Anemia in Primary Care

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Annual Primary Care Review

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Disclosure

- I have no financial disclosure or conflict of interest in relation to this presentation

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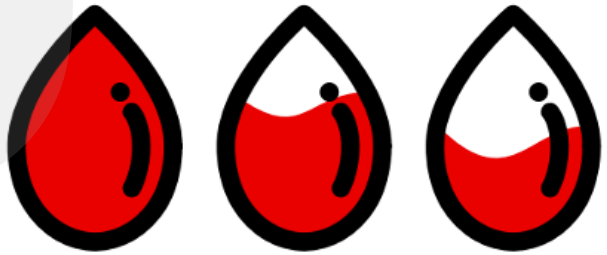
Objectives

- Describe the approach to the workup of anemia
- Differentiate between iron deficiency and anemia of chronic disease
- Review management strategies for iron deficiency anemia

Anemia

- Reduction in red blood cell mass (Hct) or hemoglobin (Hgb)

- Diagnostic approach by indices
  - Reticulocyte count: based on production
    - Lack of production vs increased losses vs premature breakdown
  - Mean corpuscular volume (MCV): based on size
    - Microcytic, normocytic, macrocytic



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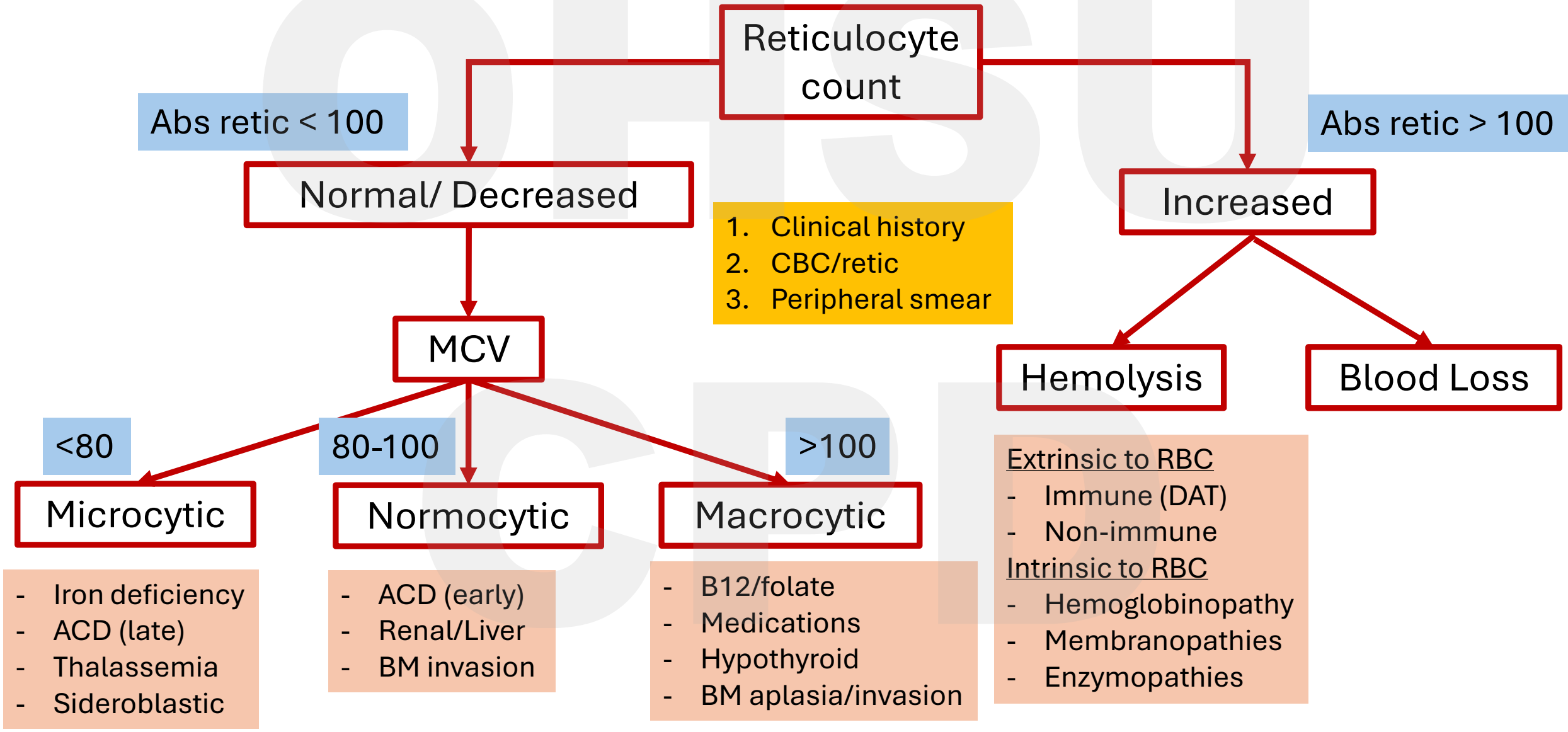
Approach to Anemia



Workup of Anemia

Etiology	First line	Second line
Comorbid condition (i.e., renal, liver, hypothyroid)	CMP, TSH	EPO, abdominal ultrasound, HIV, HCV

