Hematology for Family Practice
When to treat and when to refer

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Objectives:

1. Identify types of anemia's by analyzing indices, and appropriate tests.
2. Understand manual differential and terminology.
3. Discuss abnormalities in platelets and white cells, and determine appropriate testing.

Objectives continued:

4. Discuss treatment options for hematologic conditions and medication management.

5. Know when to refer.

1. Anemia's and Erythrocytosis

2. Low platelets and High platelets

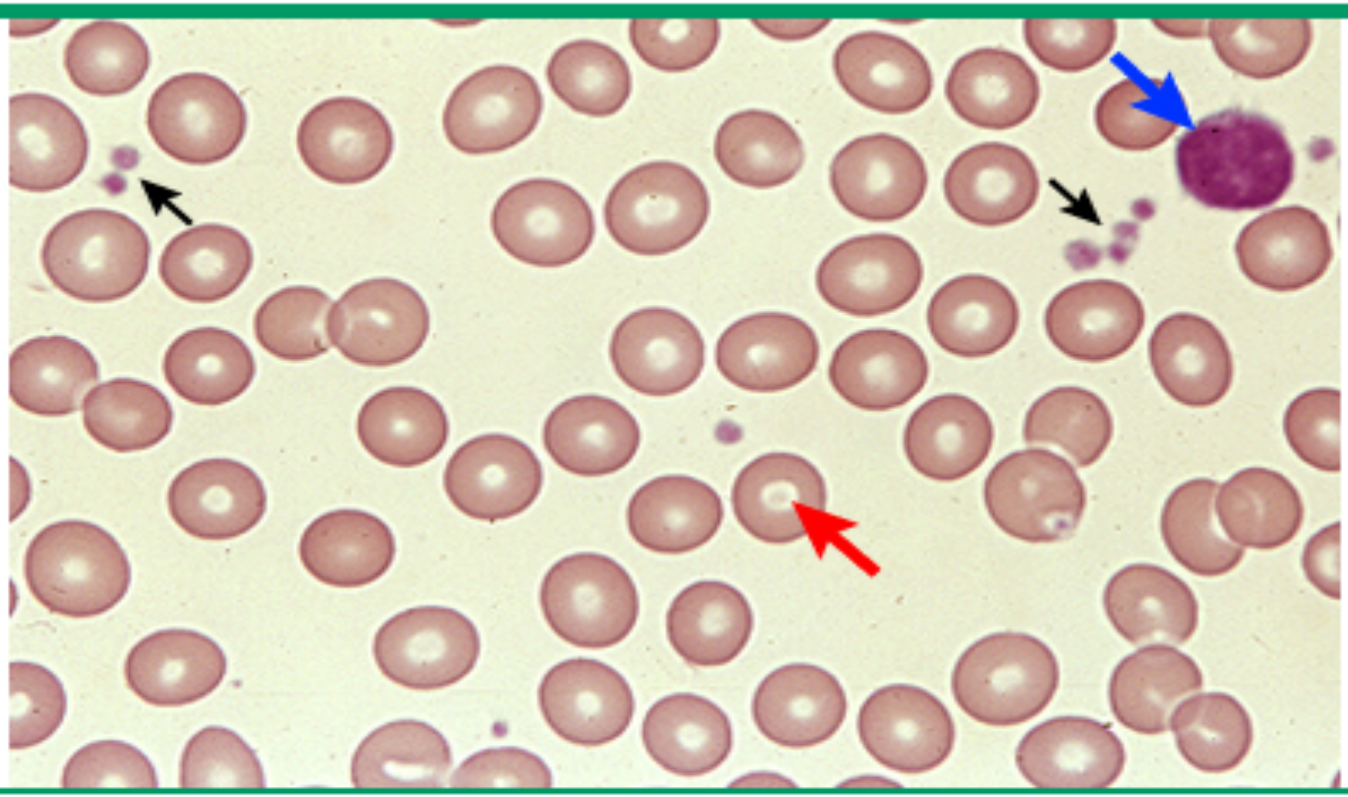
3. Leukopenia's and Leukocytosis

How long do cells live?

- Red blood cells live approximately 120 days.
- Platelets live 8 -11 days.
- White blood cells live about 4 days.

There are millions of RBCs in just one drop of blood. People who live at higher altitudes have more (like in the mountains of Peru). They are produced in the bone marrow of large bones at a rate of 2 million per second. In the minute it took you to read this, you made 120 million of them!

Normal peripheral blood smear



High power view of a normal peripheral blood smear. Several platelets (black arrows) and a normal lymphocyte (blue arrow) can also be seen. The red cells are of relatively uniform size and shape. The diameter of the normal red cell should approximate that of the nucleus of the small lymphocyte; central pallor (red arrow) should equal one-third of its diameter.

Courtesy of Carola von Kapff, SH (ASCP).

Anemia's
And Erythrocytosis

First thing to do with an abnormal CBC is to repeat it and get a smear to pathology, manual diff, and reticulocyte count.

MICROCYTOSIS:

Low MCV (mean corpuscular volume) under 80.
Low MCH (mean corpuscular hemoglobin) under 27.
Low MCHC (mean corpuscular hemoglobin concentration) under 30.

MACROCYTOSIS:

High MCV over 93
High MCH over 33
High MCHC over 37

NORMOCYTIC ANEMIA: NOMAL INDICIES

DEFINITIONS

Reticulocyte: The youngest of the circulating red cells, normally they comprise about 1% of the red cell population. They are **increased** in response to bleeding, or hemolysis, or in response to treatment with B 12, iron, of folic acid. **Decreased** in the presence of a suppressed or otherwise abnormal bone marrow, aplastic anemia, pure red cell aplasia or following chemotherapy.

Nucleated red blood cells: Are NORMOBLASTS. Are not normally seen in peripheral blood. They usually indicate the presence of severe degrees of hemolysis, profound stress, hypoxemia, or myelofibrosis.

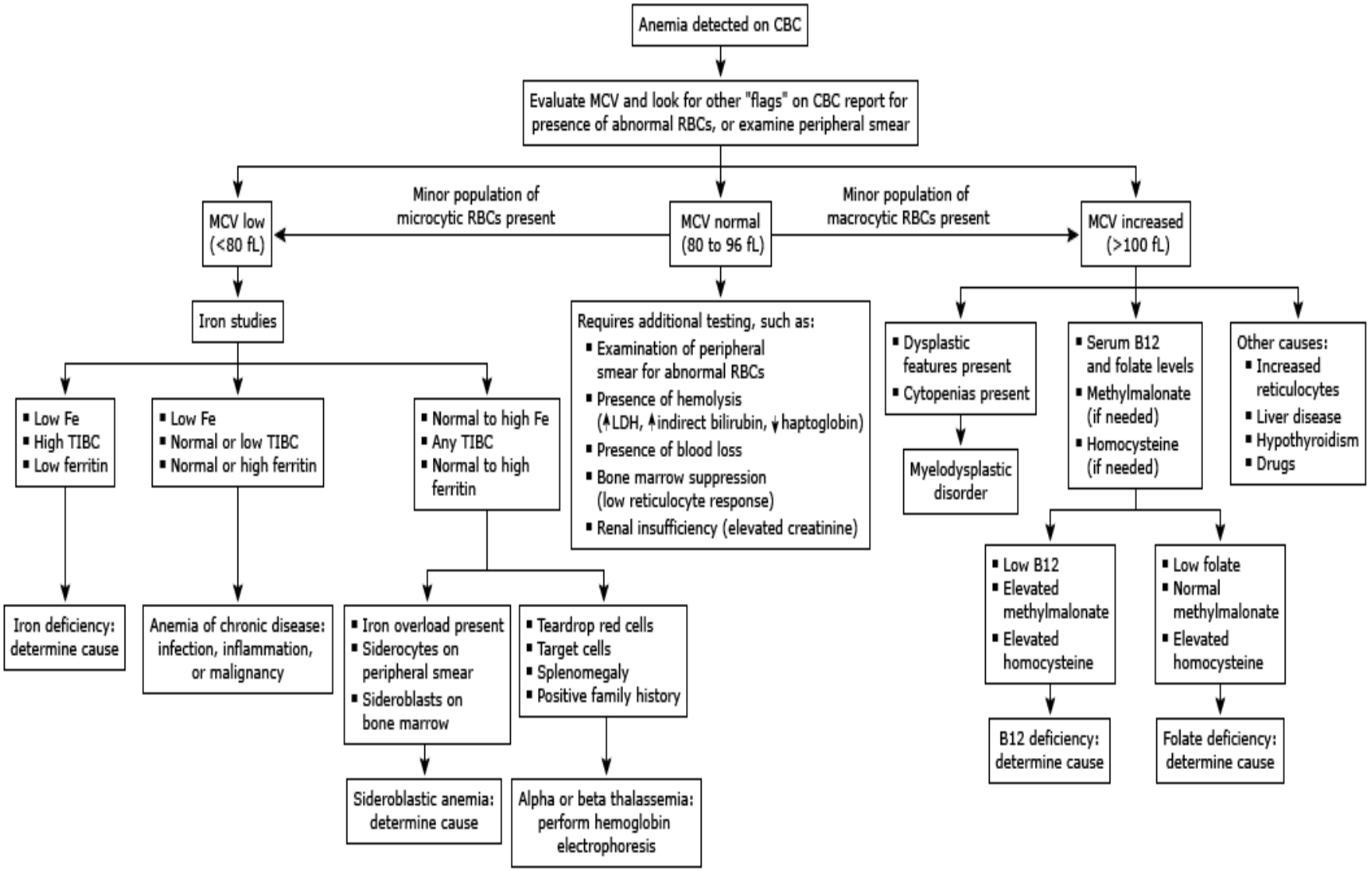
Erythrocyte: A mature red blood cell that contains hemoglobin, confined within a lipid membrane, it's main purpose is to transport oxygen.

Leukocyte: Is a white blood cell. 5 types of leukocytes are classified by the presence or absence of granules in the cytoplasm of the cell. The agranulocytes are lymphocytes and monocytes. The granulocytes are neutrophils, basophils, and eosinophil's.

Leukocytes function as phagocytes of bacteria, fungi, and viruses, detoxifiers of toxic proteins that may result from allergic reactions and cellular injury, and immune system cells.

Platelet: The smallest cells in the body, they are formed in the bone marrow and some are stored in the spleen, they do not contain hemoglobin and are essential for the coagulation of blood and in maintenance of hemostasis.

