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

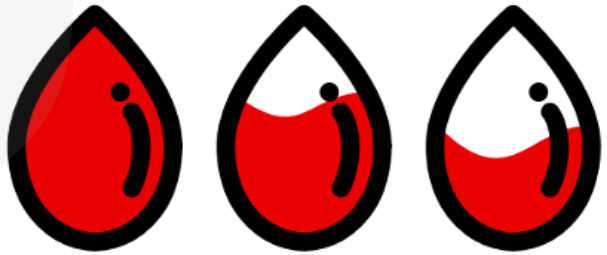
Objectives

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

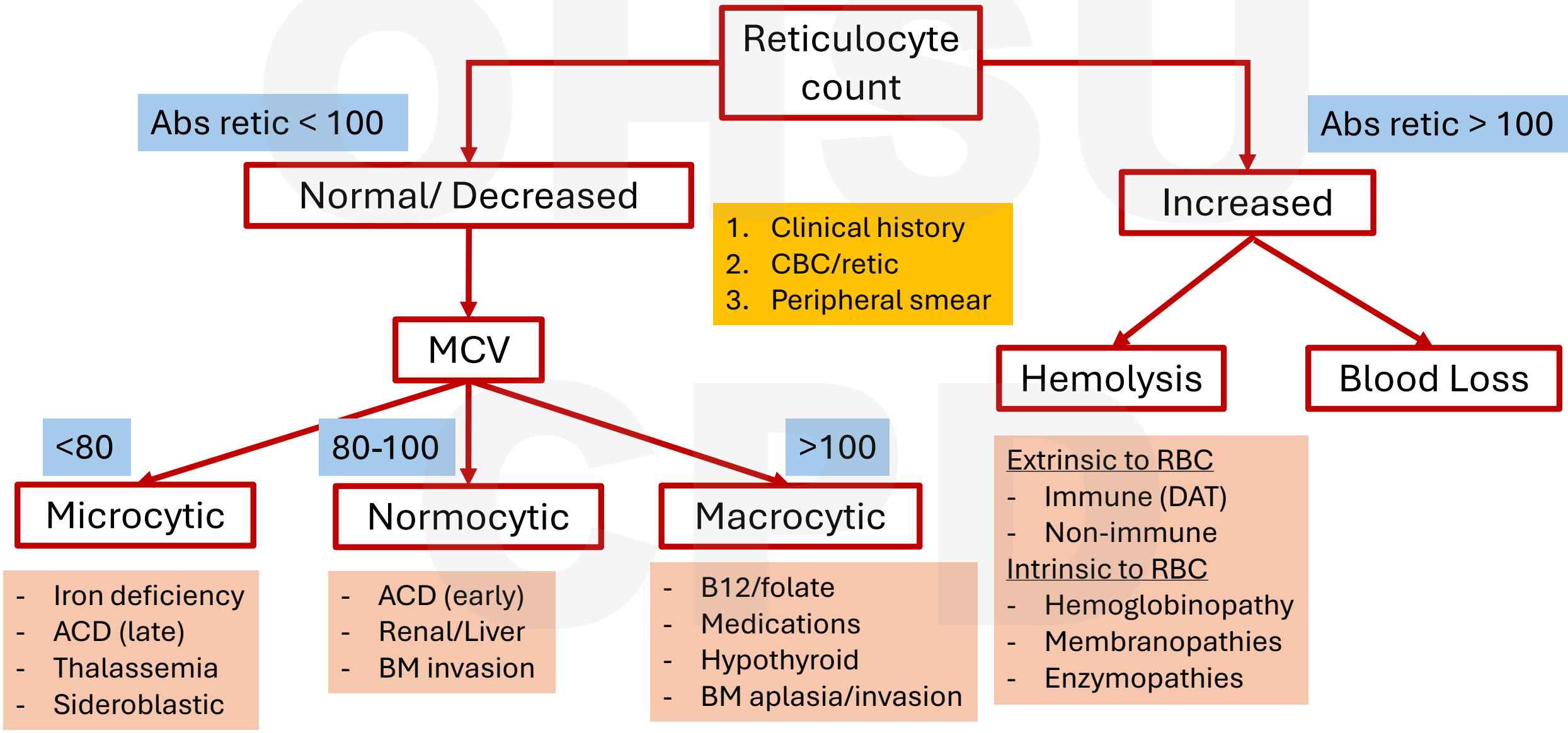
Anemia

- 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