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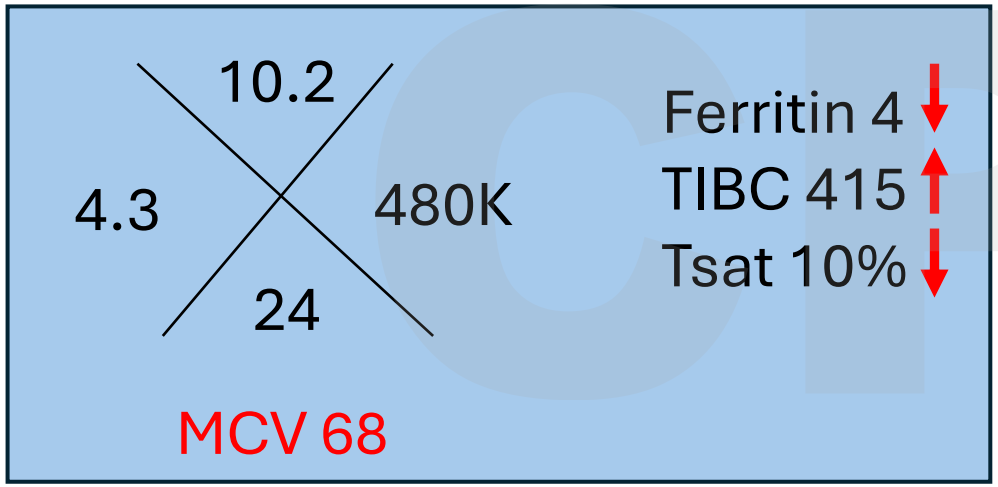
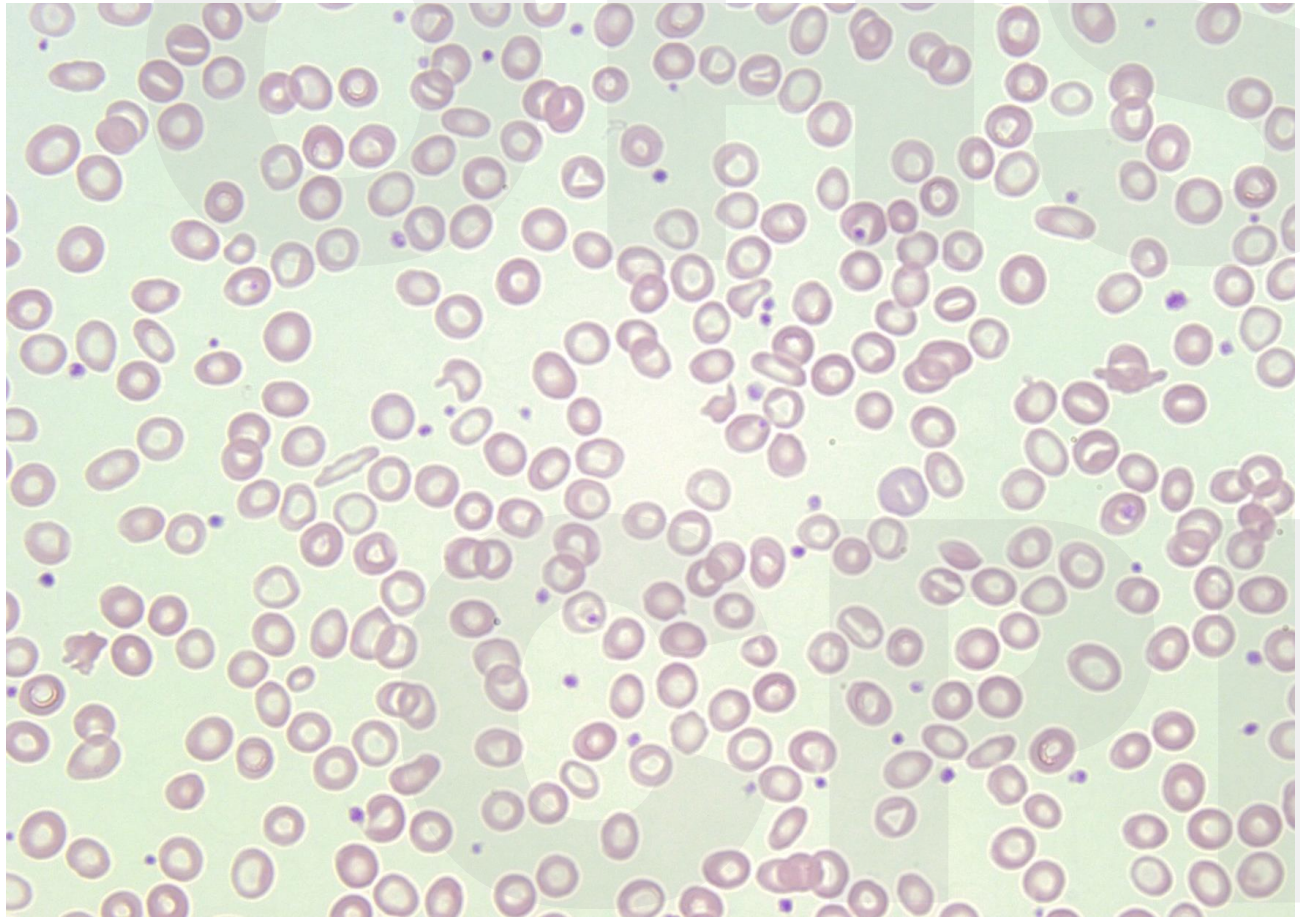
Case 1

- 28-year-old female presents to her PCP for routine evaluation
- Endorses some fatigue but attributes this to work
- Requests referral to the dentist
- Thinks she cracked a tooth while eating ice…

