Anemia in the Hospitalized Setting

Anemia is a common condition in hospitalized patients, often reflecting underlying disease processes. This pamphlet provides students with a concise guide to evaluate, diagnose, and treat anemia in the hospital setting, including a comparison of AIHA, MAHA, and PNH.

Evaluation

Definition:

• Anemia is defined as hemoglobin (Hgb) <13 g/dL (men) or <12 g/dL (women), adjusted for age, race, and altitude (e.g., African Americans: ~0.5-1 g/dL lower).

History:

- Symptoms: Fatigue, dyspnea, pallor, chest pain, syncope, dizziness.
- Risk Factors: Bleeding (GI, GU), diet (iron/B12 deficiency), chronic diseases (CKD, cirrhosis, malignancy), alcohol use, family history (sickle cell, thalassemia), recent infections, medications (e.g., chemotherapy, sulfa drugs), fever, or systemic symptoms (infections, malignancy).

Physical Exam:

- Pallor (conjunctiva, nail beds), tachycardia, flow murmur.
- **Signs of bleeding:** Petechiae, melena, hematuria.
- Jaundice (hemolysis), splenomegaly (hemolysis, cirrhosis, malignancy, infections), lymphadenopathy (malignancy, infections), fever (infections).

Initial Labs:

- • **CBC:** Hgb, hematocrit (Hct), mean corpuscular volume (MCV).
- • **Reticulocyte Count:** Low (<2%) = hypoproliferative; high (>2%) = hemolysis/ bleeding.
- • **Peripheral Smear:** See below for detailed evaluation.

Peripheral Smear Overview

Purpose:

• A peripheral blood smear examines RBC morphology, WBCs, and platelets to identify abnormalities that guide the anemia workup.

How It's Done:

• A thin layer of blood is spread on a slide, stained (Wright-Giemsa), and examined under a microscope.

Key Components:

- **• RBC Morphology:** Size, shape, inclusions, anisocytosis (variation in size), poikilocytosis (variation in shape).
- **• WBCs:** Differential (neutrophils, lymphocytes), presence of immature cells (blasts).
- **• Platelets:** Count, clumping (pseudothrombocytopenia).

Concerning Findings and Indications:

• **Schistocytes:** Fragmented RBCs; indicate microangiopathic hemolytic anemia (MAHA) → TTP, HUS, DIC (urgent hematology consult; ADAMTS13 for TTP).

• **Sickle Cells:** Crescent-shaped RBCs; indicate sickle cell disease → Hemolysis, vaso-occlusive crises (Hb electrophoresis for confirmation).

• **Spherocytes:** Small, round RBCs without central pallor; indicate hereditary spherocytosis or AIHA → Positive Coombs test in AIHA (steroids, rituximab).

• **Bite Cells:** RBCs with a "bite" taken out; indicate G6PD deficiency → Oxidative hemolysis (check G6PD assay, avoid triggers like sulfa drugs).

• **Target Cells (Codocytes):** Bullseye appearance; indicate thalassemia, liver disease (cirrhosis), or hemoglobinopathies → Hb electrophoresis, LFTs.

• **Hypersegmented Neutrophils:** >5 lobes; indicate B12/folate deficiency → Check B12/folate levels (treat deficiency, rule out MDS).

• **Blasts:** Immature WBCs (>5% concerning); indicate leukemia (AML, ALL) → Bone marrow biopsy, urgent hematology consult (chemotherapy).

• **Teardrop Cells (Dacrocytes):** Teardrop-shaped RBCs; indicate myelofibrosis or marrow infiltration (metastatic cancer) → Bone marrow biopsy, imaging (CT/PET).

• **Howell-Jolly Bodies:** Small, round inclusions in RBCs; indicate asplenia or functional hyposplenism (e.g., sickle cell, cirrhosis) → Check spleen function, vaccinate (pneumococcal).

• **Rouleaux Formation:** Stacked RBCs (like coins); indicate multiple myeloma → SPEP/UPEP for monoclonal protein (chemotherapy, bisphosphonates).