Approach to Anemia

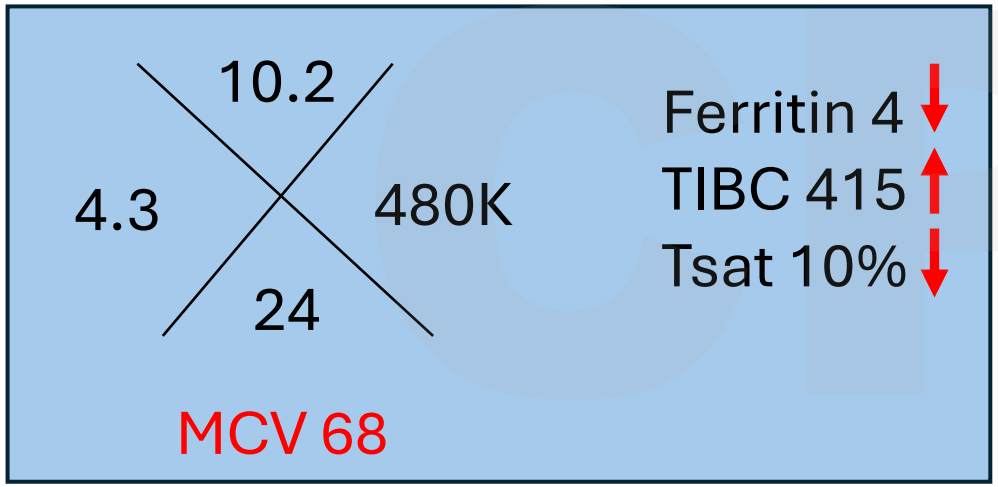


Workup of Anemia

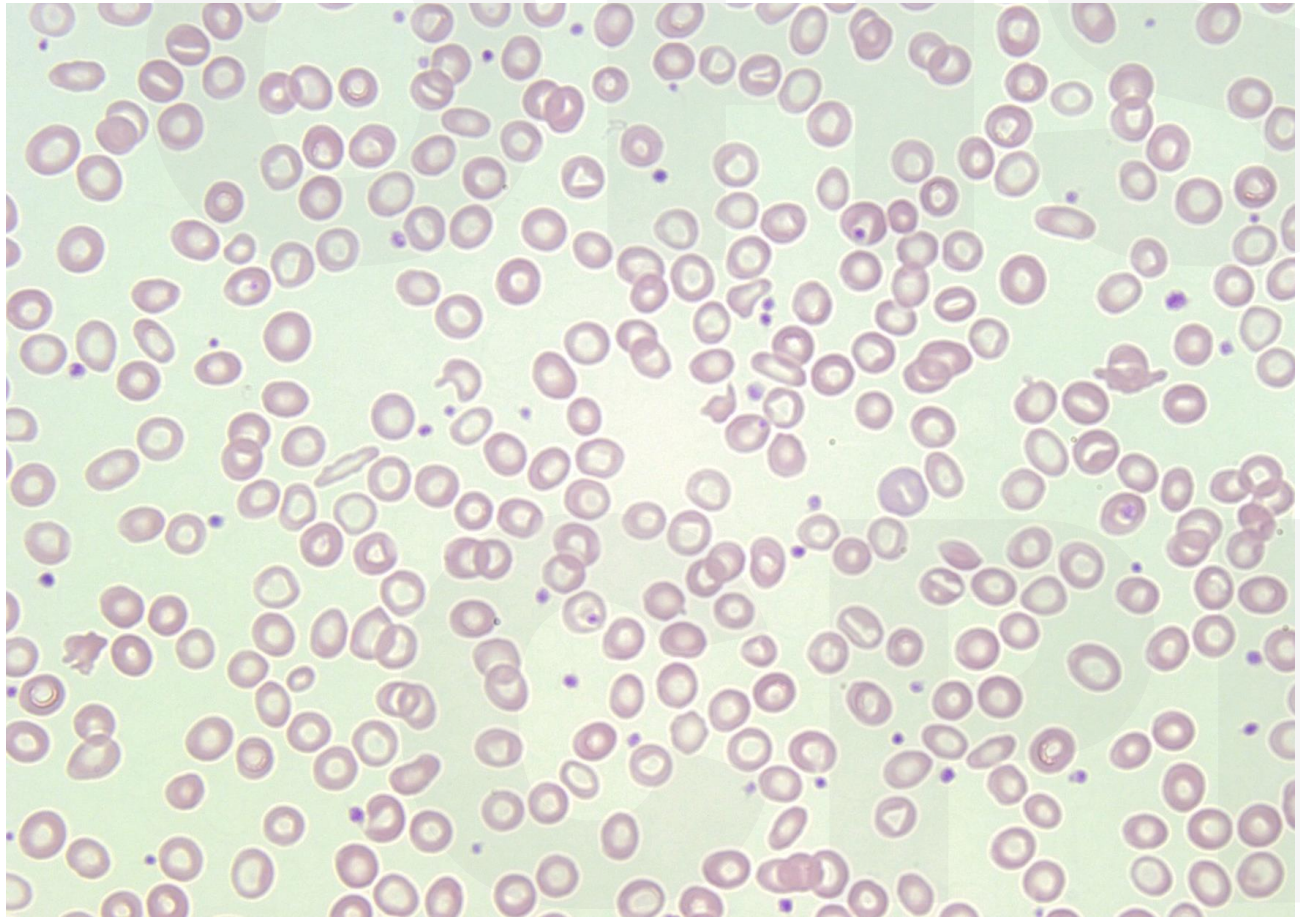
Etiology	First line	Second line
Comorbid condition (i.e., renal, liver, hypothyroid)	CMP, TSH	EPO, abdominal ultrasound, HIV, HCV