Evaluation of anemia in the adult according to the mean corpuscular volume



CBC: complete blood count; MCV: mean corpuscular volume; RBCs: red blood cells; Fe: iron; TIBC: total iron-binding capacity (transferrin); LDH: lactate dehydrogenase.

ARUP Consult

Anemia Testing

Click here for topics associated with this algorithm

INDICATIONS FOR TESTING
Fatigue, weakness, pallor, dizziness, fainting

ORDER
- CBC with Platelet Count and Automated Differential (including RBC indices and morphology on manual differential)
- Reticulocytes, Percent & Number

Anemia present on CBC (males Hgb <13g/dL, females Hgb <12g/dL)
AND
Corrected reticulocyte index ≥2.5

No

Classify by RBC indices

Normocytic, normochromic (normal MCV, MCHC) (suggests hypoproliferation)

- Bone marrow disorder (infiltration, aplasia)
- Inflammation
- Autoimmune disease
- Chronic renal disease
- Critical illness
- Chronic endocrine disorders
- Aplastic anemia, pure red cell aplasia

Microcytic, hypochromic (low MCV, MCHC) (suggests maturation defects)

- Iron deficiency
- Chronic disease
- Thalassemia – see Hemoglobinopathies topic
- Sideroblastic anemia
- Lead toxicity

Macrocytic (high MCV) (suggests maturation defects)

- B_{12} deficiency, (less commonly folate deficiency) – see Megaloblastic Anemia Testing Algorithm
- Drug effect
- Excessive alcohol use
- Hypothyroidism
- Myelodysplasia – see Myelodysplastic Syndromes Consult topic

Abnormal peripheral smear

ORDER
- Iron and Iron Binding Capacity
- Ferritin

High TIBC, Low iron, Low ferritin

Iron deficiency anemia

Low/normal TIBC, Normal/high ferritin, Low/normal iron

Suggests
- Inflammation
- Chronic disease
- Thalassemia

If no obvious chronic disease present, consider bone marrow biopsy; for Thalassemia suspicion, consider hemoglobin electrophoresis

Yes

Workup based on smear characteristics

Bone marrow biopsy may be necessary

No

Vitamin B_{12} & Folate

Yes

Fragmented cells on peripheral smear

No

Suggests acute blood loss (eg, hemmorhage)

Yes (suggests hemolysis)

- Metabolic defect (see PNH Consult topic)
- Hemoglobinopathies (eg, sickle cell) – see Hemolytic Anemias Testing Algorithm
- Autoimmune destruction
- Splenic sequestration
- RBC membrane defect – see Hemolytic Anemias Consult topic
- Intravascular hemolysis – see Hemolytic Anemias Consult topic

Abbreviations and Formula

MCV = mean cell volume
MCHC = mean cell hemoglobin concentration
TIBC = total iron binding capacity

Reticulocyte correction for anemia:

$$\text{ReticCount\%} \times \frac{\text{Hgb}}{\text{Htc}} \times \frac{1}{\text{Maturation time correction (use 2\% for most patients)}}$$

Red Cell Morphology and associated Conditions

Auer Rods: observed in Blasts associated with AML

Acanthocytosis (spur cells): Alcoholic cirrhosis, post splenectomy, hemolytic anemia

Anisocytosis: Various types of anemia

Basophilic Stippling: **Fine:** various anemias **Course**: lead toxicity and thalassemias

Bite Cells: Chemical poisoning, G-6PD deficiency, hemolytic anemia

Burr Cells: Myeloproliferative states, heparin therapy, uremia, Chronic renal disease, bleeding, peptic ulcers

Howell-Jolly bodies: Post Splenectomy, megaloblastic and hemolytic anemias

Hypochromia: Iron deficiency and thalassemia

Hypersegmented neutrophils: megaloblastic anemias, pernicious, B12, and folate deficiencies

Heinz bodies: G-6PD deficiency, thalassemia

Pelger-Huet: myelogenous leukemia

Dohle bodies: (toxic granulation are usually seen together) Acute infection, pneumonia, scarlet fever, measles, septicemia, pregnancy, burns

Reactive lymphocytes: (Downey cells) mono, CMV, viral hepatitis, chronic inflammatory disease

Smudge Cells: atypical lymphocytosis, CML

Schistocytosis: cardiac valve disease, DIC, severe burns, uremia

Spherocytes: (helmet cells) hereditary spherocytosis, thermal injuries, immune and hemolytic diseases, TTP, DIC

Rouleaux: multiple myeloma, elevated protein

Target cells: chronic liver disease, iron deficiency, post splenectomy

Tear drop cells: Thalassemias, pernicious anemia, Myeloproliferative disorders.

Band Neutrophils: normal 5-11% increased # = LEFT SHIFT (stress, infection, Myeloproliferative disease)

Basophils: <2% are normal. Allergic reaction, hypothyroid, chronic hemolytic anemia, post splenectomy

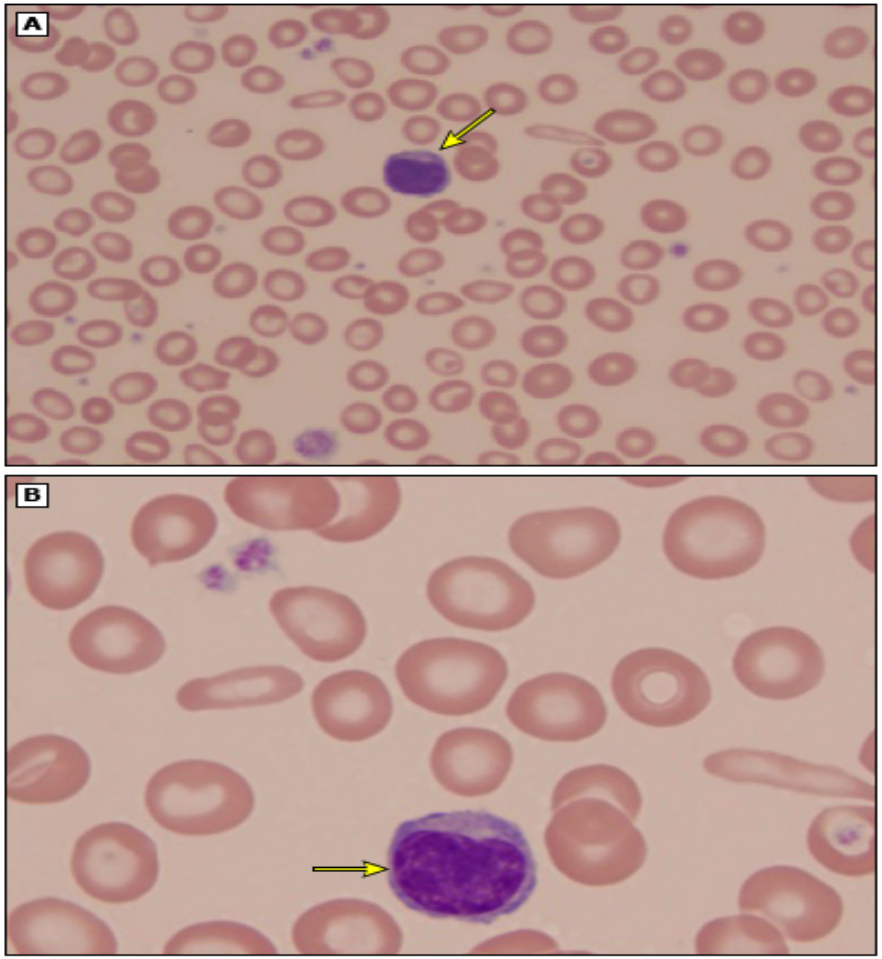
Eosinophils: increased in asthma, hay fever, extensive skin lesions, parasitic infections. Decreased in shock, severe burns, and severe infections.

Metamyelocyte: Myelocytic hyperplasia
Myelocyte: CML, AML
Plasma cells: Not usually seen in peripheral blood. Chronic infections, autoimmune disorders, alcoholic liver disease.
Monocytes: increased in chronic neutropenia, IBD, chronic infection, CMV, TB an can be elevated in AMML.

Evaluating Anemia

Number one reason for microcytic anemia is bleeding, either GU or GI. Ask the right questions. A good physical exam and a good history is essential to your investigation. Don't forget family history.

Microcytic hypochromic red cells in iron deficiency anemia



Peripheral smear at two different magnifications from a patient with iron deficiency shows small (microcytic) red cells with a thin rim of pink hemoglobin (hypochromic); occasional "pencil" shaped cells are also present. Normal red cells are similar in size to the nucleus of a small lymphocyte (arrow) and central pallor should equal about one-third of its diameter; thus, many hypochromic and microcytic cells are present in this smear.

Kindly supplied by Dr. German Pihan, Department of Pathology, Beth Israel Deaconess Medical Center, Boston, MA.

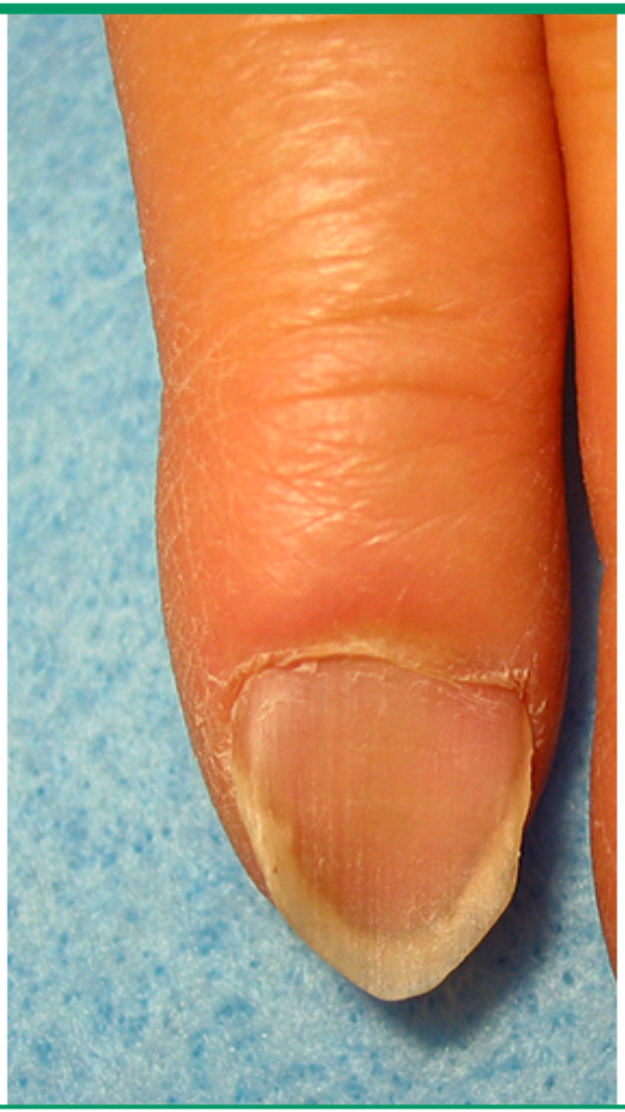
Laboratory findings in iron deficiency anemia, thalassemia, and anemia of chronic disease/inflammation

Test	Iron deficiency anemia	Alpha or beta thalassemia	Anemia of chronic disease/inflammation
Complete blood count			
Hemoglobin	Decreased	Decreased	Decreased
Mean corpuscular volume (MCV)	Decreased or normal	Decreased	Normal to decreased
Red cell distribution width (RDW)	Increased	Increased	Normal to increased
Red blood cell count	Decreased	Increased or normal	Decreased
Iron studies			
Serum iron	Decreased	Normal or increased	Decreased
Total iron-binding capacity (TIBC); transferrin	Increased	Normal	Decreased
Transferrin saturation	Decreased	Normal	Decreased
Serum ferritin	Decreased	Normal	Increased
Erythrocyte protoporphyrin*	Increased	Normal or increased	Increased
Soluble transferrin receptor*	Increased	Increased	Normal

Refer to UpToDate topics on anemia for further details of the evaluation and interpretation.