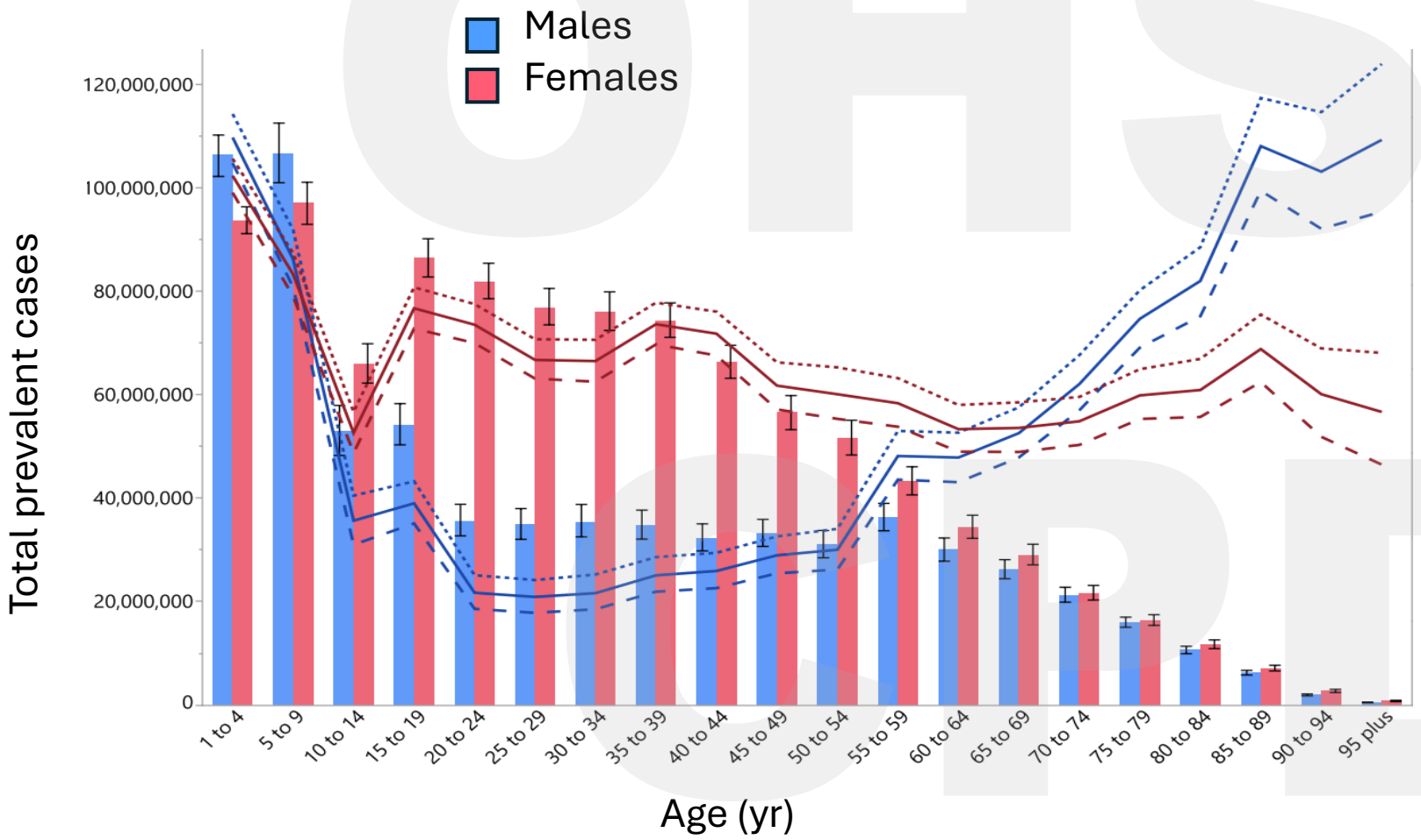


Peripheral Blood Smear



- Hypochromia
- Microcytosis
- Thrombocytosis

Epidemiology of Anemia

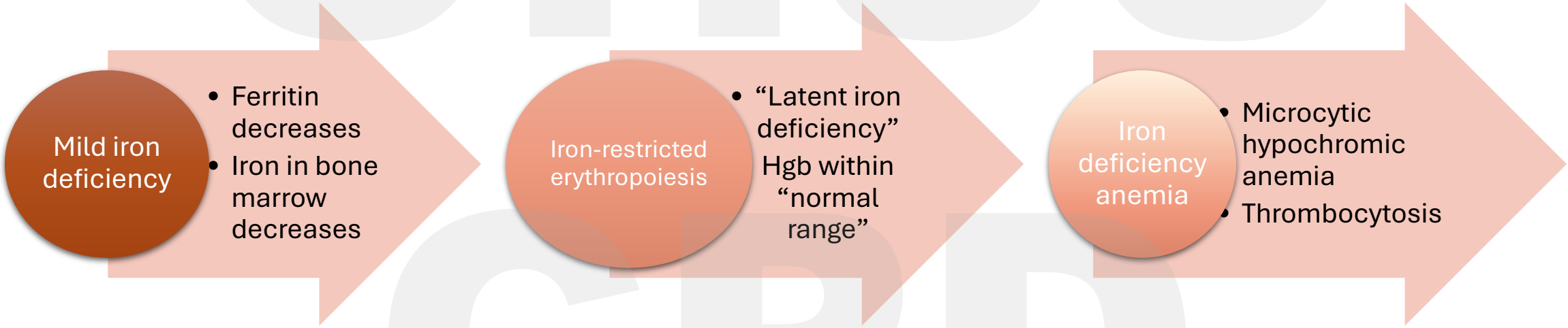


- Anemia is exceedingly common
  - >1.9 billion cases globally
  - 25% of global population
  - Iron deficiency is leading cause
- Divergence of prevalent cases by sex at menarche

Safiri et al. J Hematol Oncol 2021

Iron Deficiency Exists on a Spectrum

Iron deficiency even in the absence of anemia can be symptomatic!



