis

a. Bleeding is more likely to occur in acute while thrombosis in chronic, however both can happen in each type.
b. Common bleeding manifestations: Petechiae, purpura, ecchymoses, hematuria, hematemesis, hematochezia. Oozing of blood from surgical wounds, IV lines, catheter, mucosal surfaces. Collection of blood in body cavities (features of hemoperitoneum, hemothorax).
c. Thromboembolic manifestations: venous thromboembolism & arterial thrombosis w/ tissue or organ ischemia.

B. Organ dysfunction

a. Acute renal failure (oliguria), Hepatic dysfunction (jaundice).
b. ARDS (dyspnea, rales), Pulmonary thromboembolism (dyspnea, chest pain, hemoptysis).
c. Neurological dysfunction (altered mental status, stroke), DVT (LL edema).
d. Waterhouse Friderichsen syndrome (adrenal infarcts → adrenal insufficiency).

C. Purpura fulminans (DIC with extensive skin necrosis).

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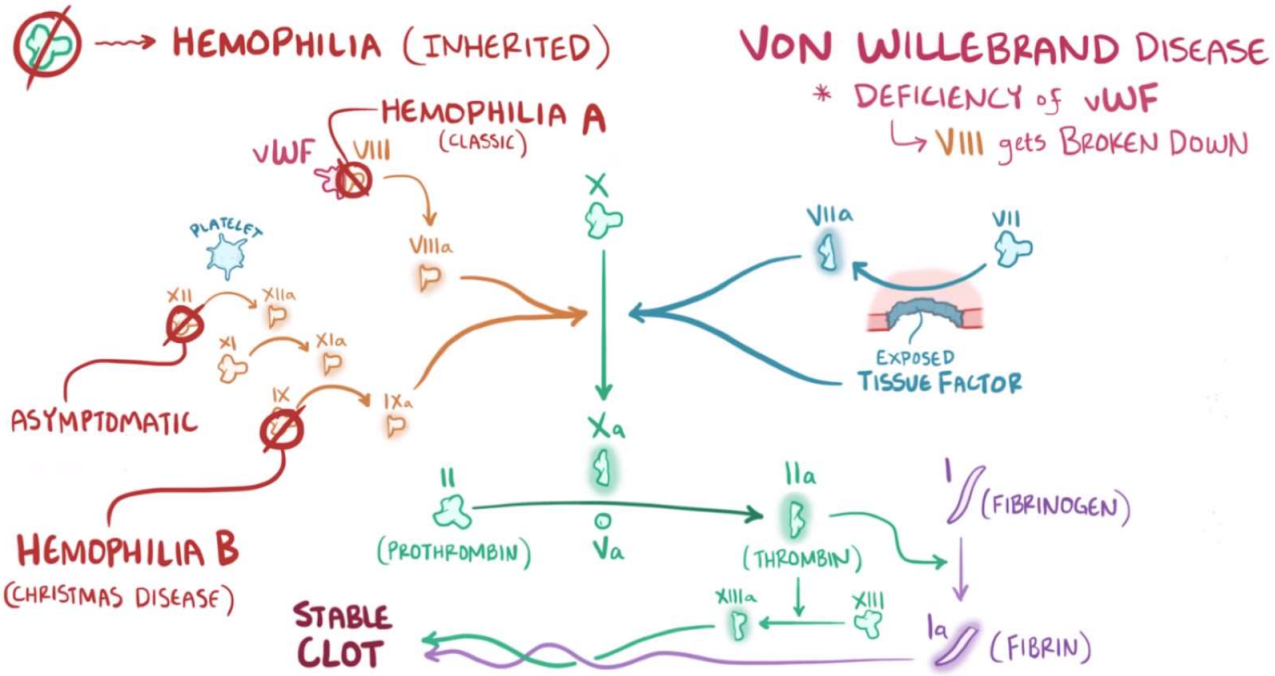
[68] Coagulation and fibrinolysis become abnormally (often massively) activated within the vasculature, leading to ongoing coagulation and fibrinolysis. Normally hemostasis ensures formation of a blood clot at the site of vessel injury, followed by resolution of the clot to allow tissue repair. There r feedbacks built into this system to prevent activation of coagulation in absence of vessel injury and restrict the clot to injury sites.
[69] Amniotic fluid embolism, Pre-eclampsia, Abruptio placenta, Retained products of conception.
[70] DIC is a dynamic process. The acuity and magnitude of ongoing intravascular coagulation determine whether consumption of coagulation factors and platelets can be compensated adequately by ongoing synthesis of coagulation factors and generation of new platelets in the bone marrow. The two ends of the spectrum between inadequate and adequate compensation are sometimes referred to as acute and chronic DIC. Acute and chronic DIC may both be associated with bleeding and/or thrombosis, along with their sequelae in affected organs. However, acute DIC is much more likely to present with bleeding, due to consumption of fibrinogen and other procoagulant factors and the disruption of normal fibrin formation and platelet function by the large amount of fibrin degradation products; whereas chronic DIC is more likely to present with thromboembolic complications because production of procoagulant factors keeps pace with ongoing generation of thrombi.
[71] Can develop when blood is exposed to large amounts of tissue factor (or other procoagulant substances) over a brief period of time, with significant generation of thrombin. This leads to rapid consumption of coagulation factors that outpaces their production. The fibrin degradation products (FDPs) that are generated in turn disrupt normal fibrin polymerization and fibrinogen binding to platelet surface , thus interfering with both fibrin clot formation and platelet aggregation, and effectively operating as pathological anticoagulant and antiplatelet agents.
[72] Can develop when blood is continuously or intermittently exposed to smaller amounts of tissue factor (or other procoagulant substances). Coagulation factors and platelets are consumed, but production is able to compensate, and the liver is able to clear the FDPs. Clotting times may be normal, and thrombocytopenia may be mild or absent. Thrombosis generally predominates over bleeding, although many patients are asymptomatic with laboratory-only evidence of increased thrombin generation and fibrinolysis.