* Not used in the routine evaluation of anemia.

Koilonychia (spoon nail) associated with iron deficiency



Megaloblastic Anemia Testing

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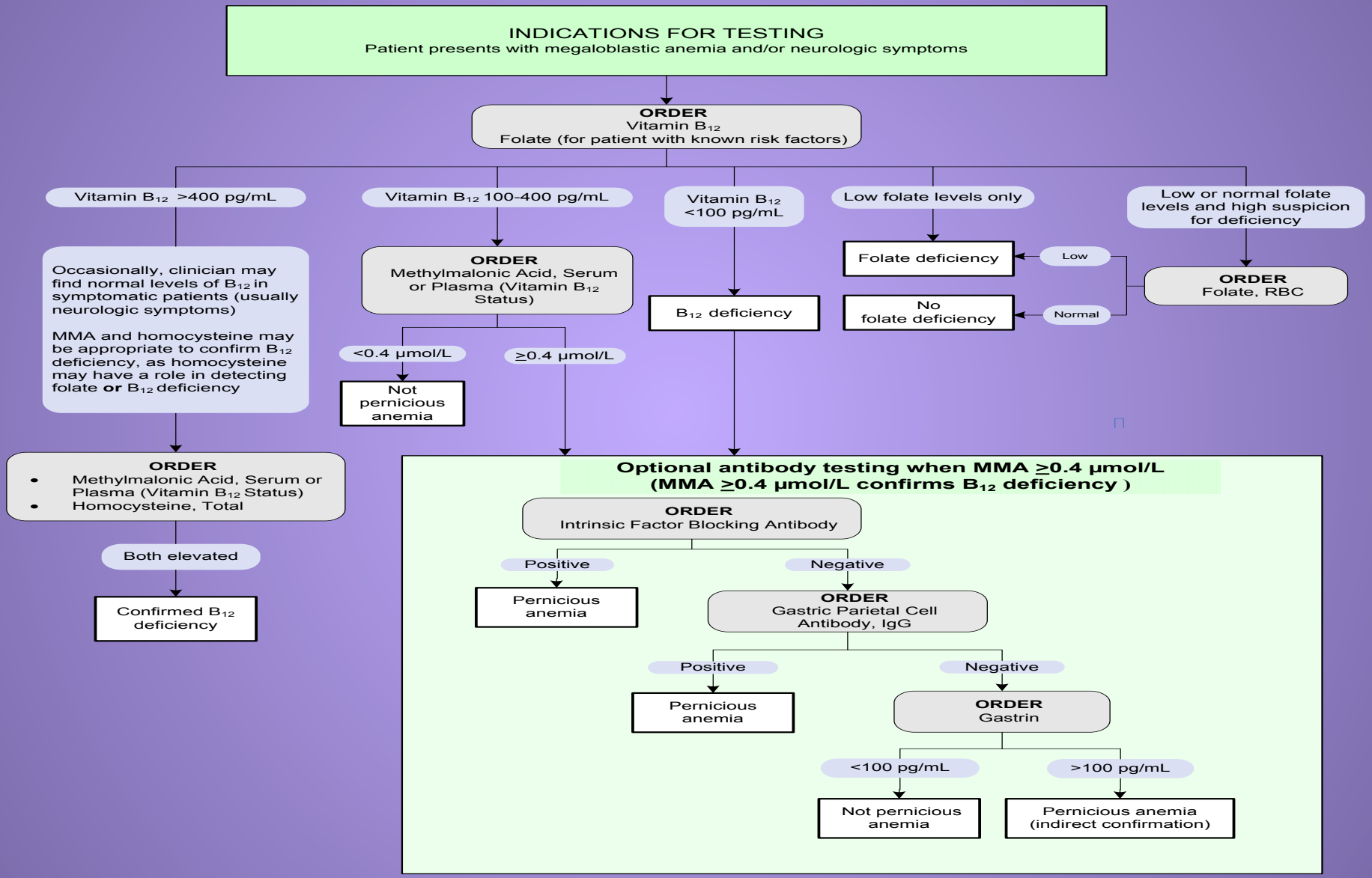

Differential diagnosis of anemia in the adult

Low mean corpuscular volume (microcytic anemia: MCV <80 fL)
Iron deficiency anemia
Thalassemic disorders
Anemia of inflammation/anemia of chronic disease (late; uncommon)
Sideroblastic anemia (eg, congenital, lead, alcohol, drugs; uncommon)
Copper deficiency, zinc poisoning (rare)
Normal mean corpuscular volume (normocytic anemia: MCV 80 to 100 fL)
Acute blood loss
Iron deficiency anemia (early)
Anemia of inflammation/anemia of chronic disease (eg, infection, inflammation, malignancy)
Bone marrow suppression (may also be macrocytic)
Bone marrow invasion (eg, leukoerythroblastic blood picture)
Acquired pure red blood cell aplasia
Aplastic anemia
Chronic renal insufficiency
Endocrine dysfunction
Hypothyroidism (most commonly normocytic)
Hypopituitarism
Increased mean corpuscular volume (macrocytic anemia: MCV >100 fL)
Ethanol abuse
Folate deficiency
Vitamin B12 deficiency
Myelodysplastic syndromes
Acute myeloid leukemias (eg, erythroleukemia)
Reticulocytosis
Hemolytic anemia
Response to blood loss
Response to appropriate hematinic (eg, iron, B12, folic acid)
Drug-induced anemia (eg, Hydroxyurea, AZT, chemotherapeutic agents)
Liver disease
Hypothyroidism (less commonly macrocytic)

This list is not meant to be exhaustive; only the most common causes are mentioned. In addition, two or more of these conditions may be present (eg, combined iron and folate deficiencies), resulting in a misleadingly normal mean corpuscular volume.

Causes for failure to respond to oral iron therapy

Coexisting disease interfering with marrow response
Infection
Inflammatory disorder (eg, rheumatoid arthritis)
Concomitant malignancy
Coexisting folate and/or vitamin B12 deficiency
Bone marrow suppression from another cause
Patient is not iron deficient, possible correct diagnoses include
Thalassemia
Lead poisoning
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 acquired malabsorption for iron (eg, sprue, atrophic or autoimmune gastritis, H. pylori infection)
Medication taken in association with an agent interfering with absorption (eg, antacids, tetracycline, tea)
Congenital cause for iron malabsorption (eg, iron-resistant iron deficiency anemia, IRIDA)
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, hereditary hemorrhagic telangiectasia [Osler-Weber-Rendu syndrome]) or need cannot be met by oral iron preparation (eg, renal failure or malignancy being treated with erythropoietin)
Switch patient to intravenous iron product

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


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Iron preparations:

Ferrous gluconate orally is less likely to cause GI upset and is more tolerated than ferrous sulfate. It is equally absorbable with less side effects. Comes in may strengths and is generally OTC. Severe iron deficiency may require 325 mg TID. Most patients don't take it as directed for a variety of reasons. Nausea and constipation are the biggest reasons.

I never order ferrous sulfate, for those reasons.

There are many conditions that can interfere with oral iron absorption and or cause iron deficiency:

Being older, poor tolerance of oral iron preparations
Inflammatory bowel disease, ulcerative colitis
Gastric surgery and gastric bypass
H. Pylori, autoimmune gastritis and celiac disease.
Chronic kidney disease and dialysis
Cancer patients

IV iron preparations: (use them when patients cannot tolerate oral)

AVOID IM: It's painful, stains the buttocks, and has variable absorption. Case reports have also described development of sarcomas.

Iron Dextran (Infed): Black Box warnings for anaphylaxis, requires pre medications and takes long to give. Usually including premeds and test dose, 4-6 hours. Dosing is by weight and Hgb. (Chart) can be up to 1.5 Gms. More than a Gram doesn't work any better.

Ferumoxytol (Feraheme): Given in 2 doses, one week apart. 510 mg Often given with premeds and has an increase in second dose reactions.

Iron sucrose (Venofer): Should have a test dose. Given in multiple doses, not over 300 mg. Used in CKD, and in the setting of dialysis.

Ferric carboxymaltose (Injectafer): is a colloidal iron hydroxide complex with a tighter binding of elemental iron. It's a 15 minute infusion and doesn't require premeds and is given in NSS 750 mg in 2 doses, one week apart.

Monitoring:

For chronic iron deficiency anemia patients that require ongoing IV iron treatments, monthly CBC's and iron studies including ferritin. Treat again when ferritin goes below 50.

Oral iron treatment F/U should be checked monthly during replacement until repleted. Continue oral iron up to 3-6 months after normalization of iron levels to replete iron stores. When ferritin is normalized, a trial off iron for 3 months and recheck CBC, iron, TIBC and ferritin.

If the cause of the iron deficiency has been treated, no further iron should be necessary. (normalization of periods, post uterine oblation, GI bleed is successfully treated, etc.)

Case Study:

71 year old female with a history of macrocytic anemia over 2 years. Supplementation with B 12 shows adequate B 12 levels and folate. She has hypothyroidism and upper and lower endoscopies were completed in 2013 and she was found to have a single benign colon polyp and mild gastritis that was treated. ECOG performance status is 0.

