Hematology In General Practice

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Today

- Iron Deficiency Anemia
- B12 Deficiency
- Approach to Leukocytosis
- Approach to Lymphadenopathy

What is Anemia?

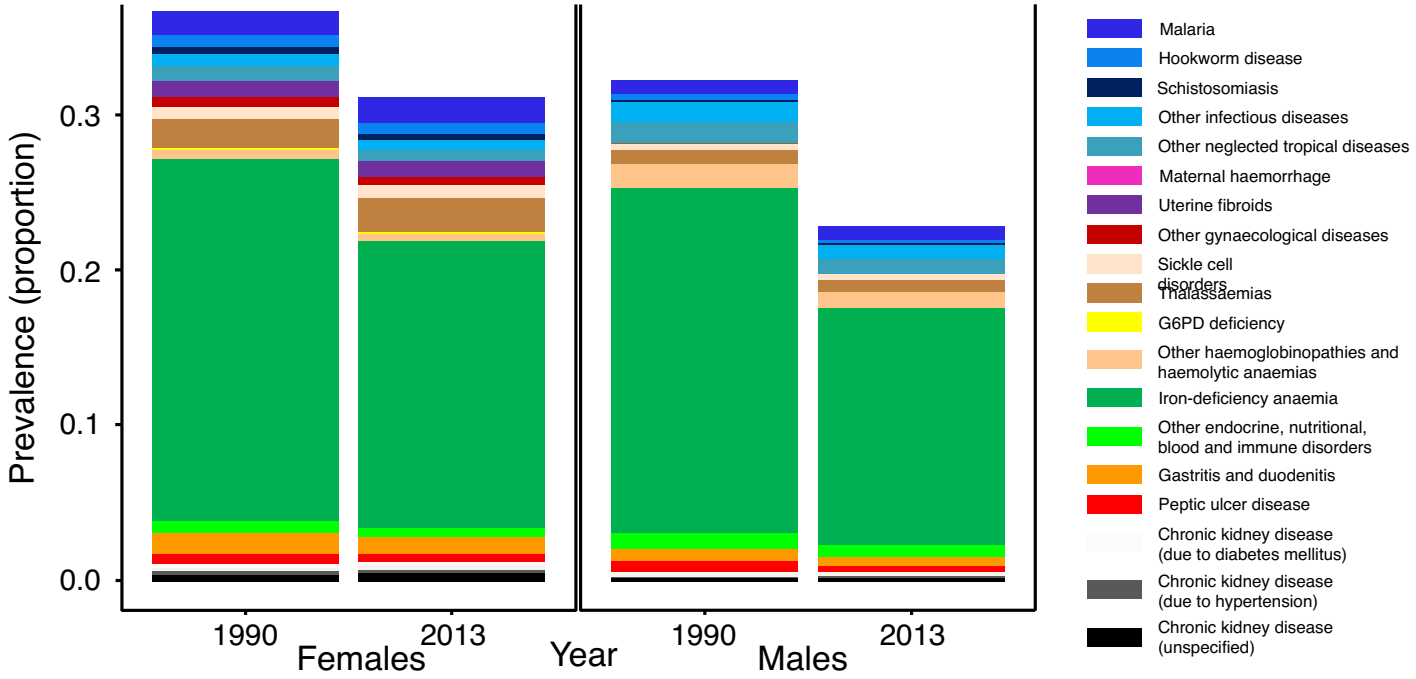
- Anemia is defined by reduction in Hg Concentration, Hct Concentration or RBC count
- Or defined as 2 standard deviations below the mean
- WHO criteria is Hg < 13 in men and Hg < 12 in women

The World Health Organization Defines The Severity of Anemia Based on Hemoglobin Levels

Population	Non-anemia (g/dL)	Mild anemia (g/dL)	Moderate anemia (g/dL)	Severe anemi (g/dL)
Children ½ to 5 years	11.0 or higher	10.0-10.9	7.0-9.9	lower than 7.0
Children 5 to 11 years	11.5 or higher	11.0-11.4	8.0-10.9	lower than 8.0
Children 12 to 14 years	12.0 or higher	11.0-11.9	8.0-10.9	lower than 8.0
Non-pregnant women (15 years of age and above)	12.0 or higher	11.0-11.9	8.0-10.9	lower than 8.0
Pregnant women	11.0 or higher	10.0-10.9	7.0-9.9	lower than 7.0
Men (15 years of age and above)	13.0 or higher	11.0-12.9	8.0-10.9	lower than 8.0

Prevalence of anaemia

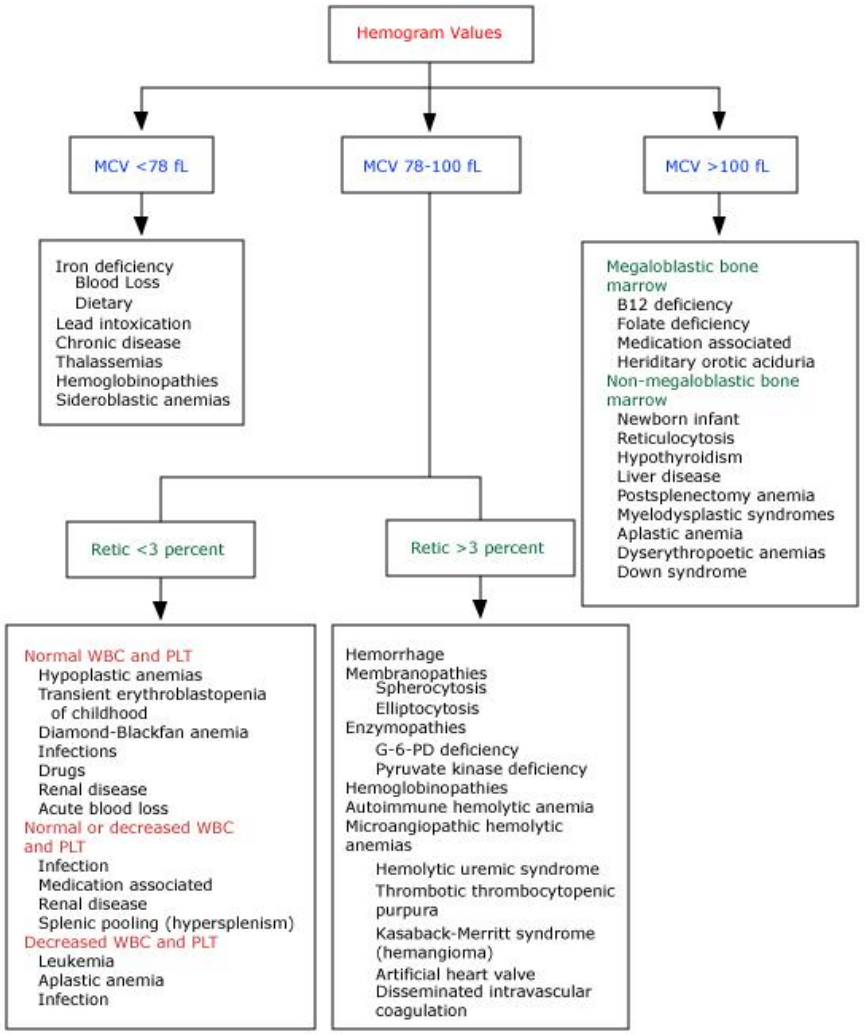
1. Iron-deficiency is the global #1 cause of anaemia and also #1 in many regions
2. Tropical infections, inherited blood disorders, chronic kidney disease, digestive diseases, and gynaecological disorders also commonly cause anaemia
3. Most causes are more common amongst females