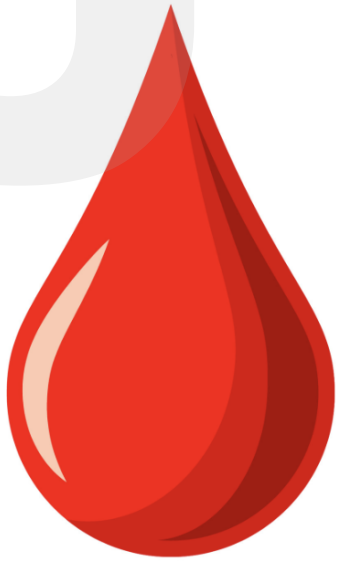
- Fatigue
- Lethargy
- Cold intolerance

- Decreased exercise capacity
- Reduced concentration
- Pica/ restless leg syndrome

- Palpitations
- Dizziness
- Shortness of breath

Approach to Management of IDA

1. Confirm the diagnosis
2. Identify the cause
3. Correct or manage the primary cause
4. Provide iron therapy, PO vs IV
5. Confirm repletion



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1. Confirm the Diagnosis

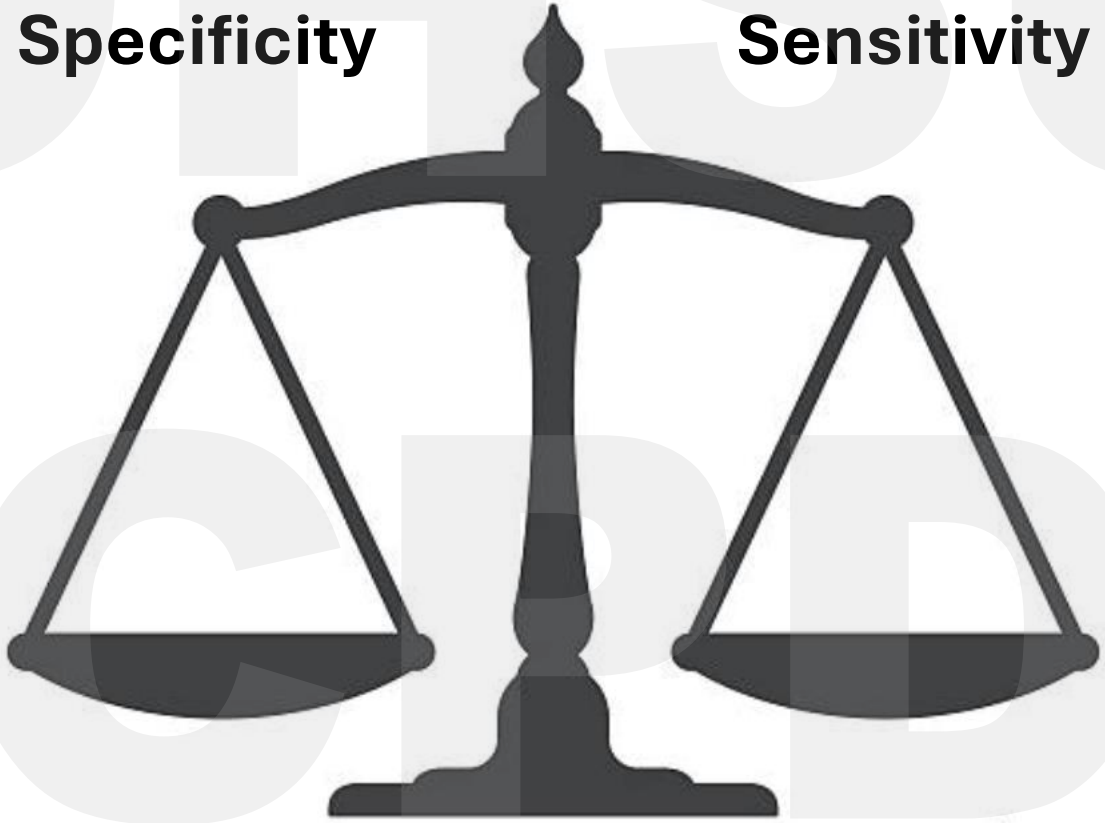
	Iron Deficiency Anemia	Anemia of Chronic Disease
Serum Iron	↓	↓
TIBC	↑	↓
Tsat	↓	↓
Ferritin	↓	↑
Transferrin Receptor	↑	–

Optimal ferritin to diagnose iron deficiency?

Specificity **Sensitivity**

WHO 2022
Ferritin < 15 ug/L

98% specific 75% sensitive



AGA Guidelines
Ferritin < 45 ug/L

92% specific 85% sensitive

*Compared to “gold standard” of bone marrow biopsy

Movement toward a higher (and standardized) threshold…

- Physiologic studies using stable iron isotope[1]
  - Increased iron absorption in GI tract in iron deficiency
  - Physiologic compensation does not return to baseline until ferritin >50

- Multiple studies demonstrating improvement in fatigue when ferritin repleted > 50[2,3]

[1]Galetti et al. E Clin Med 2021
[2]Beutler et al. Ann Intern Med 1960
[3]Vaucher et al. CMAJ 2012