Key Tips:

- Always correlate smear findings with clinical history and labs (e.g., schistocytes + thrombocytopenia = TTP).
- Urgent findings (blasts, schistocytes) require immediate hematology consult.

Causes

Microcytic (MCV <80 fL):

- Iron deficiency (bleeding, poor intake, malabsorption).
- Thalassemia (target cells on smear).
- Anemia of chronic disease (ACD; e.g., CKD, cirrhosis, malignancy, infections like TB or HIV).
- **Drug Reactions:** Methotrexate (inhibits folate metabolism), zidovudine (HIV treatment, marrow suppression).

Normocytic (MCV 80-100 fL):

- • Acute blood loss (GI bleed, trauma).
- Hemolysis:
  - Common Triggers:
    - Infections (malaria, Mycoplasma, Clostridium perfringens), drugs (penicillin, sulfonamides for G6PD deficiency, dapsone), autoimmune (SLE, lymphoma), mechanical (prosthetic valves, MAHA).
  - Causes:
    - Autoimmune hemolytic anemia (AIHA), G6PD deficiency, sickle cell disease, hereditary spherocytosis, MAHA (e.g., TTP, DIC), paroxysmal nocturnal hemoglobinuria (PNH).
- CKD:
  - Reduced erythropoietin (EPO) production; Hgb often 8-10 g/dL.
- Cirrhosis:
  - Hypersplenism (sequestration), GI bleeding (varices), folate deficiency.

- Alcohol-Related Marrow Suppression:
- Direct toxicity to bone marrow, folate deficiency, often normocytic or macrocytic.

- Infections:
  - Malaria: Intravascular hemolysis (Plasmodium falciparum), schistocytes, parasitemia on smear.
- HIV: ACD, marrow suppression (zidovudine), opportunistic infections (e.g., parvovirus B19 causing pure red cell aplasia).
- Sepsis: Hemolysis (Clostridium), ACD, marrow suppression (endotoxin-mediated).
- Drug Reactions:
  - Chemotherapy (e.g., cyclophosphamide, cisplatin): Bone marrow suppression.
- Dapsone, primaquine: Oxidative hemolysis in G6PD deficiency (bite cells on smear).

Macrocytic (MCV >100 fL):

- • B12/folate deficiency (pernicious anemia, alcoholism).
- Alcohol: Marrow suppression, folate deficiency, liver disease.
- Myelodysplastic syndrome (MDS), liver disease (cirrhosis), hypothyroidism.
- Drug Reactions:
  - Methotrexate, hydroxyurea (impairs DNA synthesis), zidovudine (marrow toxicity).
- Infections:
  - Parvovirus B19: Pure red cell aplasia (especially in sickle cell patients), low reticulocytes.
  - EBV/CMV: Marrow suppression, hemolysis (if AIHA).

Malignant Causes:

- Multiple Myeloma: Bone marrow infiltration, renal failure (light chain nephropathy).
- Leukemia: Acute leukemia (AML, ALL) → Bone marrow replacement → Pancytopenia.
- Lymphoma: Bone marrow involvement, hemolysis (AIHA in CLL/lymphoma).
- Metastatic Cancer: Marrow infiltration (breast, prostate, lung cancer).

Other Causes:

- Aplastic Anemia: Bone marrow failure (idiopathic, post-viral, drugs like chloramphenicol), pancytopenia.

- Sideroblastic Anemia: Defective heme synthesis (alcohol, lead poisoning, isoniazid), ringed sideroblasts on bone marrow.
- Vitamin C Deficiency: Scurvy (hospitalized patients with poor nutrition), microcytic anemia, bleeding gums.

Comparison: AIHA, MAHA, and PNH

Autoimmune Hemolytic Anemia (AIHA):

- **Mechanism:** Immune-mediated destruction of RBCs by autoantibodies (IgG or IgM); extravascular hemolysis (spleen/liver).
- **Causes:** Primary (idiopathic) or secondary (SLE, lymphoma, drugs like penicillin, infections like Mycoplasma).
- **Labs/Smear:** Positive direct Coombs test (DAT), spherocytes on smear, high LDH, low haptoglobin, high reticulocytes.
- **Clinical:** Jaundice, splenomegaly, anemia (Hgb <10 g/dL), no thrombosis.
- **Treatment:** Prednisone 1 mg/kg/day (taper after 4-6 weeks); rituximab (375 mg/m² IV weekly x 4) if refractory.

