MASTER REVIEWER: LABORATORY DIAGNOSIS - ERYTHROCYTIC & HEMOSTASIS DISORDERS

PART 1: ERYTHROPOIESIS & ANEMIA OVERVIEW

Erythropoiesis Stages (Must Know Sequence)

Stage	Key Features	Clinical Pearl
Pronormoblast	Largest erythroid precursor; fine chromatin; prominent nucleoli (≥1); basophilic cytoplasm; no granules	Earliest recognizable; undergoes mitosis → 2 basophilic normoblasts
Basophilic Normoblast	Smaller; coarser chromatin; parachromatin stains pink; nucleoli not visible; deeply basophilic cytoplasm; pseudopodia	Exam Trap: Nucleoli present but NOT visible
1 Pronormoblast → 16 Reticulocytes	Complete maturation cycle	High-Yield: Final reticulocyte count reflects marrow activity

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PART 2: IRON DEFICIENCY ANEMIA (IDA) - MOST COMMON CAUSE OF ANEMIA

Pathophysiology Stages (Must Memorize)

Iron Depletion → Iron Deficient Erythropoiesis → Iron Deficiency Anemia

Stage	Lab Findings
Iron Depletion	↓ Serum ferritin; ↑ TIBC/transferrin
Iron Deficient Erythropoiesis	↓ Plasma iron; ↓ Transferrin saturation (<15%); ↓ % sideroblasts in BM
Iron Deficiency Anemia	Microcytic, hypochromic RBCs

Clinical Features (Exam Pearls)

- Paresthesias (neuropathy)
- Atrophy of tongue epithelium → burning/soreness
- Angular stomatitis (cheilosis)
- Chronic gastritis
- PICA (craving dirt/ice) → Exam Pearl: Most classic symptom
- Koilonychia (spoon nails)
- Difficulty swallowing (Plummer-Vinson syndrome)

Laboratory Features

Test	Finding
CBC	Normocytic-normochromic (early) → Hypochromic, microcytic (late)
Reticulocyte count	↓ Decreased (except after iron therapy)
MCV	↓ Low
Hct/Hb	↓ Lower than RBC count
TIBC/Transferrin	↑ Increased
% Transferrin Saturation	↓ Decreased
Osmotic fragility	↓ Decreased
Platelet count	↑ Increased (blood loss) or ↓ Decreased (severe anemia)
Bone Marrow	Erythroid hyperplasia (early); ↓ Sideroblasts (<20%)
Ferritin	↓ LOW (Best test for IDA!)

Therapy

- Ferrous iron → 200 mg/day
- Iron-Refractory IDA (IRIDA) : Hereditary recessive; TMPRSS6 gene mutation; DOES NOT respond to oral iron

Exam Trap: IRIDA vs. IDA

- Both are microcytic anemia
- IRIDA fails oral iron therapy → suspect TMPRSS6 mutation

PART 3: ANEMIA OF CHRONIC DISEASE (ACD) - HIGH-YIELD DIFFERENTIAL

Pathogenesis

- Cytokines (TNF-α, ceramide) → ↓ RBC survival, altered iron metabolism, ↓ EPO, inhibited hematopoiesis
- Elevated Hepcidin → traps iron in macrophages

Laboratory Features

Parameter	Finding
PBS	Normocytic-normochromic → microcytic, hypochromic
Reticulocyte	NOT elevated
Bone Marrow	Normocellular; "frayed" hypochromic normoblasts
Sideroblasts	Decreased BUT storage iron is INCREASED

PART 4: IDA vs. ACD COMPARISON - EXAM GOLD

Parameter	IDA	ACD
Serum Iron	↓ LOW	↓ LOW
Ferritin	↓ LOW	↑ Normal/High
TIBC	↑ HIGH	↓ Low
% Transferrin Saturation	↓ LOW	↓ Normal/Low
Free Erythrocyte Protoporphyrin	↑ Increased	↑ Increased
Treatment	Iron	EPO

Exam Pearl: FERRITIN is the key discriminator!

- Low ferritin = IDA (iron stores depleted)
- Normal/High ferritin = ACD (iron trapped in macrophages)

PART 5: MEGALOBLASTIC ANEMIA

Vitamin B12 Deficiency

Absorption Site: TERMINAL ILEUM
Requires: Intrinsic Factor + Acid digestion

Causes:

1. Inadequate intake → Strict vegetarians (rare)
2. Reduced absorption → Defective intrinsic factor production (MCC!)

Folic Acid Deficiency

Sources: Green leafy vegetables
RDA: 50 μg folic acid / 400 μg food folate
Stores: ~5 mg (adequate for several months)
Absorption Site: JEJUNUM
Transport: Methyl TH4 (2/3 loosely bound to albumin, α2-macroglobulin, transferrin)
Function: Important in DNA/RNA synthesis

Key Distinction: B12 vs. Folate

Feature	B12 Deficiency	Folate Deficiency
Absorption site	Terminal ileum	Jejunum
Neurologic symptoms	YES (subacute combined degeneration)	NO
Dietary source	Animal products	Green leafy vegetables
Intrinsic factor required	YES	NO

Laboratory Tests (Know These!)