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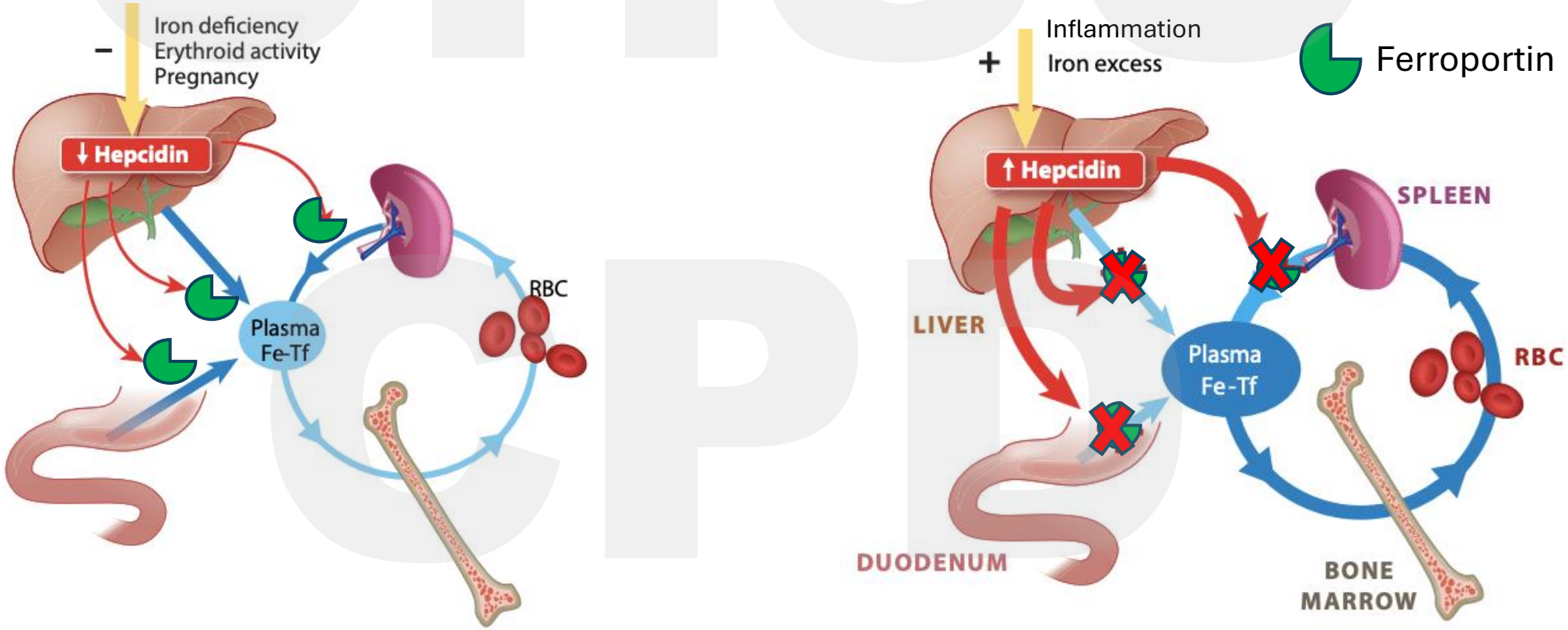
Chronic Inflammation

IL-6 → increased hepcidin → iron-restricted erythropoiesis

AKA "<u>functional iron deficiency</u>"