GBD 2013 Mortality and Causes of Death Collaborators. *Lancet* 2015;385:117–171

Kinetic Approach

- Decreased RBC production
  - Lack of nutrients (B12, folate, iron)
  - Bone Marrow Disorder
  - Bone Marrow Suppression
- Increased RBC destruction
  - Inherited and Acquired Hemolytic Anemias
- Blood Loss


Hemogram Values
MCV <78 fL
MCV 78-100 fL
MCV >100 fL
Iron deficiency
Blood Loss
Dietary
Lead intoxication
Chronic disease
Thalassemias
Hemoglobinopathies
Sideroblastic anemias
Megaloblastic bone marrow
B12 deficiency
Folate deficiency
Medication associated
Heriditary orotic aciduria
Non-megaloblastic bone marrow
Newborn infant
Reticulocytosis
Hypothyroidism
Liver disease
Postsplenectomy anemia
Myelodysplastic syndromes
Aplastic anemia
Dyserythropoetic anemias
Down syndrome
Retic <3 percent
Retic >3 percent
Normal WBC and PLT
Hypoplastic anemias
Transient erythroblastopenia of childhood
Diamond-Blackfan anemia
Infections
Drugs
Renal disease
Acute blood loss
Normal or decreased WBC and PLT
Infection
Medication associated
Renal disease
Splenic pooling (hypersplenism)
Decreased WBC and PLT
Leukemia
Aplastic anemia
Infection
Hemorrhage
Membranopathies
Spherocytosis
Elliptocytosis
Enzymopathies
G-6-PD deficiency
Pyruvate kinase deficiency
Hemoglobinopathies
Autoimmune hemolytic anemia
Microangiopathic hemolytic anemias
Hemolytic uremic syndrome
Thrombotic thrombocytopenic purpura
Kasaback-Merritt syndrome (hemangioma)
Artificial heart valve
Disseminated intravascular coagulation

Iron Deficiency

Introduction

- More than a quarter of the world's population is anemic
- one-half of this burden is a result of iron deficiency anemia
- Most prevalent among preschool children and women.
- The prevention and treatment of iron deficiency is obviously a major public health goal, especially in low- and middle-income countries.
- Successful overall management of the patient with iron deficiency anemia requires an attempt to identify and treat the underlying cause(s) of the iron deficiency

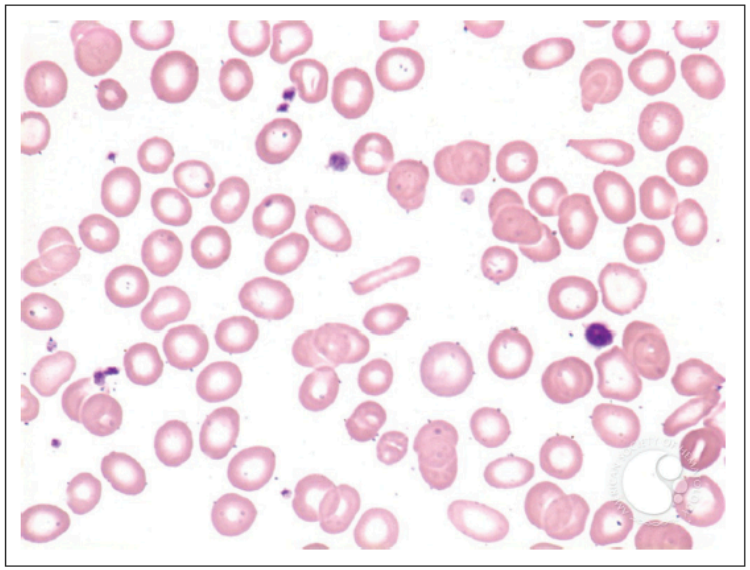
Stages of ID

- **Three stages of iron deficiency have been described.**
  - The initial stage, iron depletion, occurs when stored iron in the bone marrow diminishes due to insufficient supply of iron.
  - The second stage, iron deficiency, during which storage levels become substantially reduced and hemoglobin synthesis begins to be affected.
  - The final stage, iron deficiency anemia, develops when iron stores are insufficient to maintain hemoglobin production.
- **This advanced stage will be reflected in low hemoglobin and hematocrit values**