Dx:CBC+Smear+CoagProf	Acute	Chronic
Platelet	↓	Variable
PT	Prolonged	N
aPTT	Prolonged	N
Thrombin time	Prolonged	N/slightly prolonged
Plasma fibrinogen	↓	N/↑
Plasma factor V	↓	N
Plasma factor VIII	↓	N
FDPs	↑	↑
D-dimer	↑	↑



DVT (Deep Vein Thrombosis)

Pathophysiology

The Virchow triad: 3 main pathophysiological components of thrombus formation:

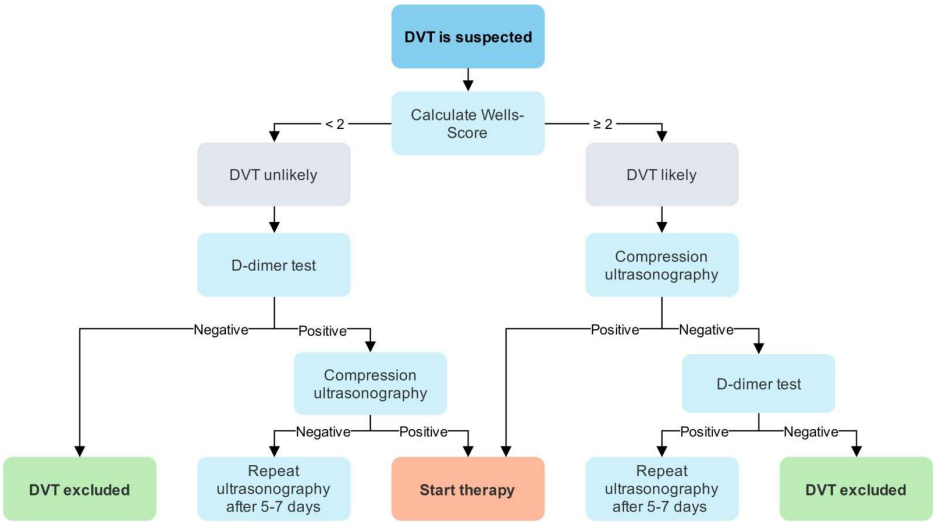
1. Alterations in the constituents of the blood (inherited or acquired hypercoagulability): increased platelet adhesion, increased clotting tendency (thrombophilia).
2. Endothelial damage: inflammatory, traumatic.
3. Alterations in blood flow (stasis): varicosis, external pressure on the extremity, immobilization, local application of heat.