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…

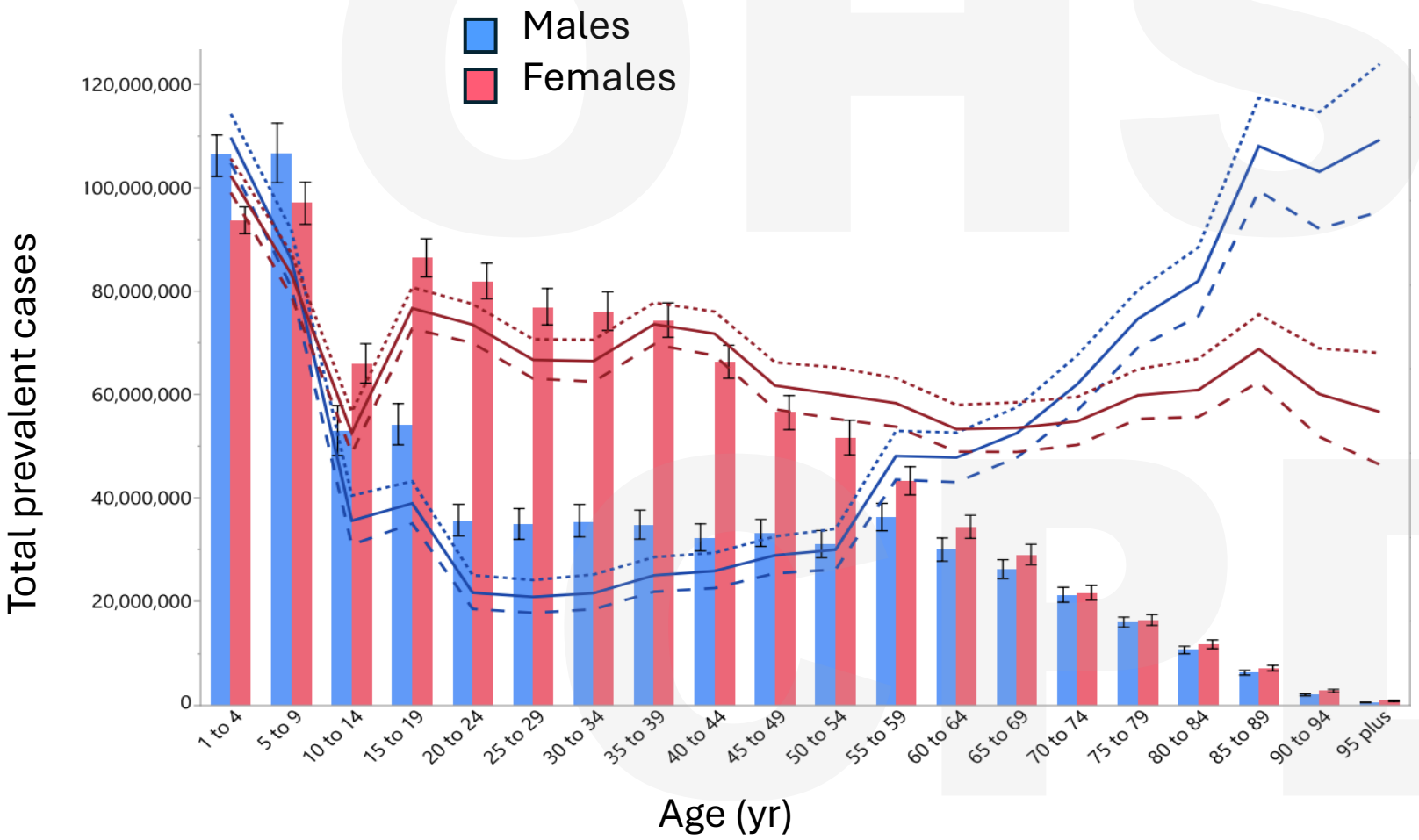


Peripheral Blood Smear



- Hypochromia
- Microcytosis
- Thrombocytosis

Epidemiology of Anemia

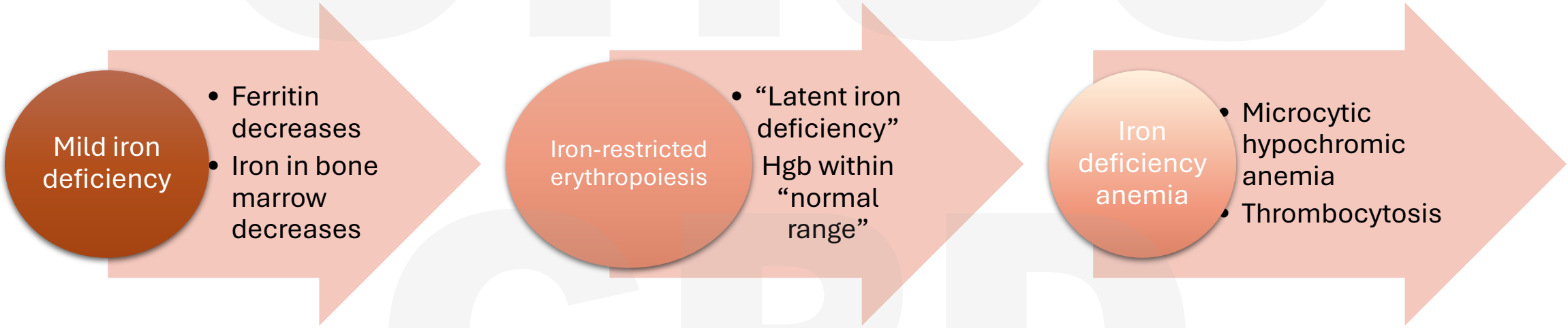


- Anemia is exceedingly common
  - >1.9 billion cases globally
  - 25% of global population
  - Iron deficiency is leading cause
- Hgb thresholds diverge at menarche
  - Females: Hgb < 12 g/dL
  - Males: Hgb < 13 g/dL

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 Iron Deficiency

Approach to Management

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

1. Confirm the Diagnosis

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

Optimal ferritin to diagnose iron deficiency?