Iron Deficiency Anemia

Peripheral Blood Film

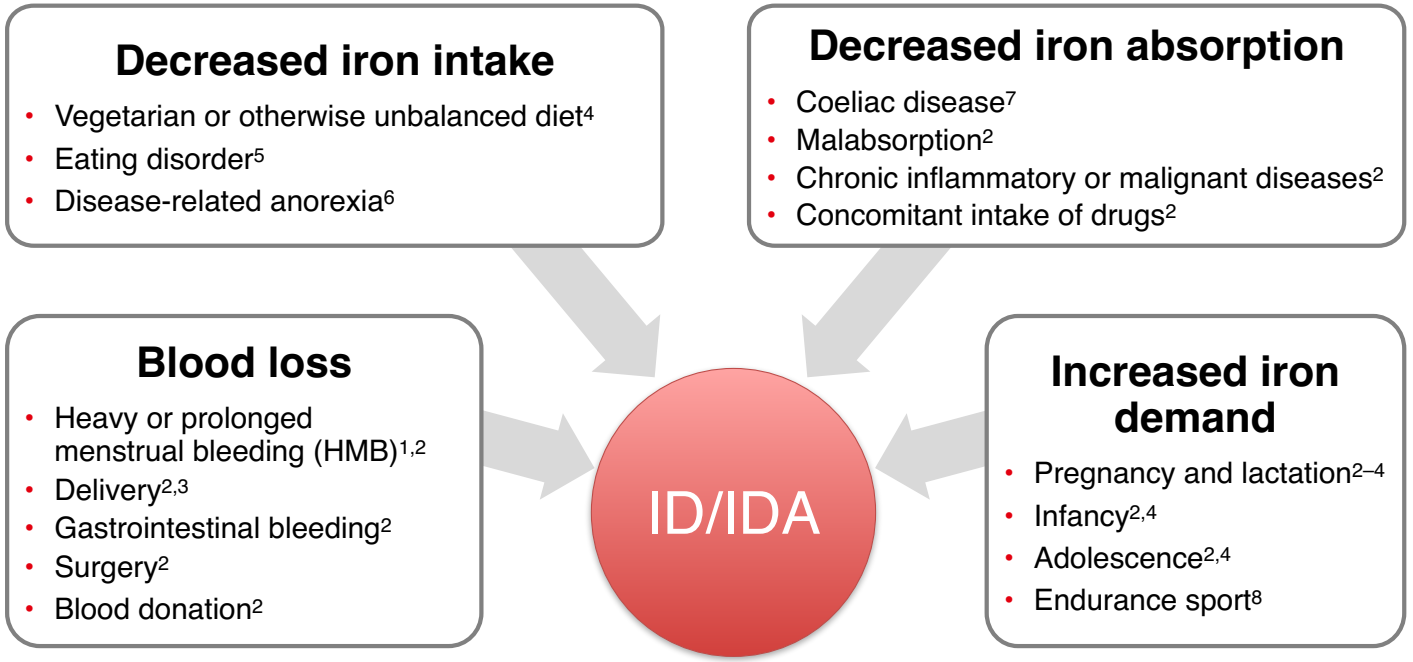
- Microcytic and hypochromic RBCs
- Anisopoikilocytosis
- bizarrely shaped erythrocytes, including characteristic cigar- or pencil-shaped cells
- Target cells can be seen but are infrequent
- +/- Thrombocytosis is common



Red Cell Parameters in IDA and Thalassemia

Parameter	IDA	Thalassemia trait
RBC	Low	Normal or High
Hb	Low	Low or Normal
MCV	Low	Low
MCH	Low	Low
RDW	High	Normal

Most Common Causes of ID/IDA



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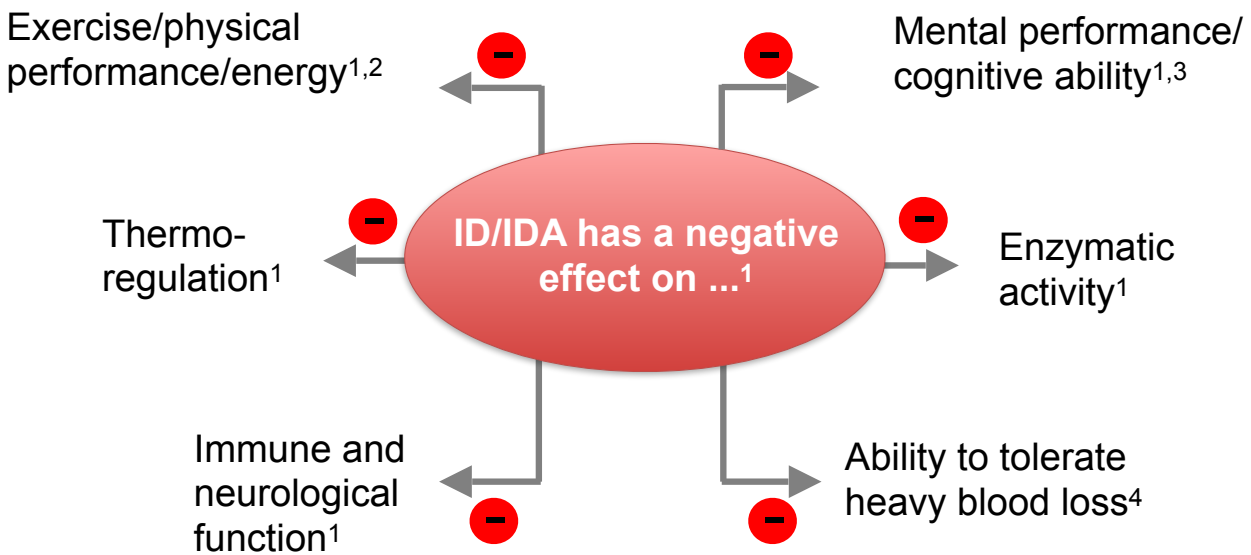
Factors that Effect Dietary Iron Absorption

Inhibit absorption	Enhance absorption
Calcium-rich foods	Ascorbic acid
Tannins in tea and coffee	Heme iron
Phytates in cereals	Germination and fermentation of legumes (removephytates)
	Ferrous iron (Fe^{2+})

General consequences of ID/IDA



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Treatment Issues

- **Oral iron therapy**
  - Because oral iron is inexpensive and effective when taken as prescribed, it is considered front line therapy.
  - There are numerous conditions, however, for which oral iron is either poorly tolerated or ineffective. As examples:
    - Gastrointestinal side effects are extremely common and may result in poor adherence to therapy.
    - Various malabsorptive states may be associated with an inability to absorb iron optimally.
  - Treatment with oral iron may take as long as six to eight weeks in order to fully ameliorate the anemia, and as long as six months in order to replete iron stores.