MCV = 125.7	(81.6 -98.3)
MCH = 43.5	(25.6-32.2)
Hgb = 9.3	
Hct = 26.9	
WBC 3.30	(3.98-10.04)
Retic count = 1.71%	(0.50-1.70)
Ferritin = 912	(11.1-264)
Iron = 188	(37-170)

Question:

What tests do you do next?

1. Repeat Upper and lower endoscopies, as she had a polyp 3 years ago.

2. Bone Marrow Biopsy with Cytogenetics.

3. She has had this for 2 years and is stable, no further work up is necessary.

4. Consider hypothyroid as a reason for her macrocytosis and follow closely.

71 Y/O female with megaloblastic anemia

Bone Marrow Biopsy showed:

Severely increased iron stores present, ringed sideroblasts present. Increased cellularity, no evidence of metastatic neoplasm.

Comment: On BMB from pathologist

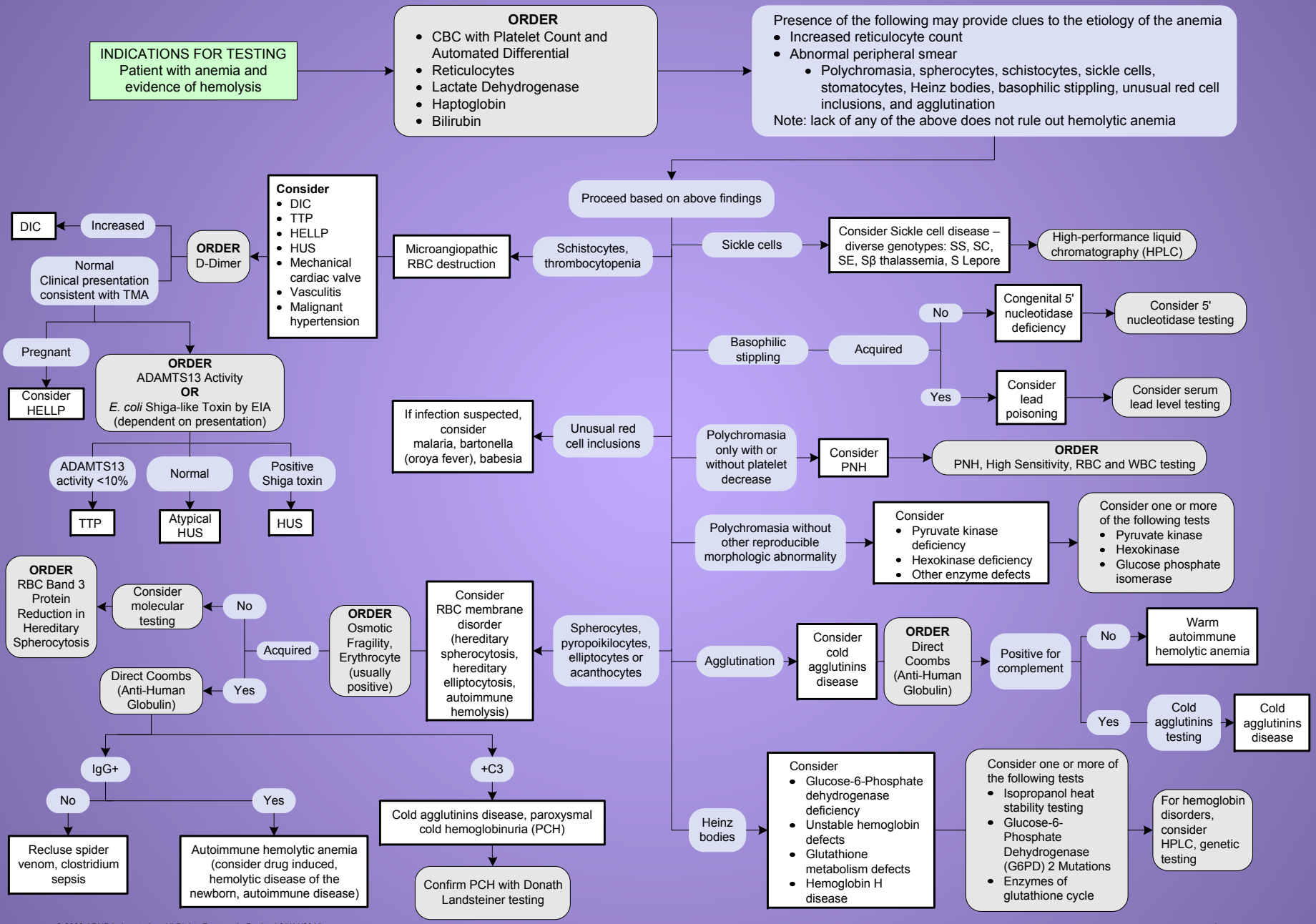
The patient developed anemia starting in 2013. She is not B 12 or folate deficient, and she is taking levothyroxine. Hypothyroidism may be associated with megaloblastic anemia; however, there is increased particulate iron without blast increase in her marrow. Cytogenetics was negative for myelodysplastic syndrome.

Treatment:

For now, she should be followed frequently with blood counts and no treatment is needed at this time. Should she continue to drop her blood counts or become symptomatic, then a trial of erythropoietin could be initiated.

Hemolytic Anemias Testing

Click here for topics associated with this algorithm



Hemolytic Anemia:

Tests: CBC, with manual diff, reticulocyte count, LDH, Haptoglobin, Bilirubin.

Findings:

Elevated reticulocyte count
Elevate LDH
Decreased Haptoglobin < 25 (if LDH and Haptoglobin are normal, 90% probability it's not hemolytic anemia)
Positive Direct Coombs test
Increased indirect Bilirubin

Peripheral smear:

Fragmented RBC (schistocytes or helmet cells
Spherocytes seen in hereditary scherocytosis
Spur cells seen in liver disease
Tear drop RBC's with circulating nucleated RBC indicating the presence of marrow involvement.

Treatment for Hemolytic Anemia (Autoimmune):

Diagnosis – Accurate diagnosis of warm agglutinin autoimmune hemolytic anemia (AIHA) requires documentation of the presence of red cell destruction (hemolysis) along with demonstration of the presence of an autoantibody or complement on the surface of the patient's red cells.

Indications for treatment – Most patients with AIHA present with an acute onset of severe hemolysis with symptomatic anemia, requiring immediate treatment. In patients with underlying cardiac disease, AIHA can present as a medical emergency, requiring immediate packed red cell transfusion.

Initial treatment – Once the diagnosis of **symptomatic** warm agglutinin AIHA is confirmed, we recommend immediate institution of treatment with glucocorticoids over splenectomy,

Poorly responsive, severe, or resistant disease

Second-line treatment – For symptomatic patients not responding to glucocorticoids, or for those who require large doses to maintain their response (eg, >15 mg/day)

CONTINUED

For adults, it is preferred splenectomy over Rituximab, as it is the only modality with potential for long-term cure, while rituximab is the treatment of choice for adults who either are not surgical candidates or refuse surgery.

Third-line treatment – For those who have failed treatment with both splenectomy and rituximab, should institute immunosuppressive or cytotoxic agents such as azathioprine (Imuran), cyclophosphamide, or cyclosporine.

Obviously you have already referred to Hematology!


THAT MOMENT WHEN
YOU REALISE
IT SPELLS HORSE.

Erythrocytosis

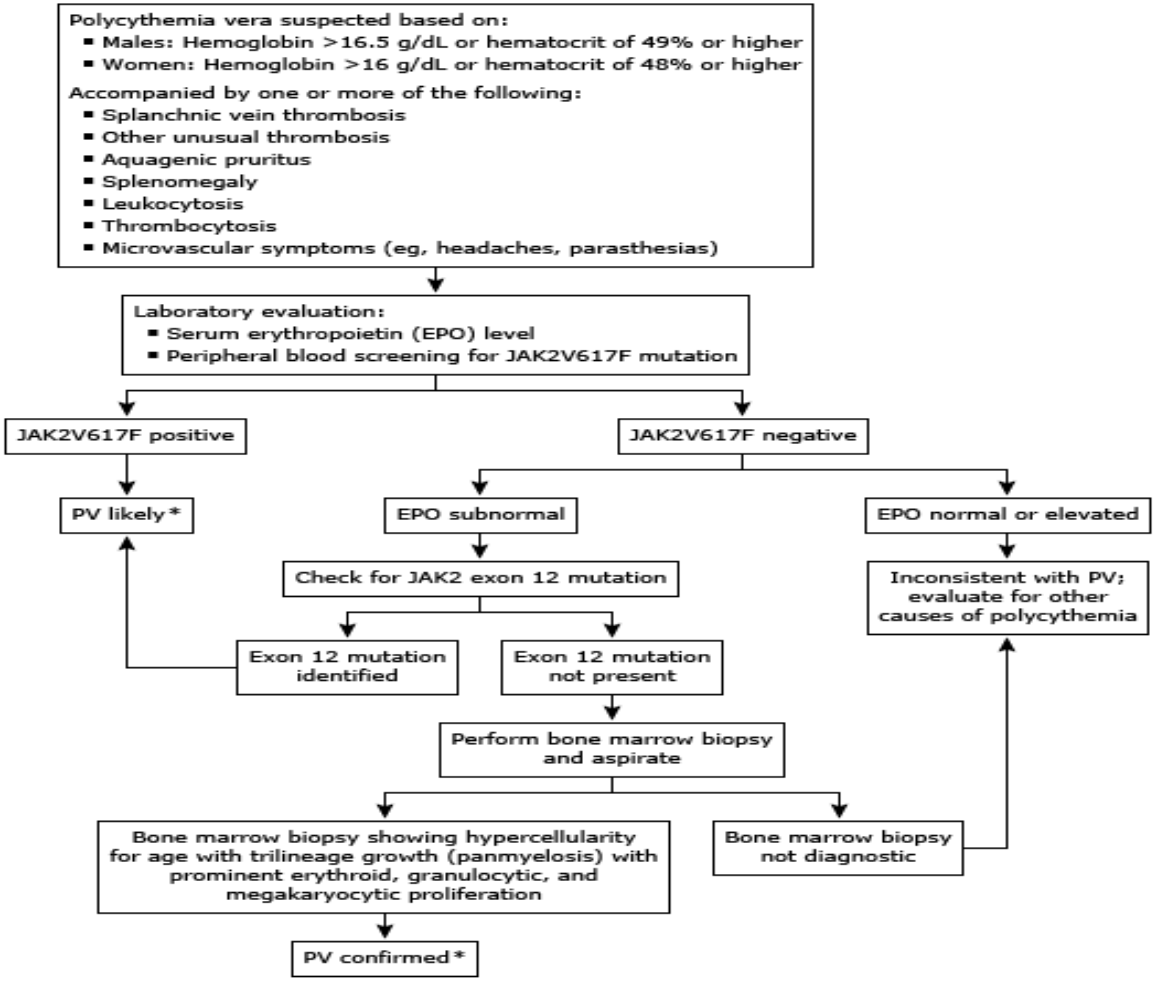
Polycythemia

Primary or Secondary

Major causes of erythrocytosis (polycythemia)