Microangiopathic Hemolytic Anemia (MAHA):

- **Mechanism:** Mechanical destruction of RBCs in small vessels due to microthrombi; intravascular hemolysis.
- **Causes:** TTP (ADAMTS13 deficiency), HUS (Shiga toxin), DIC, malignant hypertension, prosthetic valves.
- **Labs/Smear:** Schistocytes on smear, high LDH, low haptoglobin, thrombocytopenia, normal Coombs test, hemoglobinuria.
- **Clinical:** Anemia, thrombocytopenia, organ dysfunction (renal failure in HUS, neurologic symptoms in TTP), thrombosis.
- **Treatment:** TTP: Plasma exchange (daily until platelets >150,000/µL); HUS: Supportive care (dialysis if AKI); avoid platelet transfusion.

Paroxysmal Nocturnal Hemoglobinuria (PNH):

- **Mechanism:** Acquired stem cell mutation (PIGA gene) → Deficiency of complement inhibitors (CD55/CD59) → Complement-mediated intravascular hemolysis.
- **Causes:** Clonal disorder; often associated with bone marrow failure (e.g., aplastic anemia, MDS).
- **Labs/Smear:** High LDH, low haptoglobin, hemoglobinuria (dark urine, especially at night), flow cytometry (CD55/CD59-negative RBCs), bone marrow (hypocellular if aplastic anemia).

- **Clinical:** Anemia, thrombosis (e.g., hepatic vein thrombosis), pancytopenia, smooth muscle dystonia (e.g., esophageal spasm).
- **Treatment:** Eculizumab 600 mg IV weekly x 4, then 900 mg IV q2 weeks (inhibits complement); anticoagulation (e.g., enoxaparin 1 mg/kg SC BID) if thrombotic.

Key Differences:

- **AIHA:** Immune-mediated, extravascular, Coombs positive, spherocytes, no thrombosis.
- **MAHA:** Mechanical, intravascular, Coombs negative, schistocytes, thrombosis common.
- **PNH:** Complement-mediated, intravascular, flow cytometry diagnostic, thrombosis and pancytopenia prominent.

Diagnostic Workup

Step 1: Classify by MCV:

- **Microcytic:** Iron studies (ferritin, TIBC, serum iron).
- **Normocytic:** Reticulocyte count, hemolysis labs (LDH, haptoglobin, Coombs test).
- **Macrocytic:** B12/folate levels, peripheral smear (hypersegmented neutrophils).

Step 2: Peripheral Smear:

- **See Peripheral Smear Overview for findings (e.g., schistocytes, blasts, bite cells).**

Step 3: Additional Labs:

- Iron Deficiency: Ferritin <30 ng/mL, high TIBC, low serum iron.
- Hemolysis:
  - AIHA: Positive Coombs, spherocytes, high LDH, low haptoglobin.
  - MAHA: Normal Coombs, schistocytes, thrombocytopenia, high LDH.
- PNH: Flow cytometry (CD55/CD59-negative), hemoglobinuria, high LDH.
- B12/Folate Deficiency: B12 <200 pg/mL, folate <2 ng/mL; MMA/homocysteine (if equivocal).
- CKD: Cr >1.5 mg/dL, eGFR <60 mL/min, low EPO levels (not routinely measured).
- Cirrhosis: LFTs (elevated bilirubin, low albumin), PT/INR (coagulopathy), low platelets (hypersplenism).
- Alcohol-Related: High AST/ALT (2:1 ratio), GGT elevated, folate low, macrocytosis on smear.