Nemeth E, Ganz T. *Annu Rev Med* 2022

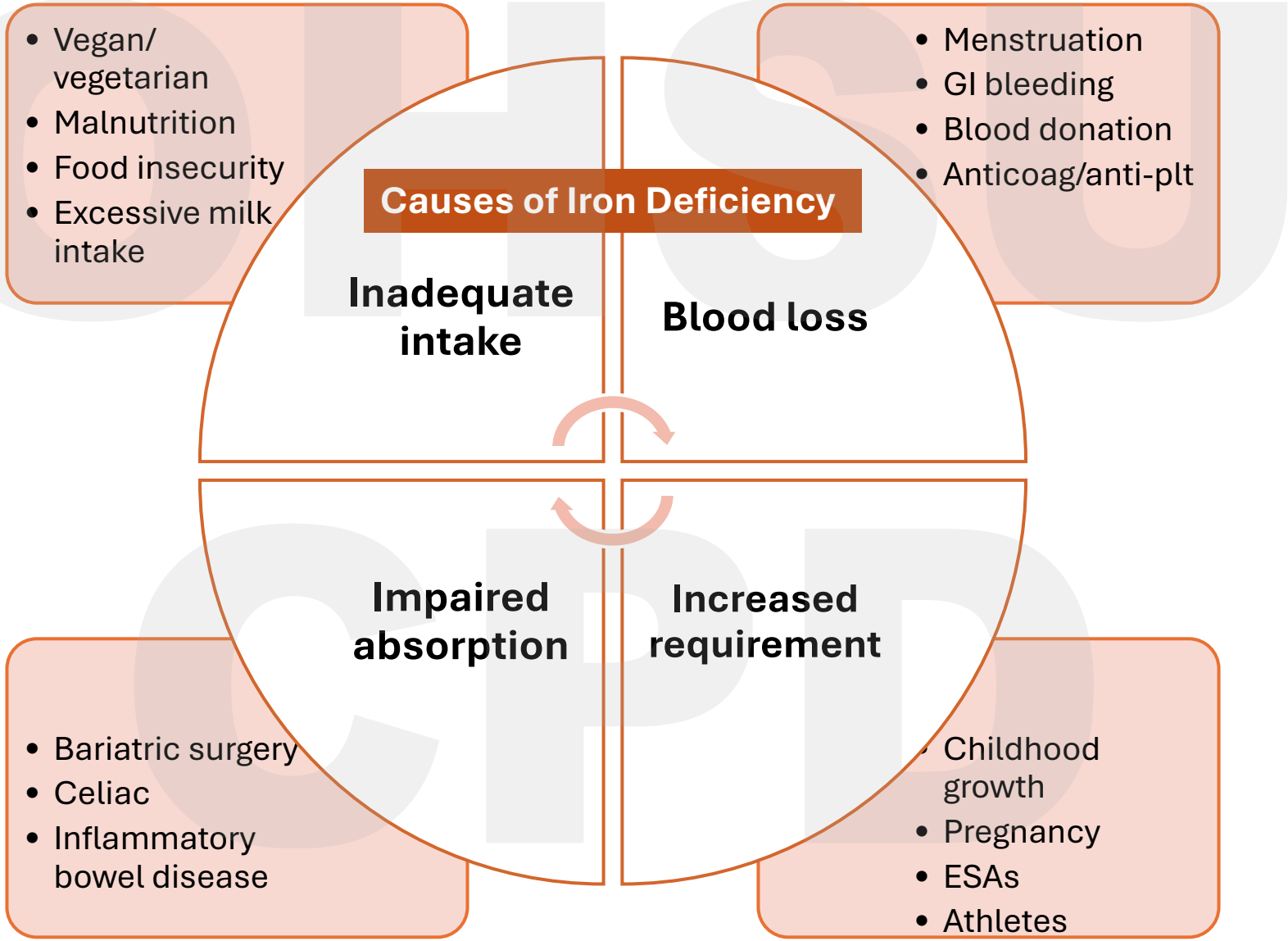
Anemia of Chronic Disease

- Ferritin is an acute phase reactant[1]
  - CRP <10 mg/L – ferritin 85 ng/mL
  - CRP 10 - 80 mg/L – ferritin 193 ng/mL
  - CRP >80 mg/L – ferritin 342 ng/mL

- Distinguishing absolute vs functional iron deficiency
  - Absolute iron deficiency unlikely if ferritin > 100[2]
  - Functional iron deficiency can still be present → Tsat can be helpful (<20%)

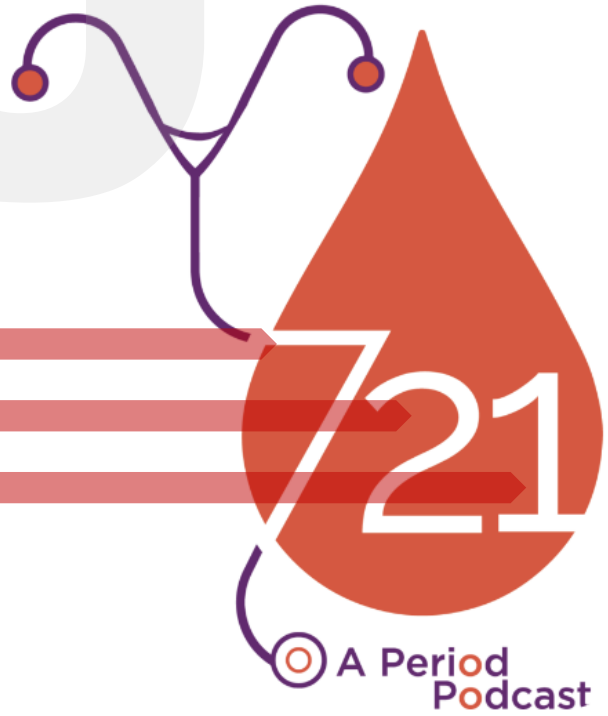
[1]McSorely et al. Transl Res 2016
[2]Guyatt et al. J Gen Intern Med 1992

2. Identify the Cause



3. Identify the Cause

- Heavy menstrual bleeding (HMB) is under-recognized
  - Historic and cultural stigmatization
  - Lack of awareness of normal vs. abnormal
  - 7-2-1 Rule
    - Cycles lasting longer than 7 days
    - Changing menstrual protection > 2hr
    - Passing clots >1 in (quarter in size)



- Don’t forget to consider occult GI bleeding
  - AGA Guidelines: endoscopy in males and postmenopausal females