Test	Purpose	Finding
Serum Microbiologic Assays	Euglena gracilis (B12); Lactobacillus casei (folate)	Subject to antibiotic interference
Immunoassay	Modern method	More specific
Deoxyuridine Suppression Test	Measures marrow ability to use deoxyuridine in DNA synthesis	Abnormal in B12/folate deficiency
Schilling Test	Measures absorption of radioactive cobalamin	Abnormal in Pernicious Anemia
Urine FIGLU	Formiminoglutamic acid	↑ Increased in folate deficiency

Correlation Table - EXAM GOLD

Clinical Situation	Serum B12	Serum Folate	RBC Folate
Normal	Normal (200-900)	Normal (5-16)	Normal (>150)
B12 Deficiency	LOW (<100)	Normal/High	LOW (<150)
Folate Deficiency	Normal	LOW	LOW
Deficiency of BOTH	LOW	LOW	LOW

Exam Pearl: RBC Folate vs. Serum Folate

- RBC folate reflects tissue stores (more accurate)
- Serum folate reflects recent intake (can be falsely normal)

PART 6: SIDEROBLASTIC ANEMIA

Causes (Acquired)

Cause	Mechanism
Lead Poisoning	Blocks ALAS, ALA dehydratase, heme synthase
Chloramphenicol	Drug-induced
Copper deficiency	↓ Copper → impaired heme synthesis

Zinc Overload	Interferes with copper absorption
Ethanol	MCC of reversible SA!
Pyridoxine (B6) deficiency	Rare

Key Feature: Ringed sideroblasts in bone marrow

- Iron accumulates in mitochondria around nucleus

PART 7: APLASTIC ANEMIA

Definition

- Bone marrow failure syndrome
- Peripheral pancytopenia + marrow hypoplasia

Etiology Classification (20% Congenital, 80% Acquired)

Congenital/Inherited	Acquired
Fanconi anemia	Drugs
Diamond-Blackfan anemia	Radiation
Familial aplastic anemia	Parvovirus
	Benzene exposure

Pathophysiology Theories

1. Absent/defective stem cells (stem cell failure)
2. Abnormal marrow microenvironment
3. Abnormal regulatory cells/factors

Exam Pearl: Fanconi Anemia

- Congenital aplastic anemia with dysmorphic features
- Thumb anomalies, short stature, hyperpigmentation
- Chromosomal breakage on DEB testing

PART 8: HEREDITARY SPHEROCYTOSIS - HIGH-YIELD

Molecular Defects (3 Important Proteins)

Protein Defect	Inheritance	Notes
Ankyrin	Autosomal recessive (25%)	MC defect (40-65%); attaches Band 3, protein 4.2
Spectrin	Autosomal dominant	Vertical defect
Protein 4.1	Autosomal dominant (75%)	Horizontal defect

Pathophysiology

- RBC membrane defect + splenic microcirculation → HEMOLYSIS
- Cells lose membrane → become spherocytes

Laboratory Findings

Special Tests:

Test	Normal	Hereditary Spherocytosis
Autohemolysis	0.2-2% (with glucose: 0-0.9%)	>2% (with glucose: less)
Osmotic Fragility	Partial: 0.45%; Complete: 0.30-0.35%	INCREASED (lysis at higher concentrations)

Osmotic Fragility Principle

- RBCs in hypotonic solution (0.9%→0%) → water influx → swelling → lysis
- Spherocytes have less surface area → lyse at higher NaCl concentrations
- Normal → partial lysis at 0.45%, complete at 0.30-0.35%

Exam Trap

- Spherocytes have INCREASED osmotic fragility
- They lyse in higher salt concentrations than normal cells

PART 9: HEREDITARY ELLIPTOCYTOSIS

Key Points

- Autosomal dominant
- MCC defect: SPECTRIN
- Horizontal defect (weakening of membrane skeleton)
- 3 groups:
    1. Common HE
    2. Hereditary Pyropoikilocytosis (HPP) → severe congenital hemolytic anemia; fragmentation at 46°C (Normal: 49°C)
    3. Spherocytic HE → both elliptocytes AND spherocytes
    4. Southeast Asian Ovalocytosis → resistance to malaria

Exam Pearl: HPP vs. Normal

- HPP red cells fragment at 46°C
- Normal cells fragment at 49°C
- This is a diagnostic test

PART 10: HEREDITARY STOMATOCYTOSIS

Key Features

- Rare, autosomal dominant
- Dehydrated stomatocytosis (DHst) → more common
- Overhydrated stomatocytosis (OHst) → less common
- DHst: RBC dehydration due to loss of K^+ → FAM38A gene mutation
- Associated with Rh deficiency syndromes (Rh null, Rh mod)

PART 11: THALASSEMIA - HIGHEST YIELD

Overview

- Quantitative reduction in globin chain synthesis
- Most common single-gene disorder in the world
- Distribution follows malaria (protective effect)

