CHAPTER 9

TREATMENT ALGORITHMS FOR HEMATOLOGIC DISORDERS

Author

Miss Veera Naga Lalitha Nakkina, Pharm D Scholar,
Koringa College of Pharmacy, Korangi, Tallarevu,
Andhra Pradesh, India

Abstract

Hematologic treatment algorithms are fundamentally dictated by cell lineage, cell maturity, and functional defects. The algorithm for anemias begins with a morphological classification (microcytic, normocytic, macrocytic) based on Mean Corpuscular Volume (MCV). This pathway then uses specific tests (e.g., iron studies, B12/folate levels, reticulocyte count) to differentiate etiologies such as iron deficiency, B12/folate deficiency, or anemia of chronic disease, with treatment aimed at targeted repletion. In contrast, algorithms for leukemias are bifurcated by acuity (acute vs. chronic) and lineage (myeloid vs. lymphoid). Acute leukemias (AML, ALL) are medical emergencies requiring immediate induction chemotherapy. Chronic myeloid leukemia (CML) is managed with a first-line algorithm of oral tyrosine kinase inhibitors. Chronic lymphocytic leukemia (CLL) often follows a "watch and wait" algorithm until symptoms or cytopenias develop. Lymphoma algorithms diverge into Hodgkin (HL) and Non-Hodgkin (NHL) pathways. HL is treated with stage-adapted chemotherapy (e.g., ABVD). NHL algorithms are highly heterogeneous based on subtype, ranging from "watch and wait" for follicular lymphoma to aggressive R-CHOP for diffuse large B-cell lymphoma. Bleeding disorder algorithms differentiate between platelet and factor deficiencies. Immune thrombocytopenia is managed with first-line corticosteroids, while hemophilias require factor replacement algorithms (prophylactic or on-demand).

Keywords: *Anemia, Leukemia, Lymphoma, Bleeding Disorders, Chemotherapy, Targeted Therapy*

Learning Objectives

After completion of the chapter, the learners should be able to:

- Classify anemias based on MCV (microcytic, normocytic, macrocytic) and identify key follow-up tests for each.
- Explain the general treatment algorithm for Acute Myeloid Leukemia (AML), including induction and consolidation phases.
- Formulate a diagnostic and treatment algorithm for a patient presenting with new-onset microcytic anemia.
- Differentiate the staging and treatment algorithms for Hodgkin Lymphoma versus non-Hodgkin Lymphoma.
- Prioritize the management steps in the algorithm for a patient with a bleeding disorder (e.g., von Willebrand disease) requiring emergency surgery.

ANEMIAS

Anemia is defined as a reduction in the concentration of hemoglobin or the number of red blood cells. The management algorithm is not a single pathway but a diagnostic algorithm based on cell morphology, which then leads to etiology-specific treatment.

Iron Deficiency Anemia (IDA)

Pathophysiology

Iron deficiency anemia is the most common anemia worldwide. The pathophysiology is a direct consequence of insufficient iron supply for hemoglobin (Hgb) synthesis. Iron is a critical component of the heme molecule, which is the oxygen-carrying moiety within Hgb. The body's iron stores (primarily as ferritin) must be depleted *before* a drop in Hgb occurs. The most common cause in pre-menopausal women is chronic blood loss (menorrhagia). In men and post-menopausal women, the most common and ominous cause is chronic gastrointestinal blood loss (e.g., from a peptic ulcer or colon cancer). In resource-poor settings, nutritional deficiency is also a primary driver. The resulting RBCs are microcytic (small) and hypochromic (pale) because there is not enough hemoglobin to fill the cell.

Anemia of Chronic Disease / Inflammation (ACD)

Pathophysiology

Anemia of Chronic Disease (ACD) is the second most common anemia and is seen in patients with chronic inflammatory states (e.g., rheumatoid arthritis, IBD, chronic infection, malignancy). The pathophysiology is *not* a deficiency of iron, but a **functional iron deficiency** driven by inflammation. The main inflammatory cytokine is **hepcidin**, which is released by the liver. Hepcidin acts as the master iron regulator. It "locks" iron away: 1) it blocks iron absorption from the gut, and 2) it prevents the release of recycled iron from macrophages. Even though the patient has abundant iron stored in their ferritin, hepcidin prevents it from being released to the bone marrow for use in new RBCs. The result is an anemia that looks similar to IDA (often microcytic/normocytic) but occurs in the setting of a high ferritin (because the iron is trapped in storage).

