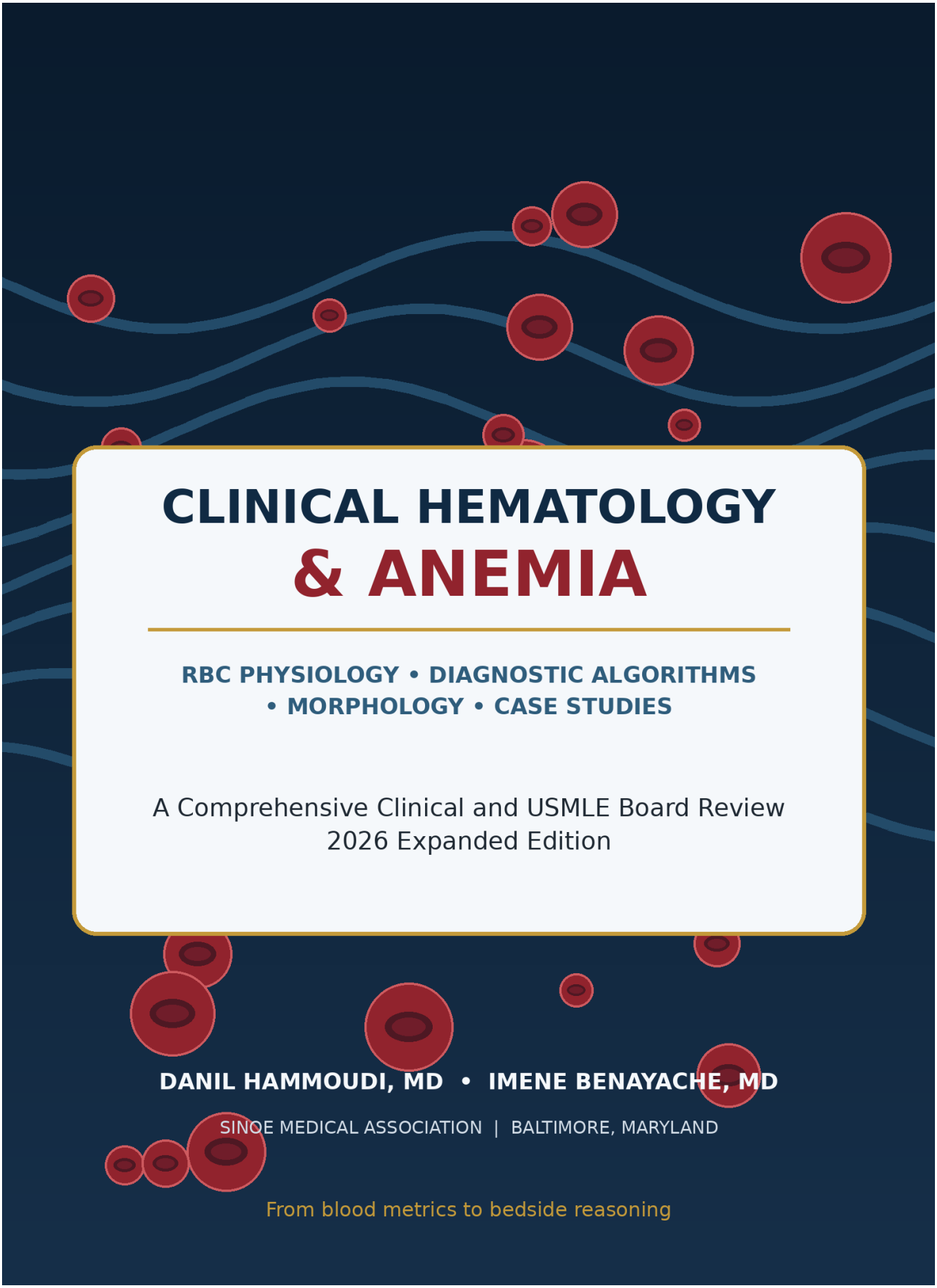

CLINICAL HEMATOLOGY & ANEMIA

RBC PHYSIOLOGY • DIAGNOSTIC ALGORITHMS • MORPHOLOGY • CASE STUDIES

A Comprehensive Clinical and USMLE Board Review
2026 Expanded Edition

DANIL HAMMOUDI, MD • IMENE BENAYACHE, MD

SINOE MEDICAL ASSOCIATION | BALTIMORE, MARYLAND

From blood metrics to bedside reasoning

CLINICAL HEMATOLOGY & ANEMIA

RBC Physiology, Diagnostic Algorithms, Morphology, and Case Studies

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Danil Hammoudi, MD • Imene Benayache, MD

Sinoe Medical Association • Baltimore, Maryland, USA

EDUCATIONAL USE ONLY

This publication is designed for medical education and board review. It does not replace individualized diagnosis, specialist consultation, institutional protocols, or treatment decisions based on the full clinical context. Laboratory reference ranges and therapeutic recommendations vary by age, pregnancy status, comorbidity, assay, and jurisdiction.

First edition compiled and expanded from eight source manuscripts supplied by the authors.

Preface: How to Use This Book

Anemia is not a single diagnosis. It is a physiologic signal that oxygen-carrying capacity is reduced, red-cell production is inadequate, red cells are being lost, or circulating cells are being destroyed prematurely. The fastest route to the correct diagnosis is not memorizing isolated diseases; it is applying a disciplined sequence: confirm anemia, measure marrow response, classify by MCV, interrogate the smear, and select targeted tests.

This expanded edition merges the strongest material from the supplied clinical briefings, microcytic-anemia manuals, iron-metabolism papers, morphology guides, sickle-cell review, and red-cell lifecycle narrative. Repetitive passages were consolidated, inconsistent formulas and legacy treatment shortcuts were corrected, and missing board-relevant topics were added.

- **For first-pass learning:** Read Chapters 1–4, then use the MCV-based chapters.
- **For clinical reasoning:** Start with the diagnostic algorithm in Chapter 3 and the case laboratory tables in Chapter 16.
- **For board review:** Prioritize the Board Traps, Tutor’s Pearls, morphology tables, buzzword appendix, and MCQs.
- **For rapid reference:** Use Appendix A for formulas, Appendix B for high-yield patterns, and Appendix C for the answer key.

> **CORE FRAMEWORK**
>
> MCV tells you cell size. Reticulocytes tell you whether the marrow is responding. The smear tells you what happened to the cell. Iron studies, hemolysis markers, and targeted biochemical tests reveal the mechanism.

Contents

CHAPTER 1

The Red Blood Cell Life Cycle

From marrow production to macrophage recycling

A mature erythrocyte is a highly specialized oxygen-delivery cell. It has no nucleus or mitochondria, maximizes intracellular hemoglobin, and remains deformable enough to cross capillaries narrower than its resting diameter. Its average lifespan is approximately 120 days.

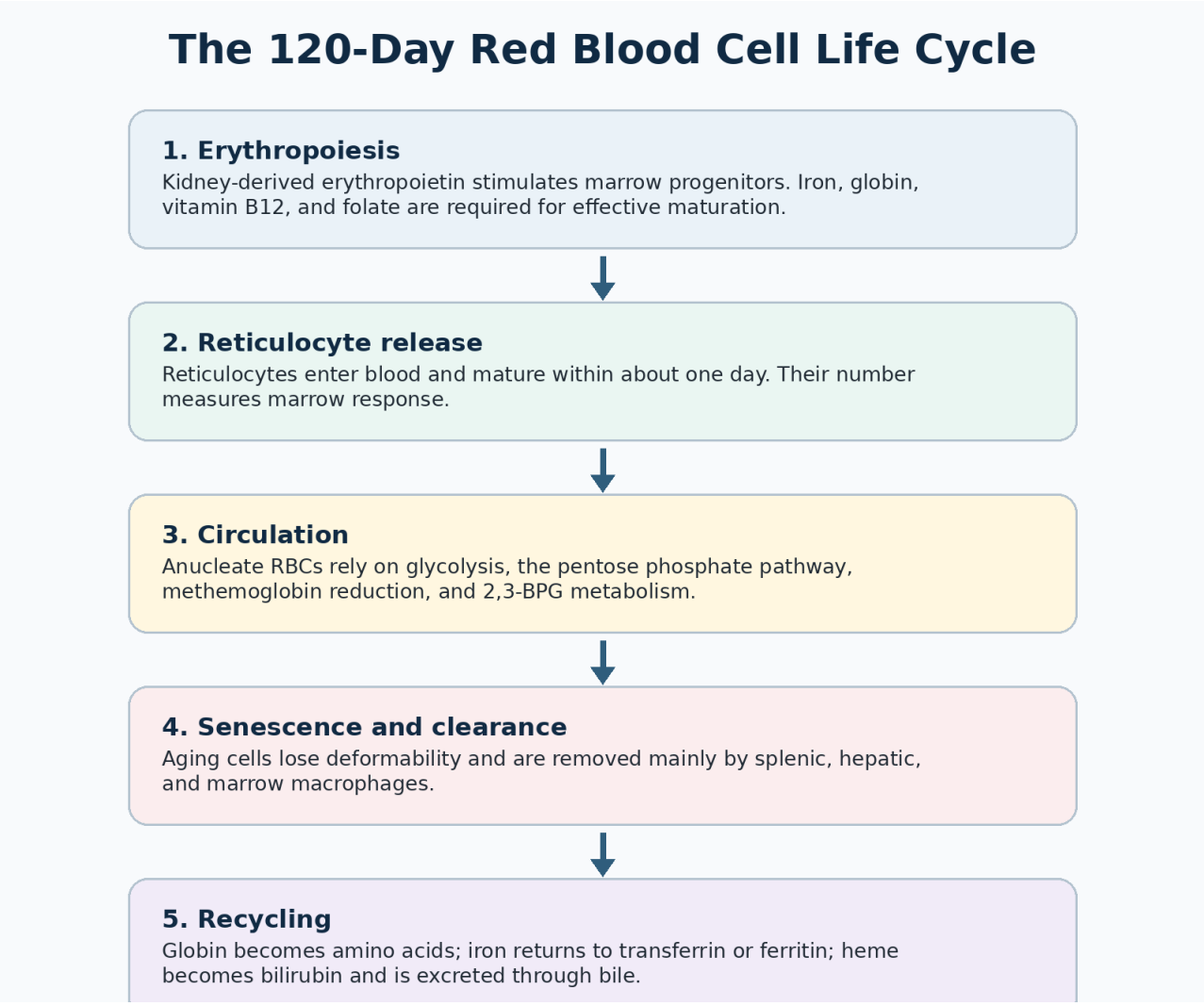

Figure 1. The RBC lifecycle connects erythropoiesis, reticulocyte response, cellular metabolism, macrophage clearance, and iron recycling.

