"Vague abnormalities" on your patient's bloodwork: What to do?

SHS/UHN Geriatrics Update Course

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Disclosures

- I have no financial/commercial or intellectual conflict of interests pertaining to the contents of this talk

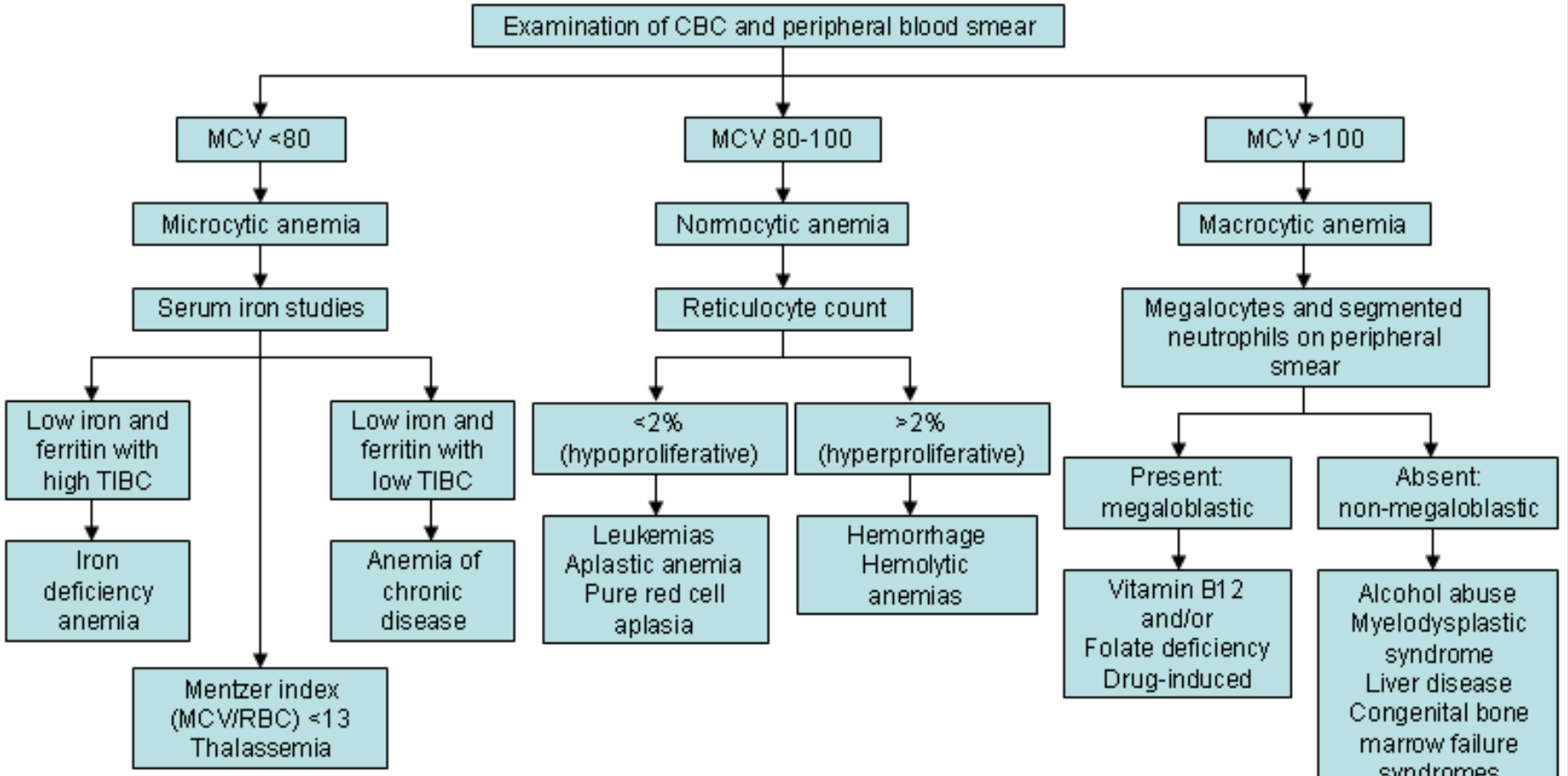
Objectives

- Through illustrative cases, explore 5 common non-malignant hematology problems encountered in older adults
- discuss initial diagnosis and management of these hematologic presentations, with particular focus on 'pearls and pitfalls', and indications for hematology consultation
- Share some hematology reference resources
- *Note: I will not be discussing transfusion medicine or thrombosis today*

Case 1

- Ms B is an 79 year old woman you are seeing in your clinic for fatigue. She notes worsening fatigue, exercise-tolerance, and difficulty concentrating. Her family has noted some cognitive concerns .
- You order bloodwork: Hb 98g/L, MCV 78, ferritin 98ug/L, Transferrin saturation 0.08., ANC 2.1, plt 160
- Diagnosis? Next steps in workup? Management?

Approach to anemia



Uptodate

HEMATOLOGIC DISEASE AT OLDER AGE

Anemia at older age: etiologies, clinical implications, and management

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Anemia in older adults

- Common (17% of patients >65)
- Associated with cardiovascular impairment, reduced mood, cognitive impairment, reduced QoL
- Often **multifactorial** in etiology (multiple comorbidities)