Alpha Thalassemia

Normal genotype: αα (2 alpha genes per chromosome = 4 total)

Syndrome	Defective Genes	Genotype	Clinical Features
Hydrops Fetalis	4	--/--	Fatal; severe edema, hepatosplenomegaly; NO HbA or HbF
HbH Disease	3	--/-α	Chronic hemolytic anemia
Thalassemia Minor	2	--/αα or -α/-α	Asymptomatic; mild anemia
Silent Carrier	1	-α/αα	NO clinical/hematologic abnormality

Exam Pearl: Hb Constant Spring

- Alpha chains produced at reduced rate
- Causes HbH disease when combined with α-thalassemia trait

Hydrops Fetalis Key Points

- Incompatible with life
- Severe edema, marked anemia, hepatosplenomegaly
- PBS: Marked anisocytosis, poikilocytosis, microcytosis, erythroblastosis
- NO HbA or HbF present

Beta Thalassemia

Pathophysiology: ↓/absent β chains → ↑ α chains → unstable aggregates → hemolysis

Beta Thalassemia Major (Cooley's Anemia)

Feature	Finding
Clinical	Jaundice, splenomegaly, prominent frontal bones (chipmunk facies), cheekbones, jaws
PBS	Extreme poikilocytosis, target cells, Cabot rings, Howell-Jolly bodies, siderocytes, normoblastosis
Iron studies	↑ Serum iron, ↑ indirect bilirubin
β0-thalassemia	HbA ABSENT; HbF ~98%; HbA2 ~2%
β+-thalassemia	HbF 60-95%; HbA present

Beta Thalassemia Minor (Trait)

- Asymptomatic (may present as refractory anemia of pregnancy)
- RBC count ↑; MCV ↓, MCH ↓; MCHC low but often normal
- HbA2 elevated (3.5-7%)
- HbF slightly elevated (1-3%) in ~50% of cases

LABORATORY INVESTIGATION OF HEMOGLOBINOPATHIES

Test	Purpose
Cation Exchange HPLC	Quantify Hb fractions
Capillary Electrophoresis	Detect Hb variants
Hb A2 Quantitation	Diagnosis of β-thal trait
Sickling Test (Metabisulfite)	Detect HbS
Sickle Solubility Test	Screen for HbS
DNA Analysis	Definitive diagnosis

Exam Trap: Beta Thalassemia Trait vs. IDA

- Both: Low MCV, low MCH
- Key difference: Beta thal trait has ↑ RBC count and ↑ HbA2
- IDA has ↓ RBC count, ↑ RDW, ↓ ferritin

PART 12: SICKLE CELL DISEASE

Molecular Defect

- HbS: Glutamic acid → Valine at 6th position of β chain
- Oxygenated: soluble
- Deoxygenated: polymerization → tactoids → sickle cells

Sickle Cell Disease (HbSS)

- Homozygous state
- Chronic hemolytic anemia
- First manifested in early childhood
- Often fatal before 30 years

Sickle Cell Trait (HbAS)

- Heterozygous state
- BENIGN - no symptoms, no hematologic abnormalities
- Protection from Plasmodium falciparum

Exam Pearl: HbS vs. HbC

- HbS: Glutamic acid → Valine (position 6)
- HbC: Glutamic acid → Lysine (position 6)

PART 13: PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH) - HIGH-YIELD

Pathogenesis

- Acquired clonal stem cell disorder
- PIG-A gene mutation
- RBCs more susceptible to complement-mediated lysis
- Deficiency in GPI-anchored complement defense proteins:
  - DAF/CD55: Antagonizes convertase
  - MIRL/CD59: Controls MAC (MCC of hemolysis in PNH!)

PNH Cell Types

Type	Sensitivity
Type I	Normal
Type II	3-5x sensitive
Type III	15-25x sensitive

Laboratory Findings

- Normocytic anemia with reticulocytosis
- DAT - negative (NOT immune-mediated)

Diagnostic Tests

Test	Description	PNH Result
Flow Cytometry (TEST OF CHOICE)	Monoclonal antibodies to CD55, CD58, CD59	↓ GPI-anchored proteins
Sucrose Hemolysis Test	Low ionic strength medium	Positive hemolysis
Acidified Serum Test (Ham's test)	Patient cells + ABO-compatible normal serum + acid	Positive hemolysis

Exam Pearl: PNH vs. Paroxysmal Cold Hemoglobinuria

- PNH: Hemolysis caused by acid produced during sleep
- PCH: IgG antibody binds in cold, fixes complement, lysis occurs at warm temperatures

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PART 14: MICROANGIOPATHIC HEMOLYTIC ANEMIA (MAHA)

Causes (Extrinsic Vascular Abnormalities)

Category	Examples
Thrombotic Microangiopathies	TTP, HUS
Renal	Malignant hypertension, glomerulonephritis, preeclampsia
Vascular	Vasculitis, polyarteritis nodosa
Infections	Rocky Mountain spotted fever
Autoimmune	Wegener's granulomatosis, scleroderma renal crisis