Autonomous (inappropriate) increase of Epo - inappropriately high serum Epo
Erythropoietin-producing neoplasms (most common)
Renal cell carcinoma
Hepatocellular carcinoma
Cerebellar hemangioblastoma
Pheochromocytoma
Uterine fibroids
Erythropoietin-producing renal lesions (eg, cysts, hydronephrosis, renal artery stenosis, distal renal tubular acidosis [rare])
Following renal transplantation (some cases are independent of erythropoietin)
Appropriate increases in erythropoietin - appropriately high serum erythropoietin
Hypoxemia secondary to:
Chronic pulmonary disease
Right-to-left cardiac shunts
Sleep apnea
Massive obesity (Pickwickian syndrome)
High altitude
Red cell defects
Some cases of congenital methemoglobinemia
Chronic carbon monoxide poisoning (including heavy smoking)
Cobalt
Germline and somatic mutational causes of polycythemia
Polycythemia vera (JAK2 mutation)
Activating mutations of the erythropoietin receptor (EPOR gene)
Chuvash polycythemia (VHL gene mutation)
Congenital methemoglobinemia
Idiopathic familial polycythemia
High oxygen affinity hemoglobins
2,3 bisphosphoglycerate (BPG) mutase deficiency
Other rare gene mutations (eg, PHD2, HIF2-alpha)
Miscellaneous causes
Use of androgens or anabolic steroids
Diuretics (reduced plasma volume rather than erythrocytosis)
Blood doping in athletes (ie, autologous blood transfusion)
Self-injection of erythropoietin
POEMS syndrome

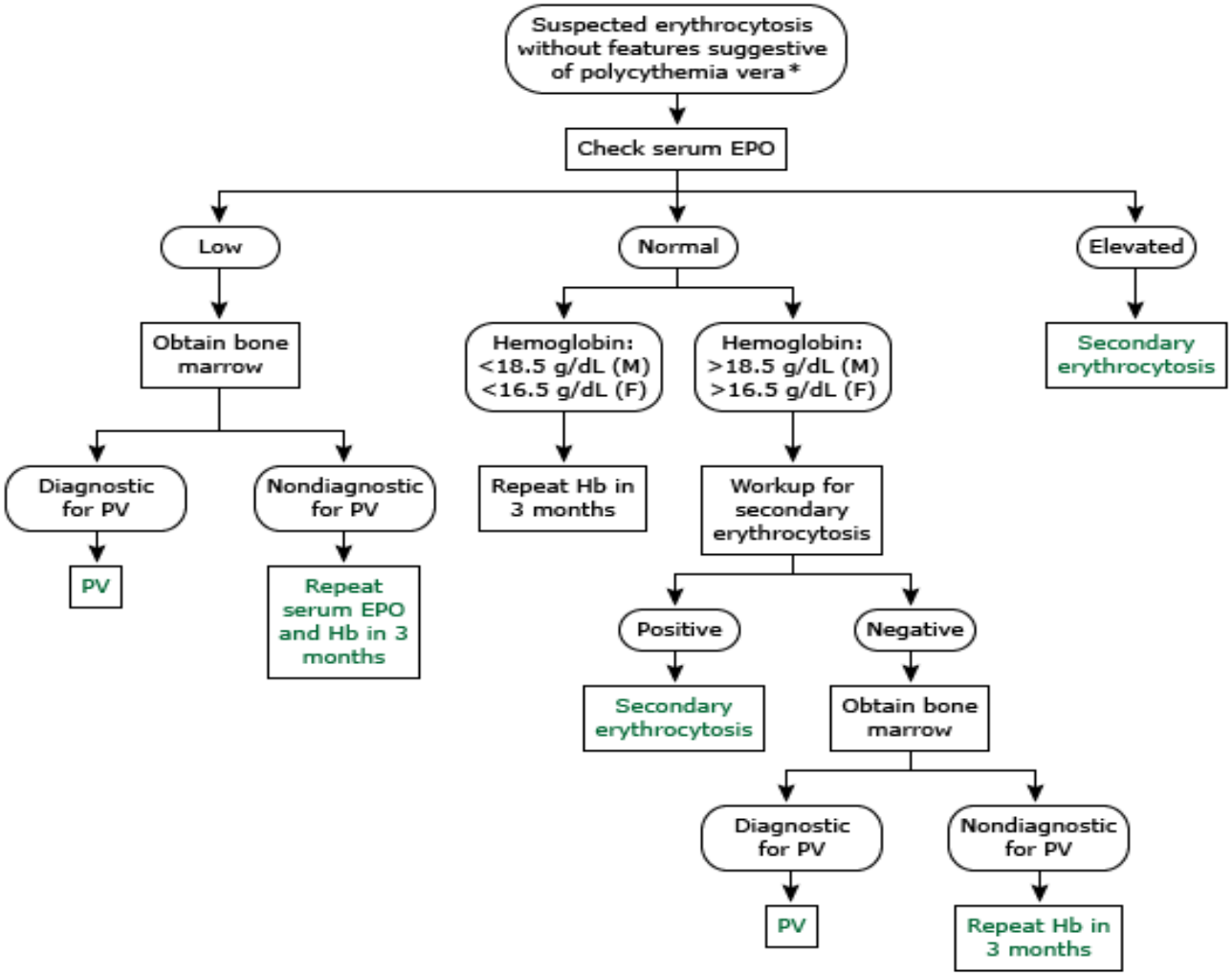
Evaluation of suspected polycythemia vera



PV: polycythemia vera; EPO: erythropoietin.

* WHO diagnostic criteria met for patients with both major criteria (hemoglobin >18.5 g/dL in men, 16.5 g/dL in women or other evidence of increased red cell volume AND presence of JAK2V617F or functionally similar mutation such as JAK2 exon 12 mutation) or the first major criterion plus two minor criteria (consistent bone marrow biopsy findings, subnormal serum EPO, or endogenous erythroid colony formation in vitro). Bone marrow biopsy might not be necessary if hemoglobin is >18.5 g/dL in men or 16.5 g/dL in women. Bone marrow biopsy is recommended for lower hemoglobin levels in order to avoid confusing PV with JAK2-mutated essential thrombocytosis. For practical purposes, PV likely and PV confirmed cases are treated similarly.

Diagnostic approach to suspected erythrocytosis in the absence of polycythemia vera-related features



PV: polycythemia vera; EPO: erythropoetin; Hb: hemoglobin; M: male; F: female.

* Features suggestive of PV include splanchnic vein thrombosis or other unusual thrombosis, aquagenic pruritus, splenomegaly, leukocytosis, thrombocytosis, and microvascular symptoms (eg, headaches, parasthesias).

QUESTION:

You have a patient, age 50ish, that you have followed for many years, who comes in complaining of fatigue, weight gain, depression, and tells you their spouse complains of their snoring is getting worse. You check labs and find that they are not anemic, in fact over the past few years, their Hgb has risen to the level of polycythemia. No other indices are abnormal. What tests do you do next?

1. Repeat CBC, with smear to path, CMP, Hgb A1c, and lipid panel.

2. Set them up for a sleep study.

3. Repeat CBC with diff and draw erythropoietin level, and make sure they are well hydrated.

4. Discuss with them about their sleep habits and activity levels, and dietary considerations, and family history of hereditary syndromes.

You find out the EPO level is elevated, now what?

Over night oximetry shows O2 saturations are under 85% frequently during testing and multiple events of apnea are noted.

Patient feels unrested upon arising, and sluggish during the day.

Exercise tolerance is poor. Diet is rich in starchy carbs and Hgb A1c is elevated at 8.0, along with high triglycerides and LDL.

Ultrasound of abdomen shows fatty liver but spleen is normal.

WHAT IS YOUR DIAGNOSIS?

How many patients in your practice fit this pattern?

You've got work to do…….