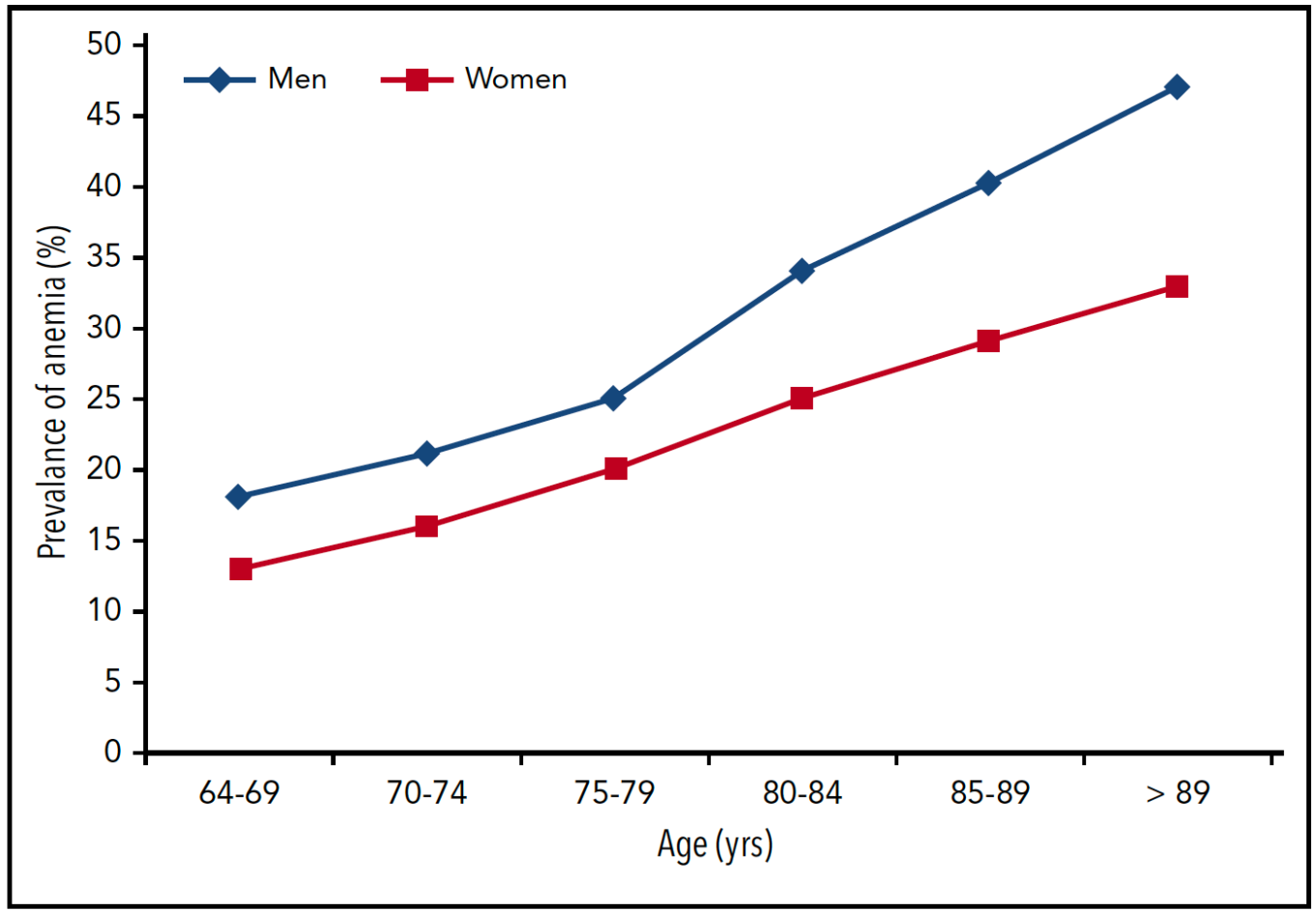

Figure 1. Increase in prevalence of late-life anemia. Increase in prevalence of anemia as defined by WHO (Hb <12 g/dL in women and <13 g/dL in men) with advanced age; cohort of 19 758 university hospital inpatients and outpatients (based on Bach et al[16]).

Table 2. Diseases frequently associated with anemia in the elderly

Category and subtypes	Specific examples
Chronic inflammatory diseases	
Rheumatologic diseases	Rheumatoid arthritis, polymyalgia rheumatica
Chronic infectious diseases	Chronic hepatitis, osteomyelitis
Inflammaging	Frailty, cachexia, geriatric syndromes
Miscellaneous	Chronic leg ulcers
Nonhematopoietic neoplasms	
Gastrointestinal tumors	Colorectal cancer, gastric cancer, etc
Multiorgan metastasis	End-stage carcinomas
BM metastasis	Various cancer types including breast and prostate
Endocrinologic and metabolic causes	
Low production of EPO	Renal anemia or pure EPO deficiency*
Thyroid dysfunction	Hypothyroidism or hyperthyroidism
Insulin deficiency	Diabetes mellitus
Blood loss	
Gastrointestinal tract bleeding	Peptic ulcer, ulcerative colitis, etc
Diffuse GI tract bleeding	Anticoagulant-mediated bleeding
Surgical procedures	Multiple abdominal surgeries
Different locations	Epistaxis, hematuria
Increased consumption or destruction of erythrocytes	
Chronic nonmechanical hemolysis	Autoimmune hemolytic anemia
Mechanical destruction of red cells	Heart valve–mediated red cell lysis
Hypersplenism	Hepato-/splenomegaly
Lack of nutrients	
Vitamin deficiency	Vitamin B_{12} and/or folate deficiency
Trace element deficiency	Copper deficiency†
Iron deficiency	Blood loss
Drug-induced anemia	
Chemotherapy	Chemotherapy-induced pancytopenia
Antimetabolites, anticonvulsants	Folate deficiency
Toxic drug reactions	Drug-induced hemolysis

- 1/3 of older patients with anemia have either CKD or a cause of anemia of inflammation (AI)
- Treatment directed at underlying etiology
- **Reasonable first-line workup**: CBC, reticulocyte count ,blood film, ferritin, iron profile, vit B12 level, SPEP, ESR/CRP, Cr, TSH, LDH, haptoglobin, bilirubin