PBS Findings

- Schistocytes (helmet cells)
- Fragmented RBCs

PART 15: IMMUNE HEMOLYTIC ANEMIAS - MUST KNOW

Warm Autoimmune Hemolytic Anemia (WAIHA)

Feature	Detail
Antibody	IgG (usually)
Complement	Fixes only to C3 (not full cascade)
Temperature	Binds at ALL temperatures
Hemolysis	Primarily extravascular (macrophages in spleen)
Associated	70% with other illnesses (SLE, lymphoma, CLL)
Treatment	Responsive to steroids and splenectomy

Cold Autoimmune Hemolytic Anemia (CAIHA)

Feature	Detail
Antibody	IgM (most common)
Temperature	Binds best at ≤30°C
Complement	Fixes ENTIRE complement cascade

Hemolysis	Intravascular (MAC formation)
Cells	Typically only complement found on cells
Associated	90% with other illnesses (infections, lymphoma)
Treatment	POOR response to steroids/splenectomy; responsive to plasmapheresis

Paroxysmal Cold Hemoglobinuria (PCH)

- Different from PNH! (PNH = acid-induced hemolysis during sleep)
- Causes: Idiopathic, post-infectious (more common)
- Mechanism: Biphasic hemolysis
  - IgG binds in cold, fixes complement
  - At warm temperatures: IgG dissociates, complement remains → lysis
- DAT: Positive with C3; usually negative with anti-IgG
- Antibody: Directed to P antigen
- Test: Donath-Landsteiner autohemolysis test

Exam Trap: DAT Patterns

Diagnosis	DAT Result
WAIHA	IgG ± C3
CAIHA	C3 only (IgM not detected)
PCH	C3 only (IgG not detected)
PNH	Negative (not immune-mediated)

PART 16: PORPHYRINS - QUICK REFERENCE

Types & Enzymes (Exam Focus)

Porphyria	Enzyme Defect	Key Feature
Acute Intermittent Porphyria (AIP)	HMBS (PBG deaminase)	Most common acute porphyria; neurovisceral symptoms ONLY; ↑ PBG, ALA in urine
ALA Dehydratase Deficiency (ADP)	ALAD	Rarest; indistinguishable from AIP; ↑ ALA ONLY
Hereditary Coproporphyria	CPOX	Neurovisceral + photosensitivity
Variegate Porphyria	PPOX	Neurovisceral + photosensitivity; erosions on sun-exposed skin
Porphyria Cutanea Tarda (PCT)	UROD	Most common in US; photosensitivity + hemolytic anemia; bullous dermatosis
Congenital Erythropoietic Porphyria	UROS	Günther disease; severe; red-pigmented urine; erythrodontia; hemolytic anemia
Erythropoietic Protoporphyria (EPP)	FECH	Photosensitivity ONLY; painful itching erythema minutes after sun exposure

Symptom Classification

Symptoms	Porphyria
Neurovisceral ONLY	AIP, ADP
Neurovisceral + Photosensitivity	Variegate, Hereditary Coproporphyria

Neurovisceral + Hemolytic Anemia	PCT, Congenital Erythropoietic
Photosensitivity ONLY	EPP, X-linked porphyria

Exam Pearls

- AIP: "Most common acute porphyria"; dark red urine upon exposure to air/light; colicky abdominal pain; psychiatric symptoms
- PCT: "Most common in US"; associated with hemochromatosis; bullous dermatosis; ↑ URO I & III
- EPP: Painful erythema within minutes of sun exposure; NORMAL urine profile
- Erythrodontia (red teeth) → Congenital Erythropoietic Porphyria

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PART 17: POLYCYTHEMIA/ERYTHROCYTOSIS

Definition

- Hb >16.5 g/dL (men), >16 g/dL (women)
- JAK2 mutation in primary polycythemias

Classification

Type	Mechanism	Examples
ABSOLUTE	↑ Total RBC mass	PV, secondary
RELATIVE	Normal RBC mass; ↓ plasma volume	Dehydration, Gaisbock's syndrome

Secondary Polycythemia (Appropriate EPO ↑)

1. ↓ O_2 loading: High altitude, pulmonary disease, cyanotic heart disease, carboxyhemoglobinemia, Hb M
2. ↓ O_2 unloading: High O_2 affinity hemoglobinopathy

Secondary Polycythemia (Inappropriate EPO ↑)

- Neoplasms: Wilms' tumor, renal carcinoma, cerebellar hemangioma, hepatoma
- Renal: Polycystic kidney, renal artery stenosis

Primary Marrow Disorders

- Polycythemia Vera (PV) - JAK2 V617F mutation

PART 18: HEMOSTASIS OVERVIEW - EXAM FOUNDATION

Three Systems of Hemostasis

System	Components	Function
Primary Hemostasis	Endothelium, platelets	Immediate plug formation
Secondary Hemostasis	Coagulation proteins	Fibrin clot formation
Fibrinolytic System	Plasminogen/plasmin	Clot dissolution