Oral Iron Therapy

	Oral Iron Therapy Recommendations [15, 23]
Indication	• Mild to moderate anemia • Clinically inactive inflammatory bowel disease
Dosage	• Adults: 120 mg of elemental iron per day (in two or three divided doses) • ≤ 100 mg elemental iron daily in inflammatory bowel disease • Premature neonates: 2 to 4 mg of elemental iron per kg per day every 12 to 24 hours with a maximum of 15 mg daily • Children with mild to moderate anemia: 3 to 6 mg of elemental iron per kg per day every 12 to 24 hours with a maximum of 60 mg daily • Children with severe anemia: 4 to 6 mg of elemental iron per kg per day every 12 to 24 hours with a maximum of 60 mg daily
Duration	• Until adequate response: expected Hb increase of 1 g/dL per week • Continue for 3 to 6 months after Hb is normalized to ensure iron store repletion

Oral Iron Therapy

	Formulation	Elemental iron
Bivalent iron salts		
Ferrous ascorbate	275-mg tablet	38 mg
Ferrous fumarate	325-mg tablet	106 mg
Ferrous gluconate	300-mg tablet	38 mg
Ferrous glycine sulphate	275-mg tablet	47 mg
Ferrous sulfate	325-mg tablet	65 mg
Trivalent iron salts		
Iron protein succinylate	800-mg tablet	40 mg
Iron polymaltose complex	370-mg tablet	100 mg

Expected Response

- An effective regimen for the treatment of uncomplicated iron deficiency with oral iron preparations should lead to the following responses:
  - If pagophagia (pica for ice) or restless leg syndrome is present, it often disappears almost as soon as oral or intravenous iron therapy is begun, well before there are any observable hematologic changes such as reticulocyte response.
  - The patient will note an improved feeling of well-being within the first few days of treatment.
  - In patients with moderate to severe anemia, a modest reticulocytosis will be seen, maximal in approximately 7 to 10 days.
  - Patients with mild anemia may have little or no reticulocytosis.

Expected Response

- An effective regimen for the treatment of uncomplicated iron deficiency with oral iron preparations should lead to the following responses:
  - The hemoglobin concentration will rise slowly, usually beginning after approximately one to two weeks of treatment, and will rise approximately 2 g/dL over the ensuing three weeks.
  - The hemoglobin deficit should be halved by approximately one month, and the hemoglobin level should return to normal by six to eight weeks.

Causes for failure to respond to oral iron therapy

Coexisting disease interfering with marrow response
Infection
Inflammatory disorder (eg, rheumatoid arthritis)
Concomitant malignancy
Coexisting folic acid and/or vitamin B12 deficiency
Bone marrow suppression from another cause
Diagnosis is incorrect, possible correct diagnoses include
Thalassemia
Lead poisoning
Anemia of chronic disease (anemia of chronic inflammation)
Copper deficiency (zinc toxicity)
Myelodysplastic syndrome/refractory sideroblastic anemia
Patient is not taking the medication
Prescription has not been filled
Prescription has been filled but patient is no longer taking the medication
Medication is being taken but is not being absorbed
Rapid intestinal transport bypasses area of maximum absorption
Enteric coated product: coating is not dissolving
Patient has malabsorption for iron (eg, sprue, atrophic gastritis)
Medication taken in association with an agent interfering with absorption (eg, antacids, tetracycline, tea)
Continued blood loss or need in excess of iron dose ingested
Cause of blood loss treatable (eg, bleeding peptic ulcer)
Initiate appropriate treatment
Cause of blood loss not treatable (eg, Osler Weber Rendu disease) or need cannot be met by oral iron preparation (eg, renal failure responding to erythropoietin)
Switch patient to parenteral iron product

Assumes that original diagnosis was iron deficiency anemia with hypochromic microcytic red blood cells, low ferritin, and low tranferrin saturation.

Side Effects

- Estimates are that up to 50 percent of patients complain of nausea, constipation, diarrhea, epigastric distress and/or vomiting after taking various oral iron preparations.
- There are a number of treatment options for such patients:
  - The patient may take an iron preparation containing a smaller dose of elemental iron (eg, switching from ferrous sulfate to ferrous gluconate), or may switch from a tablet to a liquid preparation, the dose of which (44 mg elemental iron per 5 mL) can be easily titrated by the patient
  - The patient may slowly increase the dose from one tablet per day to the recommended three times per day, as tolerated.
  - The iron may be taken with meals, although this will decrease absorption somewhat.

Parenteral Iron Therapy

	Parenteral Iron Therapy Recommendations

Indication	• Intolerance of or non-compliance with oral iron preparations
	• Malabsorption
	  • Celiac disease with insufficient absorption
	  • History of gastrectomy, gastrojejunostomy, bariatric surgery
	  • Clinically active inflammatory bowel disease
	• Unresolved bleeding
	• End-stage renal disease anemia treated with erythropoietin
	• Moderate or severe anemia with significant symptoms

Dosage	• 1,000-2,000 mg elemental iron based on the body size and anemia severity
Follow up	• Monitor Hb and iron stores after the first month of treatment

Intravenous iron preparations

Drug	Trade name	Maximum approved dose (mg elemental iron)	Total-dose infusion possible	Premedication	Test dose	Elemental iron concentration (mg/mL)	Preservative
Iron dextran (high molecular weight)*	Dexferrum	100	Yes	TDI only	Required	50	None
Iron dextran (low molecular weight)	INFeD	100	Yes	TDI only	Required	50	None
Ferric gluconate	Ferrlecit	125	No	No	Recommended if drug allergies present	12.5	Benzyl alcohol
Iron sucrose	Venofer	200 to 300	No	No	Recommended if drug allergies present	20	None
Ferumoxytol	Feraheme	510	No	No	No	30	None
Iron isomaltoside•	Monofer (not available in US)	20 mg/kg	Yes	No	No	100	None
Ferric carboxymaltose•	Ferinject (not available in US)	20 mg/kg (maximum 1000 mg)	No	No	No	50	None

* The use of high molecular weight iron dextran preparations, rather than low molecular weight iron dextran preparations, is not recommended, due to a higher incidence of adverse reactions.
• Available in certain European countries. Common European trade name shown.

Parental Iron Therapy Calculation

		Body weights												
Hemoglobin level		30kg	35kg	40kg	45kg	50kg	55kg	60kg	65kg	70kg	75kg	80kg	85kg	90kg
Hb =60g/l	AMP	9.5	12.5	13.5	15	16	17	18	19	20	21	22.5	23.5	24.5
Hb =75g/l	AMP	8.5	11.5	12	13	14	15	16	16.5	17.5	18.5	19.5	20.5	21.5
Hb =90g/l	AMP	7.5	10	11	11.5	12	13	13.5	14.5	15	16	16.5	17	18
Hb =105g/l	AMP	6.5	9	9.5	10	10.5	11	11.5	12	12.5	13	13.5	14	14.5

Hemoglobin (g/dL)	Body weight < 70 kg	Body weight > or = 70 kg
10-12 (women) 10-13 (men)	1,000 mg	1,500 mg
7-10 (women)	1,500 mg	2,000 mg

Duration Of Treatment

- Some physicians stop treatment with iron when the hemoglobin level becomes normal, and Ferritin > 40-60 mmol. And the cause of anemia is gone.
- In any inflammatory condition Ferritin should be above >100 mmol
- For hair loss in Female Ferritin level should be above >70 mmol
- Others believe that it is wise to treat for at least three to six months after the hemoglobin has normalized, in order to replenish iron stores.