Erythropoiesis: the marrow production line

- **Erythropoietin (EPO):** Produced mainly by renal interstitial cells in response to tissue hypoxia; promotes survival and differentiation of erythroid precursors.
- **Iron:** Required for heme synthesis. Deficiency limits hemoglobinization and eventually produces microcytosis.
- **Vitamin B12 and folate:** Required for DNA synthesis. Deficiency produces nuclear-cytoplasmic asynchrony and megaloblastic change.

- **Globin chains:** Quantitative defects cause thalassemia; structural variants cause hemoglobinopathies such as sickle cell disease.
- **Healthy marrow microenvironment:** Aplastic anemia, myelodysplasia, fibrosis, infiltration, and inflammatory signaling can impair production even when nutrients are adequate.

How mature RBCs survive without mitochondria

Pathway	Primary function	Failure pattern
Embden-Meyerhof glycolysis	ATP production for membrane pumps and deformability	Pyruvate kinase deficiency → chronic hemolysis
Pentose phosphate pathway	NADPH generation and reduced glutathione	G6PD deficiency → oxidant-triggered hemolysis
Methemoglobin reductase	Maintains heme iron in the Fe^{2+} state	Methemoglobinemia and impaired oxygen delivery
Rapoport-Luebering shunt	Generates 2,3-BPG to modulate oxygen affinity	Changes in 2,3-BPG shift the oxygen dissociation curve

Macrophage clearance and bilirubin formation

Senescent RBCs are removed mainly by macrophages in the spleen, liver, and bone marrow. Globin is recycled into amino acids. Iron is exported through ferroportin, transported by transferrin, or stored as ferritin. The porphyrin ring becomes biliverdin, then unconjugated bilirubin, which travels bound to albumin to the liver for conjugation and biliary excretion.

> **BOARD CONNECTION**
>
> Extravascular hemolysis increases unconjugated bilirubin and predisposes to pigment gallstones. Intravascular hemolysis more prominently produces hemoglobinemia, hemoglobinuria, hemosiderinuria, and marked haptoglobin depletion.

CHAPTER 2

Reading the CBC and Reticulocyte Response

Translate numbers into physiology

Core erythrocyte indices

Parameter	Common adult interpretation	Formula / clinical use
Hemoglobin (Hb)	Primary quantitative measure used to define anemia; interpret by age, sex, pregnancy, altitude, and laboratory range.	Measured directly; preferable to using hematocrit alone for severity decisions.
Hematocrit (Hct)	Fraction of blood volume occupied by RBCs.	Approximately 3 × Hb in many stable normocytic states, but the rule fails with marked microcytosis, macrocytosis, transfusion, or plasma-volume shifts.
MCV	<80 fL microcytic; 80–100 fL normocytic; >100 fL macrocytic.	MCV = Hct (%) × 10 / RBC count (millions/µL).
MCH	Average hemoglobin mass per RBC.	MCH = Hb (g/dL) × 10 / RBC count; usually tracks MCV.
MCHC	Average hemoglobin concentration in packed RBC volume.	MCHC = Hb × 100 / Hct. A true elevation strongly suggests spherocytosis or RBC dehydration.
RDW	Variation in RBC size.	Often high in iron deficiency, mixed deficiency, reticulocytosis, or transfusion; often normal in uncomplicated thalassemia trait.
RBC count	Number of circulating RBCs.	A relatively preserved/high RBC count despite severe microcytosis favors thalassemia trait over iron deficiency.

UPDATED DEFINITION

The World Health Organization’s 2024 guideline emphasizes age-, sex-, and pregnancy-specific hemoglobin cutoffs and appropriate adjustment for altitude and smoking. A single universal hematocrit threshold is inadequate.

The reticulocyte response

Reticulocytes are recently released RBCs. A raw reticulocyte percentage can appear falsely reassuring when the total RBC mass is low. Use the absolute reticulocyte count and, in significant anemia, a corrected reticulocyte count or reticulocyte production index (RPI).

CORRECTED RETICULOCYTE COUNT

Corrected reticulocyte % = observed reticulocyte % × (patient Hct / expected normal Hct).
RPI = corrected reticulocyte % / maturation factor. A maturation factor is needed because severe anemia causes earlier reticulocyte release and longer circulation time.

Pattern	Interpretation	Typical causes

Low or inappropriately normal reticulocytes	Hypoproliferation / ineffective erythropoiesis	Iron deficiency, B12/folate deficiency, CKD/EPO deficiency, inflammation, aplasia, marrow infiltration
High reticulocytes	Appropriate marrow response	Hemolysis, acute blood loss, recovery after nutrient replacement
High reticulocytes with macrocytosis	Reticulocytes are larger than mature RBCs	Hemolysis or blood-loss recovery; do not automatically diagnose B12/folate deficiency

Patterns that should stop you

- **Pancytopenia:** Think beyond isolated anemia—aplastic anemia, leukemia, marrow infiltration, severe megaloblastic anemia, hypersplenism, drugs, or infection.
- **High MCHC:** Verify for cold agglutinins or analytical interference; if real, hereditary spherocytosis is classic.
- **Very high RDW:** Suggests evolving deficiency, mixed populations, reticulocytosis, or recent transfusion.
- **Microcytosis with a high RBC count:** Strongly favors thalassemia trait; confirm with iron studies and hemoglobin analysis.
- **Normocytic anemia with low reticulocytes:** Do not call it “normal.” Early iron deficiency, CKD, inflammation, endocrine disease, and marrow failure commonly begin as normocytic anemia.

CHAPTER 3

The Diagnostic Architecture of Anemia

A reproducible approach for the clinic and examination room

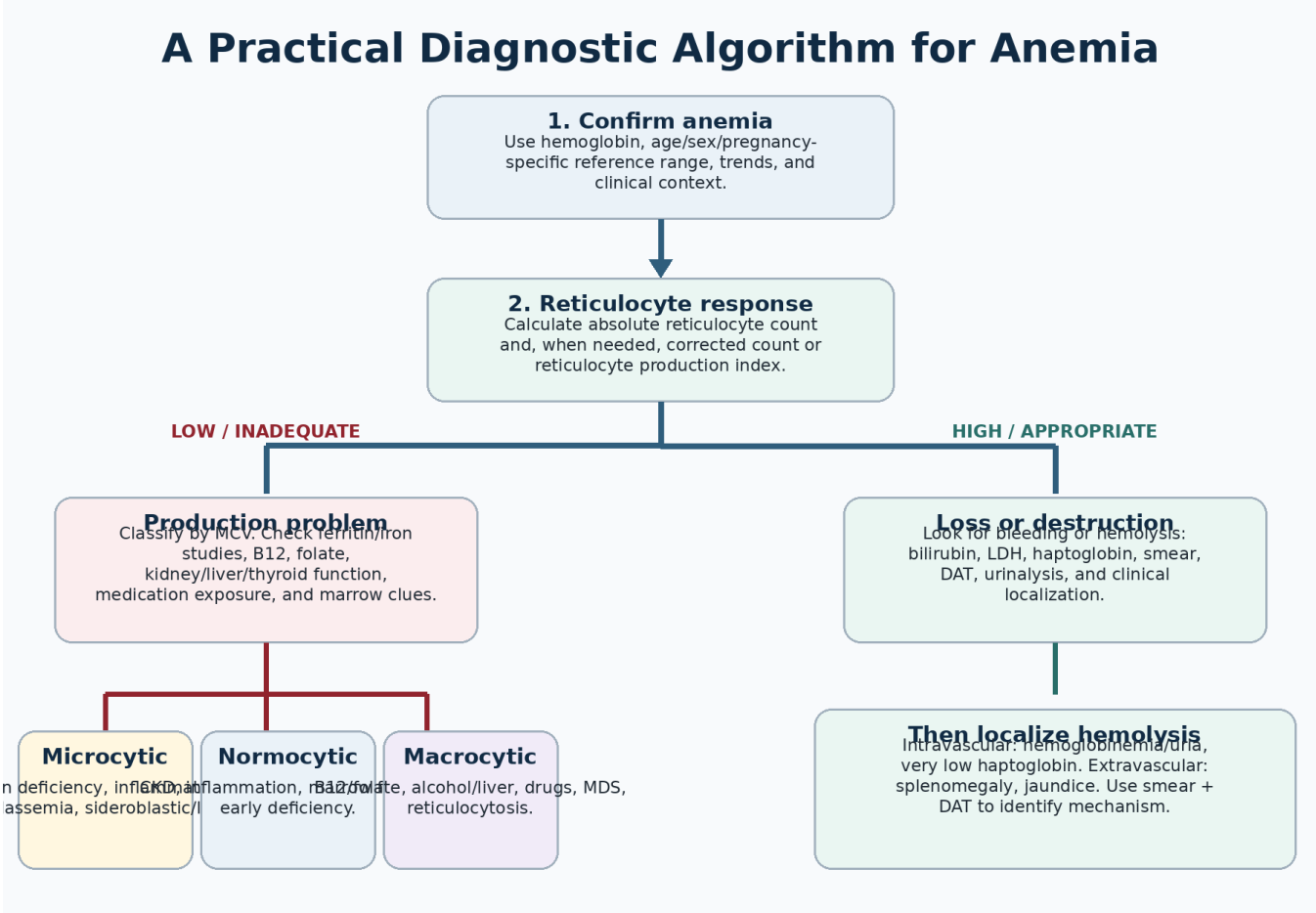

Figure 2. Anemia is solved by integrating hemoglobin, reticulocyte response, MCV, smear, and targeted testing.

Step 1: Confirm that anemia is real

- **Compare with the correct reference range:** Age, sex, pregnancy, altitude, and laboratory method matter.
- **Review prior values:** A chronic stable anemia and an acute fall require different urgency and different differential diagnoses.
- **Assess plasma volume:** Pregnancy and fluid loading can dilute Hb/Hct; dehydration can conceal anemia.
- **Look beyond the RBC line:** Leukopenia or thrombocytopenia suggests a broader marrow or systemic process.

Step 2: Decide whether the marrow is responding

An adequate reticulocyte response narrows the problem to blood loss or red-cell destruction. An inadequate response indicates defective production, inadequate substrate, impaired erythropoietin signaling, inflammation, or marrow disease.