Coagulation Cascade - Key Factors

Vitamin K-Dependent Factors (Exam Gold):

- FII (Prothrombin)
- FVII
- FIX
- FX
- Protein C
- Protein S

Contact Factors (Surface-bound zymogens):

- FXII (Hageman factor)
- Prekallikrein (Fletcher factor)
- FXI

Cofactors/Substrates:

- HMWK, FVa, FVIIIa, Protein S, TF

Exam Trap: Intrinsic vs. Extrinsic Pathway

- Intrinsic: Assessed by aPTT
- Extrinsic: Assessed by PT
- Common pathway: FII, FV, FX - prolonged in BOTH tests

PART 19: LABORATORY TESTS - MASTER TABLE

Core Coagulation Tests

Test	Pathway Assessed	Procedure	Interpretation
PT	Extrinsic + Common	Tissue thromboplastin + $CaCl_2$	Isolated prolonged = FVII def; Prolonged + aPTT = common pathway defect
aPTT	Intrinsic + Common	Contact activator + $CaCl_2$	Prolonged alone = FVIII, FIX, FXI, FXII, PK, HMWK defects
INR	PT standardization	INR = (PTR)^ISI	Only for VKA monitoring (NOT for liver disease, DIC)
Thrombin Time (TT)	Fibrinogen function	Bovine thrombin + plasma	Prolonged = hypofibrinogenemia, dysfibrinogenemia, heparin
Fibrinogen Assay	Quantitative	Clauss method (50 U/mL thrombin)	<100 mg/dL = prolonged PT & aPTT
D-dimer	Fibrinolysis	Monoclonal antibody latex agglutination	↑ = DIC, DVT, PE (rule-out for DVT/PE)

Mixing Studies - EXAM GOLD

Result	Interpretation
Complete Correction	Factor deficiency
Incomplete Correction	Circulating inhibitor (e.g., lupus anticoagulant, factor inhibitor)

Exam Pearl: PT Mixing Study

- NOT warranted for isolated prolonged PT
- Isolated prolonged PT → vitamin K deficiency → give IV vitamin K (10 mg) → both diagnostic and therapeutic

Factor Assays

- Serial dilutions of patient plasma + factor-deficient plasma
- Standard curve from NPP (100%, 50%, 25%, 12.5%)
- Diluting patient plasma dilutes out lupus anticoagulant interference

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PART 20: COAGULATION FACTOR DEFICIENCIES - MUST KNOW

Differential Diagnosis of Abnormal Screening Tests

Abnormal Test	Associated with Bleeding	NOT Associated with Bleeding
Isolated aPTT	FVIII, FIX, FXI defects	FXII, PK, HMWK, lupus anticoagulant, heparin
Isolated PT	FVII defect	-
Both PT + aPTT	Anticoagulants, DIC, liver disease, vitamin K deficiency, massive transfusion, dysfibrinogenemia, FX, FV, FII defects	-

Hemophilia A vs. B

Feature	Hemophilia A	Hemophilia B
Deficiency	FVIII	FIX
Inheritance	X-linked recessive	X-linked recessive
Prevalence	Most common severe congenital bleeding disorder	Less common
PT	Normal	Normal
aPTT	Prolonged	Prolonged
Diagnosis	FVIII assay	FIX assay
Treatment	Recombinant FVIII	Recombinant FIX

Hemophilia Severity Classification

Severity	Factor Activity	Bleeding Pattern
Severe	<1%	2-4 bleeds/month; spontaneous
Moderate	1-5%	4-6/year; minor trauma
Mild	6-30%	Uncommon; major trauma/surgery

Clinical Presentation Timeline

- Early life: Cephalhematomas at birth, post-IM vitamin K hematomas
- Toddler: Acute/recurrent hemorrhages, muscle/soft tissue hematomas
- Childhood-adulthood: Bleeding frequency ↑ with activity/trauma

Treatment Pearls

- Standard of care: Prophylaxis with clotting factor replacement
- Recombinant FVIII/FIX = treatment of choice (FFP/cryoprecipitate NO longer used)

PART 21: OTHER COAGULATION FACTOR DEFECTS

Factor XI Deficiency

- Rarely spontaneous hemorrhage
- Prolonged aPTT + Normal PT
- Treatment: FFP (20 mL/kg loading; 5-10 mL/kg maintenance q24h)

Factor Deficiencies NOT Associated with Bleeding (Exam Trap!)

Deficiency	Features
FXII Deficiency	Most common; prolonged aPTT; NO bleeding risk
Prekallikrein Deficiency	Slightly prolonged aPTT; corrects to normal after 1 hour at 37°C
HMWK Deficiency	Rare; very long aPTT; NO bleeding risk

Exam Pearl: These are "contact factor" deficiencies - prolonged aPTT but NO clinical bleeding!