RFs: Hx of immobilization or prolonged hospitalization, Recent surgery or trauma, Obesity, Previous venous thromboembolism (VTE), Malignancy or constitutional symptoms suggestive of malignancy, OCP/HRT, Pregnancy or postpartum status, Stroke with hemiplegia or immobility Age >65 years,
FHx of VTE, Heart failure, IBD.

> **DVT RFs → "THROMBOSIS"**: Travel, Hypercoagulable/HRT, Recreational drugs, Old (> 60), Malignancy, Blood disorders, Obesity/Obstetrics, Surgery/Smoking, Immobilization, Sickness (CHF/MI, IBD, nephrotic syndrome, vasculitis)!

Clinical features "May be asymptomatic"

1. Localized unilateral Sx:
   a. Typically affects deep veins of the legs, thighs, or pelvis.[73]
   b. Swelling, warmth, erythema, feeling of tightness or heaviness, and possibly livid discoloration, distention of superficial veins (Obstruction of the deep veins leads to an increase in superficial venous flow), distal pulses are normal.
   c. Progressive tenderness, dull pain (worse while walking and improves with elevation).[74]
2. General symptoms: fever.
3. Possible signs of PE: dyspnea, chest pain, dizziness, weakness.



[73] More common in the left lower extremity (Due to compression of the left iliac vein by the overlying right iliac artery). May-Thurner syndrome → compression of the left iliac vein between the right iliac artery and a lumbar vertebral spur (occurs in > 20% of adults).
[74] Homan sign → calf pain on dorsiflexion of the foot, Meyer sign → Compression of the calf causes pain, Payr sign → pain when pressure is applied over the medial part of the sole of the foot.

Diagnostics

The diagnostic approach for suspected DVT is determined by the Wells score. Compression ultrasonography and D-dimer levels are the main diagnostic tests.

Wells Criteria (identify probability)		**Score**
Hx	Active cancer (treatment ongoing or within the previous 6 m or palliative)	+1
	Previously documented DVT (this is taken into account in modified wells score)	+1
Immobilization	Paralysis or recent (cast) immobilization of LL	+1
	Recently bedridden (≥ 3 d) or Major surgery (< 12 w)	+1
SSx	Tenderness localized along the deep venous system	+1
	Swelling of the entire leg	+1
	Calf swelling ≥ 3 cm compared to asymptomatic calf	+1
	Unilateral pitting edema in symptomatic leg	+1
	Presence of collateral (non-varicose) superficial veins	+1
DDx	Alternative diagnosis at least as likely as DVT	-2

Interpretation: (A is for modified wells, 3 is wells score)
A. 2 risk group: < 2: DVT unlikely (low risk → proceed to D-dimer), ≥ 2: DVT likely (high risk → imaging).
B. OR 3 risk group: 0: low risk (D-dimer), 1–2: moderate risk of DVT (D-dimer), ≥ 3: high risk of DVT (imaging).

A. Compression ultrasonography with Doppler (**test of choice**)[75]: Indicated in clinical suspicion of a DVT or PE. Findings → noncompressibility of the obstructed vein, visible hyperechoic mass, absent or reduced flow.

B. D-dimer testing (highly sensitive but low specificity): to r/o DVT (normal values r/o DVT).[76]

C. Further diagnostic tests: Venography (angiography),[77] CT scan (suspected PE or underlying malignancy), thrombophilia screening (coagulation studies),[78] general tumor screening[79].