Point to Remember

IDA Diagnosis
All patient with microcytic anemia should have their ferritin level determined. In populations with a high frequency of alpha- and beta-thalassemia trait, many female patients have combined IDA and thalassemia trait or ID and thalassemia trait. In addition to a ferritin test, such patients could benefit from a hemoglobin analysis (e.g., electrophoresis). In patients with normal MCV, a ferritin test should be ordered in patients with severe anemia and in anemic patients with chronic inflammatory conditions.

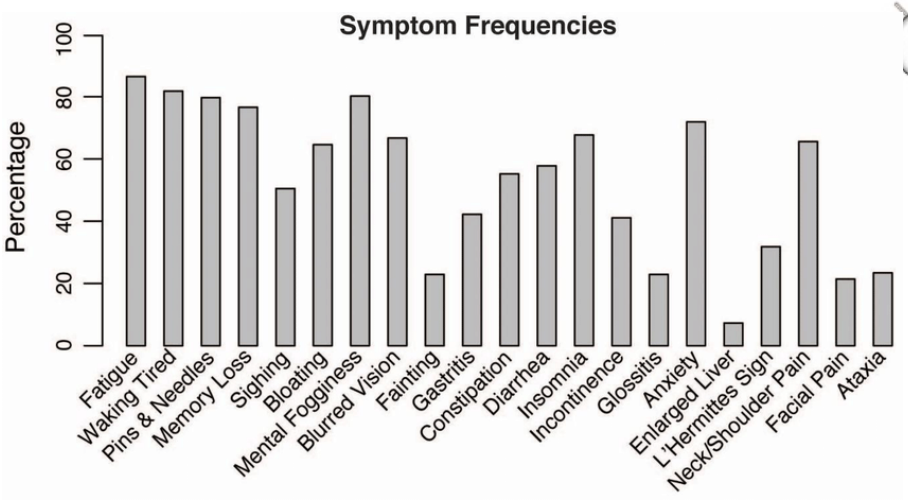
IDA screening-
The following at-risk groups should be screened for IDA: women of childbearing age, pregnant women with a history of multiple pregnancies, women undergoing pre-marital screening, men and women who had weight-reduction surgery, and one-year old children with risk factors for IDA.

Oral iron therapy-
Oral iron is an inexpensive and effective way to correct IDA and replete iron stores. An adequate response is an increase in Hb level of at least 1 g/dL per week. Therapy should be continued for 3 to 6 months after Hb level is normalized to ensure repletion of iron stores. In case of intolerance or non-compliance with the treatment, parenteral iron therapy should be considered.

Parenteral iron therapy-
Intravenous iron therapy should be used in patients who do not tolerate or improve with oral iron therapy, those with impaired iron absorption, pregnant women with severe anemia, women with anemia and heavy bleeding, and those with chronic renal failure on hemodialysis. Most patients require 1,000 – 2,000 mg of elemental iron for the correction of anemia.