Fibrinogen Disorders

Type	Defect	Findings
Type I: Afibrinogenemia	Quantitative (absent/low)	Prolonged PT, aPTT, TT; umbilical stump bleeding
Type I: Hypofibrinogenemia	Quantitative (low)	Same as above
Type II: Dysfibrinogenemia	Qualitative (dysfunctional)	Prolonged TT, reptilase time

FVII Deficiency

- Most common rare hereditary factor deficiency
- AR inheritance
- Clinical: Epistaxis, mucosal bleeding, menorrhagia
- Dx: Prolonged PT + FVII assay
- Trap: Samples should NOT be stored at 4°C (cold activation of FVII!)
- Tx: rFVIIa, FFP, 4-factor PCC

Factor XIII Deficiency

- Delayed bleeding (24-36 hours post-surgery/trauma)
- PT, aPTT, TT - ALL NORMAL
- Dx: Reduced plasma FXIII activity
- Tx: Cryoprecipitate (half-life very long)

α_2-Antiplasmin Deficiency

- Excessive fibrinolysis
- Delayed bleeding
- Normal platelet count, normal coagulation tests
- Test: Clot lysis after several hours in vitro
- Tx: Plasma transfusion, oral fibrinolysis inhibitors

PART 22: DISSEMINATED INTRAVASCULAR COAGULATION (DIC) - HIGH-YIELD

Definition

- Clinicopathologic syndrome
- Simultaneous thrombin and plasmin formation
- Consumption of coagulation factors

Clinical Features

- Widespread bleeding (especially from puncture sites, wounds, surgical sites)

ISTH Diagnostic Scoring System (Exam Focus!)

Parameter	0 Points	1 Point	2 Points
Platelet count	>100	<100	<50
D-dimer	<0.4	0.4-4.0	>4.0
PT prolongation	<3 sec	3-6 sec	>6 sec
Fibrinogen	>100	<100	-

Score ≥5 = Compatible with overt DIC

Laboratory Findings

- Prolonged PT & aPTT
- Thrombocytopenia
- Reduced fibrinogen
- ↑ D-dimer (measures plasmin-cleaved cross-linked fibrin)
- PBS: Schistocytes (microangiopathic hemolytic anemia)

Causes

- Sepsis
- Malignancy
- Obstetric complications (HELLP, abruptio placenta, placenta previa)
- Massive tissue injury

Treatment

- Non-bleeding patient with only lab evidence: Low-dose heparin (3-5 IU/kg/hour)

PART 23: LIVER DISEASE & VITAMIN K DEFICIENCY

Liver Disease

- Cirrhosis: Prolonged PT + mild-to-moderate thrombocytopenia
- Paradox: Despite abnormal labs, cirrhosis patients have rebalanced hemostasis → no excessive bleeding tendency

Vitamin K Deficiency - Causes

- Acutely ill patients on antibiotics + parenteral nutrition
- Anatomic bypass of small intestine
- Malabsorption
- Biliary tract obstruction
- Reduced dietary intake
- Warfarin therapy

Diagnosis & Treatment

- Isolated prolonged PT/INR
- Treatment: IV vitamin K (10 mg in 25-50 mL NS over 15-30 minutes) → both diagnostic AND therapeutic

PART 24: ACQUIRED FACTOR INHIBITORS

FVIII Inhibitor - MOST COMMON

- Associated with: B-cell malignancy, SLE, postpartum
- Treatment: High-dose FVIII, activated vitamin K-dependent factors, rVIIa
- Long-term: Immunosuppression (cyclophosphamide, prednisone, rituximab)

FX or FIX Inhibitor

- Associated with systemic amyloidosis
- Mechanism: Adsorption of factors onto amyloid protein

Pan-inhibitors

- Hypergammaglobulinemic states (MM, Waldenström's)

Lupus Anticoagulant (LA)

- Antibody prolonging phospholipid-dependent tests
- Associated with: SLE, recurrent abortions, thrombosis (NOT bleeding!)

PART 25: PLATELET DISORDERS - OVERVIEW

Platelet Basics

- Derived from bone marrow megakaryocytes
- Life span: ~10 days
- PBS: Number, size, distribution, structure
- Non-anticoagulated fingerstick: Some platelet clumping is normal

Platelet Function After Injury

1. Adhesion: Platelets adhere to exposed collagen via vWF + GPIb-IX-V complex
2. Activation: Shape change → spheroid with pseudopods; exocytosis of granules
3. Aggregation: GPIIb/IIIa binds fibrinogen → platelet plug formation
4. Phosphatidylserine exposure: Activates coagulation

Platelet Agonists

- Strong: Collagen, thrombin, TXA2 (induce aggregation + secretion)
- Weak: ADP, epinephrine (aggregation only)
- Ristocetin: Causes agglutination (vWF + GPIb-IX-V) → NOT aggregation

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PART 26: TESTS FOR PLATELET FUNCTION

Bleeding Time - HISTORICAL (Rarely Used)

Method	Procedure	Notes
Ivy	BP cuff at 40 mmHg; 10 mm x 1 mm forearm incision	Every 30 sec, blot until bleeding stops
Duke	Earlobe/fingertip prick (3-4 mm)	Less invasive but poor predictive value