Let's Talk White Cells

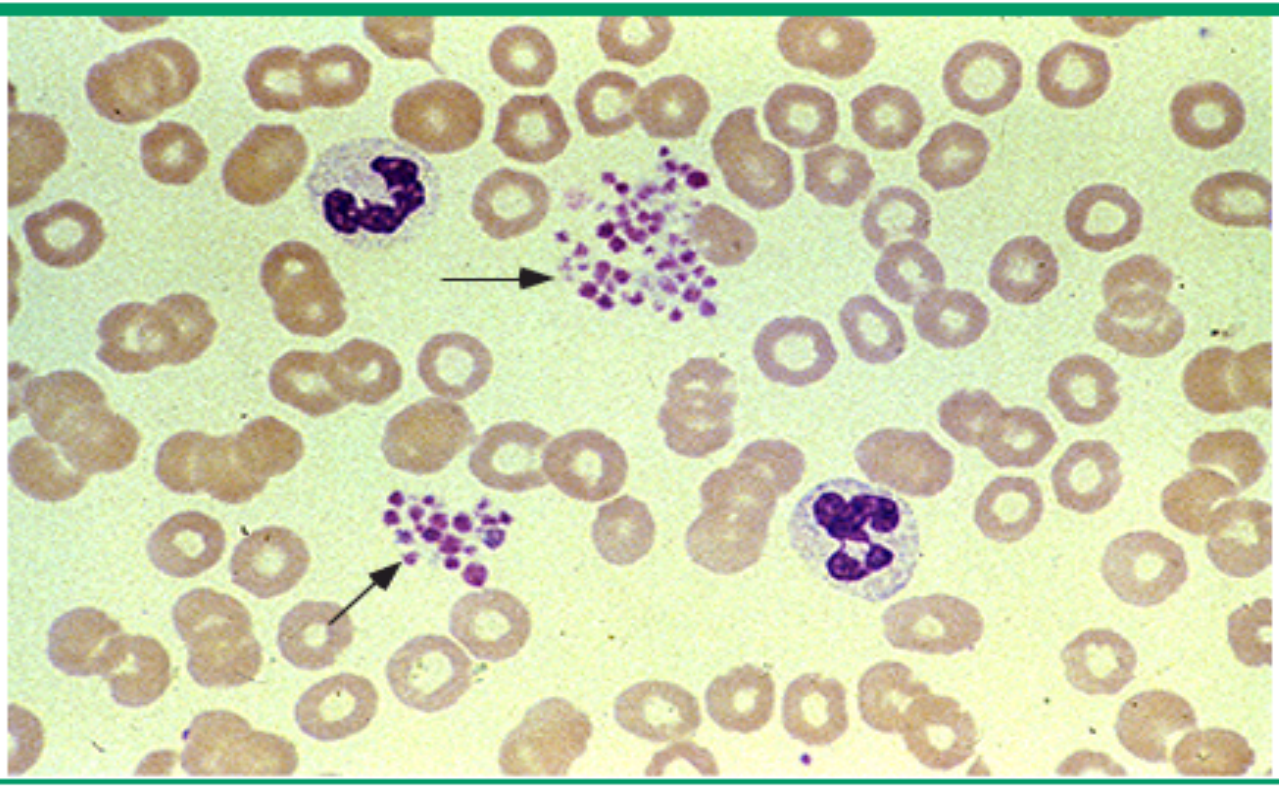
Classification of neutrophilia

Spurious
Platelet clumping
Mixed cryoglobulinemia
Primary (no other evident associated disease)
Myeloproliferative disorders (eg, CML, PV, ET)
Hereditary neutrophilia
Chronic idiopathic neutrophilia
Familial myeloproliferative disease
Congenital anomalies and leukemoid reaction
Down syndrome
Leukocyte adhesion factor deficiency
Familial cold urticaria and leukocytosis
Secondary
Infection
Stress (physical or emotional stress, vigorous exercise)
Cigarette smoking
Drugs
Glucocorticoids
Recombinant G-CSF or GM-CSF*
Catecholamines (epinephrine)
Lithium
All-trans retinoic acid
Isolated case reports for occasional other drugs
Nonhematologic malignancy
Heatstroke
Generalized bone marrow stimulation (as in hemolysis)
Asplenia and hyposplenism

Most commonly encountered causes of neutrophilia are shown in **bold**.

CML: chronic myelogenous leukemia; PV: polycythemia vera; ET: essential thrombocythemia; G-CSF: granulocyte colony-stimulating factor; GM-CSF: granulocyte-macrophage colony-stimulating factor.
* These agents are used therapeutically to raise the neutrophil count.

Pseudothrombocytopenia due to platelet clumping in EDTA



This peripheral blood smear shows platelet clumping (arrows) in an EDTA-anticoagulated blood sample. This patient had an EDTA-dependent platelet agglutinin which caused in vitro platelet clumping, resulting in an artifactually low platelet count (ie, "pseudothrombocytopenia"). No platelet clumping was seen, and the platelet count was normal, in a blood sample from this patient anticoagulated with sodium citrate.
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Major medications with a definite association with agranulocytosis

Antithyroid drugs (thionamides)
Methimazole
Carbimazole
Propylthiouracil
Antiinflammatory drugs
Sulfasalazine
Nonsteroidal antiinflammatory drugs
Gold salts
Penicillamine
Phenylbutazone
Antipyrine
Dipyrone
Phenacetin
Psychotropic drugs
Clozapine
Phenothiazines
Tricyclic and tetracyclic antidepressants
Meprobamate Cocaine/heroin (adulterated with levamisole)
Gastrointestinal drugs
Sulfasalazine
Histamine H2- receptor antagonists
Cardiovascular drugs
Antiarrhythmic agents (tocainide, procainamide, flecainide)
Ticlopidine
ACE inhibitors (enalapril, captopril)
Propranolol
Dipyridamole
Digoxin
Dermatologic drugs
Dapsone
Isotretinoin

Antibiotics
Macrolides
Trimethoprim-sulfamethoxazole
Chloramphenicol
Sulfonamides
Semisynthetic penicillins
Vancomycin
Cephalosporins
Dapsone
Antimalarial drugs
Amodiaquine
Chloroquine
Quinine
Antifungal agents
Amphotericin B
Flucytosine
Anticonvulsants
Carbamazepine
Phenytoin
Ethosuximide
Valproate
Diuretics
Thiazides
Acetazolamide
Furosemide
Spironolactone
Sulfonylureas
Chlorpropamide
Tolbutamide
Iron chelating agents
Deferiprone

Chronic Lymphocytic Leukemia

Can this be managed by primary care providers? **YES!**

You have a patient that has an elevation in lymphocytes, and you are following them over the years and now you notice a small increase in the total WBC and the lymphocyte % is higher than the neutrophil %.

What is the next test to be drawn if you suspect CLL?

Flow Cytometry.

It can confirm the diagnosis without a BMB.
Usually they will be CD 20 positive.
You can follow these patients.

Platelets, Thrombocytes those tiny little critters that keep us from bleeding out!

CAUSES OF REACTIVE THROMBOCYTOSIS

NON MALIGNANT HEMATOLOGIC CONDITIONS:

ACUTE BLOOD LOSS
ACUTE HEMOLYTIC ANEMIA
ACUTE IRON DEFICIENCY ANEMIA
TREATMENT OF VITAMIN B DEFICIENCY
REBOUND EFFECT AFTER TREATMENT OF IMMUNE THROMBOCYTOPENIA
REBOUND EFFECT AFTER ETHANOL-INDUCED THROMBOCYTOPENIA

MALIGNANT CONDITIONS:

METASTATIC CANCER
LYMPHOMA
REBOUND EFFECT FOLLOWING USE OF MYELOSUOORESSIVE AGENTS

ACUTE AND CHRONIC INFLAMMATORY CONDITIONS:

RHEUMATOLOGIC CONDITIONS, VASCULITIS, IBS, CELIAC DISEASE

TISSUE DAMAGE:

THERMAL BURNS
MYOCARDIAL INFARCTION
SEVERE TRAUMA
ACUTE PANCREATITIS
POST-SURGICAL PERIOD, ESPECIALLY POST-SPENECTOMY
CORONARY ARTERY BYPASS PROCEDURES

INFECTIONS:

CHRONIC INFECTIONS AND TUBERCULOSIS

EXERCISE

ALLERGIC REACTIONS

FUNCTIONAL AND SURGICAL ASPLENIA

REACTION TO MEDICATIONS:

VINCRISTINE
EPINEPHERINE, GLUCOCORTICOIDS
INTERLEUKIN-1B
ALL-TRANS RETINOIC ACID
THROMBOPOIETIN, THROMBOPOITIN MIMETICS
LOW MOLECULAR WEIGHT HEPARINS (ENOXAPARIN)

MEDICATIONS

THOSE
PESKY
DRUGS

Hydroxyurea:

Used mostly these days for **Essential Thrombocythemia**. It can be used in CML.
Dosing is 500 mg tablets titrated to keep the platelet count below 400K.
Monitoring CBC's should be weekly at first and then changed to every 2 weeks until stabilization occurs.
It can drop Hgb and WBC's so titration can be tricky.
Usually changes in dosing shouldn't be sooner than every 2 weeks as it takes that long to stabilize on a new dose.

It is an antineoplastic agent and is carcinogenic. Advise sun protection and monitor for malignancies.

Adjustments for lower Creatinine clearance.
Most people tolerate it without side effects.
Causes macrocytosis

Eltrombopag (Promacta):

Colony stimulating Factor; Hematopoietic Agent; Thrombopoietic Agent.
Used for Chronic immune idiopathic Thrombocytopenia (ITP)
Max dose is 150 mg daily.
Titrate to maintain platelets with lowest dose.
Weekly CBC monitoring until Platelets get up to 30K and you are seeing an upward trend, the CBC's every 2 weeks.
Pricing:

12.5 mg tabs # 30 = $4124.09
75 mg tabs # 30 = $11,509.09

Monitor liver functions
Should be taken on an empty stomach
Can be used in Hepatitis C for thrombocytopenia with caution.
Dosing is usually tolerated well.
SE: fatigue, nausea, diarrhea, elevated LFT's are the most common.

Anagrelide (Agrylin):

Antiplatelet Agent, used for **Essential Thrombocythemia (ET)**
Well tolerated, and can be used with Hydroxyurea on tough cases.
Caution in Hepatic impairment.
Initial dosing is 0.5 mg 1 to 4 times daily Max daily dose of 10 mg
Titrate up slowly, must not be increase by more than 0.5 mg a day in any one week. Most patients will stabilize between 1.5 and 3 mg daily.
Generic form available

Pricing:
0.5 mg (100) = $585.70 (generic)
1 mg (100) =$1171.35 (generic)
Monitoring parameters CBC Q 2 days during the first week with pretreatment EKG and CMP frequently during treatment.
Monitor for interstitial lung disease.
SE: palpitations, chest pain, CHF, fatigue, edema, rash, diarrhea, nausea, elevated LFT's

Hematopoietic Growth Factors:

Erythropoietin, Granulocyte and granulocyte-macrophage colony stimulating factors (G-CSF and GM-CSF), Thrombopoietin

The family of glycoproteins known as the hematopoietic growth factors (HGFs) plays a major role in the proliferation, differentiation, and survival of primitive hematopoietic stem and progenitor cells, as well as in functional activation of some mature cells. These effects are mediated by high affinity binding of the HGFs to specific receptors expressed on the surface of the target cells.