[75] A combination of ultrasonography (to **visualize** the vein) and Doppler (to assess blood **flow** abnormalities) in which examiner applies gentle pressure to normally compressible veins using US. High sensitivity & specificity in the popliteal & femoral veins, but very operator dependent.
[76] Should not be done if it is expected to be positive due to another condition such as: Arterial thromboembolic disease (MI, Stroke, Acute limb ischemia, Afib, Intracardiac thrombus) VTE (DVT, PE), DIC, recent surgery/trauma (eg, tissue ischemia, necrosis), Severe liver disease (decreased clearance), Malignancy, Renal disease, Nephrotic syndrome (eg, renal vein thrombosis), Acute renal failure, Chronic renal failure and underlying cardiovascular disease, Normal pregnancy.
[77] Most accurate assessment of calf veins & valvular competency. Indicated for obesity, severe edema, equivocal results in previous tests.
[78] Indicated for young, unusual thrombus localization, positive FHx. At earliest, tests should be performed 2 w after discontinuing anticoagulation.
[79] Indications: idiopathic thrombosis (esp. patients > 50 years). Tests (CBC, RFT, LFTurinalysis, and chest CXR). Ensure that patient is up-to-date on all age-appropriate cancer screening (e.g., colonoscopy, mammogram, digital rectal exam)

Treatment

Anticoagulation [80] [81]

A. **Acute therapy** (initial[82] "first 10 days"): **SC LMWH** (enoxaparin, dalteparin, tinzaparin), SC direct oral factor Xa inhibitor (rivaroxaban, apixaban) or SC fondaparinux.[83]

B. **Secondary prophylaxis**[84] (long-term "3-6 months"): direct oral factor Xa inhibitor (rivaroxaban, apixaban),[85] OR Warfarin with target therapeutic INR of 2.0–3.0.[86]

Additional therapy

1. **Thrombolysis** (streptokinase, urokinase, tPA)
   a. Indications: Slow response to anticoagulation, PE with hemodynamic instability, Can be considered for acute proximal DVT of the leg.
   b. Catheter-directed thrombolysis: The thrombolytic agent is administered directly at the site of obstruction via a venous catheter.
2. **Thrombectomy** (IV removal via a catheter): Indicated for Insufficient response to anticoagulation and thrombolysis, Extensive thrombus, Phlegmasia cerulea dolens. Low-dose heparin is required prior to the procedure.
3. **IVC filter** (Greenfield filter): indicated in patients with DVT at high risk of developing PE who have **CI to anticoagulation, thrombolysis, and thrombectomy** (e.g., active bleeding, recent major surgery, recent intracranial hemorrhage).
4. **Compression** therapy with bandages or compression stockings.
5. **Early mobilization** as early as tolerated, minimizes bedrest.

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[80] Absolute contraindications to anticoagulation include: Active bleeding, Severe bleeding diathesis, Recent, planned, or emergency high bleeding-risk surgery/procedure, Major trauma, Acute intracranial hemorrhage (ICH).

[81] **Selection of agent** — Options include subcutaneous low molecular weight (LMW) heparin, subcutaneous fondaparinux, the oral factor Xa inhibitors rivaroxaban or apixaban, or unfractionated heparin (UFH). A decision between these agents is usually made based upon clinician experience as well as the risks of bleeding, patient comorbidities, preferences, cost, and convenience. Warfarin cannot be administered alone as an initial anticoagulant for DVT because of the delay in depletion of the vitamin K-dependent coagulation factors.

[82] Initial refers to therapy that is administered during the first few days (up to 10 days) following a diagnosis of DVT. Long-term anticoagulant therapy is typically administered for a finite time beyond the initial period, usually three to six months, and occasionally up to 12 months.

[83] The target is to achieve and maintain an aPTT of 1.5x–2.5x the mean of the control value or upper normal limit. Simultaneous initiation of warfarin once aPTT is therapeutic.

[84] LMW heparin and fondaparinux are also effective treatments and may be preferred in some special populations without severe renal failure.

[85] For most non-pregnant patients who do not have severe renal insufficiency (ie, creatinine clearance >30 mL/minute) or active cancer, we suggest a direct oral anticoagulant (ie, apixaban, edoxaban, rivaroxaban, or dabigatran) rather than other agents. In general, these agents have similar efficacy to warfarin and a lower risk of bleeding; however, access to a reversal agent may be limited. Direct oral anticoagulants are NOT suitable for the treatment of hemodynamically unstable PE, massive iliofemoral DVT, those who are pregnant, or those with severe renal insufficiency. Regular monitoring of coagulation parameters not required → improved patient compliance.