Step 3: Use MCV as a branch—not a final diagnosis

MCV branch	Mechanistic categories	First-line tests
Microcytic	Reduced iron availability; impaired heme synthesis; reduced globin synthesis	Ferritin, serum iron, TIBC/transferrin, transferrin saturation, CRP/ESR, smear; consider hemoglobin analysis and lead level
Normocytic	Acute loss, hemolysis, CKD, inflammation, marrow failure, early nutrient deficiency	Reticulocytes, creatinine/eGFR, hemolysis panel, smear, inflammatory markers; marrow evaluation if multilineage abnormalities
Macrocytic	Megaloblastic DNA-synthesis failure or nonmegaloblastic enlargement	Smear, B12, folate, MMA, homocysteine, liver tests, TSH, medications, alcohol history; consider marrow evaluation

Step 4: Let the smear challenge the automated count

Automated indices summarize the circulating population. The smear shows individual-cell evidence: fragmentation, membrane loss, oxidant injury, marrow stress, nuclear remnants, parasites, and mixed populations. A smear can overturn a simplistic MCV diagnosis—for example, a normal average MCV may hide simultaneous microcytes and macrocytes.

> **BOARD TRAP**
> A normal MCV does not exclude two opposing processes. Combined iron deficiency and vitamin B12 deficiency may average to a “normal” MCV while RDW is high and the smear is dimorphic.

Step 5: Identify urgency before completing elegance

- **Unstable bleeding or shock:** Resuscitate and control hemorrhage while obtaining essential pretransfusion samples when feasible.
- **Chest pain, syncope, ischemia, severe dyspnea, or hemodynamic compromise:** Escalate urgently; transfusion decisions depend on symptoms, Hb, rate of decline, and comorbidity.
- **Schistocytes with thrombocytopenia:** Treat as possible thrombotic microangiopathy or DIC until proven otherwise.
- **Sickle cell disease with hypoxemia or new pulmonary infiltrate:** Consider acute chest syndrome—a medical emergency.
- **Fever in functional asplenia:** Urgent evaluation and empiric management are critical because encapsulated bacterial infection can progress rapidly.

CHAPTER 4

Peripheral Smear Morphology and RBC Inclusions

The visual language of hematology

High-yield poikilocytes

Cell	Morphology	Most useful associations
Target cell (codocyte)	Central hemoglobinized area surrounded by pallor and an outer rim	HALT: HbC disease, asplenia, liver disease, thalassemia; also sickle syndromes
Spherocyte	Small dense cell without central pallor	Hereditary spherocytosis; warm autoimmune hemolytic anemia
Schistocyte	Fragmented helmet/triangle cell	DIC, TTP/HUS, HELLP, mechanical valves, severe burns
Sickle cell	Elongated crescent or boat-shaped cell	HbS polymerization; sickle cell disease
Bite/blister cell	Semicircular “bite” or peripheral blister	G6PD deficiency after splenic removal of Heinz-body material
Teardrop cell	Dacryocyte with one tapered end	Myelofibrosis, marrow infiltration, extramedullary hematopoiesis
Macro-ovalocyte	Large oval RBC	Megaloblastic anemia; often with hypersegmented neutrophils
Pencil cell	Elongated hypochromic cell	Iron-deficiency anemia
Acanthocyte	Irregular, variably spaced spicules	Severe liver disease, abetalipoproteinemia, neuroacanthocytosis
Echinocyte	Uniform short projections	Uremia, pyruvate kinase deficiency; may be artifact
Stomatocyte	Slit-like central pallor	Hereditary stomatocytosis, liver disease, alcohol-related change
Elliptocyte	Oval/cigar-shaped cell	Hereditary elliptocytosis; may increase in iron deficiency or megaloblastic disease

RBC inclusions

Inclusion	Composition / appearance	Association
Howell-Jolly body	Nuclear DNA remnant	Asplenia/hyposplenia, post-splenectomy, megaloblastic anemia
Heinz body	Denatured oxidized hemoglobin; requires supravital stain	G6PD deficiency, unstable hemoglobins, oxidant exposure
Basophilic stippling	Aggregated ribosomal RNA	Lead toxicity, thalassemia, sideroblastic anemia, severe dyserythropoiesis

Inclusion	Composition / appearance	Association
Pappenheimer body	Iron-containing granules	Sideroblastic anemia, post-splenectomy states, iron-loading disorders
Cabot ring	Mitotic spindle/nuclear remnant	Severe megaloblastic anemia and dyserythropoiesis
Malaria parasite	Intracellular ring or other parasite forms	Plasmodium infection; species identification and parasitemia matter
Ring sideroblast	Iron-laden mitochondria encircling erythroblast nucleus in marrow	Sideroblastic anemia; not a peripheral blood cell finding

MORPHOLOGY DISCIPLINE

A finding is most powerful when it fits the full pattern. Spherocytes plus positive DAT support immune hemolysis; spherocytes plus family history, high MCHC, and negative DAT support hereditary spherocytosis.

CHAPTER 5

Iron Metabolism and Iron-Deficiency Anemia

Distinguish depleted stores from restricted availability

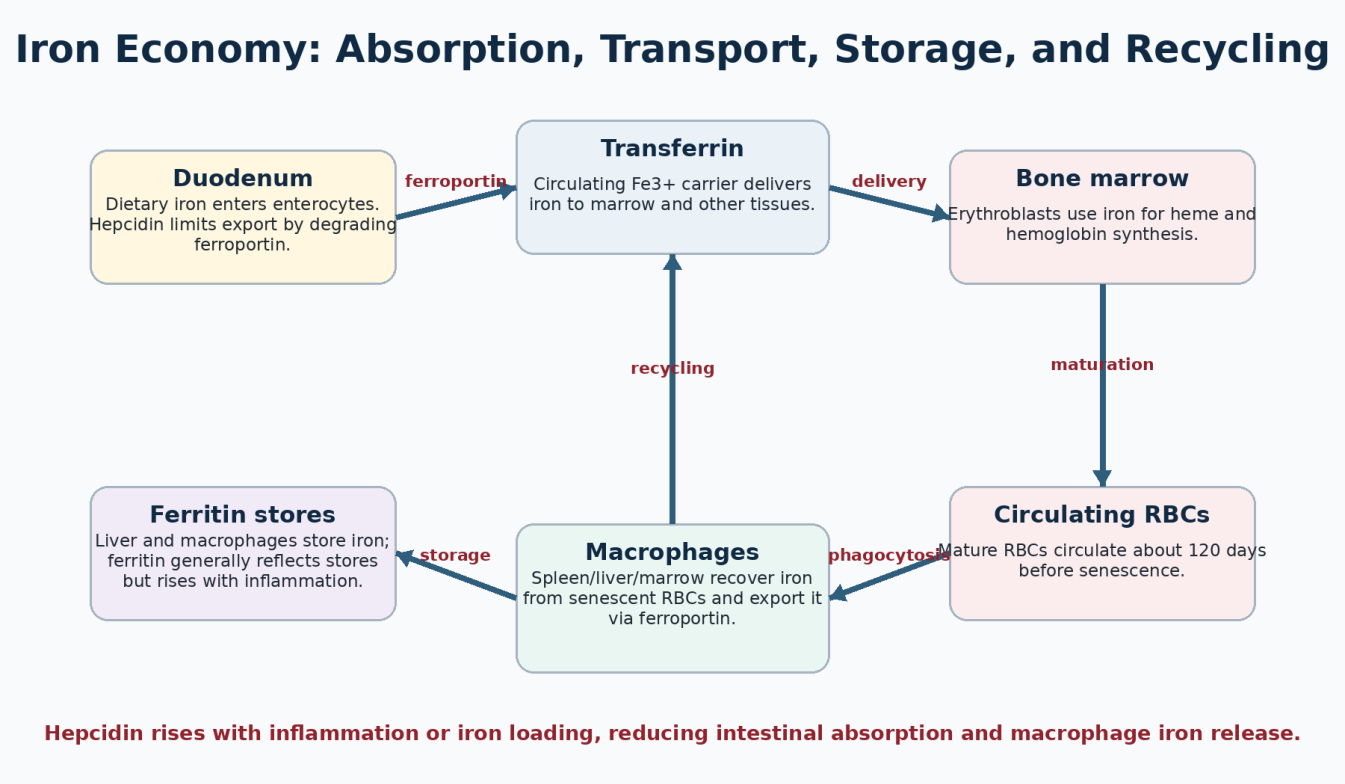

Figure 3. Iron is absorbed in the duodenum, transported by transferrin, used by marrow, stored as ferritin, and efficiently recycled by macrophages.

The hepcidin-ferroportin axis

Hepcidin is a liver-derived regulator that binds ferroportin and causes its internalization. When hepcidin is high, intestinal iron export falls and macrophages retain recycled iron. Inflammation—especially through IL-6—raises hepcidin, creating functional iron restriction despite preserved or increased ferritin. Iron deficiency, hypoxia, and increased erythropoietic drive suppress hepcidin.

Progression of absolute iron deficiency

1. Iron stores decline: ferritin falls first in uncomplicated deficiency.
2. Marrow iron becomes absent or markedly reduced.
3. Serum iron and transferrin saturation decline.
4. Transferrin/TIBC rises in classic absolute deficiency.
5. Hemoglobin falls; RDW often increases as new microcytes appear.
6. MCV may become low late—iron deficiency can initially be normocytic.

IMPORTANT CORRECTION

The body has no regulated iron-excretion pathway, but small obligatory losses occur through skin and gastrointestinal cell shedding. Clinically important iron deficiency is usually driven by blood loss, inadequate intake relative to need, or impaired absorption—not by active renal iron excretion.

Comparative iron studies

Condition	Serum iron	TIBC / transferrin	Ferritin	Transferrin saturation	Helpful clue
Iron deficiency	Low	High	Low	Low	High RDW, low reticulocyte Hb, pica, blood-loss source
Inflammation / chronic disease	Low	Low or normal	Normal or high	Low	CRP/ESR elevated; ferritin may mask coexisting deficiency
Sideroblastic anemia	High	Normal or low	High	High	Ring sideroblasts, Pappenheimer bodies
Thalassemia trait	Normal	Normal	Normal	Normal	Marked microcytosis with relatively high RBC count
Iron overload	High	Low or normal	High	High	Organ iron deposition; interpret with clinical context

Clinical features and etiologic search

- **Symptoms:** Fatigue, reduced exercise tolerance, dyspnea, palpitations, headache, restless legs, and cognitive complaints.
- **Tissue signs:** Pallor, glossitis, angular cheilitis, koilonychia, and pica—especially pagophagia.
- **Adults:** Investigate menstrual, gastrointestinal, urinary, dietary, donation, and malabsorptive causes. Iron replacement without identifying the source is incomplete care.
- **Children and pregnancy:** Rapid growth and increased demand magnify risk; screening and dosing follow age- and pregnancy-specific guidance.
- **Malabsorption:** Consider celiac disease, H. pylori-associated gastritis, autoimmune gastritis, bariatric surgery, inflammatory bowel disease, and medication effects.