WHO 2022
Ferritin < 15 ug/L

99% specific 59% sensitive

ASH Draft 2026
Ferritin < 30 ug/L

95% specific 80% sensitive

AGA 2021
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

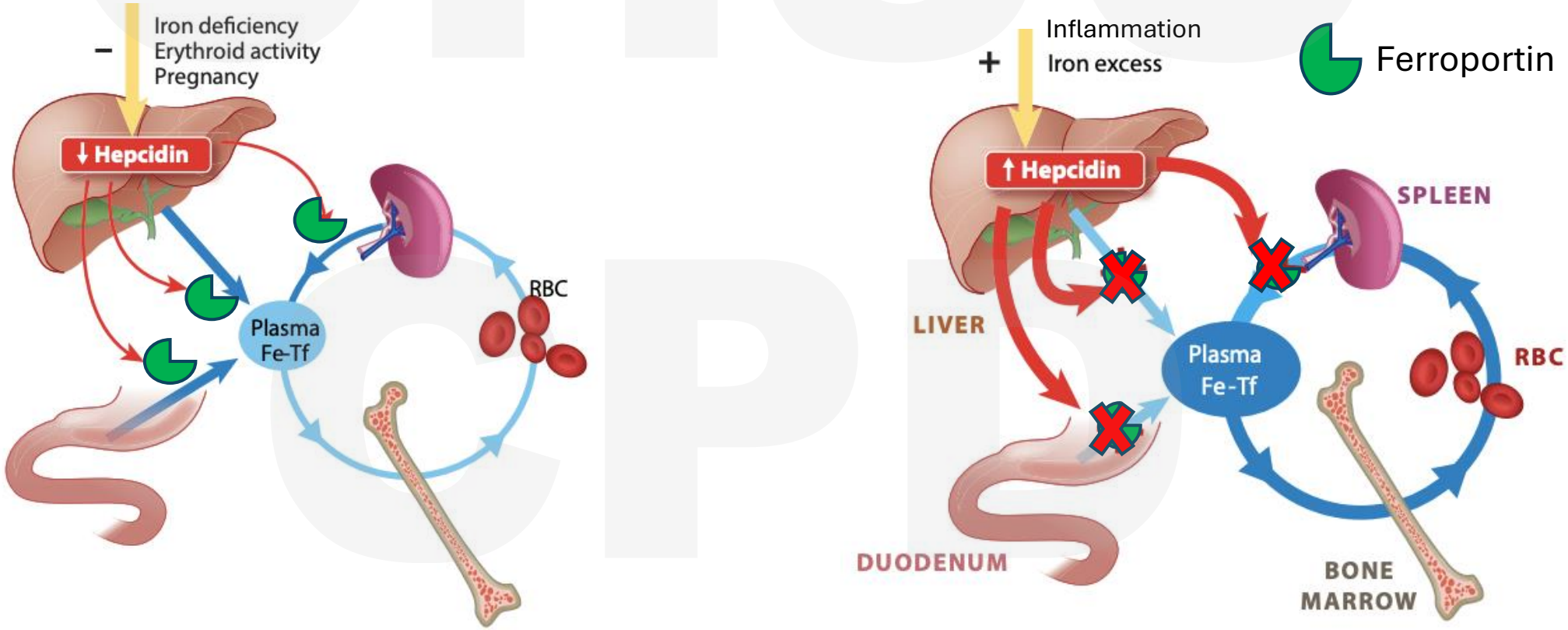
- Multiple studies demonstrating improvement in fatigue when ferritin repleted > 50[2,3]

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

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%)

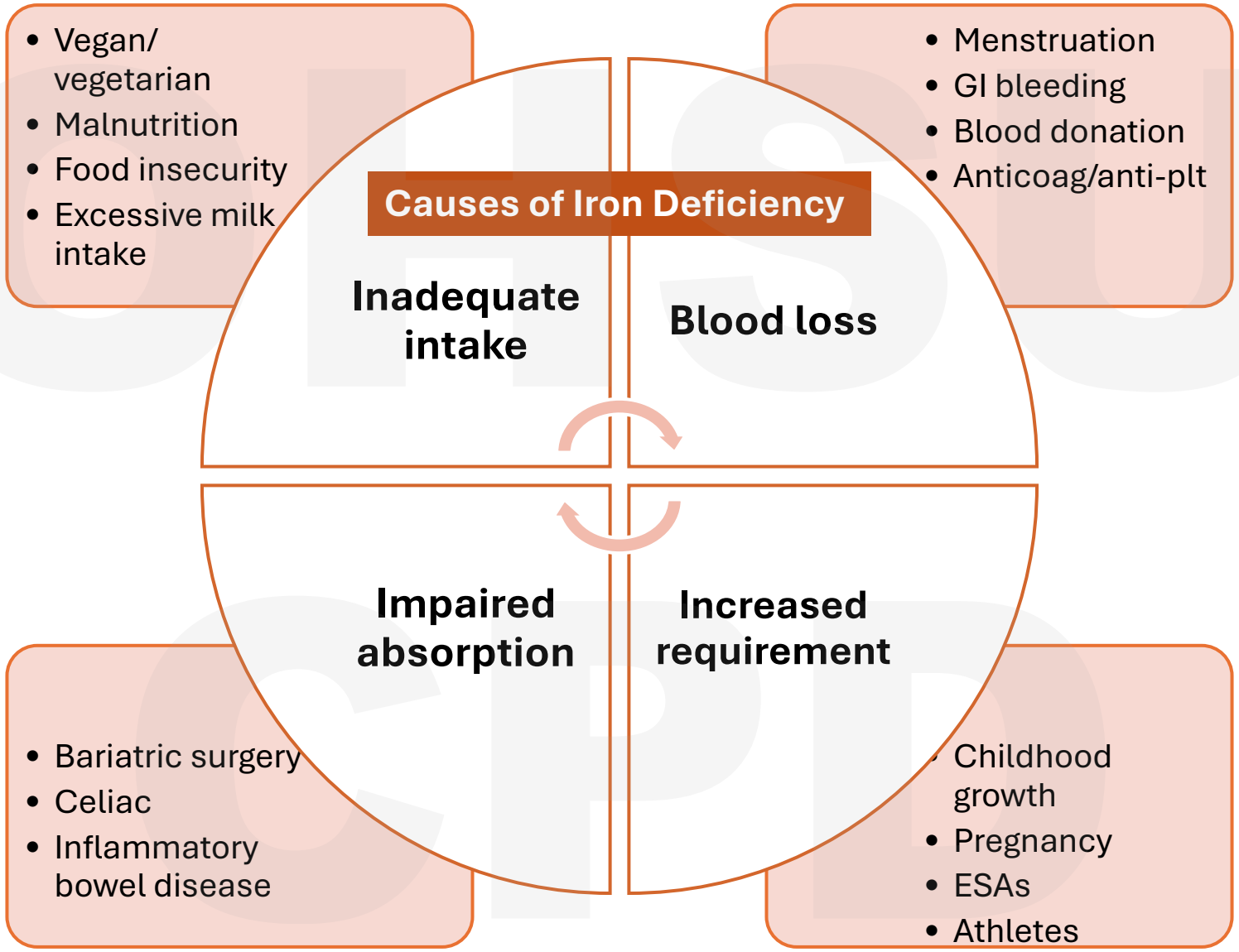
[1]McSorely et al. Transl Res 2016
[2]Guyatt et al. J Gen Intern Med 1992

Case continued

- You astutely diagnose your patient with iron deficiency
- Now what??

