SYSTEMATIC APPROACH TO PEDIATRIC ANEMIA

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Disclosure

- I have no actual or potential conflict of interest in relation to this program/presentation

Objectives

- Review the definition of anemia
- Review the initial diagnostic approach the anemic patient
- Review of diagnosis and management of microcytic anemia
  - Iron Deficiency Anemia
  - Iron Deficiency due Heavy Menstrual Bleeding
  - Thalassemia
- Review common causes of normocytic anemia in pediatric patients

Anemia

- Common
  - Increased morbidity and mortality
  - Risk for neurocognitive impairment
- 2 SD below the mean Hgb
  - Reduced Hgb/RBC cell mass not meeting cellular oxygen demands/metabolic demands

Table 1. Age-Based Hemoglobin Levels in Children and Adolescents

Age	*Mean hemoglobin level*	*–2 standard deviations*
Birth (term infant)	16.5 g per dL (165 g per L)	13.5 g per dL (135 g per L)
1 month	13.9 g per dL (139 g per L)	10.7 g per dL (107 g per L)
2 months	11.2 g per dL (112 g per L)	9.4 g per dL (94 g per L)
3 to 6 months	11.5 g per dL (115 g per L)	9.5 g per dL (95 g per L)
6 months to 2 years	12 g per dL (120 g per L)	10.5 g per dL (105 g per L)
2 to 6 years	12.5 g per dL (125 g per L)	11.5 g per dL
6 to 12 years	13.5 g per dL	11.5 g per dL
12 to 18 years		
Males	14.5 g per dL (145 g per L)	13 g per dL (130 g per L)
Females	14 g per dL (140 g per L)	12 g per dL

Information from references 3 and 4.

Wang, M. (2016). Iron deficiency and other types of anemia in infants and children. *American family physician*, *93*(4), 270-278.

Initial Approach

- Symptomatic or Asymptomatic
  - Acute versus Chronic
  - Sudden loss: Poorly Compensated
  - Chronic Redistribution: Well Compensated
  - Degree of severity