Treatment principles: updated from legacy TID regimens

- **Oral iron:** Ferrous sulfate is inexpensive and well studied. Contemporary expert guidance recommends oral iron no more than once daily; every-other-day dosing may improve tolerability with similar absorption in some patients.
- **Elemental iron matters:** A 325-mg ferrous sulfate tablet contains approximately 65 mg elemental iron. Product composition varies.
- **Administration:** Empty-stomach dosing improves absorption but may worsen gastrointestinal adverse effects. Calcium, antacids, tea, and coffee can reduce absorption when taken together.
- **Intravenous iron:** Use when oral iron is not tolerated, is unlikely to be absorbed, fails to improve indices, or when rapid repletion is clinically necessary.
- **Monitoring:** Expect reticulocytosis within days and a hemoglobin rise over subsequent weeks if the diagnosis is correct and losses are controlled. Continue long enough to restore stores, not only hemoglobin.

SOURCE-ERA CORRECTION

Older source material recommended ferrous sulfate 325 mg three times daily with routine docusate. That schedule is no longer the preferred universal teaching approach. Dose, route, frequency, and bowel management should be individualized.

Plummer-Vinson syndrome

The classic triad is iron-deficiency anemia, dysphagia, and upper esophageal webs. Glossitis and koilonychia may coexist. The syndrome is associated with increased risk of upper aerodigestive squamous carcinoma. Achlorhydria may occur but is not required as a core element of the triad.

CHAPTER 6

Anemia of Inflammation and Chronic Kidney Disease

When iron is present but unavailable—or erythropoietin is inadequate

Anemia of inflammation

Inflammation increases hepcidin, reduces ferroportin-mediated iron export, shortens RBC survival, blunts erythropoietin production and marrow responsiveness, and shifts iron into storage compartments. The anemia is often normocytic early and may become microcytic later.

Feature	Absolute iron deficiency	Inflammation / functional restriction
Ferritin	Low	Normal or high because ferritin is an acute-phase reactant
TIBC / transferrin	High	Low or normal
Serum iron / saturation	Low / low	Low / low
Soluble transferrin receptor	Often increased	Often normal unless true deficiency coexists
Response to iron alone	Usually improves if source controlled and absorption adequate	Variable; underlying inflammation and functional restriction must be addressed

BOARD TRAP

A “normal” ferritin does not reliably exclude iron deficiency during inflammation. Interpret ferritin with transferrin saturation, inflammatory markers, trends, and the clinical setting.

Anemia in chronic kidney disease

- **Reduced EPO signaling:** Declining kidney function reduces the endocrine response to anemia.
- **Iron restriction:** Inflammation, hepcidin elevation, blood loss, and dialysis-associated factors can create absolute or functional iron deficiency.
- **Shortened RBC survival:** Uremic milieu contributes to reduced erythrocyte lifespan.
- **Evaluation:** Do not assume CKD is the only cause. Check iron status, reticulocytes, B12/folate when indicated, bleeding, inflammation, and other marrow/systemic causes.
- **Management:** The 2026 KDIGO guideline integrates iron therapy, erythropoiesis-stimulating agents, HIF-prolyl hydroxylase inhibitors in selected settings, transfusion avoidance when feasible, and individualized risk-benefit decisions.

2026 UPDATE

KDIGO published updated anemia-in-CKD guidance in January 2026; follow current local protocols for drug selection and dialysis dosing.

CHAPTER 7

Thalassemias and Quantitative Globin Disorders

Microcytosis out of proportion to anemia

Core mechanism

Thalassemias are inherited quantitative defects in globin-chain production. Unbalanced chain synthesis damages erythroid precursors and circulating RBCs, producing ineffective erythropoiesis, hemolysis, target cells, and marked microcytosis. The RBC count is often relatively preserved or increased in trait states.

Alpha-thalassemia

Genotype concept	Clinical phenotype	Key laboratory clue
1 alpha-gene deletion	Silent carrier	Usually normal CBC or minimal microcytosis
2 alpha-gene deletions	Alpha-thalassemia trait	Microcytosis with mild/no anemia; electrophoresis often normal after infancy
3 alpha-gene deletions	HbH disease (beta4)	Hemolytic microcytic anemia; HbH inclusions and variable severity
4 alpha-gene deletions	Hb Bart hydrops fetalis (gamma4)	Severe fetal anemia and hydrops without effective intervention

Beta-thalassemia

Phenotype	Expected findings	Clinical implications
Beta-thalassemia trait/minor	Low MCV, high/normal RBC count, target cells; HbA2 typically elevated and HbF may increase	Usually mild; avoid unnecessary iron unless deficiency is proven
Intermedia / non-transfusion-dependent thalassemia	Variable anemia, ineffective erythropoiesis, splenomegaly, iron loading	May require episodic transfusion and specialist management
Major / transfusion-dependent thalassemia	Severe anemia after HbF declines; marrow expansion and growth complications	Regular transfusion, iron chelation, and curative options such as transplantation or gene therapy in selected patients

How to distinguish trait from iron deficiency

- **RBC count:** Often high relative to hemoglobin in thalassemia trait; often low/normal in iron deficiency.
- **RDW:** Often normal or mildly increased in trait; commonly increased in evolving iron deficiency.
- **Ferritin:** Low ferritin supports iron deficiency, but inflammation complicates interpretation.

- **Mentzer index:** MCV/RBC count <13 favors thalassemia trait; >13 favors iron deficiency. It is a screening clue, not a definitive test.
- **Hemoglobin analysis:** Beta trait usually raises HbA2. Alpha trait often requires genetic inference/testing because adult electrophoresis can be normal.

> **BOARD TRAP**
>
> Iron deficiency can lower HbA2 and obscure beta-thalassemia trait. Correct confirmed iron deficiency and repeat hemoglobin analysis if suspicion remains high.

CHAPTER 8

Sideroblastic Anemia and Lead Toxicity

Iron is available but heme synthesis fails

Sideroblastic anemia

Sideroblastic anemia is defined by ring sideroblasts in the marrow: erythroblasts whose iron-laden mitochondria encircle at least one-third of the nucleus. The phenotype can be microcytic, normocytic, macrocytic, or dimorphic depending on cause.

Category	Examples	Diagnostic / treatment clue
Inherited	ALAS2-related X-linked sideroblastic anemia; mitochondrial disorders	May respond to pyridoxine in selected ALAS2-related disease
Clonal	Myelodysplastic neoplasms with ring sideroblasts / SF3B1 mutation	Usually macrocytic or dimorphic; evaluate marrow and molecular findings
Toxic / drug-related	Alcohol, lead, isoniazid, chloramphenicol, linezolid, zinc-induced copper deficiency	Remove cause; give pyridoxine when biologically appropriate
Nutritional	Vitamin B6 or copper deficiency	Replace deficiency and identify cause

Lead toxicity

- **Heme synthesis:** Lead inhibits ALA dehydratase and ferrochelatase.
- **Smear:** Coarse basophilic stippling may appear but is not sufficiently sensitive to exclude toxicity.
- **Clinical pattern:** Abdominal pain, constipation, neurocognitive change, peripheral neuropathy, renal injury, hypertension, and developmental effects in children.
- **Diagnosis:** Venous blood lead level confirms exposure; interpret according to current public-health guidance.
- **Management:** Remove exposure. Chelation depends on concentration, symptoms, age, pregnancy, and specialist/public-health protocols.

> **MNEMONIC**
>
> LEAD: Lead lines, Encephalopathy, Anemia/abdominal pain, and wrist/foot Drop. Use the mnemonic to remember the syndrome—not to replace a blood lead level.

CHAPTER 9

Hemolysis: Mechanisms and Laboratory Localization

Prove destruction, then identify why

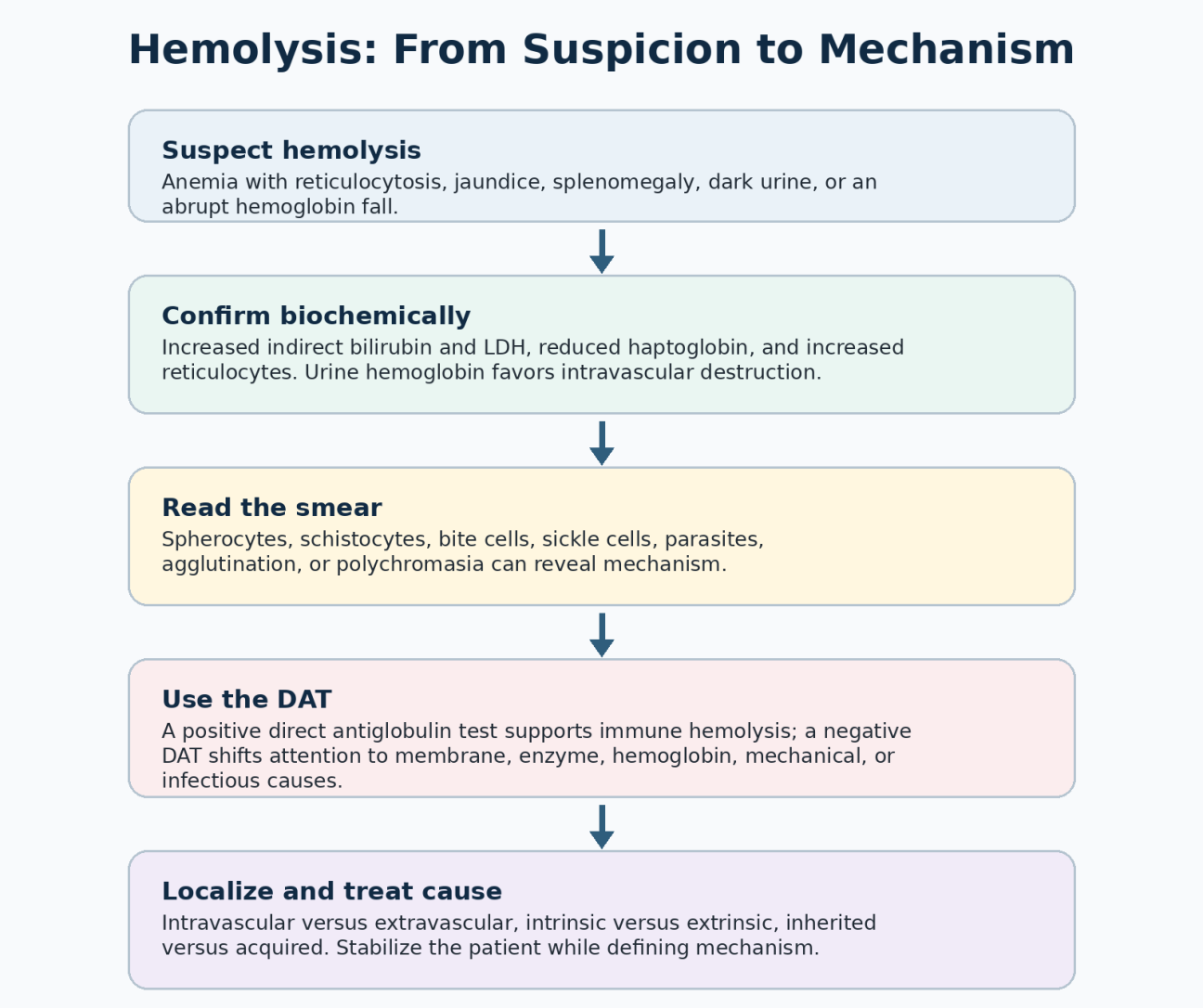

Figure 4. Hemolysis is confirmed biochemically, localized, and then classified with smear and DAT.