Distinguishing IDA from ACD

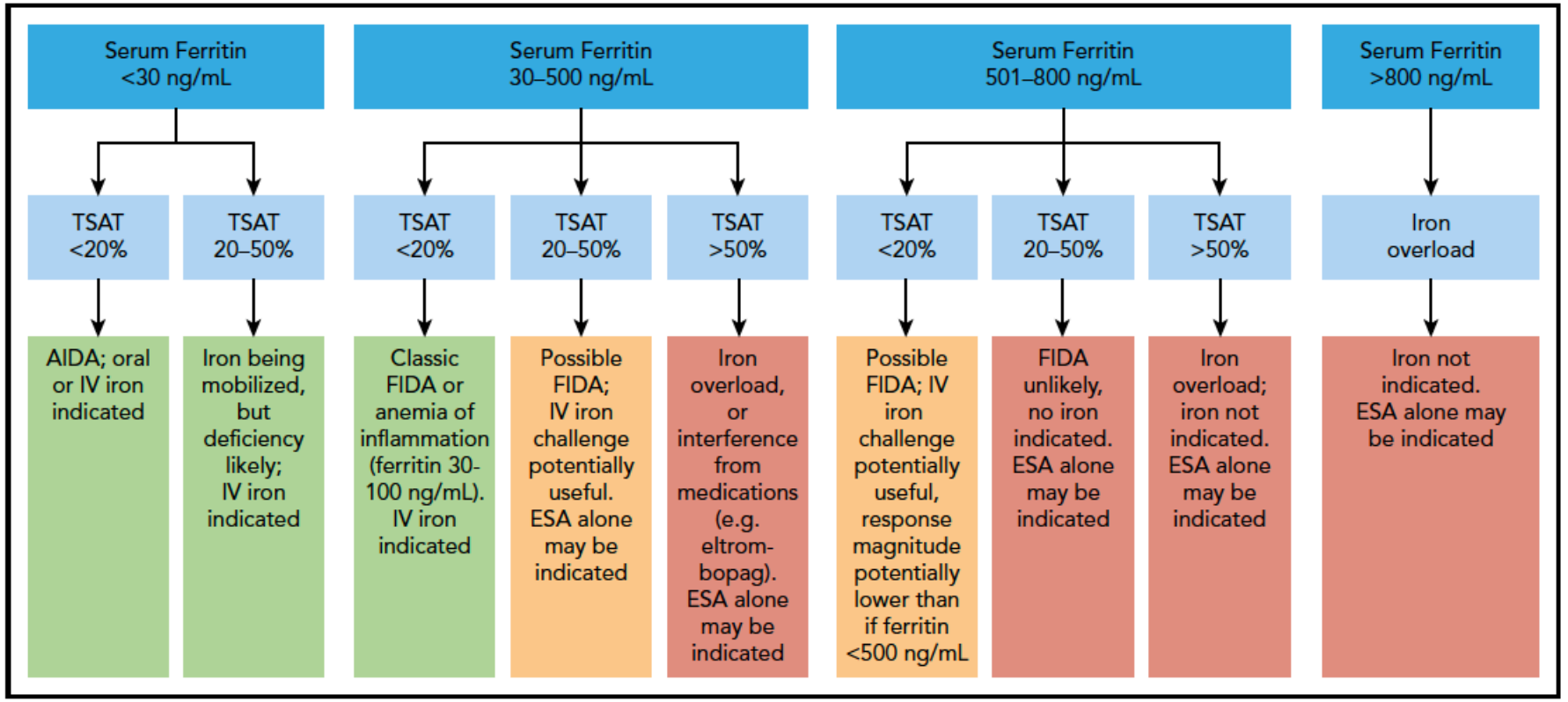

Figure 3. Algorithm using serum ferritin and transferrin saturation to predict response to iron in cancer-associated anemia. Green boxes indicate benefits of IV iron therapy. Yellow boxes indicate that an iron trial may be beneficial. Red boxes indicate that iron should not be given. Patients with TSAT <20% and inflammation elevating the serum ferritin (up to 100 ng/mL) will likely respond in a manner similar to that of classic AIDA; patients with ferritin >100 ng/mL may exhibit slightly lower Hb responses. A CHr and reticulocyte count may help to determine whether to give iron in this instance. Professional illustration by Patrick Lane, ScEYEnce Studios.

IDA – iron deficiency anemia
ACD – anemia of chronic disease

Gilreath et al 2020: How I Treat cancer-associated anemia

Treatment: oral iron

- Many options available, varying primarily in elemental iron content all roughly equivalent in terms of efficacy – I am not fussy
- Some formulations purported to have better tolerability but I find this anecdotally highly patient-specific
- My go-to are the oral iron salts: **ferrous gluconate,** ferrous sulfate, **ferrous fumarate** (bold = on ODB formulary); these are in order of increasing elemental iron content
- My approach: ferrous fumarate unless patient mentions a propensity to constipation or GI upset, in which case I use ferrous gluconate
- Dose 1 tablet (300mg) PO daily (or q2d), taken on an empty stomach, away from other cation-containing drugs/supplements (e.g. calcium, magnesium)
- Side effects: GI upset, constipation
- If unable to manage toxicities with OTC laxatives, consider q2d dosing; last resort, take with food (but will decrease absorption)

Treatment: IV iron

- Highly effective and under-used treatment option (access remains a big issue)
- Two main formulations in Canada: **iron sucrose** (Venofer) and **ferric derisomaltose** (Monoferric)
- Typical treatment dose = 1000mg (3x300mg iron sucrose or one dose 1000mg ferric derisomaltose)
- Cost for course of treatment = roughly $500 (one ferric derisomaltose dose, or $150 per iron sucrose dose); most private drug plans cover both (but ask your patient to check, some will cover one or the other)

**ferric derisomaltose available on ODB with LU code (610)!

FERRIC DERISOMALTOSE
100mg elemental iron/mL Inj Sol (Preservative-Free)

New Search

Reason For Use Code	Clinical Criteria
610	For the treatment of patients with Iron Deficiency Anemia (IDA) who meet ALL the following criteria: - Patient has documented diagnosis of IDA confirmed by laboratory testing results (e.g. hemoglobin, ferritin); AND - Patient's IDA has experienced a failure to respond, documented intolerance, or contraindication to an adequate trial (i.e. at least 4 weeks) of at least one oral iron therapy; AND - Patient does not have hemochromatosis or other iron storage disorders; AND - Monoferric is administered in a setting where appropriate monitoring and management of hypersensitivity reactions can be provided to the Patient.
	LU Authorization Period: 1 year