Vitamin B12 Deficiency

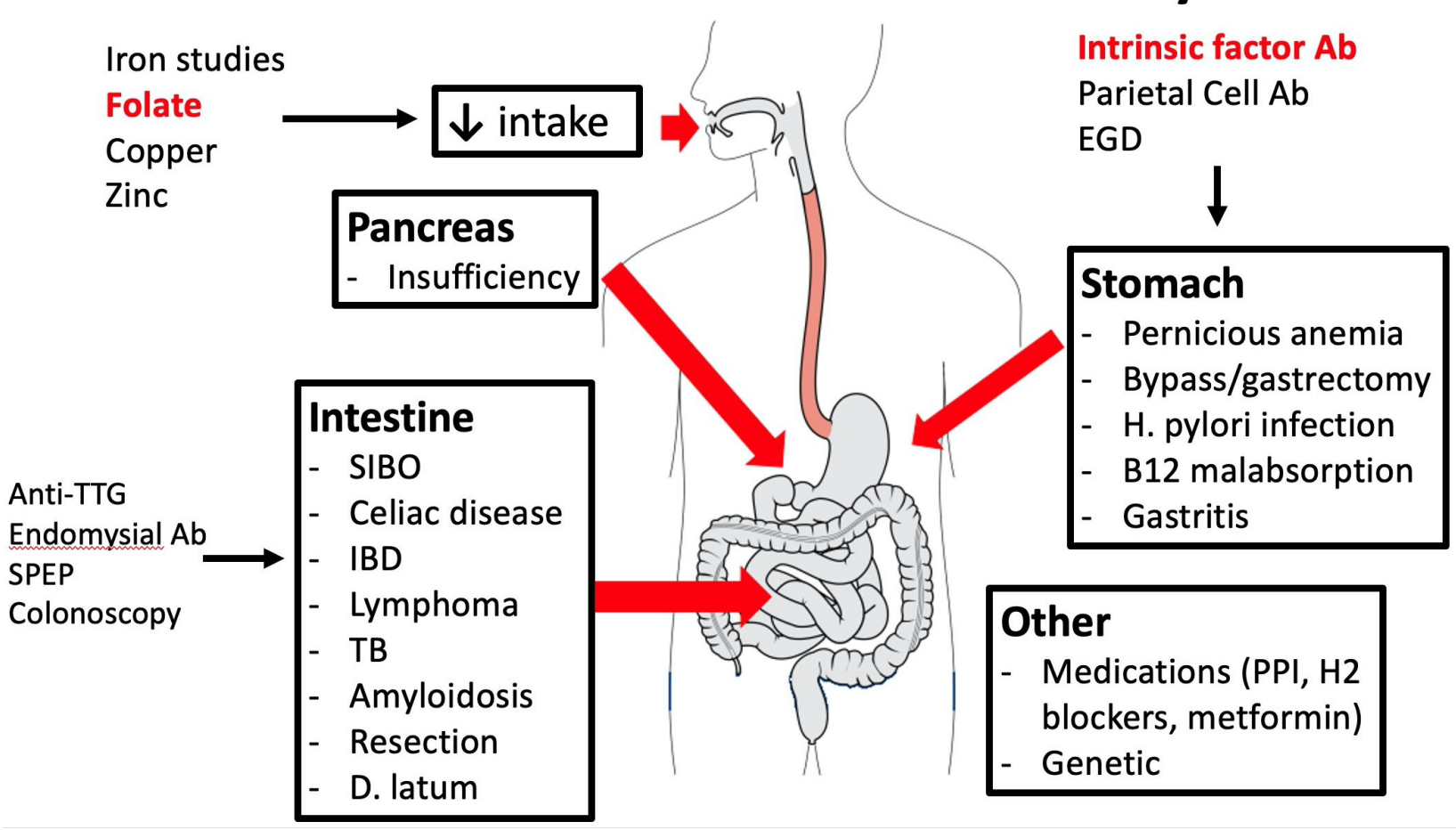
Clinical Presentation



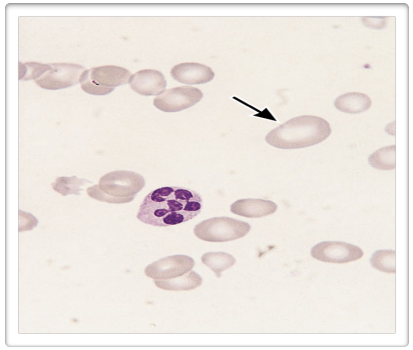
Deficiency manifestation

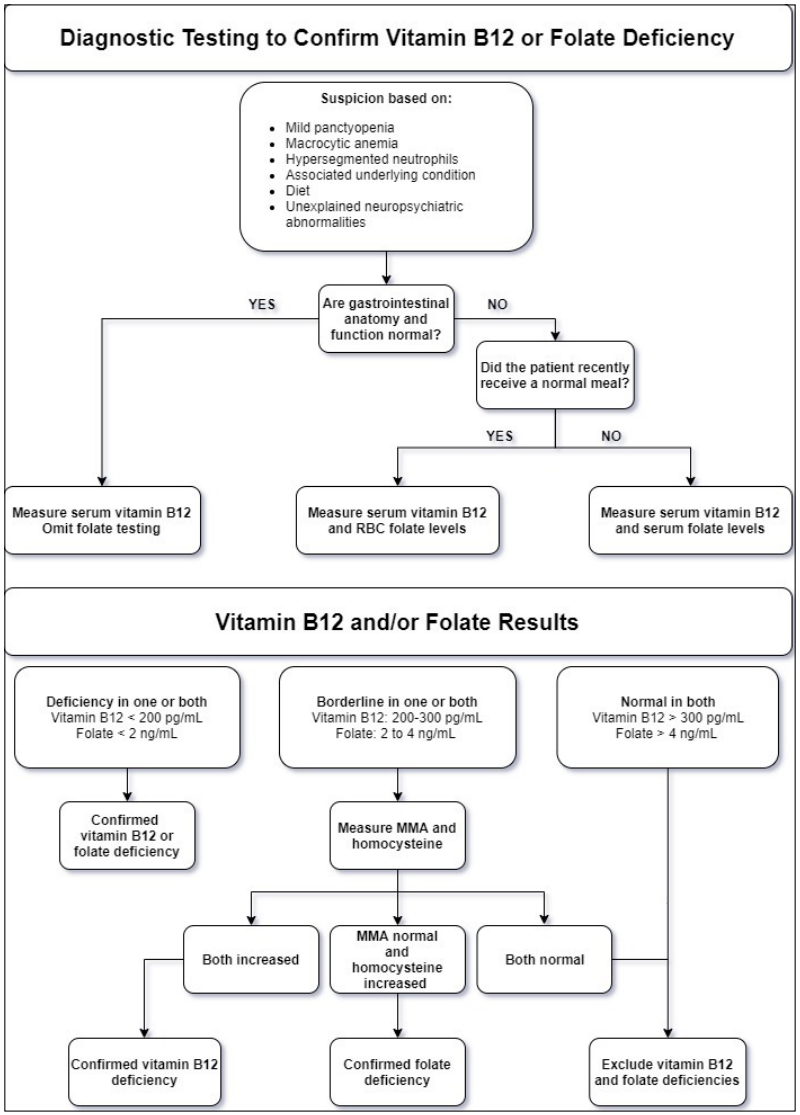
- Blood: pancytopenia, macrocytosis, hypersegmented neutrophils
- Neurological,: myelopathy, paresthesia, loss proprioception, ataxia, spasticity or autonomic dysfunction
- Tongue: glossitis (red beefy tongue), taste impairment.
- Bone marrow: hyperplasia, megaloblastic features
- Brain : impaired cognition, depression, psychosis, delusion, irritability
- Cardiac: cardiomyopathy
- Reproduction: infertility

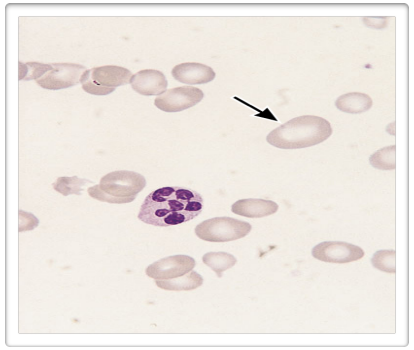
Causes of Vitamin B12 Deficiency



Investigation







Treatment

- Treat underlying cause
- Typical treatment is 1mg/day IM for 1 weeks, then 1 mg/week for 4 weeks, followed by 1mg/month thereafter
- Recent studies suggest that supplementation with oral Vit B12 may be a safe and effective treatment in some patients even when intrinsic factor is low

Approach to Leukocytosis

Hematology consultation for leukocytosis: etiologic considerations

Neutrophilia	Monocytosis	Eosinophilia	Lymphocytosis
Eclampsia	Pregnancy	Allergic rhinitis	Mononucleosis syndrome
Thyrotoxicosis	Tuberculosis	Asthma	Epstein-Barr virus
Hypercortisolism	Syphilis	Tissue-invasive parasite	Cytomegalovirus
Crohn disease	Endocarditis	Bronchopulmonary aspergillosis	Primary HIV
Ulcerative colitis	Sarcoidosis	Coccidioidal infection	Viral illness
Inflammatory/rheumatologic disease	Systemic lupus erythematosus	HIV	Pertussis
	Asplenia	Immunodeficiency	*Bartonella henselae* (cat scratch disease)
Sweet's syndrome	Corticosteroids	Vasculitides	
Granulomatous infections		Drug reaction	Toxoplasmosis
Bronchiectasis		Adrenal insufficiency	Babesiosis
Occult malignancy		Occult malignancy	Drug reaction
Trauma/burn		Pulmonary syndromes	Reactive large granular lymphocytosis
Severe stress		Gastrointestinal syndromes	
Panic		Hypereosinophilic syndrome	
Asplenia			
Cigarette smoking			
Tuberculosis			
Chronic hepatitis			
Hereditary neutrophilia			
Corticosteroids			
β-agonists			
Lithium			

HIV = human immunodeficiency virus.