Diagnosis and Classification

The diagnostic algorithm for anemia begins with a complete blood count (CBC) with differential. The first branch point is the Mean Corpuscular Volume (MCV), which classifies the anemia morphologically:

1. **Microcytic (MCV < 80 fL):** Small red blood cells.
2. **Normocytic (MCV 80-100 fL):** Normal-sized red blood cells.
3. **Macrocytic (MCV > 100 fL):** Large red blood cells.

Differential Diagnosis (Etiology)

The differential diagnosis is stratified by MCV:

- **Microcytic:** The differential includes iron deficiency anemia (IDA), thalassemia, anemia of chronic disease (ACD; can also be normocytic), and sideroblastic anemia.
- **Normocytic:** This is the broadest category. The algorithm is further stratified by the reticulocyte count. A high reticulocyte count implies hemolysis or acute blood loss (a correct bone marrow response). A low

reticulocyte count implies a production problem (e.g., ACD, aplastic anemia, renal failure).

- **Macrocytic:** The algorithm bifurcates into megaloblastic (impaired DNA synthesis) and non-megaloblastic causes. Megaloblastic anemia includes Vitamin B12 deficiency and folate deficiency. Non-megaloblastic causes include liver disease, alcoholism, and myelodysplastic syndrome (MDS).

Treatment Algorithm

The treatment algorithm is entirely dependent on the diagnosed etiology.

- **Iron Deficiency Anemia (IDA):** The algorithm begins with oral iron supplementation (e.g., ferrous sulfate) given with vitamin C to enhance absorption. For patients intolerant to oral iron or with severe malabsorption (e.g., IBD, post-bariatric surgery), the algorithm shifts to intravenous (IV) iron. It is also critical to investigate and treat the underlying cause of iron deficiency (e.g., occult GI bleeding).
- **Vitamin B12 Deficiency:** The algorithm is replacement, typically with intramuscular (IM) or subcutaneous (SC) cyanocobalamin, starting with loading doses followed by monthly maintenance. High-dose oral B12 can be used if absorption is intact.
- **Folate Deficiency:** The algorithm is simple replacement with oral folic acid.
- **Anemia of Chronic Disease (ACD):** The primary algorithm is to treat the underlying inflammatory condition (e.g., rheumatoid arthritis, IBD). If anemia is severe, particularly in the setting of CKD, the algorithm may involve erythropoiesis-stimulating agents (ESAs) after ensuring iron stores are replete.
- **Hemolytic Anemia:** The algorithm depends on the cause (e.g., corticosteroids for autoimmune hemolytic anemia, splenectomy for hereditary spherocytosis).

Table 9.1: Diagnostic Algorithm for Anemia Based on MCV

MCV Category	Initial Labs	Common Etiologies
Microcytic (< 80 fL)	**Iron Studies** (Ferritin, TIBC), Hgb Electrophoresis	Iron Deficiency, Thalassemia, Anemia of Chronic Disease (late).
Normocytic (80-100 fL)	**Reticulocyte Count,** LDH, Haptoglobin, Coombs'	**Low Retic:** Anemia of Chronic Disease, CKD, Aplastic Anemia. **High Retic:** Hemolysis, Acute Blood Loss.
Macrocytic (> 100 fL)	**B12 / Folate levels,** TSH, LFTs, Retic. Count	**Megaloblastic:** B12/Folate Deficiency. **Non-Megaloblastic:** Liver Disease, Alcoholism.