The hemolysis panel

Test	Typical hemolysis pattern	Interpretive caution
Reticulocytes	Increased if marrow reserve and substrates are adequate	May be blunted by iron/B12/folate deficiency, CKD, marrow disease, or early crisis
Indirect bilirubin	Increased	Can rise from ineffective erythropoiesis or hepatic handling abnormalities

Test	Typical hemolysis pattern	Interpretive caution
LDH	Increased, often marked in intravascular hemolysis	Nonspecific; tissue injury and megaloblastic anemia can elevate LDH
Haptoglobin	Reduced, especially in intravascular hemolysis	Can be low in liver disease and rise with inflammation
Urinalysis	Hemoglobin without proportional RBCs suggests intravascular hemolysis	Differentiate from myoglobin; microscopy and clinical context matter
DAT	Positive in many immune hemolytic anemias	A negative DAT does not exclude all immune mechanisms

Classification map

Axis	Categories	Examples
Location	Intravascular vs extravascular	MAHA/PNH/mechanical vs hereditary spherocytosis/warm AIHA
Origin	Intrinsic RBC defect vs extrinsic injury	Membrane/enzyme/hemoglobin vs antibody/microangiopathy/infection
Timing	Inherited vs acquired	G6PD or sickle vs AIHA, DIC, malaria, drug-induced
Immune status	DAT-positive vs DAT-negative	Warm/cold AIHA vs hereditary or mechanical causes

Immune hemolytic anemia

- **Warm AIHA:** Usually IgG-mediated, extravascular, and associated with spherocytes. Consider autoimmune disease, lymphoproliferative disorders, drugs, or idiopathic disease.
- **Cold agglutinin disease:** Usually complement-mediated IgM activity with cold-induced symptoms and RBC agglutination. May distort automated CBC indices.
- **Drug-induced immune hemolysis:** Mechanisms vary; recognize temporal association and stop the culprit agent.
- **Transfusion reaction:** Acute or delayed immune hemolysis requires immediate transfusion-medicine evaluation.

Microangiopathic hemolytic anemia

Schistocytes indicate mechanical fragmentation but are not a diagnosis. TTP, HUS, DIC, HELLP syndrome, malignant hypertension, mechanical circulatory devices, and severe valve disease are key contexts. Thrombocytopenia plus MAHA is an emergency pattern.

> **CLINICAL SAFETY**
>
> Suspected TTP requires urgent plasma-exchange-based management and hematology consultation; do not delay definitive treatment while waiting for every confirmatory test.

CHAPTER 10

Membrane and Enzyme Disorders

Spherocytes, bite cells, and chronic hemolysis

Hereditary spherocytosis

- **Defect:** Usually autosomal dominant abnormalities of spectrin, ankyrin, band 3, or protein 4.2 cause membrane loss and reduced surface-area-to-volume ratio.
- **Smear and CBC:** Spherocytes, increased MCHC, polychromasia, and reticulocytosis.
- **Clinical features:** Anemia, jaundice, splenomegaly, pigment gallstones, and variable severity.
- **Crises:** Parvovirus B19 can cause transient aplastic crisis; infection or stress may precipitate hemolytic worsening.
- **Testing:** Eosin-5-maleimide binding by flow cytometry is commonly used; osmotic fragility is less specific and often supplemented/replaced by modern assays.
- **Management:** Folate support, transfusion when needed, and selective splenectomy after careful risk assessment; vaccination and infection-prevention planning are essential around splenectomy.

> **KEY DISCRIMINATOR**
>
> Hereditary spherocytosis and warm AIHA both produce spherocytes. The DAT is usually negative in hereditary spherocytosis and positive in warm AIHA.

G6PD deficiency

- **Mechanism:** X-linked reduction in NADPH impairs glutathione recycling and leaves RBCs vulnerable to oxidant injury.
- **Triggers:** Infection is common; drugs and foods vary by variant and exposure. Classic teaching includes primaquine, dapsone, sulfonamides, nitrofurantoin, rasburicase, and fava beans.
- **Morphology:** Heinz bodies on supravital stain; bite and blister cells after splenic pitting.
- **Testing pitfall:** During acute hemolysis, the oldest and most deficient cells are destroyed first, and reticulocytes have higher enzyme activity. A test can be falsely normal; repeat after recovery if suspicion persists.
- **Management:** Remove trigger, treat infection, provide supportive care, and transfuse if clinically indicated.

Pyruvate kinase deficiency

Pyruvate kinase deficiency impairs glycolytic ATP production, destabilizing the RBC membrane and causing chronic extravascular hemolysis. Findings include anemia, jaundice, splenomegaly, echinocytes, and increased 2,3-BPG, which shifts the oxygen dissociation curve to the right and can partially improve tissue oxygen unloading.

CHAPTER 11

Sickle Cell Disease and Hemoglobin C

Polymerization, vaso-occlusion, hemolysis, and modern therapy

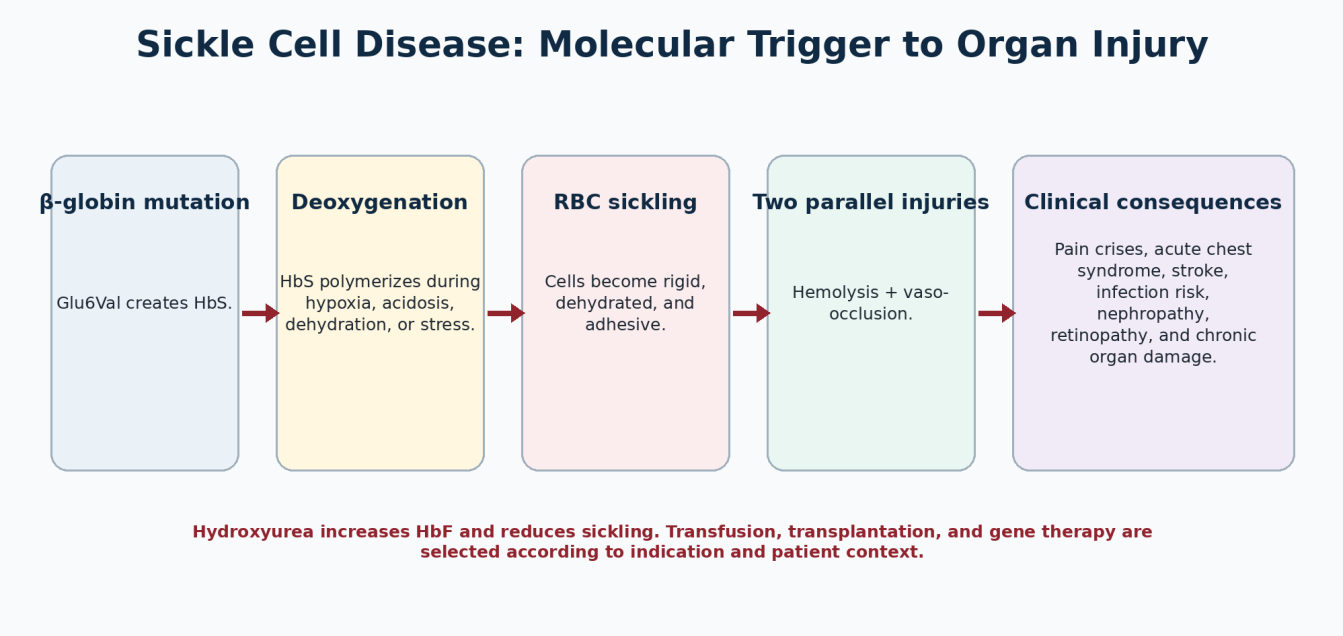

Figure 5. HbS polymerization links a single amino-acid substitution to hemolysis, vaso-occlusion, and multiorgan injury.

Molecular basis and inheritance

Sickle hemoglobin results from substitution of valine for glutamic acid at position 6 of the beta-globin chain. Deoxygenated HbS polymerizes, distorting RBCs. Repeated sickling causes membrane injury, dehydration, hemolysis, endothelial activation, inflammation, and vaso-occlusion. Disease genotypes include HbSS, HbSβ0-thalassemia, HbSβ+-thalassemia, and HbSC disease; phenotype varies widely.

Acute complications

Complication	Presentation	Immediate reasoning
Vaso-occlusive pain episode	Acute severe pain without another clear cause	Rapid analgesia, hydration tailored to status, oxygen only if hypoxemic, and evaluation for precipitating complications
Acute chest syndrome	New pulmonary infiltrate plus respiratory symptoms, chest pain, fever, or hypoxemia	Antibiotics, incentive spirometry, oxygen as needed, transfusion strategy according to severity; monitor closely
Stroke / TIA	Focal neurologic deficit, seizure, altered mental status	Emergency neuroimaging and urgent exchange transfusion pathway with specialist coordination
Splenic sequestration	Acute splenic enlargement, hypovolemia, abrupt Hb fall—usually in children before autosplenectomy	Urgent volume and transfusion management; recurrence planning
Aplastic crisis	Abrupt anemia with low reticulocytes, often parvovirus B19	Supportive care/transfusion; distinguish from sequestration or hemolysis

Complication	Presentation	Immediate reasoning
Infection / sepsis	Fever in functional asplenia	Urgent cultures and empiric antibiotics according to age and protocol

Chronic complications

- **Neurologic:** Overt stroke, silent cerebral infarction, cognitive effects.
- **Pulmonary/cardiac:** Recurrent acute chest syndrome, pulmonary hypertension phenotype, cardiopulmonary strain.
- **Renal:** Hyposthenuria, hematuria, albuminuria, progressive CKD.
- **Ophthalmologic:** Proliferative retinopathy, especially in HbSC disease.
- **Musculoskeletal:** Avascular necrosis, chronic pain, osteomyelitis risk.
- **Hepatobiliary:** Pigment gallstones, hepatic complications, transfusional iron overload.
- **Reproductive:** Priapism, pregnancy-related risk, fertility effects from disease and therapy.