- Infections:
  - Malaria: Thick/thin smear (parasitemia), rapid diagnostic test (PfHRP2).
- HIV: HIV viral load, CD4 count, opportunistic infections (e.g., parvovirus PCR).
- Parvovirus B19: PCR (in immunocompromised), IgM/IgG (acute infection), low reticulocytes.
- Sepsis: Blood cultures (Clostridium), lactate (elevated in hemolysis/sepsis).
- Drug Reactions:
  - G6PD Deficiency: G6PD enzyme assay (avoid during acute hemolysis), bite cells on smear.
- Chemotherapy: Bone marrow biopsy (hypocellular), CBC (pancytopenia).
- Methotrexate: Folate levels (low), macrocytosis, bone marrow suppression.
- Malignant Causes:
  - Multiple Myeloma: SPEP/UPEP (monoclonal spike), serum free light chains (kappa/lambda ratio), calcium (hypercalcemia), Cr (renal failure).
- Leukemia: Peripheral smear (blasts >20%), bone marrow biopsy (hypercellular, blast predominance).
- Lymphoma: Lymph node biopsy, bone marrow biopsy (if involved), PET/CT (staging).
- Metastatic: Bone marrow biopsy (marrow infiltration), tumor markers (e.g., PSA for prostate).
- Aplastic Anemia: Bone marrow biopsy (hypocellular), pancytopenia.
- Sideroblastic Anemia: Bone marrow (ringed sideroblasts), iron studies (high ferritin).
- Vitamin C Deficiency: Serum ascorbic acid (<0.2 mg/dL), clinical signs (bleeding gums, perifollicular hemorrhages).
- Other: Cr (CKD), LFTs (cirrhosis), TSH (hypothyroidism), lead levels (if sideroblastic anemia suspected).

Step 4: Imaging/Tests:

- • **Endoscopy/colonoscopy:** For GI bleeding (e.g., melena, hematochezia).
- • **Bone marrow biopsy:** For MDS, leukemia, myeloma, aplastic anemia, or metastatic disease.
- • **CT/PET:** For malignancy (lymphoma, metastatic cancer).

Diagnosis

Microcytic Anemia:

- • **Iron Deficiency:** Ferritin <30 ng/mL, low serum iron, high TIBC.

- • **Thalassemia:** Normal/high ferritin, Hb electrophoresis (elevated HbA2 or HbF), target cells on smear.
- • **ACD:** High ferritin, low TIBC (e.g., CKD, cirrhosis, malignancy, TB/HIV).
- • **Sideroblastic:** Ringed sideroblasts on bone marrow, high ferritin (e.g., alcohol, isoniazid).

Normocytic Anemia:

- Blood Loss: High reticulocyte count, history of bleeding (e.g., melena).
- Hemolysis:
  - AIHA: Positive Coombs, spherocytes on smear, high LDH.
  - MAHA: Normal Coombs, schistocytes on smear, thrombocytopenia.
- PNH: Flow cytometry (CD55/CD59-negative), hemoglobinuria, pancytopenia.
- CKD: eGFR <60 mL/min, Hgb 8-10 g/dL, normal/low reticulocytes.
- Cirrhosis: Hypersplenism (platelets <150,000/µL), LFT abnormalities, Howell-Jolly bodies on smear.
- Alcohol-Related: Macrocytosis (if chronic), folate deficiency, normal/low reticulocytes.
- Infections: Malaria (parasitemia on smear), HIV (low CD4, parvovirus PCR positive), sepsis (positive cultures, hemolysis markers).
- Aplastic Anemia: Pancytopenia, hypocellular bone marrow, no abnormal cells on smear.

Macrocytic Anemia:

- B12/Folate Deficiency: Low B12/folate, hypersegmented neutrophils on smear, high MMA (B12 deficiency).
- MDS: Dysplastic cells on smear, bone marrow biopsy (hypercellular, abnormal maturation).
- Drug Reactions: Methotrexate (low folate, macrocytosis), zidovudine (marrow suppression).

Malignant Causes:

- Multiple Myeloma: Monoclonal spike on SPEP, rouleaux formation on smear, lytic lesions (skeletal survey).
- Leukemia: Blasts on smear, bone marrow biopsy (AML: >20% blasts).
- Lymphoma: Bone marrow involvement, AIHA (positive Coombs), lymph node biopsy (e.g., Hodgkin's: Reed-Sternberg cells).