PFA-100/-200 (Modern Screening)

- Citrated blood aspirated through membrane coated with collagen + epinephrine OR collagen + ADP
- Affected by: vWF level (inverse), platelet count (inverse), Hct (inverse)
- Must be performed within 4 hours; transported on ice
- Advantage: High negative predictive value

Platelet Aggregation/Light Transmission Aggregation (LTA)

Parameter	Finding
Strong Agonists	Collagen, thrombin, TXA2 → induce secretion + aggregation
Weak Agonists	ADP, epinephrine → aggregation only
Panel Recommended	ADP, epinephrine, collagen, thrombin, TXA2, arachidonic acid, ristocetin

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PART 27: INHERITED PLATELET DISORDERS - EXAM FOCUS

Disorders of Platelet Adhesion: Bernard-Soulier Syndrome

Feature	Detail
Defect	Abnormal/absent GP Ib-IX-V complex
Inheritance	Autosomal recessive
Adhesion	Impaired (can't bind vWF)
Platelet count	Moderately decreased
Platelet size	INCREASED (macrothrombocytopenia)
Bleeding time	Prolonged
LTA - Ristocetin	ABSENT/DECREASED
LTA - Other agonists	Normal (ADP, epinephrine, collagen, thrombin)
Differential	vWD (similar ristocetin response but ↓ vWF and FVIII)

Disorders of Platelet Aggregation: Glanzmann Thrombasthenia

Feature	Detail
Defect	Quantitative/qualitative defect in GPIIb/IIIa
Inheritance	Autosomal recessive
Chromosome	17
Aggregation	Impaired (can't bind fibrinogen)
Platelet count	Normal
PBS	Platelets remain isolated (no clumping)
LTA - All agonists	ABSENT/DECREASED (no primary or secondary waves)
LTA - Ristocetin	Normal (vWF binding intact)
Differential	Congenital afibrinogenemia (similar LTA pattern but with prolonged PT, aPTT, TT)

Exam Trap: Bernard-Soulier vs. Glanzmann

Feature	Bernard-Soulier	Glanzmann
Defect	GPIb-IX-V	GPIIb/IIIa
Ristocetin	Absent	Normal
Other agonists	Normal	Absent
Platelet size	Large	Normal

Storage Pool Diseases

Type	Defect	Features
δ-SPD	Dense granule deficiency	First wave present; second wave ABSENT (ADP/epinephrine); ATP:ADP >2.5
α-SPD (Gray Platelet Syndrome)	α-granule deficiency	Deficient PF4, βTG, vWF, thrombospondin; EM shows decreased α-granules
Quebec Platelet Syndrome	↑ uPA → proteolysis of α-granules	Delayed bleeding; unresponsive to platelet transfusion; responsive to fibrinolysis inhibitors

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PART 28: VON WILLEBRAND DISEASE (vWD) - HIGH-YIELD

vWF Functions

1. Primary hemostasis: Binds GPIb-IX-V on platelets + subendothelial collagen
2. Secondary hemostasis: Carries FVIII (free FVIII is unstable and rapidly cleared)

vWD Classification

Type	Defect	Key Features
Type 1	Quantitative	70% of cases; ↓ vWF levels
Type 2A	Qualitative	10-20%; Loss of large MW multimers (↑ proteolysis by ADAMTS13 or defective multimerization)
Type 2B	Qualitative	Increased affinity to GPIb-IX-V; large multimers spontaneously bind platelets → consumed
Type 2M	Qualitative	Decreased platelet receptor binding
Type 2N	Qualitative	Impaired FVIII binding ("autosomal hemophilia")
Type 3	Quantitative	Absent/nearly absent vWF

Exam Pearl: Type 2B vWD

- Called "pseudo vWD"
- Increased vWF affinity for platelets → thrombocytopenia due to platelet consumption
- Can be confused with platelet-type vWD (mutation in GPIBA)

vWD vs. Hemophilia

- vWD: Bleeding from mucocutaneous sites
- Hemophilia: Bleeding into joints/muscles

PART 29: THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP)

Pathogenesis

- Deficiency of ADAMTS13 metalloprotease
- ADAMTS13 normally cleaves ultralarge vWF multimers
- Deficiency → persistence of ultralarge vWF → binds endothelial cells + platelets → microvascular thrombi

Clinical Features

- Neurologic manifestations
- Fatigue, bleeding, petechiae
- Fever
- Hemoglobinuria

Laboratory Diagnosis

Test	Finding
CBC	↑ WBC, ↓ Hgb, ↓ Platelets
PT/PTT	Normal
BUN/Creatinine	To rule out HUS
LDH/Bilirubin	↑ (hemolysis)
PBS	Schistocytes
ADAMTS13 activity	↓ (not routinely available)

TTP vs. HUS - EXAM GOLD

Feature	TTP	HUS
ADAMTS13	Severely decreased	Less severely decreased
Renal	Less severe	More severe
CNS	More severe	Less severe
Diarrhea history	Usually absent	Present (E. coli O157:H7, Shigella)