Disease-modifying and curative strategies

- **Hydroxyurea:** Raises HbF and reduces vaso-occlusive events and acute chest syndrome; remains foundational therapy.
- **Transfusion therapy:** Simple or exchange transfusion is used for selected acute events and chronic prevention indications, especially stroke prevention.
- **Other disease-modifying agents:** L-glutamine and crizanlizumab may be considered according to indication, age, access, and evolving guidance.
- **Hematopoietic stem-cell transplantation:** Potentially curative; candidacy depends on disease severity, donor options, organ status, age, and shared decision-making.
- **Gene therapy:** Autologous gene-modified stem-cell therapies now provide additional potentially curative options but require intensive conditioning, specialized centers, and long-term follow-up.

2026 UPDATE

FDA approval for CASGEVY was expanded in July 2026 to patients aged 2 years and older with recurrent vaso-occlusive crises; the product also has an indication for transfusion-dependent beta-thalassemia. LYFGENIA remains an approved gene therapy for patients aged 12 years and older with a history of vaso-occlusive events.

MEDICATION SAFETY UPDATE

Voxelotor (Oxbryta) was voluntarily withdrawn from the market in September 2024 because of safety concerns and should not appear as an active current treatment option.

Hemoglobin C

HbC substitutes lysine for glutamic acid at beta-globin position 6. HbC trait is generally asymptomatic. Homozygous HbCC may produce mild hemolysis, splenomegaly, target cells, and intracellular crystals. HbSC disease combines polymerizing HbS with HbC-associated dehydration and can cause serious vaso-occlusive, ocular, and thrombotic complications despite a higher hemoglobin than HbSS.

CHAPTER 12

Acute Blood Loss, Marrow Failure, and Infiltrative Disease

Normocytic anemia is a category, not a reassurance

Acute blood loss

Hemoglobin and hematocrit may initially remain near baseline during abrupt whole-blood loss because both cells and plasma are lost. The measured concentration falls after interstitial fluid shifts or crystalloid resuscitation. Reticulocytosis takes several days. Management prioritizes hemostasis, perfusion, and source control.

Aplastic anemia

- **Pattern:** Pancytopenia, low reticulocytes, and a hypocellular fatty marrow without malignant infiltration.
- **Causes:** Often immune-mediated and idiopathic; drugs/toxins, viral infections, radiation, pregnancy, and inherited marrow-failure syndromes are important.
- **Clinical risk:** Bleeding and infection may dominate over anemia symptoms.
- **Management:** Remove causative exposure when possible; definitive therapy may involve hematopoietic stem-cell transplantation or immunosuppressive therapy depending on age, severity, and donor availability.

Marrow infiltration and myelophthisis

Cancer, granulomatous disease, fibrosis, storage disease, and other infiltrative processes can replace marrow. A leukoerythroblastic smear—nucleated RBCs, immature myeloid cells, teardrops—and a “dry tap” or fibrotic marrow are classic clues.

Pure red cell aplasia

Pure red cell aplasia produces severe anemia and reticulocytopenia with relative preservation of platelets and neutrophils. Causes include parvovirus B19, thymoma, autoimmune disease, lymphoproliferative disorders, drugs, and anti-EPO antibodies.

Endocrine and systemic causes

Cause	Mechanism / clue
Hypothyroidism	Reduced metabolic demand and marrow stimulation; may be normocytic or macrocytic
Hypogonadism	Reduced androgen stimulation of erythropoiesis
Chronic liver disease	Macrocytosis, target cells, bleeding, hypersplenism, nutritional deficiency, or hemolysis may coexist
Chronic infection/inflammation	Hepcidin-mediated restriction, shortened survival, reduced EPO response
Malignancy	Inflammation, bleeding, marrow infiltration, renal dysfunction, or treatment toxicity

CHAPTER 13

Megaloblastic Anemia: Vitamin B12 and Folate

DNA-synthesis failure with systemic consequences

Morphology and pathophysiology

Impaired thymidylate and DNA synthesis delays nuclear maturation while cytoplasmic development continues, producing nuclear-cytoplasmic asynchrony. The marrow becomes hypercellular but ineffective; intramedullary precursor death can markedly elevate LDH and indirect bilirubin.

Feature	Vitamin B12 deficiency	Folate deficiency
Common causes	Pernicious anemia, gastric surgery, ileal disease/resection, malabsorption, vegan diet without supplementation, nitrous oxide exposure	Poor intake, alcohol use, pregnancy, hemolysis/increased demand, malabsorption, antifolate drugs
Neurologic findings	Can cause paresthesias, loss of vibration/proprioception, gait and cognitive changes	Classically absent; neurologic symptoms suggest another/additional diagnosis
Methylmalonic acid	Increased	Normal
Homocysteine	Increased	Increased
Treatment principle	Replace B12; route depends on cause/severity and absorption	Replace folate after excluding or simultaneously treating B12 deficiency

Smear and laboratory clues

- **Macro-ovalocytes and hypersegmented neutrophils:** Classic megaloblastic pattern.
- **Pancytopenia:** Severe deficiency can suppress all cell lines and mimic marrow failure.
- **High LDH and bilirubin:** Reflect ineffective erythropoiesis and intramedullary destruction.
- **Low reticulocytes:** Despite hypercellular marrow, mature-cell output is ineffective.
- **Normal MCV does not exclude deficiency:** Coexisting iron deficiency, thalassemia, or inflammation can mask macrocytosis.

> **CLINICAL SAFETY**
>
> Never treat suspected folate deficiency alone when vitamin B12 deficiency has not been excluded. Folate may correct anemia while neurologic injury progresses.

Pernicious anemia

Autoimmune parietal-cell loss and intrinsic-factor deficiency impair terminal ileal B12 absorption. Intrinsic-factor antibodies are specific; parietal-cell antibodies are less specific. Autoimmune gastritis may coexist with iron deficiency and warrants individualized gastric surveillance.

CHAPTER 14

Nonmegaloblastic Macrocytosis and Myelodysplasia

Not every high MCV is a vitamin deficiency

Common nonmegaloblastic causes

Cause	Mechanism / clue
Alcohol use	Direct marrow toxicity; macrocytosis may precede anemia or liver-test abnormalities
Liver disease	Membrane lipid changes produce round macrocytes and target cells
Reticulocytosis	Reticulocytes are larger; hemolysis or blood-loss recovery can elevate MCV
Hypothyroidism	Reduced erythropoietic drive; often mild macrocytosis
Medications	Hydroxyurea, zidovudine, methotrexate, anticonvulsants, chemotherapy, and others
Myelodysplastic neoplasm	Clonal ineffective hematopoiesis, cytopenias, dysplasia; often older adults
Spurious macrocytosis	Cold agglutinins, marked hyperglycemia, leukocytosis, or delayed sample processing

When to suspect myelodysplasia

- **Persistent unexplained macrocytosis:** Especially with anemia plus neutropenia or thrombocytopenia.
- **Dysplastic smear:** Hypogranular/hyposegmented neutrophils, anisopoikilocytosis, abnormal platelets.
- **Low reticulocyte response:** Ineffective clonal hematopoiesis rather than compensatory production.
- **Bone marrow and cytogenetics:** Required to classify disease and distinguish from reversible deficiency, drug effect, copper deficiency, or alcohol toxicity.

BOARD TRAP

Macrocytosis in a patient taking hydroxyurea can reflect the expected pharmacologic effect and adherence; it does not automatically indicate B12 deficiency.

CHAPTER 15

Transfusion Reasoning, Special Populations, and Safety

Treat the patient, not an isolated hematocrit

Red-cell transfusion principles

- **Decision variables:** Hemoglobin, symptoms, rate of decline, bleeding, hemodynamics, cardiopulmonary reserve, ischemia, age, and procedure.
- **Restrictive practice:** Many stable adults use restrictive thresholds, but no single number applies universally.
- **Expected increment:** One unit of packed RBCs commonly raises Hb by about 1 g/dL and Hct by about 3 percentage points in a nonbleeding average-sized adult.
- **Pretransfusion samples:** Obtain CBC, type/screen, and etiologic tests before transfusion when feasible—but never delay lifesaving stabilization.
- **Reassess:** Transfuse one unit at a time in stable nonbleeding adults when appropriate, then reassess symptoms and Hb.
- **Complications:** Alloimmunization, hemolysis, febrile/allergic reactions, TACO, TRALI, infection, and chronic iron overload.

> **CORRECTION OF SOURCE SHORTHAND**
>
> Symptoms cannot be predicted reliably from hematocrit bands alone. Chronic adaptation, age, cardiovascular reserve, and rate of decline profoundly change presentation.

Iron studies and recent transfusion

Recent transfusion can alter serum iron, saturation, RBC indices, hemoglobin analysis, and smear interpretation. Ferritin is influenced by inflammation and cumulative transfusion. Draw diagnostic samples first when clinically feasible and document timing.

Pregnancy

- **Physiologic dilution:** Plasma volume expands more than RBC mass, lowering measured Hb/Hct.
- **Iron demand:** Maternal blood-volume expansion and fetal/placental needs increase iron requirements.
- **Do not dismiss anemia:** Use pregnancy-specific thresholds; evaluate iron status and other causes rather than attributing every low value to dilution.
- **Hemoglobinopathies:** Carrier screening and counseling may be indicated by history, ancestry, CBC pattern, and local guidance.

Children and older adults

- **Children:** Use age-specific cutoffs; consider nutrition, growth, occult loss, lead, inherited disorders, and infection.
- **Older adults:** Anemia is not normal aging; investigate CKD, inflammation, deficiency, occult bleeding, marrow disease, malignancy, and drugs.
- **Frailty and cognition:** Moderate anemia may impair function; balance cause, goals, comorbidity, and procedural risk.

Transfusion in sickle cell disease

Do not reflexively normalize hemoglobin in sickle cell disease because hyperviscosity can be harmful. Choose simple versus exchange transfusion by indication, baseline Hb/HbS fraction, severity, and volume status; use extended antigen matching and specialist coordination.

Rapid recognition of an acute transfusion reaction

IMMEDIATE FIRST STEP

Stop the transfusion, maintain intravenous access with compatible saline, recheck patient and unit identification, assess vital signs, and notify the transfusion service. Do not restart the implicated unit until the reaction is evaluated.

Pattern	Key clues	Immediate priorities
Acute hemolytic reaction	Fever, chills, pain, hypotension, hemoglobinuria; often incompatibility	Stop transfusion; blood-bank workup, DAT and hemolysis studies; supportive care
Bacterial contamination	High fever, rigors, hypotension or shock	Culture patient and unit; begin empiric antibiotics and resuscitation
TACO	Dyspnea, hypertension, JVD, pulmonary edema; volume overload	Oxygen, upright position, diuresis; use slower/smaller future transfusions
TRALI	Acute hypoxemia and bilateral infiltrates without circulatory overload	Respiratory support; avoid reflex diuresis unless overload also exists
Allergic / anaphylactic	Urticaria and pruritus; severe cases cause bronchospasm or hypotension	Antihistamine for mild reaction; epinephrine and airway support for anaphylaxis
Febrile nonhemolytic	Fever or chills without hemolysis after dangerous causes are excluded	Evaluate first for hemolysis and sepsis; symptomatic management after exclusion

CHAPTER 16

Integrated Clinical Cases

Apply indices, morphology, and mechanism

CASE 1: Pagophagia and microcytosis

A 34-year-old woman reports fatigue and a compulsive desire to chew ice. Hb is 8.9 g/dL, MCV 69 fL, RBC count 3.9 million/µL, RDW 19%, ferritin 5 ng/mL, and TIBC is elevated.