Kahn, M. J. et al. ASH-SAP 2010;2010:27-74

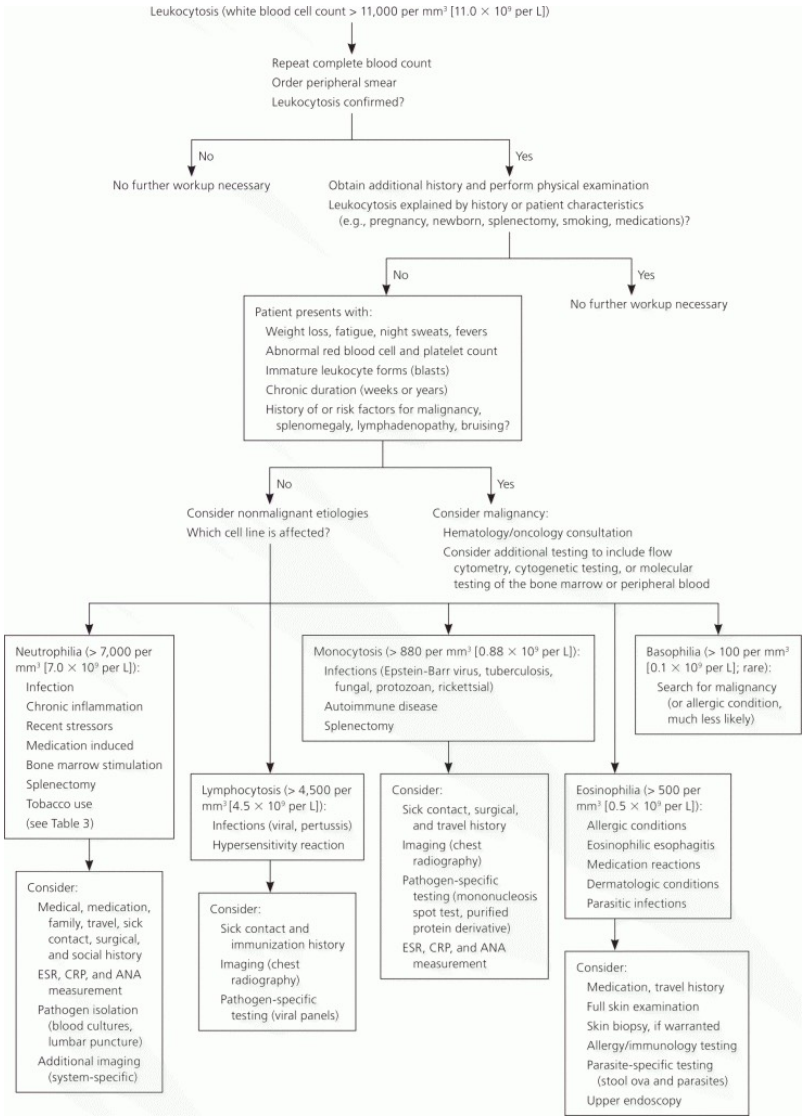
Table 1. Characteristics of Major Subtypes of Leukemia

Subtype	*Description*	*Typical group(s) affected*	*Common presenting features*	*Five-year relative survival rate**
Acute lymphoblastic leukemia	Blast cells on peripheral blood smear or bone marrow aspirate	Children and young adults (53% of new cases occur in persons < 20 years)	Symptoms: fever, lethargy, bleeding, musculoskeletal pain or dysfunction Signs: hepatosplenomegaly and lymphadenopathy	< 50 years: 75% ≥ 50 years: 25%
Acute myelogenous leukemia	Blast cells on peripheral blood smear or bone marrow aspirate; Auer rods on peripheral smear	Adults (accounts for 80% of acute leukemia in adults)	Symptoms: fever, fatigue, weight loss, bleeding or bruising Signs: hepatosplenomegaly and lymphadenopathy (rare)	< 50 years: 55% ≥ 50 years: 14%
Chronic lymphocytic leukemia	Clonal expansion of at least 5,000 B lymphocytes per µL (5.0×10^9 per L) in the peripheral blood	Older adults (85% of new cases occur in persons > 65 years)	Symptoms: 50% of patients are asymptomatic Signs: hepatosplenomegaly and lymphadenopathy	< 50 years: 94% ≥ 50 years: 83%
Chronic myelogenous leukemia	Philadelphia chromosome (*BCR-ABL1* fusion gene)	Adults	Symptoms: 20% of patients are asymptomatic Signs: splenomegaly	< 50 years: 84% ≥ 50 years: 48%

**—Relative survival compares a cohort of leukemia survivors (diagnosis made in 2005) to a similar cohort of cancer-free individuals.*

Information from references 1, and 9 through 18.

Approach Algorithm



ApproachTo Lymphadenopathy

Causes of Lymphadenopathy

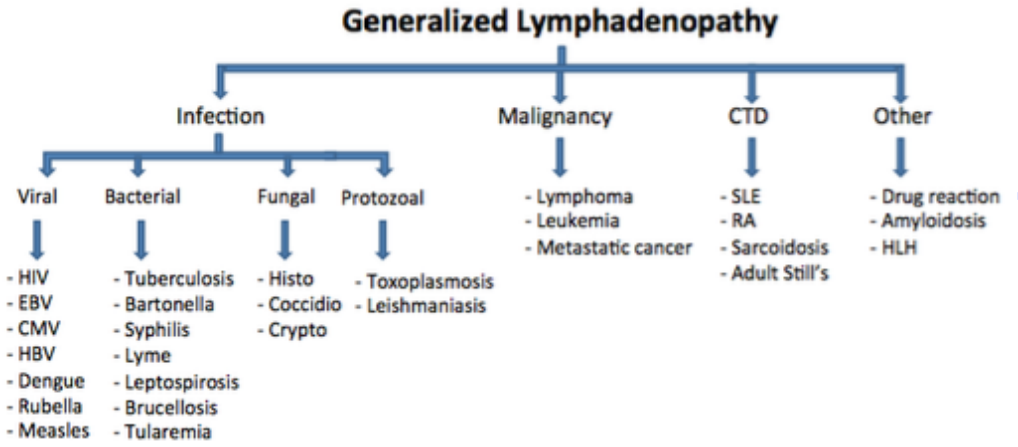


Table 2. Drugs Linked to Lymphadenopathy
Allopurinol
Aspirin
Atenolol
Captopril
Carbamazepine
Cephalosporins
Gold
Hydralazine
Indomethacin and other nonsteroidal anti-inflammatory drugs
Isoniazid
Penicillins
Phenytoin
Primidone
Pyrimethamine
Quinidine
Sulfonamides
Tetracyclines