Approach to Management

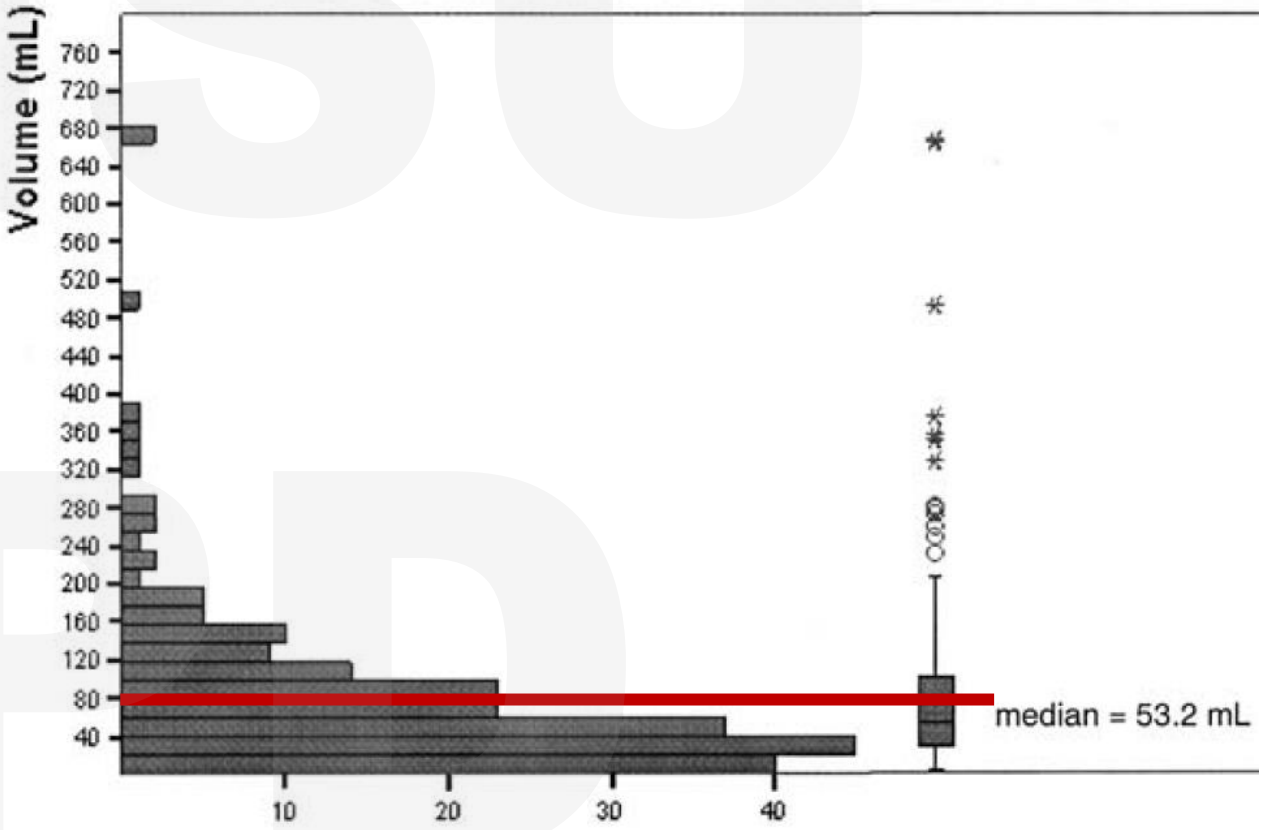
1. Confirm the diagnosis
2. Identify the cause
3. Correct or manage the cause
4. Provide iron therapy, IV or PO
5. Confirm repletion and monitor


Causes of Iron Deficiency
Inadequate intake
Blood loss
Impaired absorption
Increased requirement
• Vegan/ vegetarian
• Malnutrition
• Food insecurity
• Excessive milk intake
• Menstruation
• GI bleeding
• Blood donation
• Anticoag/anti-plt
• Bariatric surgery
• Celiac
• Inflammatory bowel disease
• Childhood growth
• Pregnancy
• ESAs
• Athletes

Menstrual bleeding: normal vs abnormal?