Treatment: IV iron cont'd

- Must be administered in an infusion clinic (but not necessarily prescribed by a hematologist – institution policies vary)
- Toxicity: rash, anaphylaxis (1:1000), Fishbane infusion reaction, delayed reactions (arthralgia/myalgia/low-grade fever), hypotension (mainly with ferric derisomaltose)
- Assess for response about 4-6 weeks following infusion; if iron stores not adequately replenished, can give additional dose(s)

Anemia: Pearls and Pitfalls

- Anemia is a finding not a diagnosis – always think of etiology
- 'Jumping the gun' – sometimes tendency to assume 'anemia' = 'iron deficiency'; send a ferritin, Tsat, consider ddx
- Ignoring iron deficiency without anemia – patients can still be symptomatic (and this could still be a sign of significant pathology)
- Dosing oral iron more than once daily – no role for this (no added benefit, increases side effects)
- Pushing oral iron too hard – if inadequate response after a 3 month trial of oral iron, or intolerance to oral iron, should strongly consider parenteral iron (*especially* in patients unlikely to absorb iron well, e.g. post-bariatric surgery, IBD patients)

Anemia: When to refer?

- Undifferentiated anemia: Hb<110 without obvious cause after first line evaluation
- Macrocytic anemia (especially if no clear B12 deficiency, liver disease, alcohol use, medication cause, or hypothyroid)
- Iron deficiency: Inadequate response to a 3-month trial of oral iron therapy or intolerance of oral iron
- Oral iron relatively contra-indicated or very unlikely to be effective (IBD, bariatric surgery, anyone who really must not get constipated e.g. post-op, anal fissure, etc)
- Need for rapid optimization (e.g. pregnant, pre-op)
- Combined hematinic deficiencies (e.g. iron + B12) – suggests possible malabsorption syndrome

Case 2

- Mr. S is a 71M in your practice with long-standing EtOH use disorder. He does not have a known history of liver disease. He was recently admitted to hospital with EtOH-induced pancreatitis, and you are seeing him in follow-up post discharge. You notice that on his inpatient bloodwork, his platelet count has been persistently low in the 50-60 range. What are your next steps in working this up? What do you think is/are the most likely possible cause(s)

Approach to thrombocytopenia

How to approach thrombocytopenia

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Thrombocytopenia is a common hematologic finding with variable clinical expression. A low platelet count may be the initial manifestation of infections such as HIV and hepatitis C virus or it may reflect the activity of life-threatening disorders such as the thrombotic microangiopathies. A correct identification of the causes of thrombocytopenia is crucial for the appropriate management of these patients. In this review, we present a systematic evaluation of adults with thrombocytopenia. The approach is clearly different between outpatients, who are frequently asymptomatic and in whom we can sometimes indulge in sophisticated and relatively lengthy investigations, and the dramatic presentation of acute thrombocytopenia in the emergency department or in the intensive care unit, which requires immediate intervention and for which only a few diagnostic tests are available. A brief discussion of the most common etiologies seen in both settings is provided.

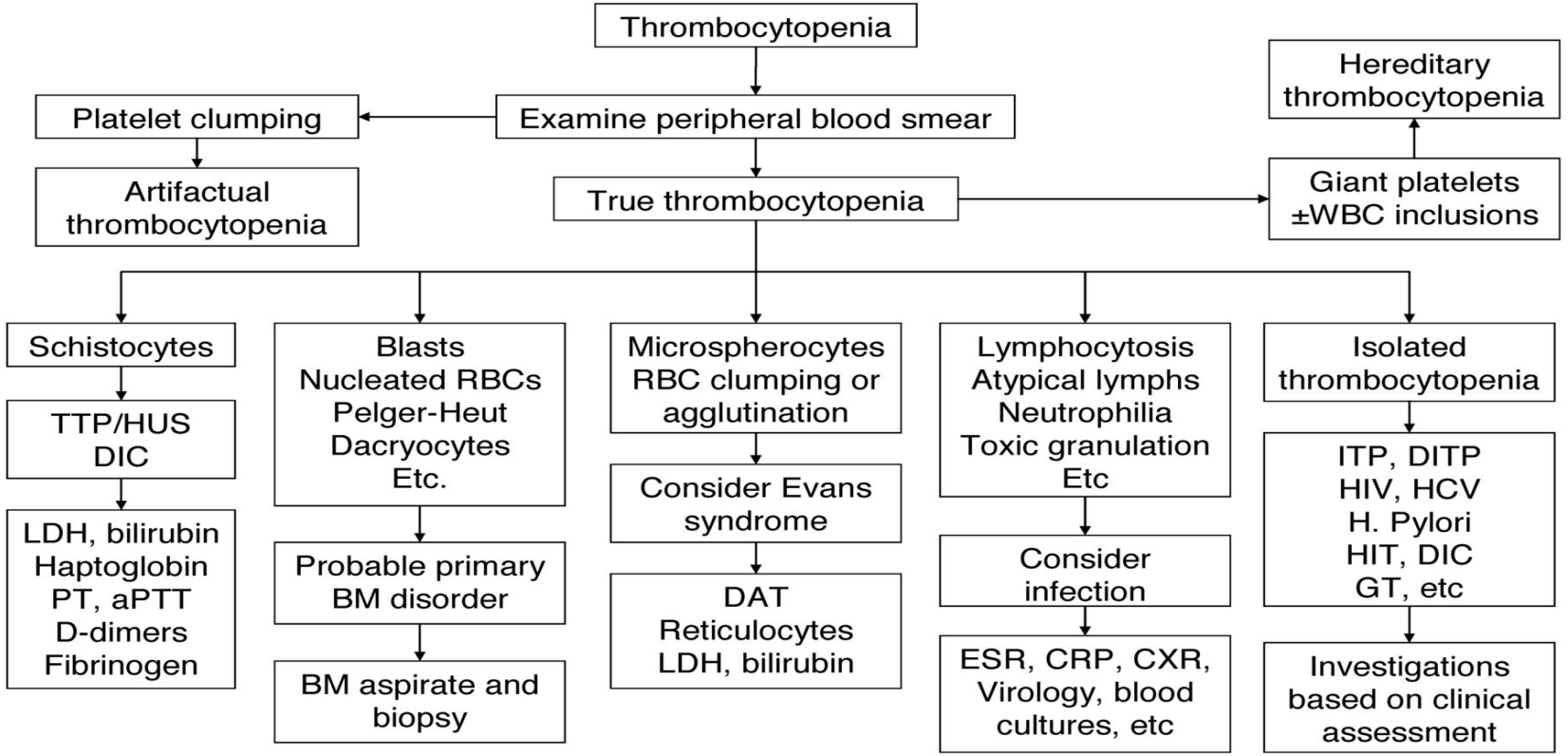
Table 1. Clinical scenarios and most common causes of thrombocytopenia