Clues That might Help in the Diagnosis

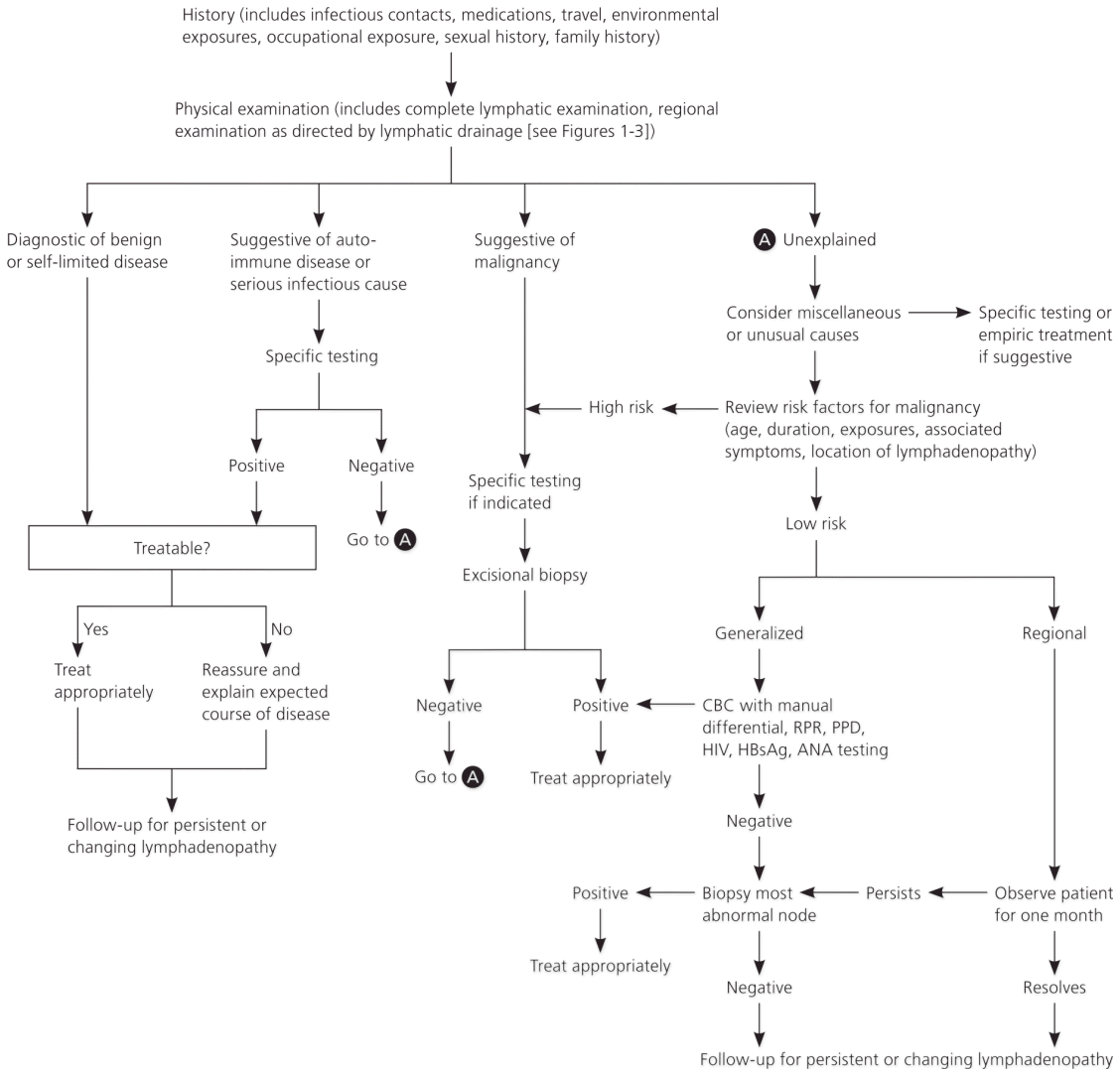
Table 2. Clues and Initial Testing to Determine the Cause of Lymphadenopathy

Historical clues	*Suggested diagnoses*	*Initial testing*
Fever, night sweats, weight loss, or node located in supraclavicular, popliteal, or iliac region, bruising, splenomegaly	Leukemia, lymphoma, solid tumor metastasis	CBC, nodal biopsy or bone marrow biopsy; imaging with ultrasonography or computed tomography may be considered but should not delay referral for biopsy
Fever, chills, malaise, sore throat, nausea, vomiting, diarrhea; no other red flag symptoms	Bacterial or viral pharyngitis, hepatitis, influenza, mononucleosis, tuberculosis (if exposed), rubella	Limited illnesses may not require any additional testing; depending on clinical assessment, consider CBC, monospot test, liver function tests, cultures, and disease-specific serologies as needed
High-risk sexual behavior	Chancroid, HIV infection, lymphogranuloma venereum, syphilis	HIV-1/HIV-2 immunoassay, rapid plasma reagin, culture of lesions, nucleic acid amplification for chlamydia, migration inhibitory factor test
Animal or food contact		
Cats	Cat-scratch disease (*Bartonella*)	Serology and polymerase chain reaction
	Toxoplasmosis	Serology
Rabbits, or sheep or cattle wool, hair, or hides	Anthrax	Per CDC guidelines
	Brucellosis	Serology and polymerase chain reaction
	Tularemia	Blood culture and serology
Undercooked meat	Anthrax	Per CDC guidelines
	Brucellosis	Serology and polymerase chain reaction
	Toxoplasmosis	Serology
Recent travel, insect bites	Diagnoses based on endemic region	Serology and testing as indicated by suspected exposure
Arthralgias, rash, joint stiffness, fever, chills, muscle weakness	Rheumatoid arthritis, Sjögren syndrome, dermatomyositis, systemic lupus erythematosus	Antinuclear antibody, anti-doubled-stranded DNA, erythrocyte sedimentation rate, CBC, rheumatoid factor, creatine kinase, electromyography, or muscle biopsy as indicated

CBC = complete blood count; CDC = Centers for Disease Control and Prevention; HIV = human immunodeficiency virus.

Information from reference 2.

Approach Algorithm



Thank You