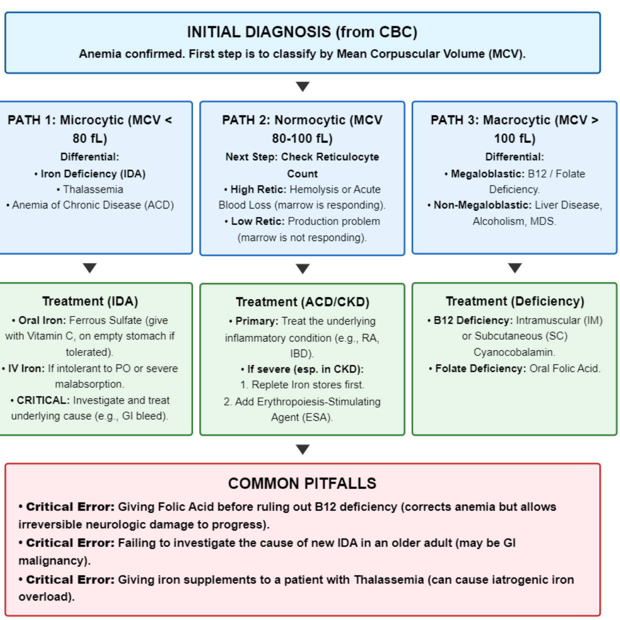

Figure 9.1: Anemia Diagnostic and Treatment Algorithm

Monitoring and Follow-Up

The primary monitoring parameter is the **hemoglobin** level, which should begin to rise within 2-3 weeks of starting iron supplementation. A complete blood count (CBC) and reticulocyte count should be checked at 4 weeks to confirm a response (a rise in reticulocytes, or new RBCs, should be seen within 7-10 days). A failure to respond suggests non-adherence, malabsorption, or incorrect diagnosis. More importantly, **ferritin** must be monitored. The goal is not just to normalize the Hgb, but to *replete the iron stores*. Oral iron should be continued for 3-6 *months* after the Hgb has normalized to fully replenish the ferritin stores.

Long-Term Management / Secondary Prevention

Long-term management is focused on identifying and **treating the underlying cause of iron loss**. In a man or post-menopausal woman with new IDA, the diagnostic algorithm *must* include an upper endoscopy and colonoscopy to rule out a GI malignancy. For a pre-menopausal woman, management of menorrhagia is crucial. Secondary prevention in high-risk groups (e.g., pregnant women, bariatric surgery patients) involves prophylactic low-dose iron supplementation.

Patient Counseling Points

1. **Iron Dosing and Side Effects:** "This is a critical counseling point. You should take your iron pill on an *empty stomach* to absorb it best, often with a glass of orange juice, as Vitamin C helps absorption. However, iron is very hard on the stomach and commonly causes constipation, nausea, and dark stools. If you can't tolerate it on an empty stomach, it is better to take it *with food* than to not take it at all."
2. **Constipation Management:** "You will almost certainly become constipated. You should start a stool softener (like docusate) or a gentle laxative (like Miralax) at the same time you start your iron."
3. **Duration of Therapy:** "This is not a quick fix. We are checking your blood count in a few weeks, but you will

need to take this pill for *many months*. Our goal is first to fix your blood count, and then to re-fill your body's 'iron savings account' (ferritin), which takes time."

Common Pitfalls in Management

A very common pitfall is prescribing iron supplementation to a patient with thalassemia; these patients are microcytic but often iron-overloaded, and iron can cause organ damage. Another error is initiating folic acid supplementation in a patient with severe macrocytic anemia *before* ruling out B12 deficiency; this can correct the anemia hematologically but allow irreversible neurologic damage from B12 deficiency to progress. Finally, failing to investigate the *cause* of iron deficiency in an older adult is a critical omission that can miss a GI malignancy.

Case Study

A 35-year-old pre-menopausal female (Ms. Yang) presents with a 6-month history of progressive fatigue, pallor, and "brain fog." She notes her menstrual periods have been very heavy. On exam, she has pale conjunctivae. Her CBC shows: Hgb **9.2 g/dL** (low), Hct 28% (low), and **MCV 74 fL** (low).

Discussion

The patient's CBC reveals a **microcytic anemia** (MCV < 80). The diagnostic algorithm for microcytic anemia is to first differentiate Iron Deficiency Anemia (IDA) from thalassemia or anemia of chronic disease. Given her history of heavy menses (chronic blood loss), IDA is the leading cause.

Treatment Algorithm

1. **Diagnosis (MCV-based):** Microcytic Anemia.
2. **Algorithm Step 1 (Diagnostic Labs):** You order **iron studies**.
    - **Ferritin: 5 ng/mL** (very low, < 15-30)
    - **Serum Iron:** Low
    - **TIBC:** High
    - This lab profile confirms the diagnosis of **Iron Deficiency Anemia**.

3. **Algorithm Step 2 (Treatment):**
   - **Repletion:** Start **oral Ferrous Sulfate 325 mg daily**.
   - **Counseling:** You counsel her to take it on an empty stomach with a glass of orange juice (Vitamin C) to enhance absorption, and warn her about expected side effects (constipation, dark stools).
4. **Algorithm Step 3 (Address Cause):** The anemia will recur unless the cause is treated. You refer her to a GYN to manage her menorrhagia.
5. **Follow-up:** Re-check CBC in 4 weeks to see a rise in Hgb. The algorithm *requires* continuing iron for **3-6 months *after*** her Hgb normalizes to replete her ferritin stores.

Outcome

Ms. Yang is started on oral iron supplementation and referred to GYN to manage the underlying cause of her chronic blood loss.

LEUKEMIAS

Leukemias are malignant proliferative disorders of hematopoietic cells. The treatment algorithms are highly specific and are bifurcated by acuity (acute vs. chronic) and cell lineage (myeloid vs. lymphoid).