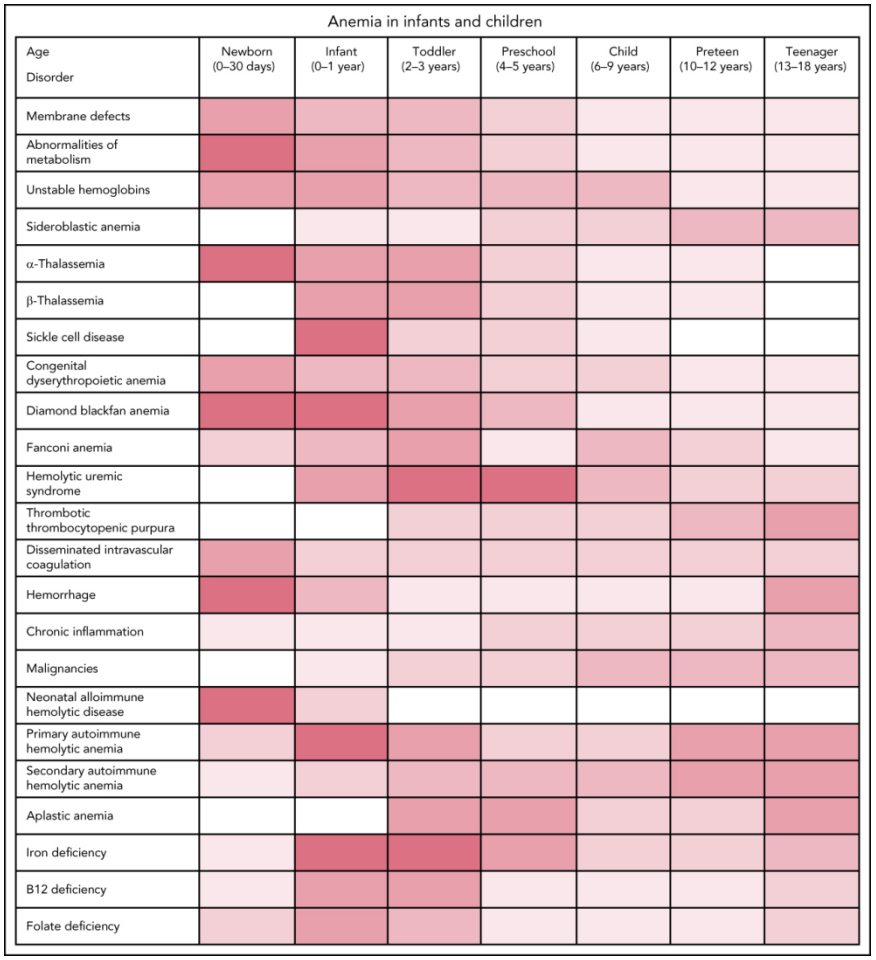
- Symptoms

  - Pallor, Weakness, dyspnea, fatigue, dizziness, cold intolerance syncope
    - HEMOLYSIS: Jaundice, dark urine, abdominal pain

Initial Approach

- Causes
  - Acquired or Inherited
    - Blood loss
    - Production/Failure of erythropoiesis
    - Destruction/Hemolysis
    - Combined/Mixed etiology

Anemia in the pediatric patient



Anemia in infants and children

Age Disorder	Newborn (0–30 days)	Infant (0–1 year)	Toddler (2–3 years)	Preschool (4–5 years)	Child (6–9 years)	Preteen (10–12 years)	Teenager (13–18 years)
Membrane defects							
Abnormalities of metabolism							
Unstable hemoglobins							
Sideroblastic anemia							
α-Thalassemia							
β-Thalassemia							
Sickle cell disease							
Congenital dyserythropoietic anemia							
Diamond blackfan anemia							
Fanconi anemia							
Hemolytic uremic syndrome							
Thrombotic thrombocytopenic purpura							
Disseminated intravascular coagulation							
Hemorrhage							
Chronic inflammation							
Malignancies							
Neonatal alloimmune hemolytic disease							
Primary autoimmune hemolytic anemia							
Secondary autoimmune hemolytic anemia							
Aplastic anemia							
Iron deficiency							
B12 deficiency							
Folate deficiency							

Patrick G. Gallagher, Anemia in the pediatric patient, Blood, 2022,

Initial approach

- Comprehensive history and exam
  - Age
  - Gender
  - Ethnicity
  - Diet**
  - Neonatal/NBS
  - Family history
  - Weight loss/GI
  - Mucosal bleeding symptoms
  - Medications
  - Recent trauma/injury/surgical procedures

Clinical History
CBC with diff
Retic count

Family History

History RED FLAGS

- Unexplained fevers
- Unexplained weight loss
- For HMB– pelvic pain
- Boney pain
- Seizure
- Worst headache
- Refractory emesis
- Severe mucosal bleeding symptoms
  - Bloody Stools
  - Severe and/or Recurrent Epistaxis

Exam RED FLAGS

- HSM
- Cardiorespiratory compromise
  - Respiratory Distress
  - Hypoxia
- Focal Neuro Deficits
- Petechia or purpura
- Active bleeding
- Adenopathy
- Lethargy

Initial Lab evaluation

Initial Labs

- CBCD with Diff
- Retic Count
- Peripheral smear

- Microcytic
  - Iron studies including ferritin
  - Lead
  - Hemoglobinopathy evaluation
- Macrocytic
  - B12/Folate