	Inpatient		
Outpatient	**Multisystem illness/ICU**	**Cardiac patient**	**Pregnancy/postpartum**
ITP	Infections	HIT	GT
DITP	TTP/HUS	Cardiac bypass	ITP
Infections	DITP	GPIIb/IIIa inhibitors	HELLP syndrome
HIV	DIC	Other DITP	Preeclampsia
Hepatitis C virus	Liver disease	Dilutional	Abruptio placentae
Helicobacter pylori	HIT		TTP/HUS
CMV	MAS		
Other recent viral infections	BM disorders		
Connective tissue disorders	CIT		
Systemic lupus erythematosus			
Rheumatoid arthritis			
Antiphospholipid syndrome			
Vaccinations			
Myelodysplastic syndromes			
Congenital thrombocytopenia			
Common variable immunodeficiency			

TTP/HUS indicates thrombotic thrombocytopenic purpura/hemolytic uremic syndrome; MAS, macrophage activation syndrome (including hemophagocytic syndrome); CIT, chemotherapy-induced thrombocytopenia; HELLP, hemolysis, elevated liver enzymes, and low platelets.

Also myelosuppressive drugs (septra, MTX, chemotherapy, etc)

Approach to Thrombocytopenia



Always order a blood film for any new thrombocytopenia (*especially* if concurrent anemia) – should be reflexed by the lab

The presence of **fragments (schistocytes)** or **blasts** on the blood film is a *medical emergency* → send patient to ED

Thrombocytopenia Pearls and Pitfalls

- "Platelet clumping" in EDTA tubes is an artifactual phenomenon of no clinical significance – order a **citrate tube platelet count** (usually solves the problem)
- Platelet counts >100 are generally **not** associated with adverse clinical sequelae and can be safely observed (unless associated with other cytopenias, or abnormal clinical bleeding)
- Platelets are often an 'innocent bystander' ; consider intercurrent illness (especially infection/sepsis) in patients with acute moderate thrombocytopenia
- Abdo U/S reasonable to get in virtually everyone with unexplained thrombocytopenia; I have picked up *many* new diagnoses of cirrhosis this way!

Thrombocytopenia When to refer?

- Platelet count <100
- If platelet count >100, refer if there is a co-existent cytopenia, or abnormal clinical bleeding phenotype (may suggest type 2b VWD or a congenital platelet disorder)

Case 3

- Ms. J is a 74 year old woman who is new to your practice. She is a recent immigrant from Guyana. You are doing an intake visit with her in your falls prevention clinic, and order some baseline bloodwork. You find her ANC is low at 0.9. She is entirely well with no other PMHx and is on no medications. What do you do?

Neutropenia

- Defined as ANC<1.5 (mild), <1 (moderate), <0.5 (severe)
- Anxiety-provoking for clinicians and patients alike
- Challenging: ddx spans completely clinically insignificant entities to life-threatening ones

Neutropenia: causes

Table 1. Causes of neutropenia in adults

Congenital*	
Constitutional neutropenia	
Ethnic neutropenia	Duffy-associated neutrophil count (DANC)
Benign familial neutropenia	
Cyclic neutropenia	
Acquired	
Infection-associated	
Post-infectious	
Active infection (sepsis, viruses)	
Drug-induced	
Agranulocytosis	
Mild neutropenia	
Autoimmune	
Primary autoimmune	
Secondary autoimmune	
Felty syndrome	
Malignancy	
Acute leukemia	
Myelodysplasia	
LGL leukemia	
Myeloma, lymphoma	
Myelophthisic processes	
Dietary	
B_{12}, folate deficiency	
Copper deficiency	
Global caloric malnutrition	

*Excludes forms of congenital neutropenia that would be diagnosed in childhood (eg, severe congenital neutropenia or neutropenia occurring in the context of a larger congenital syndrome).

Think of ddx in terms of 'buckets': drugs, autoimmune conditions, malignancy, infections (especially viral, acute or chronic)