Recombinant HGFs are administered in the following clinical settings:

Transient bone marrow failure following chemotherapy
Hematopoietic stem cell and progenitor cell mobilization
Recovery from hematopoietic cell transplantation
Myelodysplastic syndrome
Aplastic anemia
Some forms of neutropenia
Inherited bone marrow failure syndromes
Human immunodeficiency virus (HIV) infection-associated neutropenia
Chronic anemias (eg, renal failure, prematurity, chronic disease/ inflammation, HIV infection)
Reducing the need for perioperative blood transfusion

Potential toxicities of the recombinant HGFs include the following (see 'Toxicity of colony-stimulating factors' above and 'Toxicity of erythropoietin' above):

Transient leukopenia

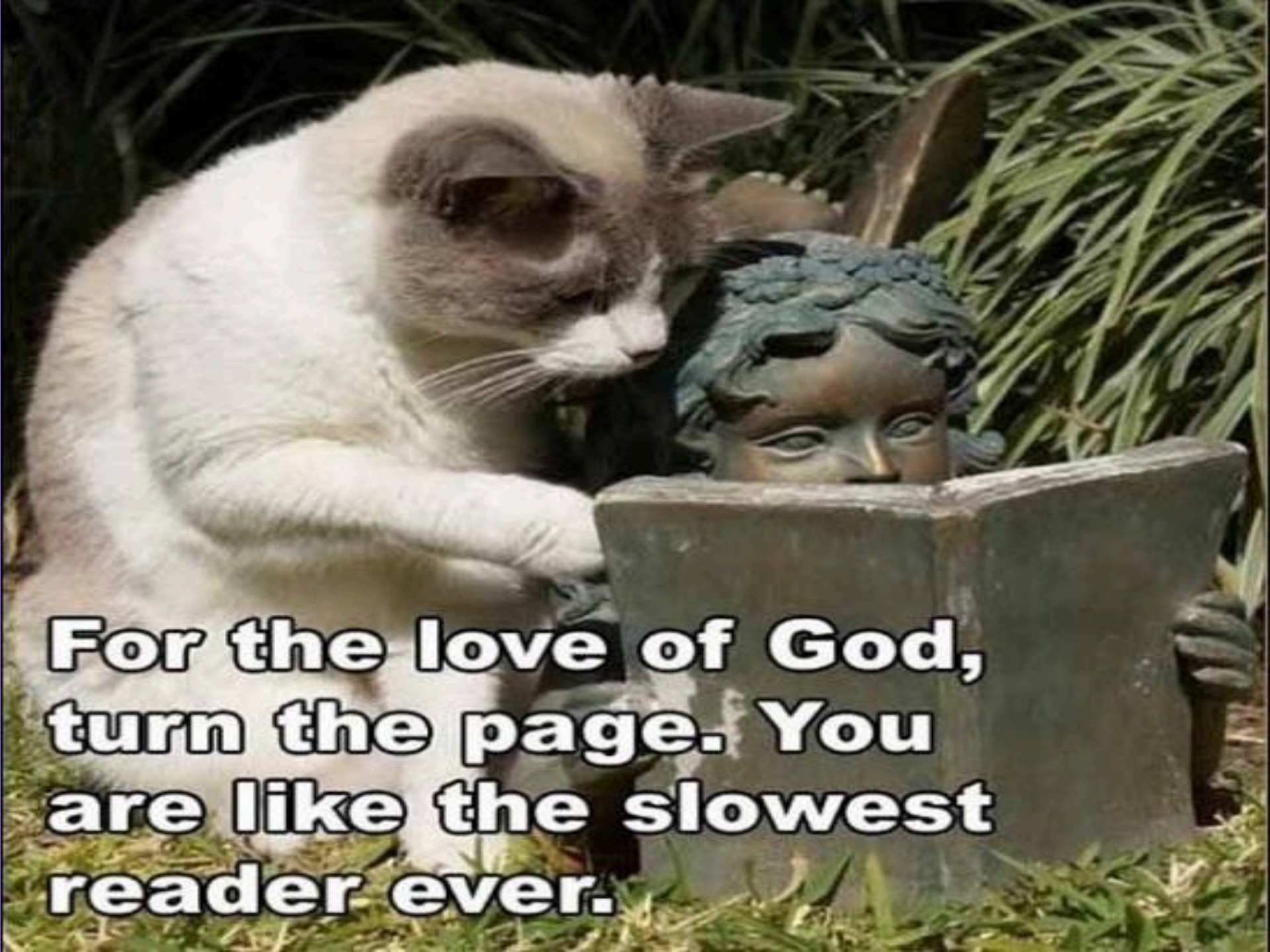
Systemic reactions (eg, flu-like symptoms, capillary leak, hypertension, thrombosis)

Production of deleterious neutralizing antibodies

Possible stimulation of malignancy

Possible enhancement of HIV replication

Multiorgan failure when used in sickle cell syndromes


For the love of God, turn the page. You are like the slowest reader ever.

PEARLS:

1. ANC (absolute neutrophil count) is the neutrophil # on the differential of a CBC. Always order CBC with diff so you can find this number. If it is < 1.5 or below 1500 you have neutropenia.
2. Thrombocytopenia alone, may be due to platelet clumping. Have the lab do a manual diff to verify if there is clumping. If so have the next CBC, have drawn in a sodium citrate tube. Clumping can be seen with EDTA tube.

Case Study:

73 Y/O female with anemia, severe monocytosis, elevated WBC, low platelets. Hx of DM, HTN, multiple UTI's.

WBC	43.81	HH
RBC	3.09	L
HGB	9.2	L
HCT	28.7	L
MCV	92.9	H
MCH	29.8	
PLTS	20	LL
ANC#	0.34	LL
Lymph #	9.78	H
MONO#	33.53	HH
EOS #	0.01	L

BUN	24	(7 – 17)
Creatinine	2.5	(0.7 – 1.2)

Blood sugar and electrolytes were normal

Bone Marrow Biopsy:

Peripheral Blood:

Normocytic, normochromic anemia with anisocytosis. Atypical monocytosis with dysplastic morphology. Few monoblasts. Few variant lymphocytes.

Bone Marrow:

Acute myeloid leukemia with monocytic differentiation with infiltration of marrow about 85% cellularity of the marrow is close to 100%

Flow Cytometry:

Markedly increased immunophenotypically atypical monocytes detected. Blast count is 3.4%. Manual count with 5% immature monocytes noted.

Monocytosis:

A number of conditions which cause neutrophilia can also cause monocytosis, making this combination a relatively nonspecific finding. These include pregnancy, the asplenic state, inflammatory (eg, sarcoidosis, inflammatory bowel disease) and autoimmune conditions, depression, and treatment with corticosteroids or colony stimulating factors. Monocytosis may also accompany conditions associated with neutropenia, presumably as a compensatory mechanism.

A large number of infections have been associated with monocytosis including brucellosis, varicella-zoster, bacterial endocarditis, tuberculosis, malaria, typhoid fever, syphilis, and trypanosomiasis.

Monocytosis may also be seen in certain malignancies, such as Hodgkin lymphoma. Neutrophilia with monocytosis may also suggest chronic myelomonocytic leukemia, one of the myelodysplastic disorders. Additional associated findings in this condition are anemia, thrombocytopenia and abnormal cellular maturation (eg, macrocytic red cells, defective lobulation in neutrophils, and abnormal size and granulation in platelets).

In this case study, at the time of the BMB, she had declining platelets and she was quite weak. She was instructed to be very careful about injuries and falls!

Within 2 days she was in the ER and transported to Albuquerque.
She neglected to tell anyone she had fallen and hit her head.
She became obtunded and a CT revealed a subdural hematoma.

She went into a blast crisis with her Acute myelomonocytic leukemia and passed.

Case Study:

63 Y/O male with elevated LFT's, macrocytosis, Hx of colon cancer, in to F/U on colon cancer.

WBC	8.75		
RBC	3.92		
HGB	14.6		
HCT	40.2		
MCV	102.6	H	
MCH	37.2	H	
PLTS	175		(163-369)
Glucose	111.0	non fasting	
BUN	5	L	
Creat	0.7	L	
Sodium	131	L	
AST	106	H	(17-59)
ALT	89	H	(13-69)
CEA	7.9	H	

Ordered the following:

Restaging CT Chest, Abd, and pelvis
Hepatitis panel
Colonoscopy

All were negative.

Patient smokes 2 pks per day
Patient drinks 12 pk beer per day

CEA is elevated in smokers
Macrocytosis and elevated liver functions from alcohol intake.

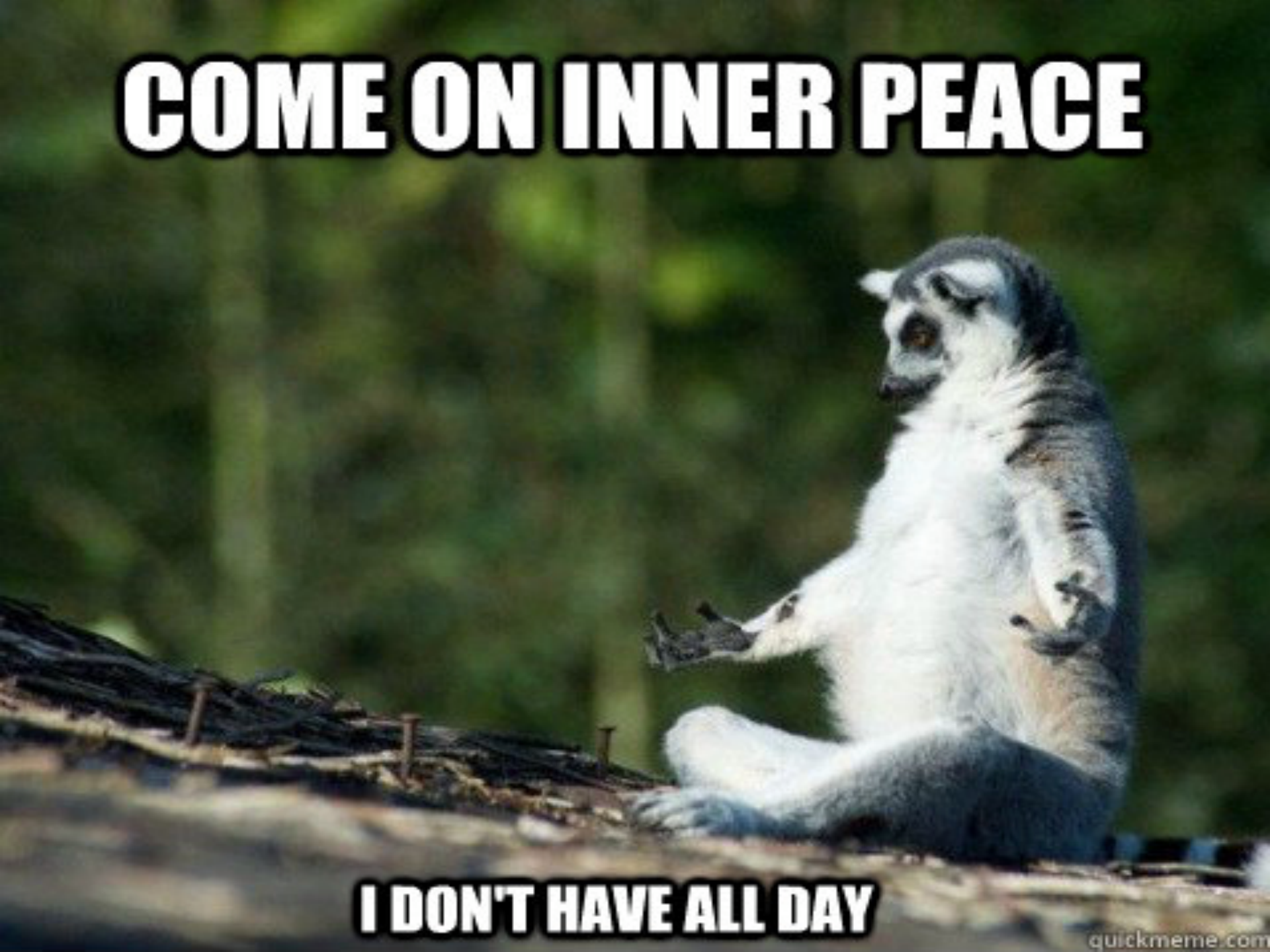
Case Study:

67 Y/O male who had orthopedic surgery and required 2 units of blood post op. He was discharged and 6 weeks later returned to the ER with purpura lower extremities, blood blisters in his mouth. Platelet count was 4K, Hgb was 11.4 The next day platelet count was 0.
He has a Hx of high risk prostate cancer and is on Lupron injections every 6 months. Otherwise he is healthy for his age.