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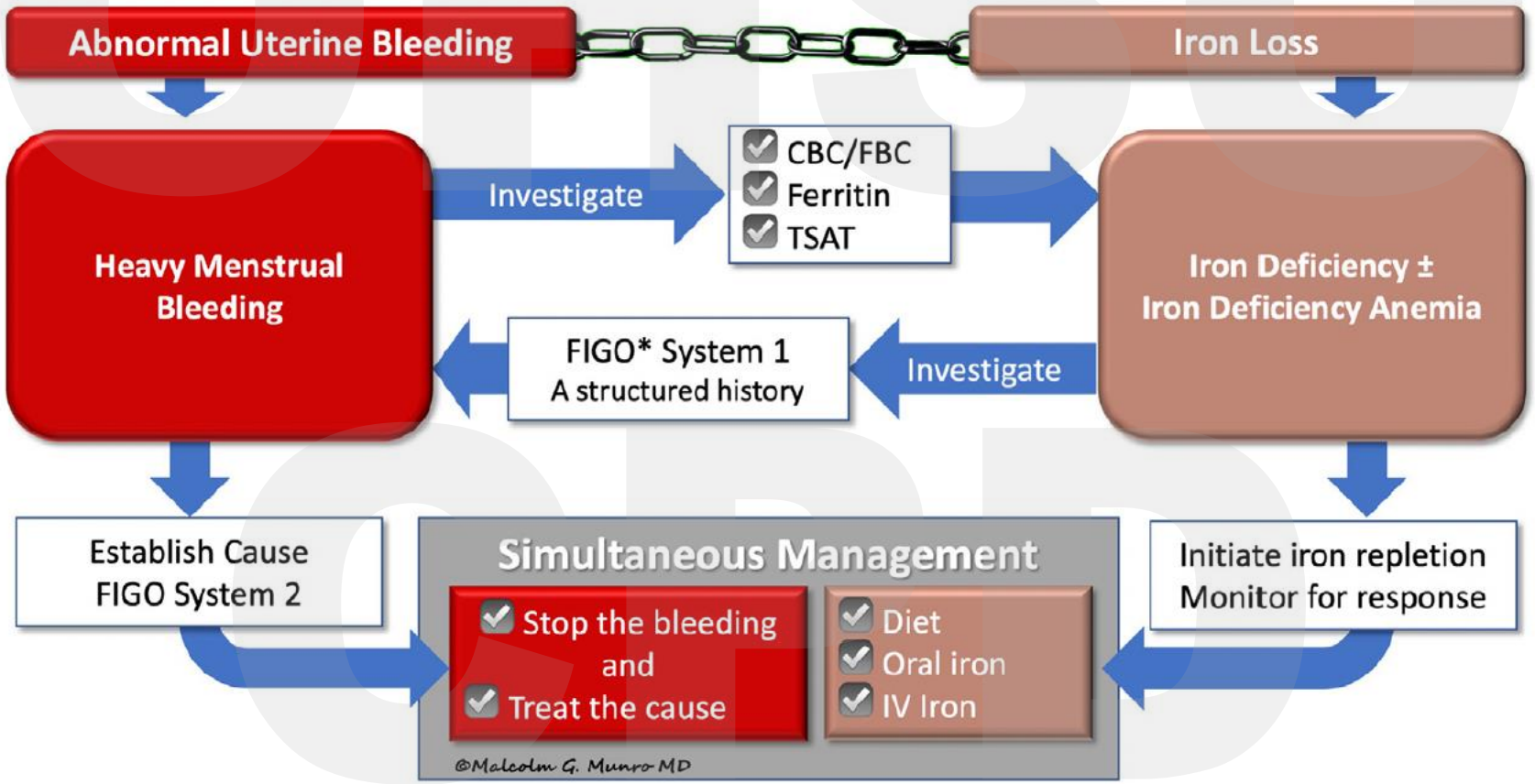
4. Correct the Cause



Munro et al. Am J Obstet Gynecol 2023

Case 1 continued

- Cycles last 7-8 days in duration
- Changes pad and tampon every 2-3 hr
- Passes clots > 1 inch
- Significant impact on QoL

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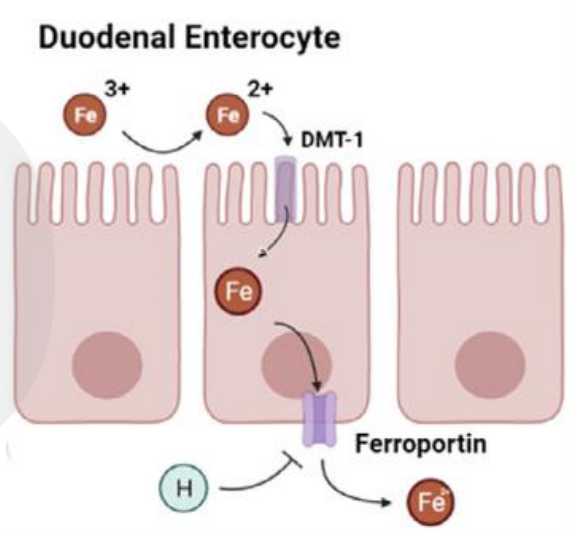
4. Provide Iron Therapy: Oral Iron

- Formulation
  - Iron salt (ferrous gluconate, sulfate, fumarate)
  - Elemental dose: 60 – 110 mg
  - Avoid enteric-coated and slow-release formulations

- Side Effects
  - Common GI side effects: constipation, nausea
  - Consider alternate day dosing if intolerant

- Best Practices
  - Avoid tannins (coffee/tea), Ca and Mg
  - Consider taking with Vitamin C

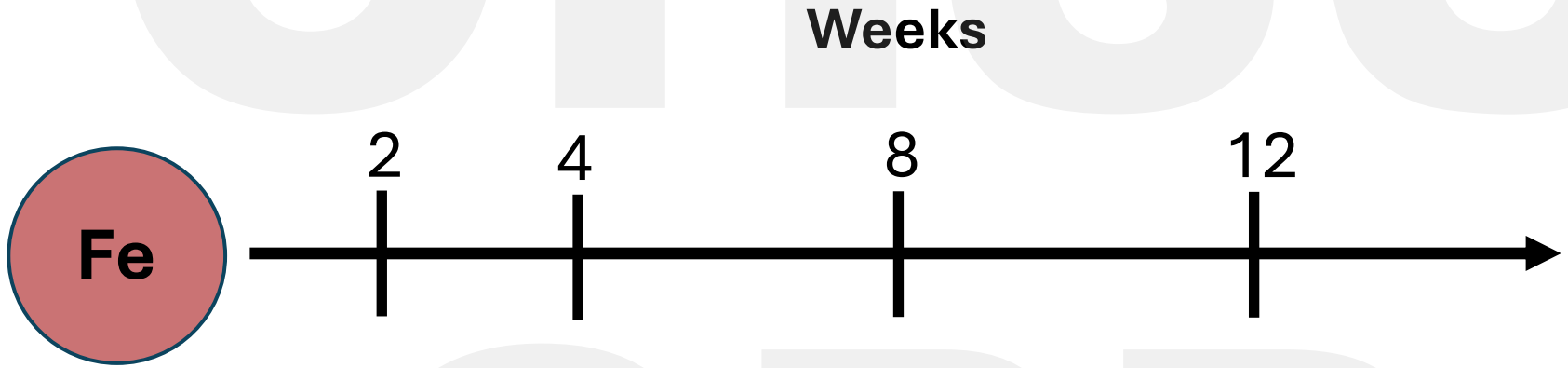


4. Provide Iron Therapy: IV Iron

- Indications
  - Refractory or intolerant
  - Time restraints (i.e., pregnancy, preoperative)
  - Impaired absorption (i.e., IBD, gastric bypass)
  - Chronic and/or rapid blood loss (i.e., menstrual bleeding, AVMs)