Additional Considerations

Concern for Acute Hemolysis
-DAT, LDH, Haptoglobin, CMP, UA

Concern for anemia of chronic inflammation/disease
-ESR/CRP, CMP

Concern for Occult Loss
-UA to screen for occult loss, Fecal occult blood,

Concern for bleeding disorder
-VWD panel, PT/INR, aPTT, Fibrinogen, PFA

Concern for hematologic malignancy
-PONC panel, Immunophenotyping, COAGs

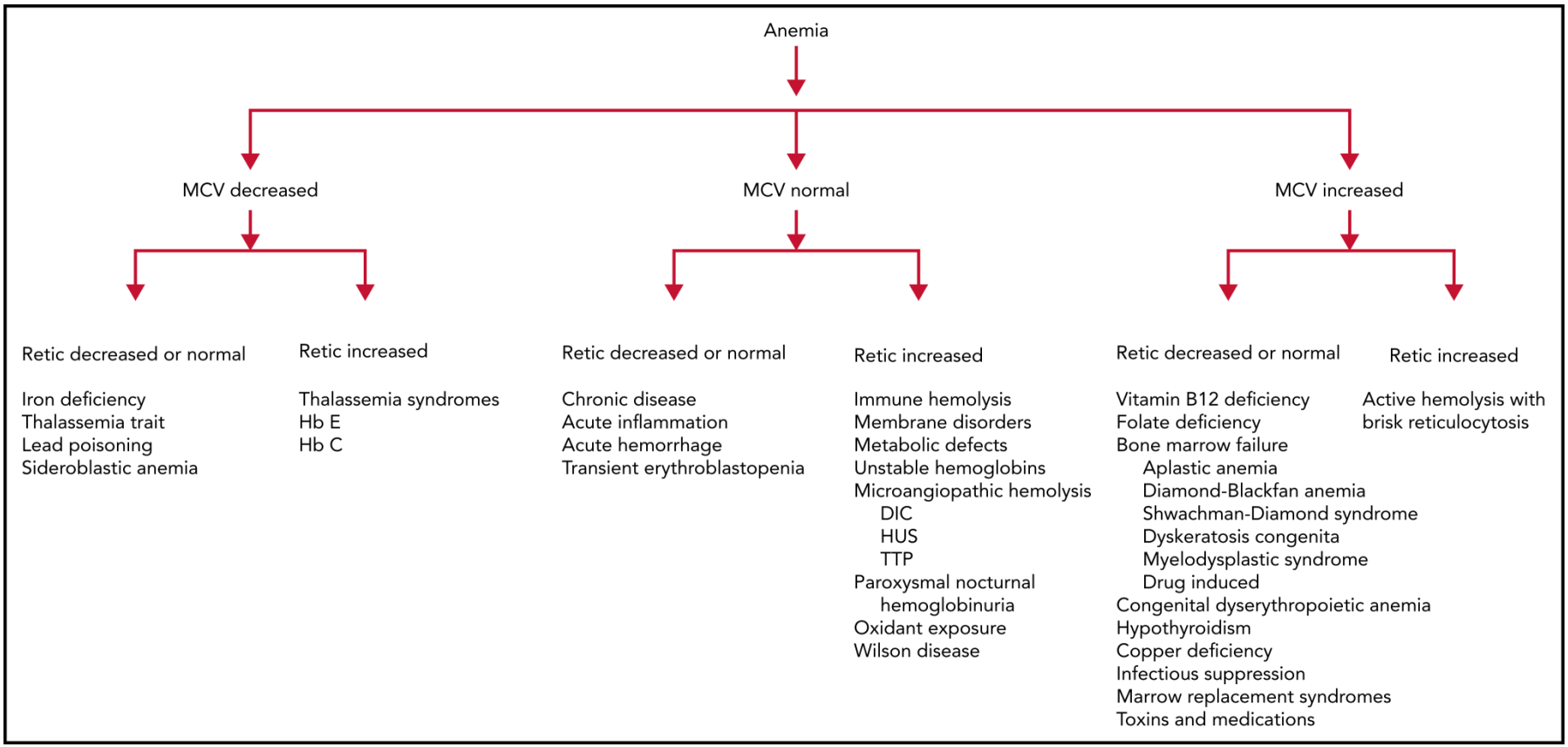
RBC indices

- MCV: Mean corpuscular volume (size)
  - Microcytic MCV <70-75
    - IDA, lead elevation, Thalassemia
  - Normocytic MCV 70s-90s
  - Macrocytic MCV >90/100
- RDW
  - Red cell distribution width
    - High in IDA
- MCH
  - Mean Cell Hemoglobin Content -- How much Hgb per RBC
    - Low == hypochromic

Role of the Retic Count

- Reticulocytopenia, relative to anemia suggests impaired red cell production
- Elevated can point to chronicity or underlying hemolytic process

Anemia in the pediatric patient



Patrick G. Gallagher, Anemia in the pediatric patient, Blood, 2022, Figure 2.

Case #1

8 week old F infant seen at PCP for routine evaluation. As part of the evaluation Hgb 9, MCV83 and retic could is low-normal. Peripheral smear notable for anemia but no dysmorphology.