Treatment

- Plasma exchange with FFP = Treatment of choice

PART 30: QUANTITATIVE PLATELET DISORDERS - THROMBOCYTOPENIA

Inherited Thrombocytopenias - EXAM FOCUS

Syndrome	Mutation	Features
MYH9-related	MYH9	Large platelets, Döhle-like inclusions; May-Hegglin, Fechtner, Epstein, Sebastian syndromes
RUNX1/AML1	RUNX1	Normal platelet size; abnormal function; predisposition to AML
Platelet-type vWD	GPIBA	Enhanced ristocetin responsiveness
Velocardiofacial/DiGeorge	22q11 deletion	Cardiac abnormalities, parathyroid/thymus insufficiency, cognitive impairment
Paris-Trousseau/Jacobsen	11q23-24 deletion	Large platelets with large α-granules
Bernard-Soulier	GPIB/IX/V	Autosomal recessive; large platelets
Congenital amegakaryocytic	MPL	Severe thrombocytopenia; absence of megakaryocytes
Gray Platelet	NBEAL2	Absent α-granules
Wiskott-Aldrich	WAS	Small platelets; X-linked

Immune Thrombocytopenia (ITP)

Types:

- Primary: Diagnosis of exclusion
- Secondary: Associated with HIV, HCV, H. pylori

Pathogenesis:

- Viral attachment/antigenic alteration → platelet autoantibodies (IgG)
- IgG-coated platelets destroyed by splenic macrophages

Presentation:

- Children: Usually post-viral; self-limited
- Adults: Chronic course

Work-up:

- Isolated thrombocytopenia (<100,000/μL) = Hallmark

Treatment:

- Children: Often no treatment needed (resolves spontaneously)
- Adults: Corticosteroids = initial drug of choice
- Splenectomy = rapid, complete, long-term remission

PART 31: THROMBOCYTOSIS - QUICK REFERENCE

Types

Type	Cause	Examples
Acquired (most common)	Autonomous clonal	MPNs, Essential Thrombocythemia
Reactive	Secondary	Infection, chronic inflammation, malignancy, hemolysis, IDA, splenectomy
Congenital	Mutation in TPO/MPL	-

Reactive Conditions with ↑ Platelets (Box 4-5)

- Transient: Acute blood loss, recovery from thrombocytopenia, acute infection, exercise
- Sustained: Iron deficiency, hemolytic anemia, post-splenectomy, cancer, chronic inflammation, connective tissue disorders, TB, drug reactions

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EXAM HIGH-YIELD SUMMARY TABLES

Quick Differential: Microcytic Anemias

Feature	IDA	ACD	Thalassemia	Sideroblastic
Ferritin	↓	↑/N	N/↑	↑
TIBC	↑	↓	N	N/↓
% Sat	↓	↓	N	↑
RDW	↑	N	N/↑	N/↑
RBC count	↓	N	↑	N
Ringed sideroblasts	No	No	No	Yes

Quick Differential: Hemolytic Anemias

Test	HS	HE	G6PD	Sickle	PNH
Osmotic fragility	↑	N	N	N	N
Autohemolysis	↑	N	N	N	N
Coombs (DAT)	-	-	-	-	-
Special	OF test	Heat fragility	Enzyme assay	Hb electrophoresis	Flow cytometry (CD55/59)

Quick Differential: Coagulation Tests

Condition	PT	aPTT	TT	Platelets
Hemophilia A/B	N	↑	N	N
vWD	N	↑ (Type 1/2)	N	N (↓ in Type 2B)
FVII deficiency	↑	N	N	N
FXII deficiency	N	↑	N	N
Vitamin K deficiency	↑	↑	N	N
DIC	↑	↑	↓/N	↓
Liver disease	↑	↑	↑	↓
Fibrinogen deficiency	↑	↑	↑	N

Exam Pearls - Quick Review

1. Ferritin = Best test for IDA (low = IDA, normal/high = ACD)
2. Reticulocyte count = Best indicator of marrow response
3. aPTT mixing study = Complete correction = factor deficiency; Incomplete = inhibitor
4. Schistocytes = MAHA (TTP, HUS, DIC)
5. Ringed sideroblasts = Sideroblastic anemia
6. Howell-Jolly bodies = Hyposplenism
7. Target cells = Thalassemia, liver disease, Hb C disease
8. ADAMTS13 deficiency = TTP
9. CD55/59 deficiency = PNH (flow cytometry)
10. JAK2 V617F = PV, ET, PMF

TEST-TAKING STRATEGY

1. Start with CBC → Classify anemia (microcytic, macrocytic, normocytic)
2. Reticulocyte count → Is it hypoproliferative or hyperproliferative?
3. Iron studies → Ferritin, TIBC, % Sat → IDA vs. ACD
4. Hb electrophoresis → Thalassemia vs. hemoglobinopathy
5. Coagulation cascade → PT vs. aPTT → Which pathway is affected?
6. Platelet function → vWD vs. platelet disorder
7. Mixing studies → Factor deficiency vs. inhibitor