Approach to neutropenia

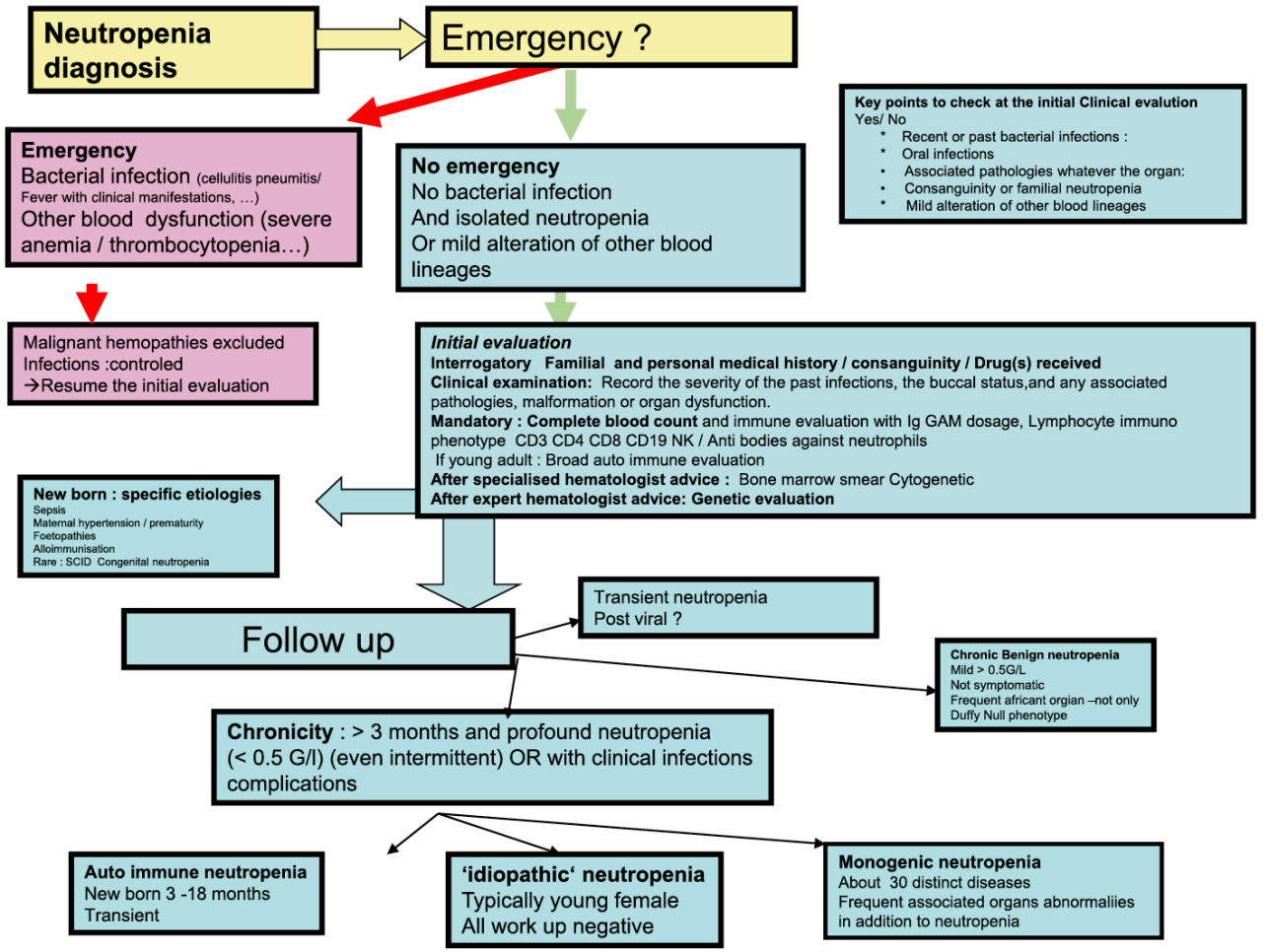


Figure 1. Evaluation of neutropenia: an overview.

Duffy-associated neutrophil count (DANC)

When non-Whiteness becomes a condition

Lauren E. Merz[1] and Maureen Achebe[2,3]

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The term "benign ethnic neutropenia" describes the phenotype of having an absolute neutrophil count (ANC) <1500 cells/μL with no increased risk of infection. It is most commonly seen in those of African ancestry. In addition, ANC reference ranges from countries in Africa emphasize that ANC levels <1500 cells/μL are common and harmless. The lower ANC levels are driven by the Duffy null [Fy(a-b-)] phenotype, which is protective against malaria and seen in 80% to 100% of those of sub-Saharan African ancestry and <1% of those of European descent. Benign ethnic neutropenia is clinically insignificant, but the average ANC values differ from what are typically seen in those of European descent. Thus, the predominantly White American medical system has described this as a condition. This labeling implicitly indicates that common phenotypes in non-White populations are abnormal or wrong. We believe that it is important to examine and rectify practices in hematology that contribute to systemic racism. (*Blood.* 2021; 137(1):13-15)

- Formally called 'benign ethnic neutropenia'
- Below reference-range neutrophil count in an individual with African or Middle Eastern ancestry (areas of historical or ongoing malaria endemicity)
- **NO** history of infection/constitutional symptoms
- Associated with the 'Duffy null' minor RBC antigen phenotype
- Is of no clinical significance

Neutropenia: pearls and pitfalls

- Consider DANC in a patient of typical ancestral background with mild-moderate neutropenia (0.5-1.5) who is otherwise *completely well* ; this entity has no clinical significance and should not be over-investigated
- ANC <0.5 – counsel on febrile neutropenia (ED if T>38C) while patient is under active diagnostic evaluation/awaiting consultation
- In a well patient with moderate neutropenia, suggest repeat CBC in 1-2 months (transient neutropenia is common with many viral illnesses; if resolves, referral not needed)

Neutropenia: When to refer?

- ANC <1 is a reasonable threshold (ANC <0.5 reasonable threshold in a patient with typical ancestry for DANC if otherwise asymptomatic)
- ANC <1.5 if co-existing cytopenia, recurrent infections, constitutional symptoms

Case 4

- Ms. L, an 86 year old woman in your practice, was recently admitted to hospital with diarrhea and acute kidney injury. During her stay, a serum protein electrophoresis (SPEP) was ordered. It was pending at time of discharge. You are seeing her in clinic at a regular follow-up visit and see the report in your EMR. The comment reads "a discrete band, IgG kappa, is identified at 2g/L". You wonder what you should do next.