Pt was full term. No hx of hyperbilirubinemia at the time of birth. Appropriate weight gain and development. Normal Hgb at time of birth. Normal NBS. Famhx reassuring. Exam reassuring.

What is the most likely cause of the low Hgb?

-IDA

-Sickle Cell Anemia Hgb SS

-Physiologic Nadir

-Anemia of Chronic Inflammation

Physiologic Nadir

- 8-12 weeks of age
- Normal: 9-11 mg/dL
- Decreased viability of RBCs (60-70 days at birth)
- Transition from fetal erythropoiesis

- Increase in tissue oxygen → decreased EPO
  Rate of Hgb synthesis decreases
- Production reaches minimum during 2nd week of life
- Increased – maximum at ~3 months of age

What is the most appropriate next step?

- Serial CBC to confirm recovery

  OR

- Provide Reassurance

Serial CBCs are not required if the patient is otherwise well appearing without clinical concerns; repeat Hgb at routine WCC

Case #2

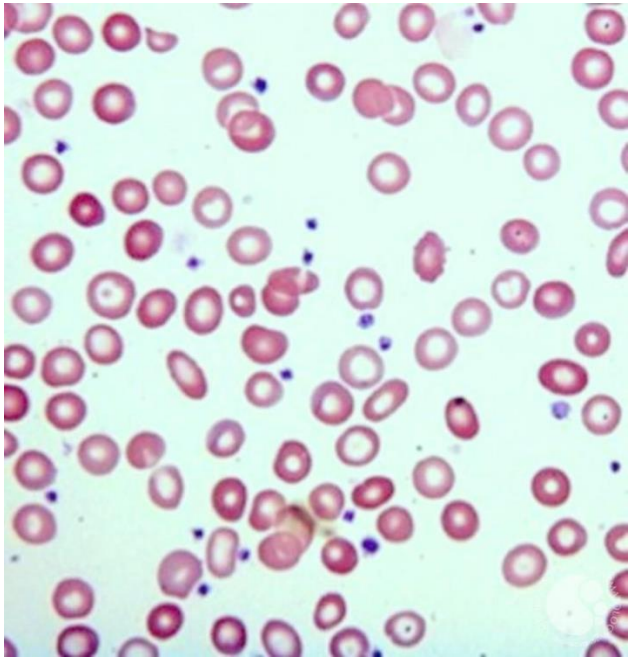
- 4 yo F at her WCC; per mother no acute concerns but saw grandmother at Thanksgiving and she was worried her child looked “pale.”
- Exam: mildly elevated HR; BP, SP02, and RR are appropriate
- Pallor, mild tachycardia, 2/6 Systolic flow murmur; otherwise non-focal exam

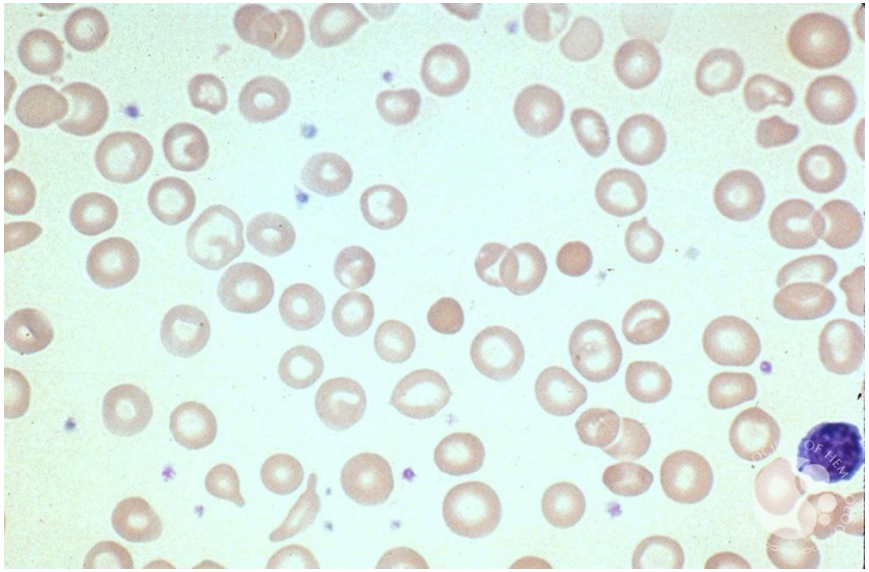
- Additional history elements?