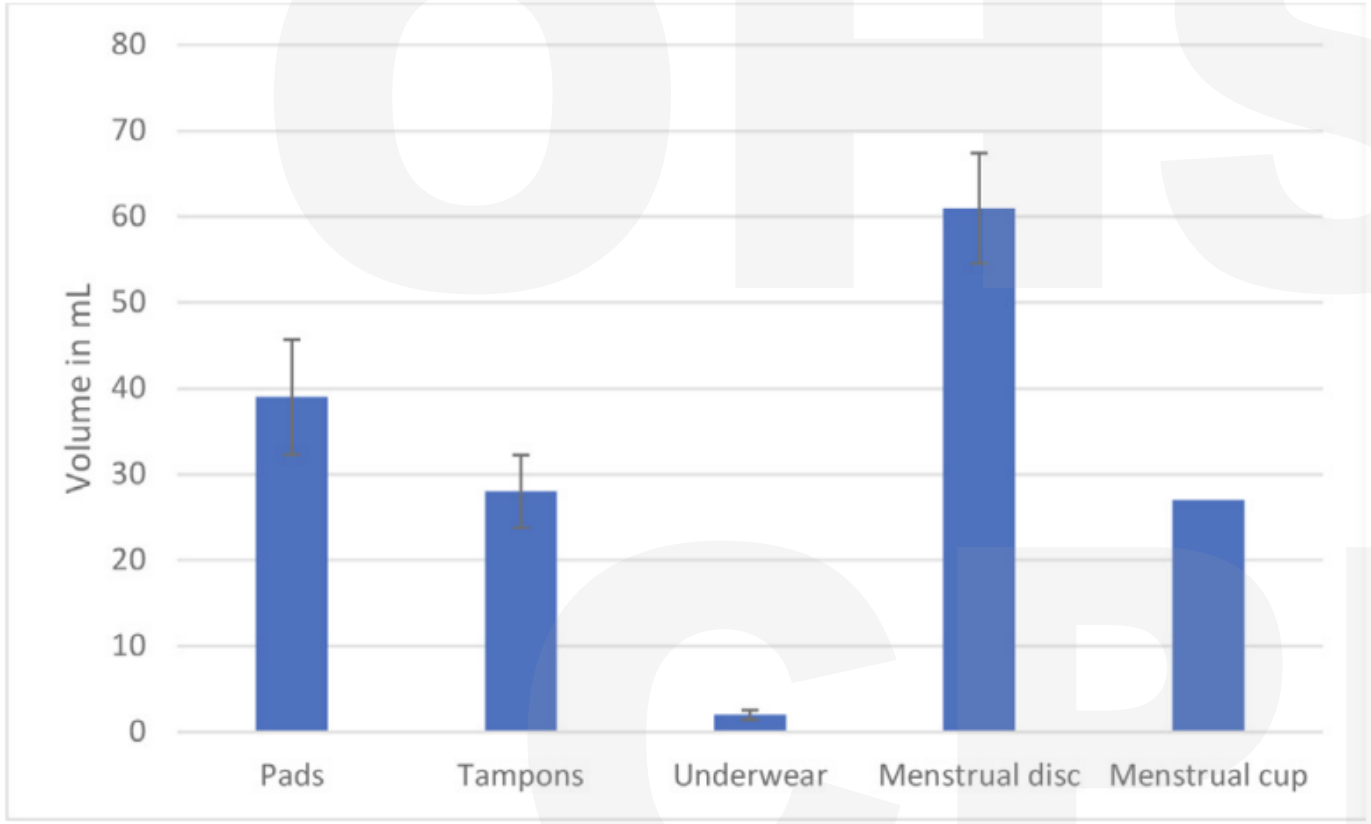
- Menorrhagia I Study
  - 226 individuals completed menstrual blood collection
  - 34% had losses **>80 mL/cycle**

- Clinical predictors
  - Low ferritin
  - Clots > 1 inch in diameter
  - Changing protection > hourly



Warner et al. Am J Obstet Gynecol 2004

Three questions



Deloughery et al. BMJ Sex Reprod Health 2024

- How often do you change protection?
  - Including "doubling up" on protection
  - And the *type* of protection
- Do you pass clots > 1 inch?
- Have you ever been diagnosed with iron deficiency?
  - Check a ferritin!

7-2-1 Rule

- Cycles lasting longer than 7 days
- Changing menstrual protection more often than every 2 hours
- Passing clots > 1 inch (or a quarter in size

When to consider GI workup?

- In postmenopausal women and men with iron-deficiency anemia, the AGA recommends bidirectional endoscopy over no endoscopy

- In premenopausal women with iron deficiency anemia, the AGA suggests bidirectional endoscopy over iron replacement therapy only

CLINICAL PRACTICE GUIDELINES

AGA Clinical Practice Guidelines on the Gastrointestinal Evaluation of Iron Deficiency Anemia

Cynthia W. Ko,[1] Shazia M. Siddique,[2] Amit Patel,[3] Andrew Harris,[4] Shahnaz Sultan,[5] Osama Altayar,[6] and Yngve Falck-Ytter[7,8]