Post transfusion purpura

He was first treated with plasmaphoresis which failed. Then treated with steroids and IVIG which also failed. He was then placed on Eltrombopag (Promacta).

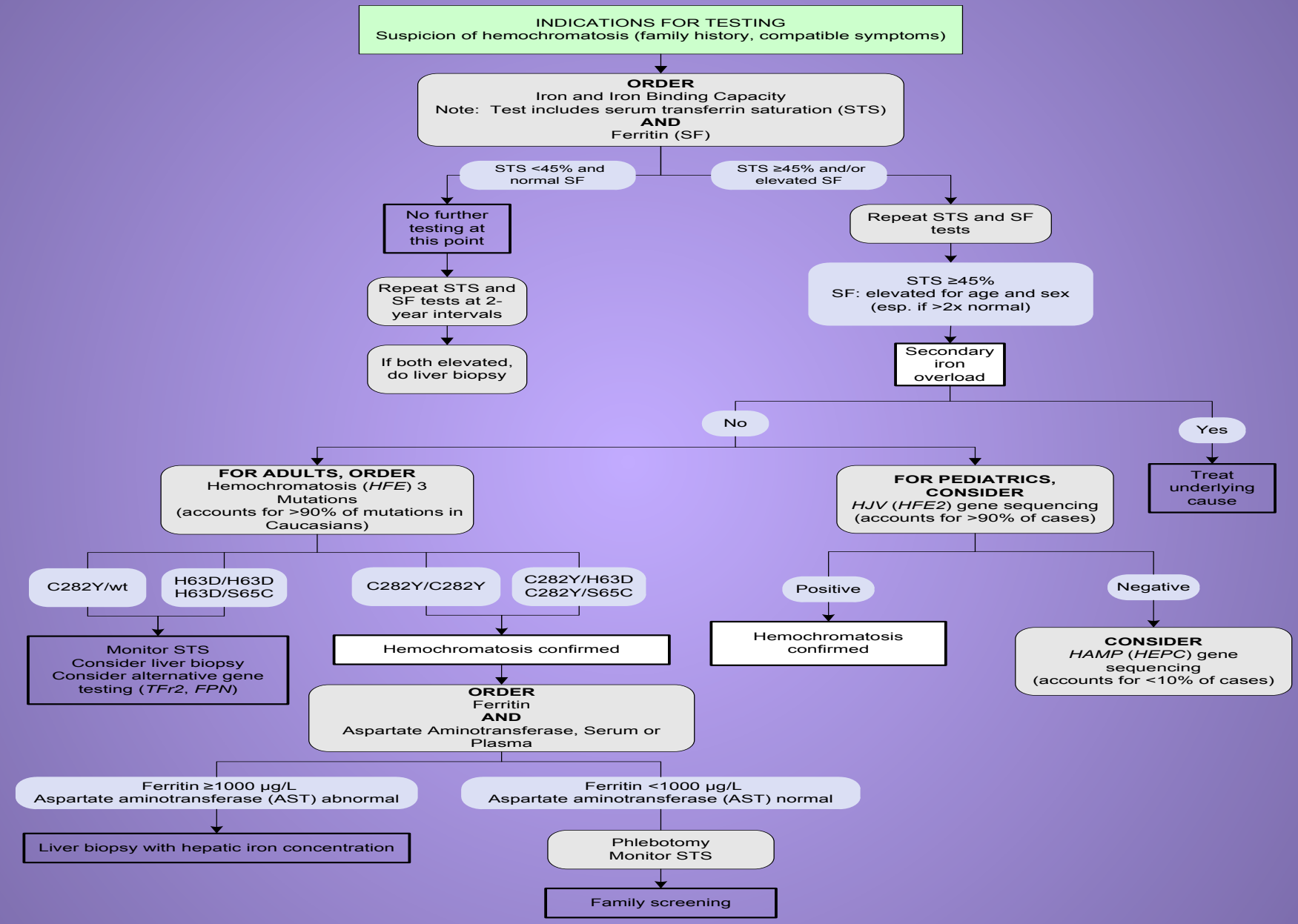
Started at 50 mg daily, CBC's followed weekly platelets took about 4 weeks to recover to 79 K.
Discontinued Promacta in February when his Platelets were 265K.


COME ON INNER PEACE
I DON'T HAVE ALL DAY
quickmeme.com

ARUP Consult

Hemochromatosis Testing

Click here for topics associated with this algorithm



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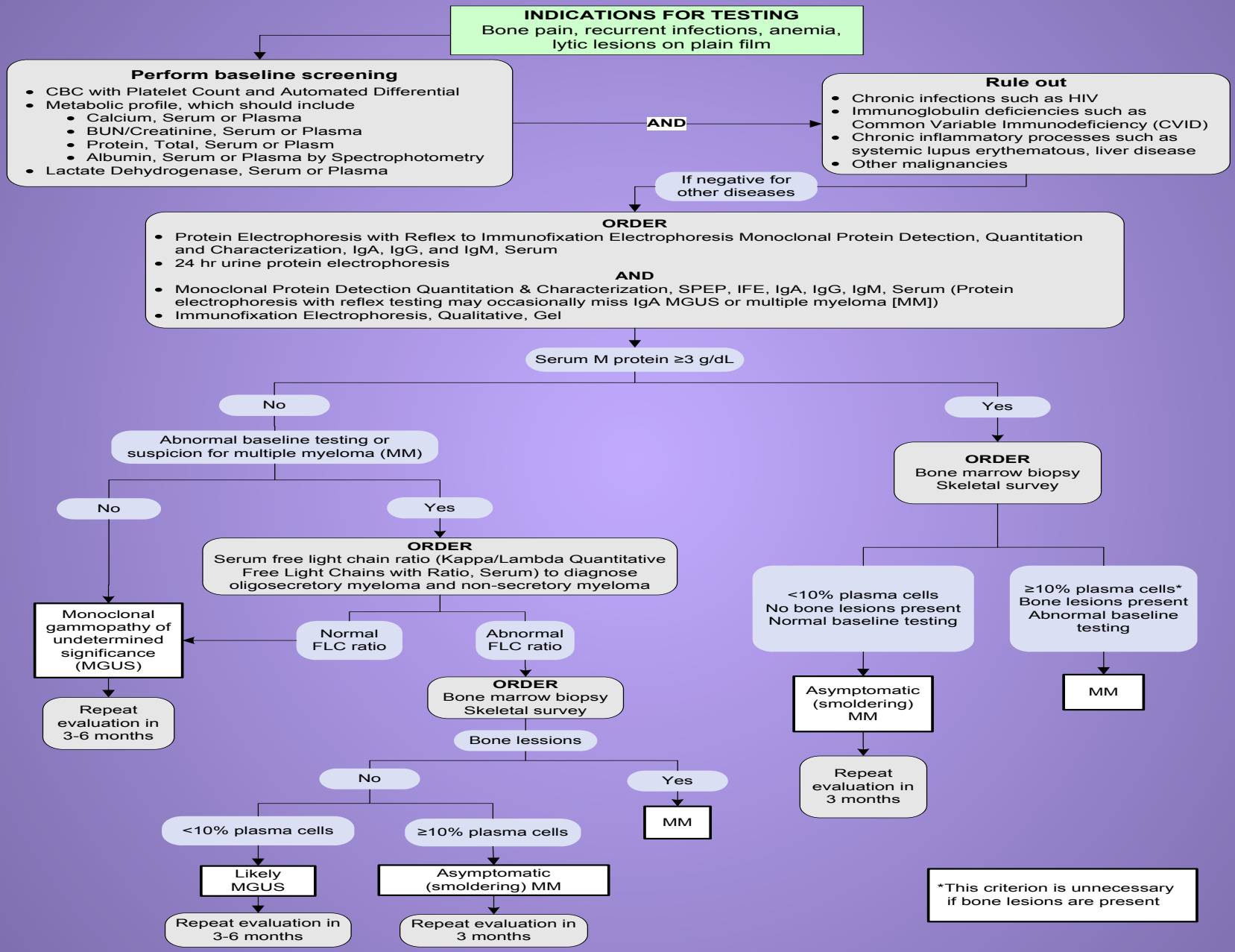
Plasma Cell Dyscrasias

Click here for topics associated with this algorithm



RESCOURCES :

UP TO DATE has apps for cell phone, expensive but great!

ARUP Consult apps for cell phone, great reference for algorithms.

iHematology apps for cell phone, quick reference to describe smear morphology.

Medical Lab Tests for cell phones

labtestsonline.org

WHEN TO REFER

1. PANCYTOPENIA
2. PLATELETS TREND DOWN OVER TIME AND ARE STAYING UNDER 100 K
3. YOU CAN'T FIND A REASON FOR IRON DEFICIENCY
4. UNEXPLAINED LEUKOCYTOSIS
5. UNEXPLAINED ADENOPATHY…. GET IT BIOPSIED!
6. INTOLERANCE TO ORAL IRON AND PERSISTANCE OF IRON DEFICIENCY WITH NEGATIVE WORKUP
7. YOU HAVE A BAD FEELING AND TOO MAY ABNORMALS ON THE SMEAR...

MY ADVICE:

GET TO KNOW YOUR LOCAL HEMATOLOGIST AND ASK FOR ADVICE. THEY MAY HAVE A FRIENDLY NP TO TALK TO. SHE OR HE MAY HAVE GOOD ADVICE!!!