- POCT Hgb 6.9
- CBC
  - WBC 6.1; Diff Appropriate
  - PLT **850K**
  - Hgb 6.0
  - MCV 51
  - HCT 18%

  + hypochromia
  + anisocytosis
  + microcytosis

  - Retic WNL





Most likely diagnosis:

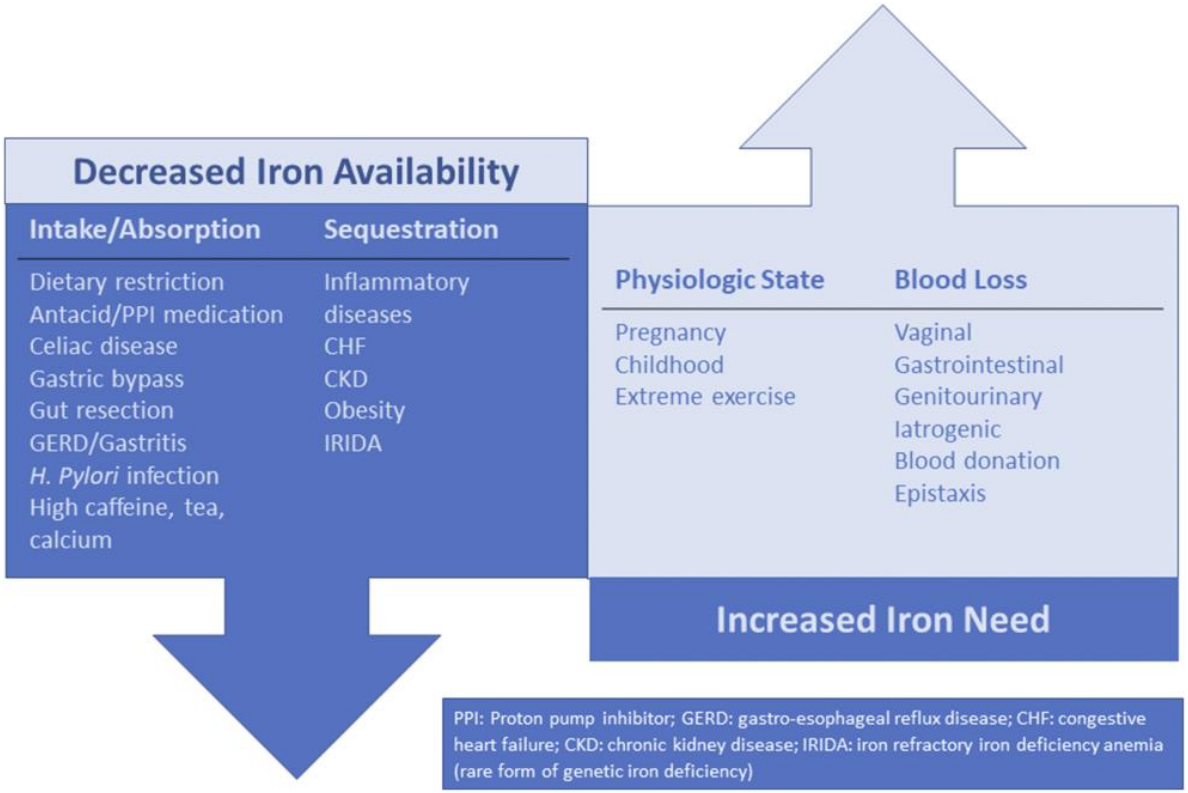
- Iron deficiency Anemia

Microcytic Anemia/IDA work-up

- What other labs would you obtain?
  - Reticulocyte count
  - Iron Studies
    - TIBC
    - Transferrin
    - **Ferritin**
    - Iron sat
- Path review of peripheral smear
- +/- Hgb electrophoresis
- +/- Bilirubin, LDH, haptoglobin, DAT+