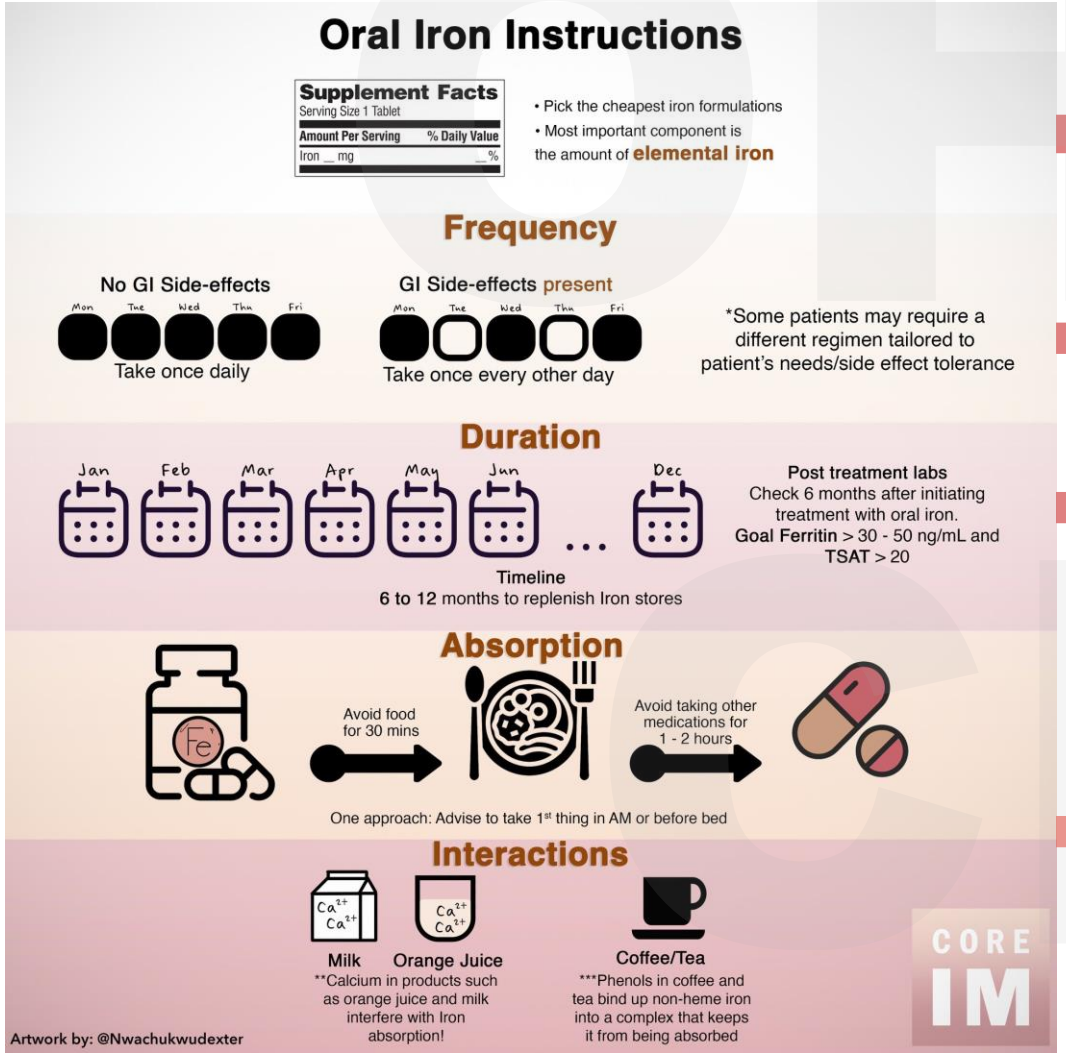
Case 1 continued

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

Approach to Management

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

Best practices for oral iron administration



Formulation: iron salt (i.e., ferrous sulfate, gluconate)
Dosing: 60-110mg **elemental** iron daily

Frequency: daily dosing = faster time to correction
Consider QOD if GI side effects (nausea, constipation)

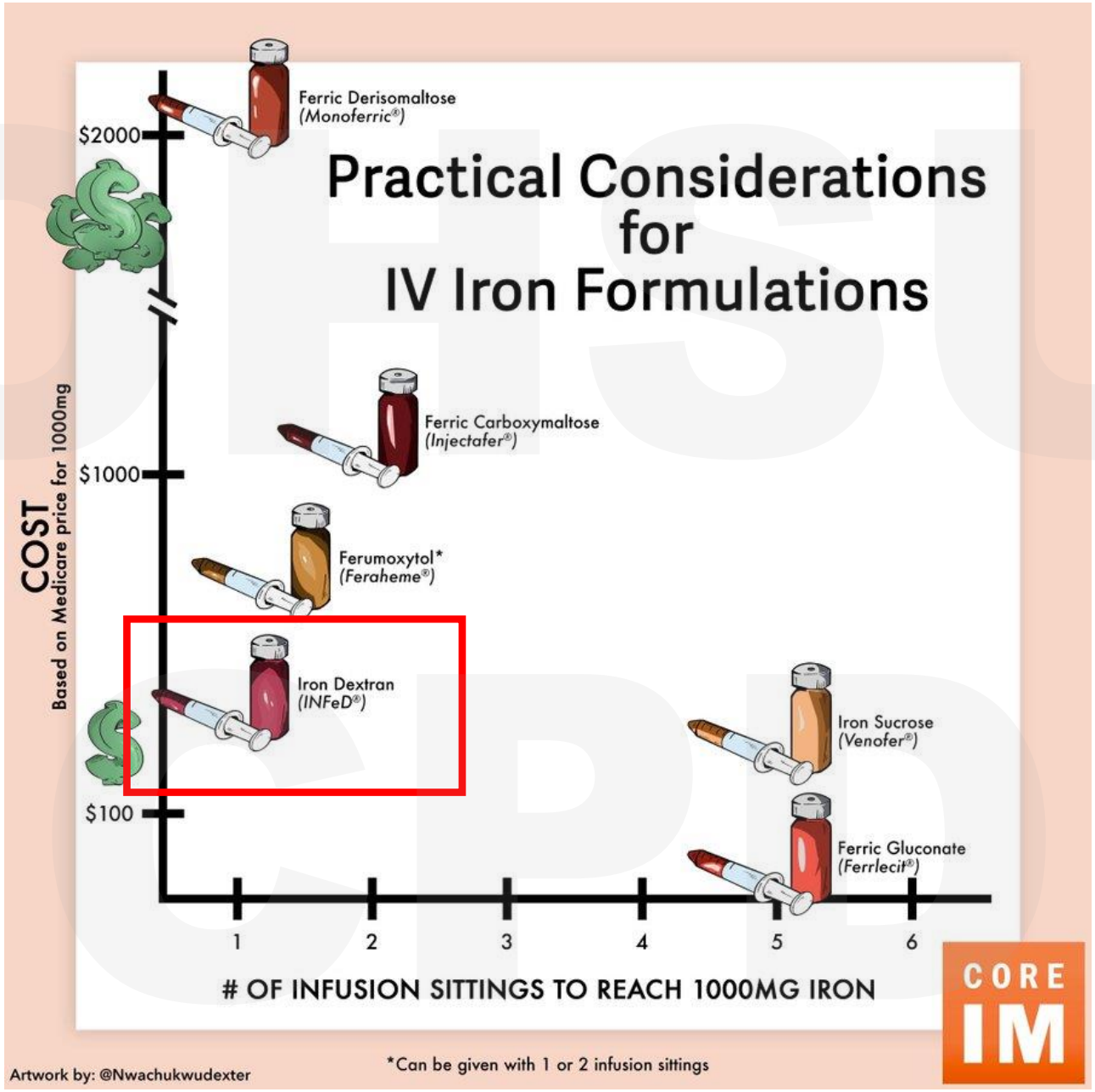
Labs: check ferritin and CBC in 4 weeks
Expect Hgb rise ~1g/dL

Absorption inhibited by:
- divalent cations (Ca and Mg)
- phytates (seeds and grains)
- tannins (tea and coffee)
- medications (PPIs, H2 blockers)

https://www.coreimpodcast.com/2024/03/27/fe-deficiency-treatment-5-pearls-segment/