MGUS

- MGUS stands for "monoclonal gammopathy of uncertain significance"
- Also referred to as a **paraprotein**
- Indicates the presence of a plasma cell clone
- Why do we care? Plasma cell clones can become cancerous (myeloma), or otherwise cause end-organ damage (even if criteria for myeloma are not met)
- **Very common**: 3-5% of the population >50 years of age!
- The clinical challenge is sorting out which patients require further evaluation/closer surveillance

Plasma Cell Dyscrasias

MGUS	Smoldering Multiple Myeloma (SMM)[2]	Multiple Myeloma (MM)
M-protein < 3 g/dL (30 g/L) **AND** Clonal bone marrow plasma cells < 10% **AND/OR** Urine monoclonal protein < 500 mg/ 24 hours	M-protein ≥ 3 g/dL (30 g/L) **AND/OR** Urine monoclonal protein ≥ 500 mg/24 hours **AND/OR** Clonal bone marrow plasma cells ≥ 10% Patients with SMM may require additional imaging including PET-CT, low-dose whole-body CT, or MRI of whole body or spine/pelvis	End-organ disease (CRAB) including one or more osteolytic lesions on radiography, but more than one lesion is required if < 10% marrow plasma cells. From MRI imaging, there must be more than one lesion of > 5 mm in size. **AND/OR** Clonal bone marrow plasma cells > 60% **AND/OR** An involved serum free light chain (kappa or lambda) > 100 mg/L with the ratio of the involved/uninvolved free light chains also > 100 mg/L

https://www.hematology.org/education/clinicians/guidelines-and-quality-care/pocket-guides

MGUS: lab evaluation and risk factors for progression

Test	Comment
CBC	For a diagnosis of MGUS, results are within normal limits. Abnormal results may be indicative of an alternate diagnosis (see Table 3).
Calcium	
Creatinine	
LDH (lactate dehydrogenase)	
LFTs (liver function tests)	
Qualitative test for urine protein	
Serum and urine protein electrophoresis (UPE) with immunofixation (IFE)	May be diagnostic for a clonal plasma cell disorder. If the above qualitative test for urine protein is abnormal, check 24 hour urine collection for UPE and IFE.

Risk factors for progression per Mayo criteria[3]
M-protein > 1.5 g/dL (15 g/L)
Non-IgG isotype (IgA or IgM)
FLC Ratio < 0.26 or > 1.65

Bone marrow biopsy recommended!

IgM MGUS is usually associated with **lymphomas** rather than myeloma; examine for lymphadenopathy and consider abdominal imaging (ultrasound or CT)

MGUS: Pitfalls

- Ordering an SPEP without a clear indication (unexplained anemia, unexplained renal dysfunction, hypercalcemia, *lytic* bony lesions, unexplained neuropathy)
- Ordering serum free light chain assay without an established finding of a monoclonal gammopathy (*community labs also charge for this – very reasonable to leave for the specialist)
- *Elevated serum free light chains without an abnormal serum free light chain **ratio** are NOT indicative of a clonal process*
- *'polyclonal gammopathy' is indicative of inflammation and is not indicative of a primary hematologic disorder*

MGUS: When to refer?

- Reasonable to refer any established monoclonal gammopathy (discrete band identified on SPEP and/or immunofixation)
- Low risk MGUS (per Mayo criteria) – consider OTN econsult service
- Higher-risk MGUS should be seen formally by a hematologist as a bone marrow evaluation is indicated per guidelines
- MGUS in the presence of unexplained skin changes, renal dysfunction, cardiomyopathy, neuropathy (possible "monoclonal gammopathy of clinical significance" or MCRS)

Case 5

- Mr. T is a 68M in your practice. He tells you that his father had hemochromatosis. His primary care provider had ordered a ferritin level, and you see it is elevated (550ug/L). What do you do next?

Approach to high ferritin

- Serum ferritin is a marker of the body's **iron stores**, however it is also an **acute phase reactant** and is **primarily stored in the liver**
- The concern when high ferritin is seen is **hemochromatosis** (genetic); while this is relatively common (particularly in individuals of northwestern/northern European ancestry), *inflammation* and *liver disease* are much more common reasons for high ferritin seen in clinical practice
- Ask about: alcohol use, family history of hemochromatosis (or unexplained liver/cardiac disease), recent infections
- The **transferrin saturation (TS)** is a much better screening test for hemochromatosis than ferritin for these reasons: **a TS >45%** is suggestive of true iron overload and should be followed by genetic testing (**HFE gene**)
- If TS not >45% and there is no family history of hemochromatosis, symptoms suggestive of hemochromatosis, or liver enzyme elevation, evaluate for alternate causes