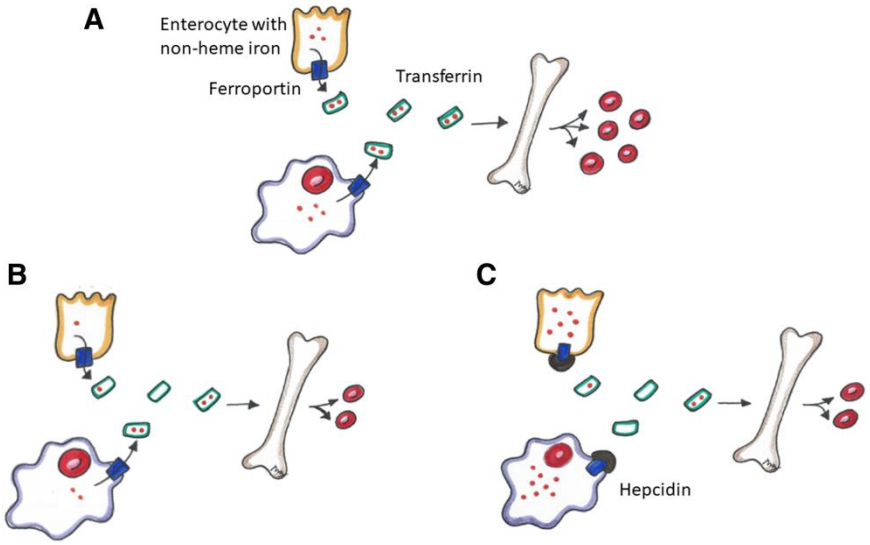
- What other history elements would you obtain?
  - Dietary history
  - NBS result
    - Concern for thalassemia
  - Concern for bleeding history/occult loss
    - Menorrhagia, IBD, celiac
  - Concern for hemolytic process