- **What is the diagnosis?**
- **What must be investigated beyond prescribing iron?**

Reasoned answer: Absolute iron-deficiency anemia. The low ferritin, high TIBC, elevated RDW, and pagophagia are classic. Assess menstrual and gastrointestinal blood loss, pregnancy, donation, diet, and malabsorption.

Board pearl: Ferritin usually falls before MCV. Iron deficiency can be normocytic early.

CASE 2: Microcytosis with a high RBC count

A 22-year-old asymptomatic man has Hb 12.2 g/dL, MCV 62 fL, RBC count 6.3 million/µL, normal ferritin, and target cells.

- **Which category is most likely?**
- **What test is next?**

Reasoned answer: Thalassemia trait is most likely because microcytosis is profound while the RBC count is high and iron stores are normal. Obtain hemoglobin analysis; if adult electrophoresis is normal and suspicion persists, evaluate for alpha-thalassemia.

Board pearl: Do not prescribe iron for microcytosis unless deficiency is demonstrated.

CASE 3: Inflammatory arthritis and anemia

A patient with active rheumatoid arthritis has Hb 9.8 g/dL, MCV 82 fL, low serum iron, low TIBC, ferritin 240 ng/mL, and elevated CRP.

- **What mechanism explains the pattern?**
- **Could true iron deficiency coexist?**

Reasoned answer: Inflammation-driven hepcidin elevation traps iron in macrophages and reduces intestinal export. Yes—ferritin may be misleadingly normal/high, so use saturation, trends, soluble transferrin receptor or reticulocyte hemoglobin where available, and bleeding history.

Board pearl: Anemia of inflammation may begin normocytic and become microcytic.

CASE 4: Jaundice, splenomegaly, and spherocytes

A teenager has intermittent jaundice, splenomegaly, pigment gallstones, Hb 10.5 g/dL, reticulocytes 9%, high MCHC, spherocytes, and a negative DAT.

- **What is the diagnosis?**
- **What infection can precipitate an aplastic crisis?**

Reasoned answer: Hereditary spherocytosis. Parvovirus B19 can transiently suppress erythropoiesis and cause profound anemia with reticulocytopenia.

Board pearl: Spherocytes + negative DAT + high MCHC strongly favor hereditary spherocytosis.

CASE 5: Oxidant exposure and dark urine

A man develops jaundice and dark urine two days after taking an oxidant medication. Smear shows bite cells; LDH and indirect bilirubin are high and haptoglobin is low.

- **What enzyme defect is likely?**
- **Why might the enzyme assay be falsely normal now?**

Reasoned answer: G6PD deficiency. During crisis, the most deficient older cells are destroyed and reticulocytes have higher G6PD activity, causing a false-negative assay.

Board pearl: Repeat testing after recovery when suspicion remains high.

CASE 6: Anemia plus thrombocytopenia

A woman develops confusion, petechiae, Hb 7.9 g/dL, platelets 18,000/μL, elevated LDH, undetectable haptoglobin, and schistocytes.

- **What emergency pattern is present?**
- **What action should not be delayed?**

Reasoned answer: Microangiopathic hemolytic anemia with severe thrombocytopenia suggests TTP until proven otherwise. Urgent plasma-exchange-based management and hematology involvement should not await all confirmatory testing.

Board pearl: Schistocytes are a mechanism clue; thrombocytopenia and organ findings define urgency.

CASE 7: Macrocytosis and neuropathy

A 61-year-old has gait instability, paresthesias, glossitis, Hb 8.7 g/dL, MCV 116 fL, macro-ovalocytes, and hypersegmented neutrophils.

- **Which deficiency is most concerning?**
- **Which metabolites help distinguish it from folate deficiency?**

Reasoned answer: Vitamin B12 deficiency is most concerning because neurologic findings accompany megaloblastic anemia. Methylmalonic acid and homocysteine rise in B12 deficiency; only homocysteine rises in folate deficiency.

Board pearl: Folate alone may improve anemia while neurologic damage progresses.

CASE 8: Sickle cell disease and new infiltrate

A patient with HbSS presents with fever, chest pain, cough, oxygen saturation 88%, and a new lower-lobe infiltrate.

- **What is the diagnosis?**
- **What broad treatment elements are required?**

Reasoned answer: Acute chest syndrome. Provide close monitoring, analgesia, incentive spirometry, oxygen for hypoxemia, antibiotics, and simple or exchange transfusion according to severity and baseline hemoglobin.

Board pearl: Acute chest syndrome is a leading cause of sickle-related morbidity and can worsen rapidly.

CASE 9: Abrupt severe anemia with low reticulocytes in HbSS

A child with HbSS develops profound fatigue after a viral prodrome. Hb falls from 8.5 to 4.8 g/dL and reticulocytes are nearly absent.

- **What is the likely complication?**
- **How does it differ from splenic sequestration?**

Reasoned answer: Transient aplastic crisis from parvovirus B19. Splenic sequestration causes splenic enlargement and usually a reticulocyte response; aplastic crisis produces reticulocytopenia.

Board pearl: Reticulocytes distinguish production arrest from accelerated destruction/sequestration.

CASE 10: Pancytopenia and hypocellular marrow

A patient has fatigue, recurrent infections, bruising, pancytopenia, very low reticulocytes, and a markedly hypocellular fatty marrow.

- **What is the diagnosis?**
- **Why is this not isolated anemia?**

Reasoned answer: Aplastic anemia. The stem-cell/marrow process affects erythroid, myeloid, and megakaryocytic production, creating pancytopenia and infection/bleeding risk.

Board pearl: Always inspect the white-cell and platelet lines before labeling an anemia by MCV alone.

CASE 11: Dimorphic cells and a normal MCV

A patient with chronic malabsorption has Hb 9.2 g/dL, MCV 91 fL, RDW 24%, and a smear containing both microcytes and macro-ovalocytes.

- **Why is the MCV misleading?**
- **What deficiencies should be tested?**

Reasoned answer: The MCV is an average of two opposing cell populations. Test iron status, vitamin B12, and folate; mixed deficiency is likely.

Board pearl: A normal MCV with a very high RDW can conceal mixed anemia.

CASE 12: Lead exposure

A renovation worker has abdominal pain, constipation, wrist weakness, microcytic anemia, and coarse basophilic stippling.

- **What test confirms exposure?**
- **Which enzymes are inhibited?**

Reasoned answer: A venous blood lead level confirms exposure. Lead inhibits ALA dehydratase and ferrochelatase in heme synthesis.

Board pearl: Do not rely on stippling alone; it is neither perfectly sensitive nor specific.

CHAPTER 17

USMLE-Style Review Questions

Single-best-answer questions with integrated reasoning

1. A 28-year-old woman has Hb 10.1 g/dL, MCV 72 fL, RDW 18%, ferritin 7 ng/mL, and platelets 520,000/µL. Which finding is most likely?

A. Decreased TIBC
B. Increased hepcidin
C. Reactive thrombocytosis
D. Elevated HbA2
E. Ring sideroblasts

Answer: C. Iron deficiency commonly produces elevated RDW and can cause reactive thrombocytosis. TIBC is typically high, ferritin low, and hepcidin suppressed.

2. A patient has Hb 11.5 g/dL, MCV 60 fL, RBC count 6.6 million/µL, and normal ferritin. Which diagnosis is most likely?

A. Iron-deficiency anemia
B. Beta-thalassemia trait
C. Anemia of inflammation
D. Aplastic anemia
E. Acute blood loss

Answer: B. Severe microcytosis with a relatively high RBC count and normal iron stores strongly suggests thalassemia trait.

3. Which pattern best supports anemia of inflammation?

A. Low iron, high TIBC, low ferritin
B. High iron, low TIBC, high ferritin
C. Low iron, low TIBC, high ferritin
D. Normal iron, high TIBC, low ferritin
E. High iron, high TIBC, low ferritin

Answer: C. Inflammation raises hepcidin, sequesters iron, lowers serum iron and transferrin/TIBC, and raises or preserves ferritin.

4. A patient with jaundice and splenomegaly has spherocytes and a positive DAT. Which process is most likely?

A. Hereditary spherocytosis
B. Warm autoimmune hemolysis
C. G6PD deficiency
D. TTP
E. Pyruvate kinase deficiency

Answer: B. Both hereditary spherocytosis and warm AIHA show spherocytes, but a positive DAT supports immune hemolysis.

5. Which smear finding most specifically suggests oxidant injury in G6PD deficiency?

A. Target cells
B. Macro-ovalocytes
C. Bite cells
D. Teardrop cells

E. Rouleaux

Answer: C. Splenic macrophages remove Heinz-body material, creating bite cells; blister cells may also be present.

6. A patient has anemia, thrombocytopenia, renal injury, and schistocytes. Which mechanism produces the RBC morphology?

A. Reduced globin synthesis
B. Splenic membrane loss
C. Mechanical fragmentation in small vessels
D. Antibody-mediated agglutination
E. Impaired DNA synthesis

Answer: C. Fibrin strands and abnormal microvascular shear fragment RBCs in thrombotic microangiopathy.

7. Which laboratory result distinguishes vitamin B12 deficiency from folate deficiency?

A. Increased homocysteine
B. Increased LDH
C. Increased indirect bilirubin
D. Increased methylmalonic acid
E. Macro-ovalocytes

Answer: D. Methylmalonic acid rises in vitamin B12 deficiency but not isolated folate deficiency. Homocysteine rises in both.

8. A patient with severe anemia has a reticulocyte count of 4%. Why can this still represent an inadequate marrow response?

A. Reticulocytes are smaller than mature RBCs
B. The percentage is inflated because the RBC denominator is reduced
C. Reticulocytes do not contain hemoglobin
D. Haptoglobin interferes with the assay
E. Ferritin suppresses reticulocyte release

Answer: B. Correct the reticulocyte percentage for the degree of anemia and, in severe anemia, account for prolonged reticulocyte maturation.

9. Which finding is most characteristic of hereditary spherocytosis?

A. Low MCHC and positive DAT
B. High MCHC and negative DAT
C. Schistocytes and low platelets
D. Target cells and high HbA2
E. Bite cells and Heinz bodies

Answer: B. Membrane loss produces dense spherocytes and elevated MCHC; DAT is negative because the process is nonimmune.