Pathophysiology

A. Acute Myeloid Leukemia (AML)

Acute Myeloid Leukemia (AML) is a cancer of the myeloid bloodline. The pathophysiology is a **maturation arrest**. A hematopoietic stem cell in the bone marrow acquires a genetic mutation (e.g., *FLT3*, *NPM1*) that causes it to proliferate uncontrollably and, critically, *fail to differentiate* into a mature cell (like a neutrophil). This results in the massive overproduction and accumulation of immature, non-functional "blasts." These blasts crowd out the entire bone marrow, leading to a failure of all other cell lines. This "bone marrow failure" is what causes the clinical presentation: **anemia** (from lack of RBCs, causing fatigue), **thrombocytopenia** (from lack of platelets, causing bleeding/bruising), and **neutropenia** (from lack of *functional* neutrophils, leading to severe infections, even though the total WBC count may be high).

Chronic Myeloid Leukemia (CML

Chronic Myeloid Leukemia (CML) is a myeloproliferative neoplasm. The pathophysiology is elegant and specific: it is driven by a single, hallmark genetic mutation known as the **Philadelphia chromosome**. This is a translocation between chromosomes 9 and 22, t(9;22), which creates a new, fused "fusion gene" called **BCR-ABL**. This new gene produces a new, constitutively "on" tyrosine kinase enzyme. This BCR-ABL kinase acts as a powerful, non-stop "gas pedal" for the myeloid cell line, causing the massive overproduction of *all* mature and maturing myeloid cells, especially neutrophils. This results in a spectacularly high WBC count (often > 100,000) and splenomegaly (as the spleen fills with these excess cells).

Diagnosis and Classification

Diagnosis is made by peripheral blood smear and confirmed by bone marrow aspiration and biopsy, which includes cytogenetics, flow cytometry, and molecular studies.

1. **Acute Leukemias (AML, ALL):** Characterized by > 20% blasts (immature cells) in the bone marrow and a rapid, fulminant course with cytopenias.
2. **Chronic Leukemias (CML, CLL):** Characterized by an overproduction of mature-appearing but dysfunctional cells and a more indolent course.

Differential Diagnosis

The differential for acute leukemia includes aplastic anemia or severe viral infections (e.g., EBV, HIV) which can also cause profound pancytopenia. The differential for CML (high WBC with mature neutrophils) includes a "leukemoid reaction" (a benign response to severe infection or inflammation). The differential for CLL (high lymphocyte count) includes other lymphoproliferative disorders.

Treatment Algorithm

- **Acute Myeloid Leukemia (AML):** AML (except Acute Promyelocytic Leukemia) is a medical emergency. The algorithm is emergent induction chemotherapy, most commonly the "7+3" regimen (7 days of cytarabine and 3 days of an anthracycline). The goal is to achieve remission. This is followed by a consolidation algorithm (e.g., high-dose cytarabine) or allogeneic stem cell transplant based on risk stratification (cytogenetics, molecular markers).
- **Acute Promyelocytic Leukemia (APL):** This AML subtype has a unique algorithm and is also an emergency due to high risk of DIC. The algorithm is immediate initiation of All-Trans-Retinoic Acid (ATRA) and arsenic trioxide (ATO), even on suspicion, which induces differentiation of the malignant promyelocytes.
- **Acute Lymphoblastic Leukemia (ALL):** The algorithm is also emergent induction chemotherapy, but with a different, multi-agent regimen (e.g., vincristine, prednisone, anthracycline, asparaginase). A critical component is CNS prophylaxis (intrathecal chemotherapy), as ALL commonly relapses in the CNS.
- **Chronic Myeloid Leukemia (CML):** The algorithm for CML was revolutionized by targeted therapy. The first-line treatment is an oral Tyrosine Kinase Inhibitor (TKI) that targets the *BCR-ABL* fusion protein, such as Imatinib. The algorithm then involves routine molecular monitoring (quantitative PCR for *BCR-ABL* transcripts) to ensure treatment milestones are met.
- **Chronic Lymphocytic Leukemia (CLL):** The algorithm for asymptomatic, early-stage CLL is "watch and wait," as treatment does not improve survival. Treatment is initiated only for "active disease" (e.g., significant B symptoms, progressive cytopenias, massive lymphadenopathy). The modern first-line algorithm involves oral targeted agents, such as a BTK inhibitor (e.g., ibrutinib, acalabrutinib) or a BCL-2 inhibitor (venetoclax).