Iron Balance

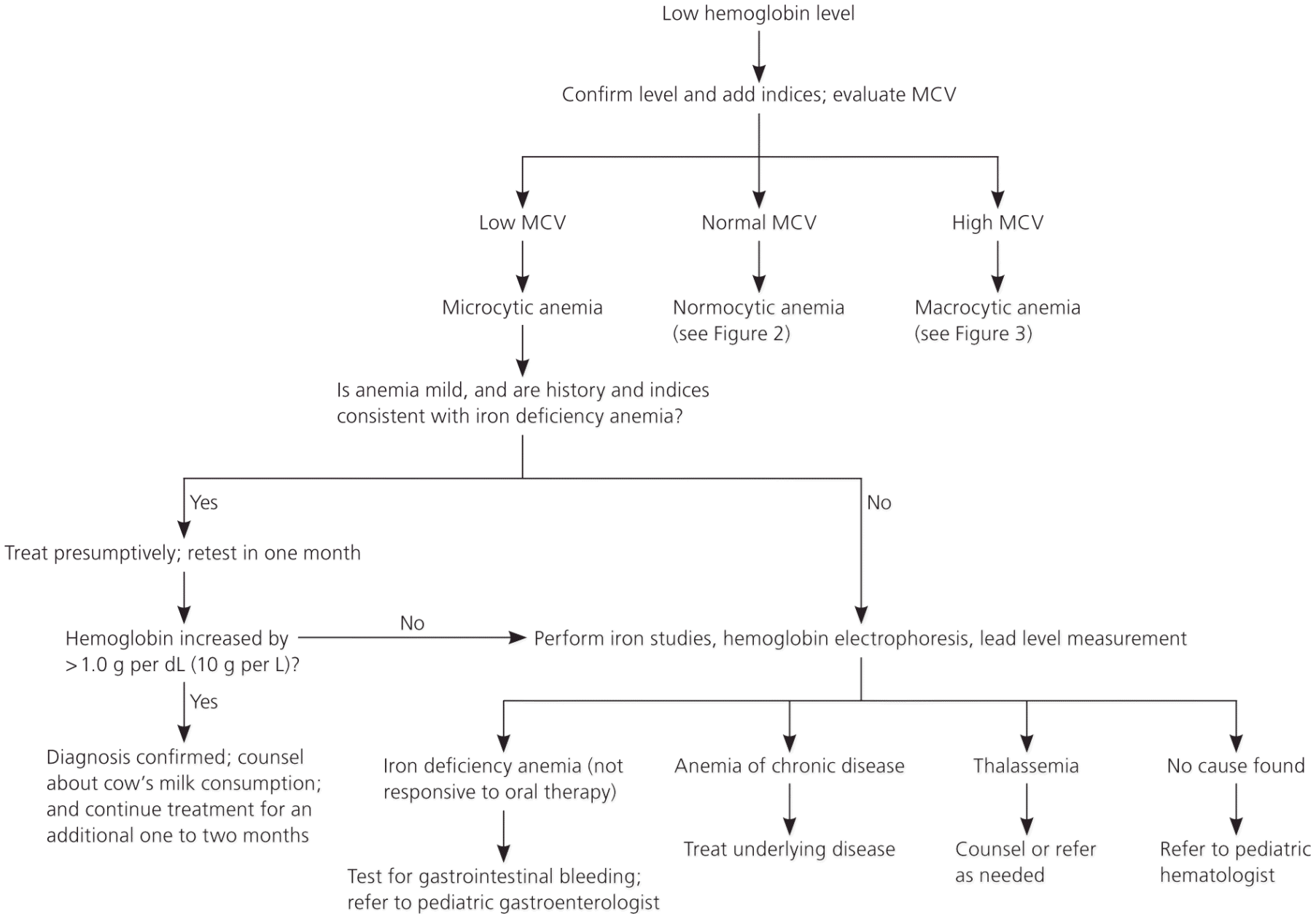


Shuoyan Ning,Michelle P. Zeller, Management of iron deficiency, Hematology Am Soc Hematol Educ Program, 2019, Figure 2.

Iron Balance



1. Shuoyan Ning,Michelle P. Zeller, Management of iron deficiency, Hematology Am Soc Hematol Educ Program, 2019, Figure



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Case #2

Hgb 6.0
MCV 51
Ferritin <2
TIBC/Transferrin elevated
Iron/Iron Sat: decreased
PLT850K

- How would you like to manage this patient?
  - Admit to SF for pRBC transfuse and PO iron start
    - Slow transfusion 5 cc/kg over 4 hours or if Hgb <5 Hgb X Weight (Kg) over 4 hours
  - Admit to SF to IV iron infusion followed by PO iron start
    - max 100 mg for first dose
  - Start oral iron in the outpatient setting; return to clinic in 72 hours for recheck
  - Start oral iron in the outpatient setting; return to clinic in 4 weeks

Management IDA

- 3-6 mg/kg elemental iron for 3 months
  - Daily
  - Inexpensive; readily available
  - Optimize adsorption with Vit C
- IV iron to replacement calculated deficit by Gazoni equation
  - Involved ~3-4 sessions for replacement
  - Risk of anaphylaxis
  - Requires IV placement
  - Most insurances require a failure of oral iron outpatient

- Either will typically lead to rapid increase in Hgb level
  - Minimum 1 g/L after 4 weeks – if mild hopefully resolved

- **ADDRESS the underlying cause**
  - Excessive cows milk or other dietary lack
  - GI losses– Celiac, IBD, ect..
  - Ongoing loss such as **menorrhagia**

Table 4. Oral Iron Formulations and Dosing

Formulation	*Dosing (elemental iron)*
Ferrous fumarate	Tablet: 90 (29.5) mg, 324 (106) mg, 325 (106) mg, 456 (150) mg
Ferrous gluconate	Tablet: 240 (27) mg, 256 (28) mg, 325 (36) mg
Ferrous sulfate	Drops and oral solution: 75 (15) mg per mL
	Elixir and liquid: 220 (44) mg per 5 mL
	Syrup: 300 (60) mg per 5 mL
	Tablet: 300 (60) mg, 324 (65) mg, 325 (65) mg
	Extended-release tablets: 140 (45) mg, 160 (50) mg, 325 (65) mg
Polysaccharide-iron complex and ferrous bisglycinate chelate	Capsule: elemental iron (50 mg, 150 mg with or without 50 mg vitamin C)
	Elixir: elemental iron (100 mg per 5 mL)