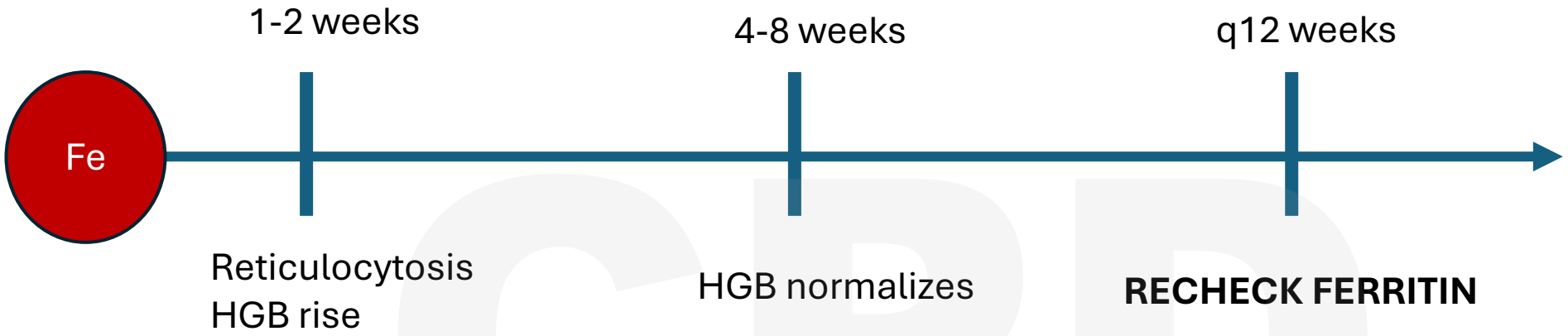
Indications for IV iron

- Inadequate response or intolerance to oral iron
  - 3 month trial of oral iron
- Rapid repletion indicated
  - Pregnancy (2nd and 3rd trimesters)
  - Preoperative
- Chronic and/or rapid blood loss
- Impaired GI absorption
  - Inflammatory bowel disease
  - Bariatric surgery
- Chronic inflammatory conditions
  - HFrEF
  - CKD


Practical Considerations for IV Iron Formulations
COST
Based on Medicare price for 1000mg
$2000
$1000
$100
Ferric Derisomaltose (Monoferric®)
Ferric Carboxymaltose (Injectafer®)
Ferumoxytol* (Feraheme®)
Iron Dextran (INFeD®)
Iron Sucrose (Venofer®)
Ferric Gluconate (Ferrlecit®)
1
2
3
4
5
6
OF INFUSION SITTINGS TO REACH 1000MG IRON
Artwork by: @Nwachukwudexter
*Can be given with 1 or 2 infusion sittings
CORE IM

Monitoring

- Confirm repletion and monitor for recurrence

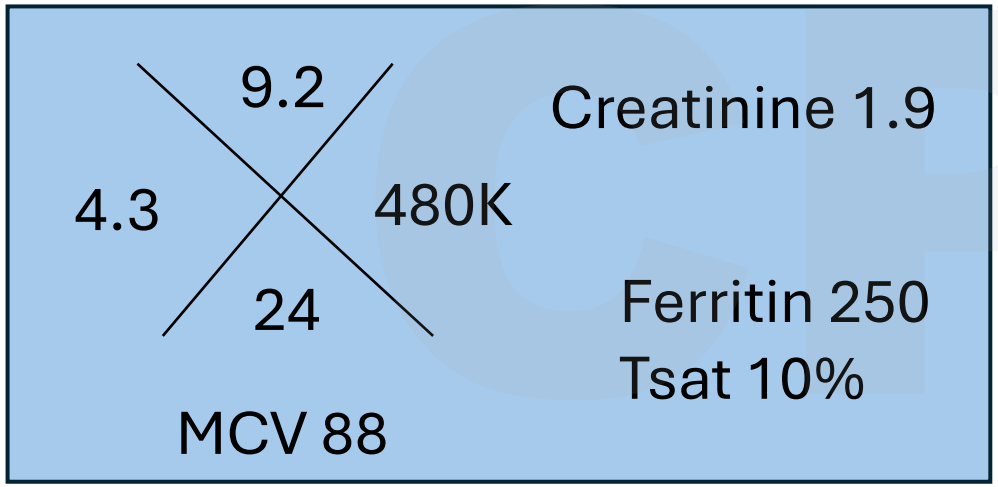


Case 1 continued

- 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

Case 2

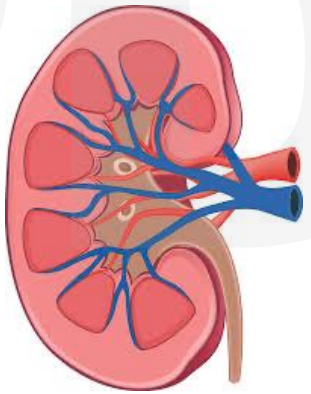
- 28-year-old male with SLE and CKD
- Endorses chronic fatigue
- Renal requests assistance with interpreting iron indices and indication for iron therapy prior to ESA



Special Considerations: CKD

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

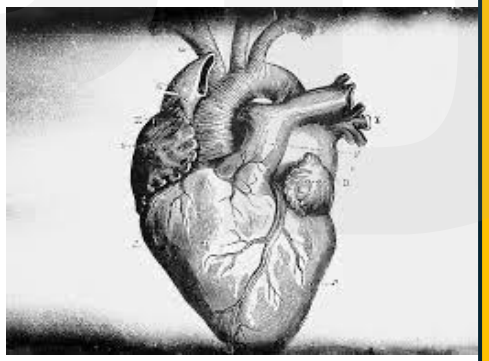
- KDIGO Guidelines
  - Absolute: Tsat ≤ 20% and ferritin ≤ 100
  - Functional: Tsat ≤ 20%, ferritin 100-500 may still benefit



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

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

Questions