[86] Warfarin is an alternative if there is concern about the poor availability of reversal agents and in those with severe renal insufficiency (although apixaban may be used in those with a CrCl <15mL/m). Warfarin should be overlapped with heparin until the international normalized ratio (INR) is therapeutic for 24 hours. In cases of malignancy, increased risk of bleeding, or PUD, continue heparin instead of warfarin.

Hypercoagulable state

Thrombophilia is characterized by recurrent thromboembolism:

1. Venous thromboembolism (most common): blood clots that form within the venous vascular system, dislodge, and travel to a distant location (DVT, PE).
2. Arterial thromboembolism: blood clots that form within the arterial vascular system, dislodge, and travel to a distant location
    - Usually, an acute event that results in ischemic tissue damage (e.g., stroke, acute mesenteric ischemia, acute limb ischemia, acute coronary syndrome, pulmonary infarction)

Etiology	Pathophysiology
Surgery	Extended immobilization during procedure → blood stasis. Vessel instrumentation → endothelial damage.
Trauma	↓venous blood flow, immobilization (stasis), release of tissue factor (hypercoagulability) → ↑clotting.
Malignancy	Cancers excrete procoagulant factors (e.g., tissue factor and cancer procoagulant).
Immobilization	Prolonged immobilization (e.g., extended travel, hospitalization, bed rest) → ↑ venous stasis.
Smoking	Causes endothelial damage. Risk is significantly higher in women who also use OCP.
Obesity	Leads to chronic systemic inflammation and impaired fibrinolysis, risk increases as BMI increases.
Antiphospholipid syndrome	Acquired antibodies directed against plasma proteins bound to phospholipids (e.g., lupus anticoagulant, anti-cardiolipin, beta2-glycoprotein I antibodies) → aggregation of plasma proteins (e.g., clotting factors) → induces venous and arterial clotting → miscarriages, DVTs, portal vein thrombosis, and strokes. Associated with SLE and RA.
Nephrotic syndrome	Loss of plasma antithrombin in urine and ↑ blood viscosity due to extravasation of fluid from albumin loss in urine.
OCP/HRT	↑ estrogen and progestin → ↑ in prothrombin and fibrinogen and a ↓ in protein S.
Heparin-induced thrombophilia	Abs against platelet factor 4 → activation of platelets (hypercoagulability) → depletion of platelets.
Pregnancy	↑ Clotting factors (hypercoagulability), ↓ Protein C/S, uterus enlarges (venous stasis).
Advanced age	Progressive endothelial damage, ↑ pro-clotting factors w/o concomitant ↑ in protein C, ↑ in other pro-clotting comorbidities (e.g., malignancy), ↓ physical activity.

Laboratory results of coagulation pathway disorders						
Defective pathway	**Disorders**	**Platelets**	**Bleeding time**	**INR**	**PT**	**aPTT**
Primary hemostasis	Platelet deficiency	↓	↑	=	=	=
	Platelet dysfunction: Hereditary (vWD), Drug-induced (ASS and other platelet aggregation inhibitors, several chemotherapeutic drugs).	=	↑	=	=	=
Secondary hemostasis	**Extrinsic system**: Factor VII deficiency.	=	=	↑	↑	=
	Intrinsic pathway: Hemophilia, Heparin therapy.	=	=	=	=	↑
	Hyperfibrinolysis	=	=	↑	↑	↑
Combined defects	vWD	=	↑	=	=	n/↑
	Decrease in vitamin K-dependent coagulation factors II, VII, IX, and X.[87]	=	=	↑	↑	↑
	DIC	↓	↑	↑	↑	↑

Note: Lymphomas and leukemias are not included in this file.
Best wishes 💪😎
Adel Al Shihri ^-^

[87] Impaired hepatic production: e.g., liver cirrhosis/Vitamin K deficiency: e.g., malabsorption syndrome, malnutrition (e.g., due to alcohol use disorder)./Vitamin K antagonists: warfarin therapy./Autoantibodies against coagulation factors (SLE).