10. A patient taking isoniazid develops a microcytic anemia with high serum iron and ring sideroblasts. Which cofactor is deficient?

A. Vitamin B1
B. Vitamin B2
C. Vitamin B6
D. Vitamin B12
E. Folate

Answer: C. Pyridoxal phosphate (vitamin B6) is required by ALA synthase. Isoniazid can cause functional B6 deficiency.

11. A child with HbSS has an abrupt hemoglobin fall and absent reticulocytes after a viral illness. Which pathogen is most likely?

A. EBV
B. Parvovirus B19
C. CMV
D. Influenza B
E. RSV
Answer: B. Parvovirus B19 infects erythroid precursors and can cause transient aplastic crisis in chronic hemolytic states.

12. Which statement about modern oral iron therapy is most accurate?

A. It must always be given three times daily
B. It should never be taken every other day
C. Once-daily dosing at most is often recommended, with alternate-day dosing for tolerability in some patients
D. Intravenous iron is always first-line
E. Treatment should stop as soon as hemoglobin normalizes
Answer: C. Contemporary expert guidance favors no more than once-daily oral iron; alternate-day dosing may improve tolerability. Stores must also be replenished.

13. A patient has macrocytosis, high LDH, indirect hyperbilirubinemia, and low reticulocytes. Which mechanism best explains the laboratory pattern?

A. Intravascular destruction of mature RBCs only
B. Ineffective erythropoiesis with intramedullary precursor death
C. Acute hemorrhage
D. Iron sequestration
E. Splenic pooling
Answer: B. Severe megaloblastic anemia causes ineffective erythropoiesis and intramedullary destruction, raising LDH and bilirubin despite low reticulocytes.

14. Which hemoglobin pattern is expected in beta-thalassemia trait?

A. Increased HbA2
B. Absent HbA2
C. HbH tetramers only
D. Hb Bart as the dominant adult hemoglobin
E. Normal HbA2 in all cases
Answer: A. Beta-thalassemia trait typically increases HbA2. Coexisting iron deficiency may lower HbA2 and mask the trait.

15. Which current treatment statement is correct for sickle cell disease?

A. Voxelotor remains a routine active option in 2026
B. Hydroxyurea decreases HbF
C. Gene-modified autologous stem-cell therapy is an approved option for selected patients
D. Exchange transfusion is never used for stroke
E. Transfusion should always normalize Hb
Answer: C. Gene therapies are approved for selected patients. Voxelotor was withdrawn; hydroxyurea raises HbF; exchange transfusion is central to acute stroke management.

16. Which finding most strongly suggests marrow infiltration?

A. Pencil cells only
B. Teardrop cells with nucleated RBCs and immature myeloid cells
C. Isolated target cells
D. Bite cells after infection
E. High reticulocytes with normal smear

Answer: B. A leukoerythroblastic smear with teardrops suggests myelophthisis or marrow fibrosis/infiltration.

17. A patient with CKD has anemia. Which approach is best?

A. Attribute anemia to CKD without additional testing
B. Give folate without checking B12
C. Evaluate iron status and other causes before selecting iron or erythropoietic therapy
D. Transfuse to a normal Hb in all cases
E. Diagnose hemolysis from creatinine alone
Answer: C. CKD commonly causes anemia, but iron deficiency, inflammation, bleeding, nutrient deficiency, and marrow disease must still be considered.

18. A normal MCV with marked anisocytosis most strongly suggests which possibility?

A. No anemia mechanism is present
B. Mixed microcytic and macrocytic populations
C. Pure thalassemia trait only
D. Analytical impossibility
E. Isolated plasma-volume expansion only
Answer: B. MCV is an average. Opposing cell populations can normalize the mean while RDW and smear reveal the mixture.

19. Which condition classically produces Pappenheimer bodies?

A. Sideroblastic anemia
B. Hereditary elliptocytosis
C. Cold agglutinin disease only
D. Acute hemorrhage
E. Folate deficiency only
Answer: A. Pappenheimer bodies are iron-containing granules and are classically associated with sideroblastic and post-splenectomy states.

20. What is the most appropriate interpretation of ferritin in systemic inflammation?

A. A normal ferritin always excludes iron deficiency
B. Ferritin is unaffected by inflammation
C. Ferritin may be elevated and can conceal coexisting iron deficiency
D. Ferritin falls in all inflammatory states
E. Ferritin directly measures circulating transferrin
Answer: C. Ferritin is an acute-phase reactant; integrate it with saturation, inflammation, trends, and clinical context.

CHAPTER A

Appendix A — Formulas and Diagnostic Shortcuts

Use shortcuts to organize reasoning, not replace definitive testing

Tool	Formula / pattern	Use and limitation
MCV	Hct (%) × 10 / RBC (millions/μL)	Classifies cell size; an average can conceal mixed populations
MCH	Hb (g/dL) × 10 / RBC	Tracks hemoglobin mass per cell; usually parallels MCV
MCHC	Hb × 100 / Hct	True elevation suggests spherocytosis/dehydration; verify analytical interference
Corrected reticulocyte %	Observed retic % × patient Hct / normal Hct	Adjusts for reduced RBC denominator
Reticulocyte production index	Corrected retic % / maturation factor	More accurate in moderate-to-severe anemia
Mentzer index	MCV / RBC count	<13 favors thalassemia trait; >13 favors iron deficiency; not definitive
Transferrin saturation	Serum iron / TIBC × 100	Low in absolute or functional deficiency; high in iron-loading states
Expected PRBC increment	~1 g/dL Hb or ~3% Hct per unit in average nonbleeding adult	Varies with size, bleeding, hemolysis, volume status, and sampling time

CHAPTER B

Appendix B — High-Yield Buzzwords and Board Traps

Rapid pattern recognition

Buzzword / clue	Think of	Why it matters
Pagophagia + low ferritin	Iron deficiency	Pica may precede severe anemia
Microcytosis + high RBC count	Thalassemia trait	Disproportionate microcytosis
Low iron + low TIBC + high ferritin	Inflammation	Hepcidin-mediated sequestration
Ring sideroblast	Sideroblastic anemia	Mitochondrial iron encircles marrow precursor nucleus
Coarse basophilic stippling	Lead / thalassemia / sideroblastic	Aggregated ribosomal RNA
Spherocyte + DAT negative	Hereditary spherocytosis	Intrinsic membrane defect
Spherocyte + DAT positive	Warm AIHA	Antibody-mediated membrane loss
Bite cell + Heinz body	G6PD deficiency	Oxidized hemoglobin and splenic pitting
Schistocytes + thrombocytopenia	TMA / DIC emergency	Mechanical fragmentation
Macro-ovalocyte + hypersegmented neutrophil	Megaloblastic anemia	Impaired DNA synthesis
B12 deficiency + neurologic signs	Subacute combined degeneration pattern	Treat B12; folate alone is unsafe
HbSS + new infiltrate + hypoxemia	Acute chest syndrome	Requires urgent multimodal therapy
HbSS + acute anemia + no retics	Parvovirus aplastic crisis	Production arrest
Target cells: HALT	HbC, Asplenia, Liver, Thalassemia	Membrane-to-volume imbalance
Teardrops + leukoerythroblastosis	Marrow fibrosis/infiltration	Myelophthisic pattern

CHAPTER C

Appendix C — Answer Key

Questions 1–20

1. C — Iron deficiency commonly produces elevated RDW and can cause reactive thrombocytosis. TIBC is typically high, ferritin low, and hepcidin suppressed.

2. B — Severe microcytosis with a relatively high RBC count and normal iron stores strongly suggests thalassemia trait.

3. C — Inflammation raises hepcidin, sequesters iron, lowers serum iron and transferrin/TIBC, and raises or preserves ferritin.

4. B — Both hereditary spherocytosis and warm AIHA show spherocytes, but a positive DAT supports immune hemolysis.

5. C — Splenic macrophages remove Heinz-body material, creating bite cells; blister cells may also be present.

6. C — Fibrin strands and abnormal microvascular shear fragment RBCs in thrombotic microangiopathy.

7. D — Methylmalonic acid rises in vitamin B12 deficiency but not isolated folate deficiency. Homocysteine rises in both.

8. B — Correct the reticulocyte percentage for the degree of anemia and, in severe anemia, account for prolonged reticulocyte maturation.

9. B — Membrane loss produces dense spherocytes and elevated MCHC; DAT is negative because the process is nonimmune.

10. C — Pyridoxal phosphate (vitamin B6) is required by ALA synthase. Isoniazid can cause functional B6 deficiency.

11. B — Parvovirus B19 infects erythroid precursors and can cause transient aplastic crisis in chronic hemolytic states.

12. C — Contemporary expert guidance favors no more than once-daily oral iron; alternate-day dosing may improve tolerability. Stores must also be replenished.

13. B — Severe megaloblastic anemia causes ineffective erythropoiesis and intramedullary destruction, raising LDH and bilirubin despite low reticulocytes.

14. A — Beta-thalassemia trait typically increases HbA2. Coexisting iron deficiency may lower HbA2 and mask the trait.

15. C — Gene therapies are approved for selected patients. Voxelotor was withdrawn; hydroxyurea raises HbF; exchange transfusion is central to acute stroke management.

16. B — A leukoerythroblastic smear with teardrops suggests myelophthisis or marrow fibrosis/infiltration.

17. C — CKD commonly causes anemia, but iron deficiency, inflammation, bleeding, nutrient deficiency, and marrow disease must still be considered.

18. B — MCV is an average. Opposing cell populations can normalize the mean while RDW and smear reveal the mixture.

19. A — Pappenheimer bodies are iron-containing granules and are classically associated with sideroblastic and post-splenectomy states.

20. C — Ferritin is an acute-phase reactant; integrate it with saturation, inflammation, trends, and clinical context.

CHAPTER D

Selected References and 2026 Guideline Updates

Authoritative sources used for expansion and correction

1. World Health Organization. Guideline on haemoglobin cutoffs to define anaemia in individuals and populations. Geneva: WHO; 2024.

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Source manuscripts integrated into this edition

- Anemia Classification and Diagnosis: A Comprehensive Clinical Briefing
- Clinical Practice Manual: The Differential Diagnosis of Microcytic Anemia
- Diagnostic Reference Paper: Clinical Synthesis of Iron Metabolism Disorders and Anemic Pathologies
- Hematology and Anemia Classification Study Guide
- Sickle Cell Anemia USMLE Board Review and Case Studies
- The Aspiring Hematologist’s Guide to Blood Metrics and Anemia
- The Blood Map: 6 Surprising Insights Into the Hidden World of Anemia
- The Life and Legacy of a Red Blood Cell: A Journey of Recycling

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