Diagnostic Approach Table

MCV Category	Key Labs	Diagnosis	Notes
Microcytic (<80 fL)	Iron studies, bone marrow (if sideroblastic)	-Iron deficiency: Ferritin <30 ng/mL -Sideroblastic: Ringed sideroblasts	Check for TB/HIV in ACD; lead levels if sideroblastic.
Normocytic (80-100 fL)	Reticulocyte count, LDH, Coombs, HIV, malaria smear	AIHA: Positive Coombs, spherocytes -MAHA: Schistocytes, normal Coombs	PNH: Flow cytometry (CD55/CD59-negative); check Cr (CKD).
Macrocytic (>100 fL)	B12/folate, peripheral smear, SPEP	-B12 deficiency: Hypersegmented neutrophils -Myeloma: Rouleaux formation	Parvovirus PCR in sickle cell; blasts on smear for leukemia.

Treatment

General Principles:

- • Treat underlying cause (e.g., stop bleeding, correct deficiency).
- • Transfuse only if Hgb <7 g/dL or symptomatic (chest pain, syncope, hemodynamic instability: HR >100 bpm, SBP <90 mmHg).

Specific Treatments:

- Iron Deficiency:
  - **Oral:** Ferrous sulfate 325 mg PO TID (with vitamin C).
  - **•IV:** Ferric carboxymaltose 750 mg IV (if malabsorption or intolerance).
- B12 Deficiency:
  - •Cyanocobalamin 1000 mcg IM daily x 7 days, then weekly x 4 weeks, then monthly.
- Folate Deficiency:
  - Folic acid 1-5 mg PO daily (ensure B12 is normal).
- Hemolysis:
  - AIHA: Prednisone 1 mg/kg/day (taper after 4-6 weeks); rituximab (375 mg/m² IV weekly x 4) if refractory.
  - MAHA (TTP): Plasma exchange (daily until platelets >150,000/µL); steroids (prednisone 1 mg/kg/day).
- PNH: Eculizumab 600 mg IV weekly x 4, then 900 mg IV q2 weeks; anticoagulation (e.g., enoxaparin 1 mg/kg SC BID) if thrombotic.

- Sickle Cell: Hydration (NS 100 mL/h IV), pain control (morphine 0.1 mg/kg IV q2h PRN), transfusion if severe.
- G6PD Deficiency: Avoid triggers (e.g., sulfa drugs, dapsone), supportive care (hydration, transfusion if severe).
- CKD: Epoetin alfa 50-100 units/kg IV 3x/week (Hgb <10 g/dL); iron supplementation (ferritin <100 ng/mL).
- Cirrhosis: **Treat bleeding (varices:** octreotide 50 mcg/h IV, endoscopy), folate (1 mg PO daily), minimize alcohol.
- Alcohol-Related: Abstinence, folate 1 mg PO daily, nutritional support (thiamine 100 mg IV before glucose).
- Infections:
    - Malaria: Artemisinin-based combination therapy (e.g., artemether-lumefantrine 20/120 mg, 4 tabs PO BID x 3 days); transfusion if severe.
    - HIV: Antiretroviral therapy (e.g., tenofovir + emtricitabine + dolutegravir); treat opportunistic infections (e.g., IVIG for parvovirus).
    - Parvovirus B19 IVIG 0.4 g/kg IV daily x 5 days (in immunocompromised or sickle cell).
- Sepsis: Broad-spectrum antibiotics (piperacillin-tazobactam 4.5 g IV q6h), supportive care (transfusion, fluids).
- Drug Reactions:
    - G6PD Deficiency: Stop offending drug (e.g., dapsone), supportive care.
    - Chemotherapy; Hold drug if possible, G-CSF (filgrastim 5 mcg/kg/day SC) for neutropenia, transfusions.
- Methotrexate: Folinic acid (leucovorin) rescue 15 mg IV q6h (if toxicity), folate supplementation.
- Malignant Causes: Multiple Myeloma:
    - Chemotherapy (lenalidomide 25 mg PO daily + dexamethasone 40 mg weekly), bisphosphonates (zoledronic acid 4 mg IV monthly).
- Leukemia (AML): Induction chemotherapy (cytarabine 100 mg/m² IV daily x 7 days + daunorubicin 60 mg/m² IV x 3 days).
- Lymphoma: **Chemotherapy (CHOP:** cyclophosphamide 750 mg/m² IV, doxorubicin 50 mg/m² IV, vincristine 1.4 mg/m² IV, prednisone 100 mg PO daily x 5 days).
- Aplastic Anemia: Immunosuppression (ATG + cyclosporine); bone marrow transplant (if <40 years).
- Sideroblastic Anemia: Pyridoxine 50-100 mg PO daily (if responsive), stop offending drug (e.g., isoniazid).
- Vitamin C Deficiency: Ascorbic acid 500 mg PO BID x 2 weeks, then 100 mg daily.