- Several different formulations
  - Iron dextran 1,000 mg
  - Low cost, single total dose infusion
  - Safety: major reaction/anaphylaxis <1:200,000

5. Confirm Repletion and Monitor



- Reticulocytosis
- Hgb rise 1g/dL

- Repeat ferritin + CBC ~4-6 weeks

- Monitor ferritin + CBC q3 mo thereafter

Hgb normalizes prior to ferritin

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Case 1 continued

- Receives iron replacement therapy
- Labs:
  - Hgb improves 14.0 g/dL
  - Ferritin normalizes > 50 ug/L
- Referral to gynecology → levonorgestrel IUD
- Routine q3mo ferritin monitoring plan in place

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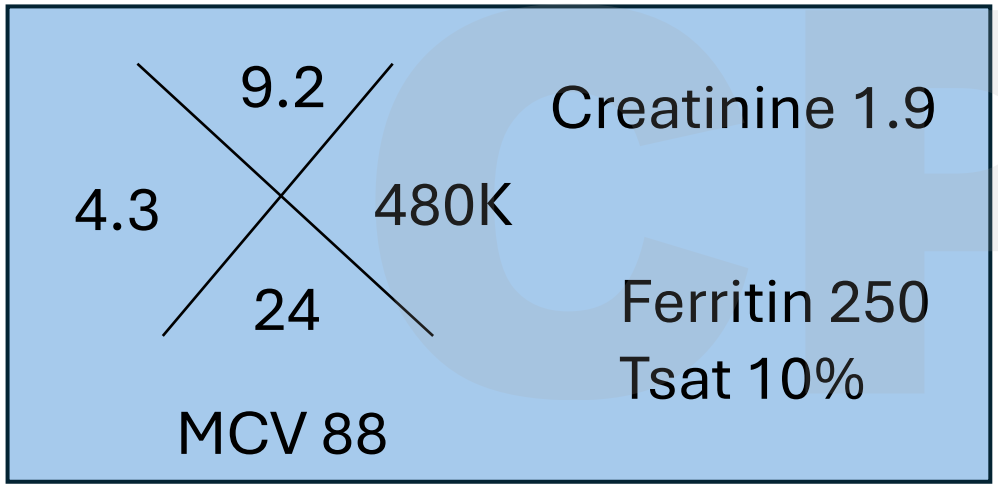
Case 2

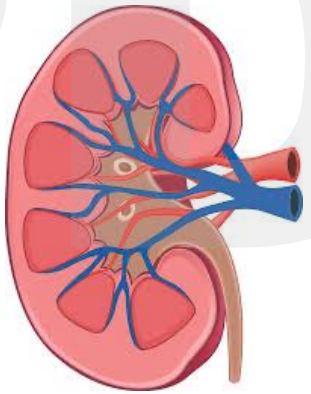
- 28-year-old male with SLE and CKD
- Endorses chronic fatigue
- Renal requests assistance with interpreting iron indices and indication for iron therapy prior to ESA



Special Considerations: CKD

- Absolute (reduced stores) vs functional (insufficient availability) iron deficiency

- KDIGO Guidelines
  - Absolute: Tsat ≤ 20% and ferritin ≤ 100
  - Functional: Tsat ≤ 20%, ferritin 100-500 may still benefit



<u>CKD and anemia</u>
Tsat ≤ 20% and ferritin ≤ 500 may benefit from IV iron repletion prior to ESA

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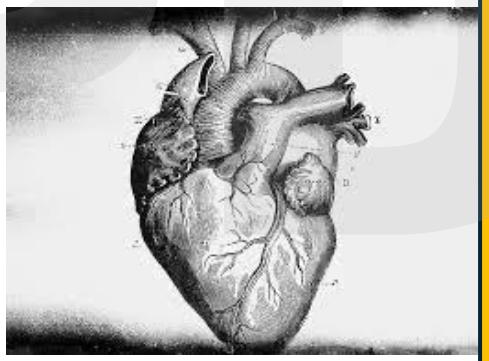
Special Considerations: HFrEF

- 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure
  - Patient population: NYHA class II-IV heart failure with an EF ≤45%
- Diagnosis: ferritin < 100 or ferritin 100-300 with TSAT < 20%
- Outcomes of IV iron:
  - Improved exercise capacity/QoL
  - Reduction in hospitalization
- PO iron is <u>insufficient</u>



<u>HFrEF and anemia</u>
Ferritin <100 or Tsat < 20%
and ferritin 100-300
may benefit from IV iron

Heidenreich et al. Circulation 2022

Special Considerations: Pregnancy

- Epidemiology
  - Iron deficiency anemia affects >40% of pregnancies
  - Racial and socioeconomic disparities
  - Significant fetal and maternal complications

- Pathophysiology → total iron requirements 1 gm
  - Fetal growth
  - Increased RBC mass

<u>Pregnancy and anemia</u>

Check ferritin and if <50:

- PO iron 1st trimester
- IV iron for 2nd / 3rd trimester

Takeaways

- The differential diagnosis of anemia is broad and requires simultaneous consideration of production (retic) and size (MCV)

- Ferritin is the most important iron parameter; Tsat can be helpful if interpreting concurrent iron deficiency and anemia of chronic disease

- Identifying and correcting the underlying cause is as critical as providing appropriate iron repletion therapy

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Questions