Signs and symptoms of hemochromatosis

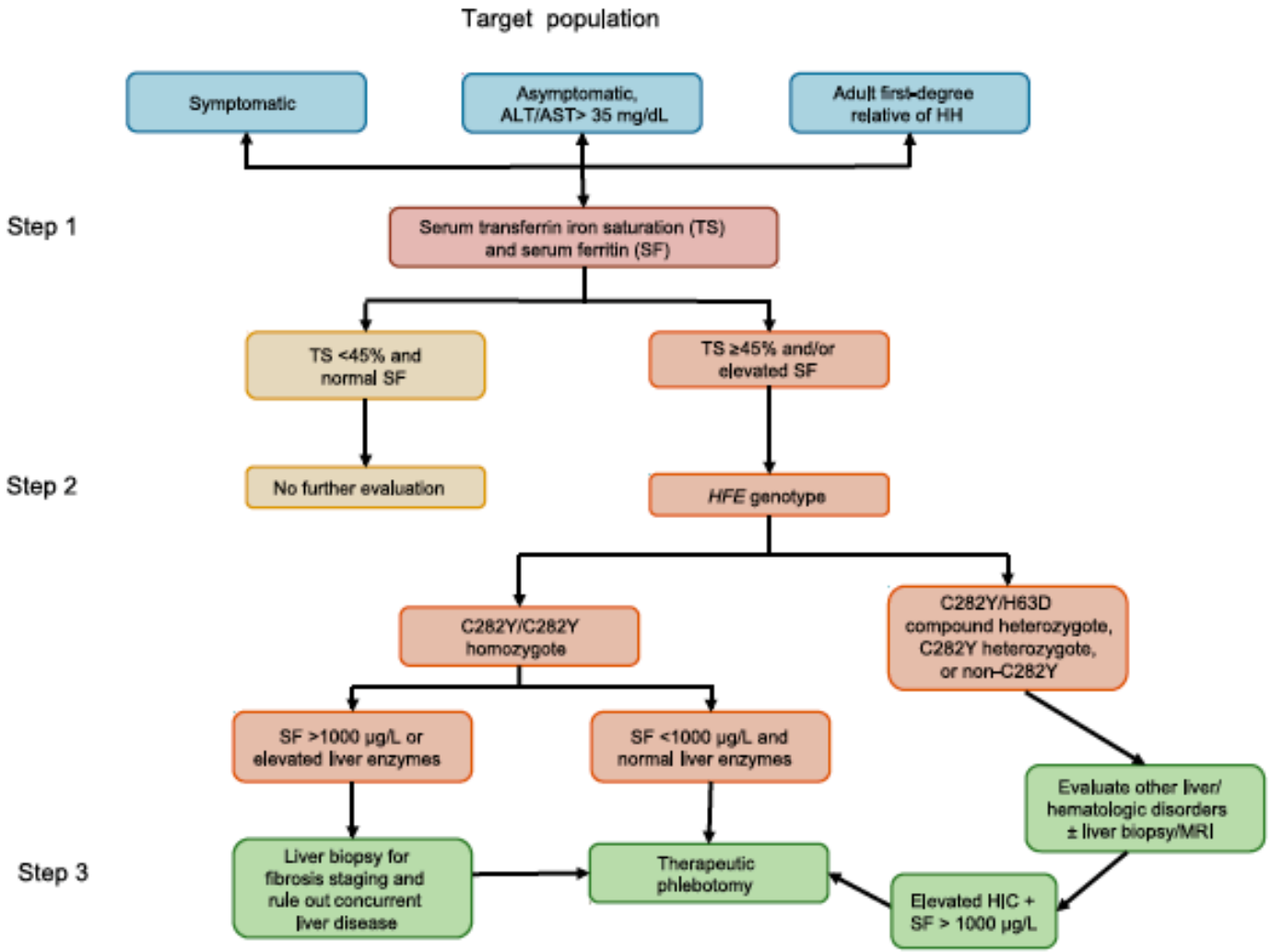
Table 4. Clinical manifestations of HH

Organ	Manifestations
Liver	Elevated liver enzymes Hepatomegaly Fibrosis Cirrhosis HCC
Endocrine	Hyperglycemia Diabetes mellitus Hypogonadism Testicular atrophy Amenorrhea Loss of libido Hypopituitarism
Skin	Hypermelanotic pigmentation (bronze skin)
Joints	Arthralgia Arthritis Chondrocalcinosis
Heart	Cardiomyopathies Arrhythmias Heart failure

HCC, hepatocellular carcinoma; HH, hereditary hemochromatosis.

ACG Clinical Guideline: Hereditary Hemochromatosis

Suspected hemochromatosis: algorithm



HFE gene mutations: C282Y, H63D (C282Y more pathogenic)

ACG Clinical Guideline: Hereditary Hemochromatosis

High ferritin: pitfalls

- Not ordering a TS (*must indicate "hemochromatosis" on MOH requisition for community labs to process)
- Over-referral/over-investigation of asymptomatic mild-moderate ferritin elevation (especially if TS normal) – consider reactive causes, especially **alcohol** and **liver disease**
- Inappropriate genetic testing: follow the ACG algorithm
- Patients heterozygous for an HFE gene mutation are **not** at risk for clinical iron overload (and these are *common* – allelic frequency 6-7% in people of European descent!)
- HFE gene testing is less informative in patients without European ancestry – testing for other implicated genes not routinely available

High ferritin: when to refer?

- TS>45%
- Ferritin >500 if TS <45%
- Anyone with a first degree relative with hemochromatosis who has high ferritin OR TS>45%
- Patients with anemia and high ferritin – consider iron overloading anemia syndromes (e.g. beta thalassemia) → refer

Referral parameters for other hematologic abnormalities

Hematologic Issue	We will only see if
Isolated neutropenia	ANC ≤ 1.0 on two or more readings
Isolated neutrophilia with no left shift	ANC ≥ 15.0
Isolated thrombocytopenia	Platelets ≤ 100
Macrocytosis and normal CBC	MCV ≥ 110
Anemia NYD	Hb ≤ 110
Iron deficiency	Not anemic: Ferritin < 10 If anemic: Ferritin ≤ 30 If pregnant: Ferritin ≤ 50
Lymphocytosis	Absolute Lymphocyte Count ≥ 5.0
Lymphopenia	Absolute Lymphocyte Count ≤ 0.5
Marrow infiltration on MRI	Concomitant abnormal CBC History of solid tumour malignancy or hematologic disorder
Eosinophilia	Eosinophils ≥ 1.0 (if other accompanying adenopathy or cytopenias, Malignant Heme)
High ferritin	If no TSAT provided: Ferritin > 500 If TSAT > 45%: Ferritin > 200
High IgG, IgA, or IgM	Monoclonal protein present on SPEP or abnormal serum free light chains
MGUS, confirmed	Malignant Heme
Erythrocytosis	< 50%, any age, Non-malignant Heme <55%, age less than 50, Non-malignant Heme (otherwise, Malignant Heme)
Splenomegaly	Benign Heme, unless pancytopenia or discrete lesions
Lymphadenopathy	>3.5cm, Malignant Heme 2-3.5cm with red flags (e.g. abnormal architecture, Bsx), Malignant Heme < 2 cm, Non-malignant Heme
Thrombocytosis	< 500 Non-malignant Heme > 500 Malignant Heme unless iron deficiency or clear reactive cause

Useful websites

- https://thrombosiscanada.ca/
- https://transfusionontario.org/en/category/bloody-easy-e-tools-publications/bloody-easy-for-healthcare-professionals/
- https://www.hematology.org/education/clinicians/guidelines-and-quality-care/pocket-guides
- https://www.wolterskluwer.com/en/solutions/uptodate

Concluding thoughts

- For many mild CBC abnormalities in a patient that is otherwise well, repeating the CBC in a few months to evaluate for persistence is a reasonable first step
- There is a major shortage of non-malignant hematologists in this province and wait-times are long; consider e-consult service (OTN) for non-urgent referrals (many can be safely managed without formal consultation)
- If you are not sure if something should be referred, reach out to your local hematologist to ask; we tend to be pretty friendly people ☺

Thank you!
Questions?

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