Transfusion:

- **PRBCs:** 1 unit IV over 2-4h (increases Hgb by 1 g/dL); use leukoreduced blood.

- **Monitoring:** Hgb q4-6h post-transfusion, watch for reactions (fever, hemolysis, TRALI).

Key Tips:

- • Avoid transfusion in iron overload (e.g., thalassemia); treat underlying cause first.
- • Avoid platelet transfusion in MAHA (e.g., TTP) unless life-threatening bleeding.

Treatment Guidelines Table

these are managed by hematology consultants

Cause	Treatment Agent/ Dose	Notes	
AIHA	Steroids, rituximab	-Prednisone 1 mg/kg/ day -Rituximab 375 mg/m² IV weekly x 4	Taper steroids; rituximab if refractory.
MAHA (TTP)	Plasma exchange, steroids	-Daily PLEX -Prednisone 1 mg/kg/ day	Continue PLEX until platelets >150,000/µL.
PNH	Eculizumab, anticoagulation	-Eculizumab 600 mg IV weekly x 4 -Enoxaparin 1 mg/kg SC BID	Monitor for thrombosis; vaccinate (meningococcal).
Myeloma	Chemotherapy, bisphosphonates	-Lenalidomide 25 mg PO daily -Zoledronic acid 4 mg IV monthly	Manage hypercalcemia, renal failure.

Complications

Acute:

- **Hypoxia:** MI, stroke, organ failure (Hgb <7 g/dL).
- **Transfusion Reactions:** Hemolysis, TRALI, TACO.

Chronic:

- **Iron Overload:** In transfusion-dependent anemia (e.g., thalassemia); liver/heart damage.
- **Neurologic:** Subacute combined degeneration (B12 deficiency; numbness, ataxia).

Underlying Disease:

- **Sickle Cell:** Vaso-occlusive crises, stroke, acute chest syndrome.
- **PNH:** Thrombosis (30-40% risk), bone marrow failure.
- **Malignancy:** Progression (MDS → AML, 10-30%), infections (chemotherapy-related).

Key Pearls

- **Classify anemia by MCV:** Microcytic (iron deficiency, ACD), normocytic (hemolysis, CKD), macrocytic (B12 deficiency, MDS).
- **Peripheral Smear:** Schistocytes (MAHA), spherocytes (AIHA), blasts (leukemia)—urgent findings require hematology consult.
- **AIHA vs. MAHA vs. PNH:** AIHA (immune, Coombs positive), MAHA (mechanical, schistocytes), PNH (complement, thrombosis risk).
- **Reticulocyte count:** Low (<2%) = hypoproliferative (CKD, cirrhosis); high (>2%) = hemolysis/bleeding.
- **Hemolysis:** Check LDH, haptoglobin, Coombs; identify triggers (infections, drugs like dapsone).
- Transfuse only if Hgb <7 g/dL or symptomatic; avoid in iron overload states.

References

• **UpToDate:** “Approach to Anemia in Adults” (2025).

• **AAFP:** “Evaluation and Management of Anemia” (2024).

• **NEJM:** “Autoimmune Hemolytic Anemia: Diagnosis and Treatment” (2023).

• **Blood:** “Paroxysmal Nocturnal Hemoglobinuria: Diagnosis and Management” (2024).