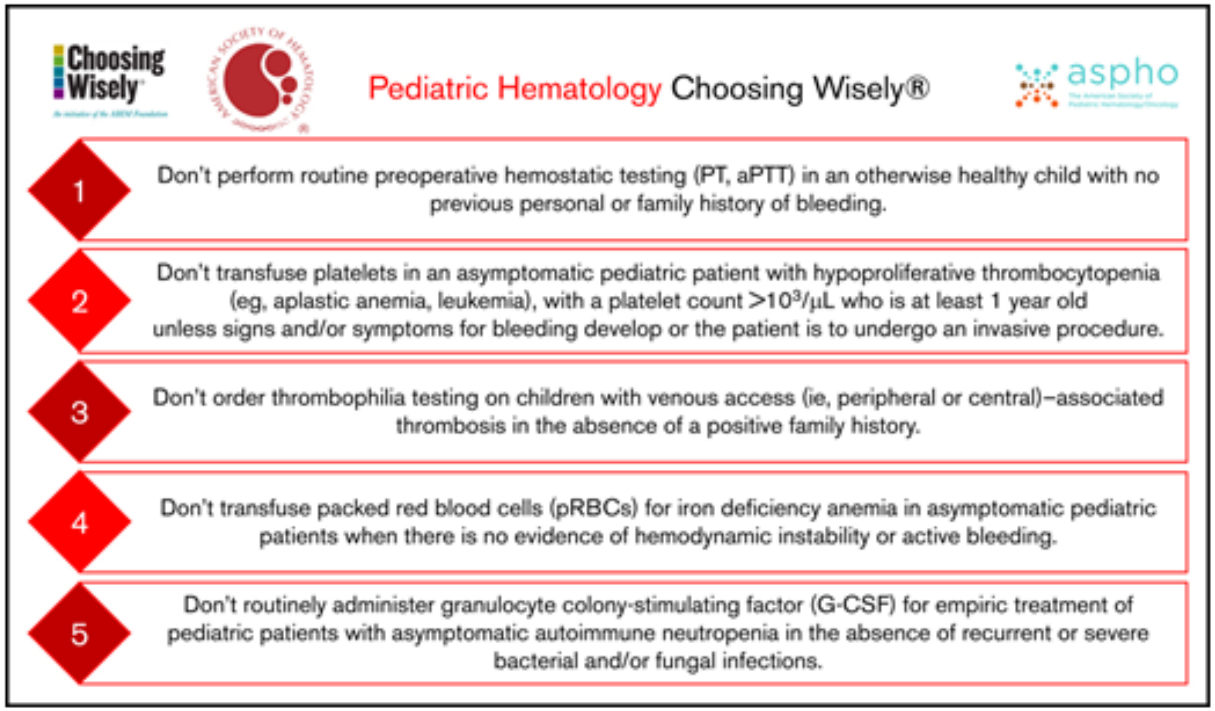
Information from reference 3.

Wang , M. (2016). Iron deficiency and other types of anemia in infants and children. *American family physician*, *93*(4), 270-278.70-278.

Time points to follow with oral iron replacement

- Baseline → start therapy
- 72 hours-1 week→ reticulocytosis
- 1 month → CBCd, retic; ideally anemia resolved if mild
- 3 months → CBCd, retic, ferritin – assess if you can stop therapy

Choosing Wisely



Limitations with pRBC transfusion

- Limited pRBC supply
  - Cost

- Risks with transfusion
  - Transfusion Associated Transfusion Overload
  - Transfusion Related Lung Injury
  - Allergic Reactions
  - Delayed/Acute hypersensitivity reactions
  - All immunization

Transfusion in IDA

- Transfuse Symptomatic, bleeding or otherwise unstable patients with documented Iron Deficiency
  - Considerations of compliance and feasibility for close interval outpatient follow-up
  - Generally in stable patients with confirm IDA WITHOUT active bleeding transfusion should not be omitted for those with Hgb 5 or less

Cause of poor response to oral iron

- **Noncompliance**
  - Oral iron challenge – can be done in office or while admitted
- Incorrect dose or insufficient duration
- Occult blood loss
- High gastric pH– antacids
- Incorrect diagnosis
  - Thalassemia; ACI; sideroblastic anemia
- Something inhibiting absorption
  - Ongoing cows milk
  - Lead
  - Chronic inflammation
  - Underlying GI condition
- Least likely: IRIDA (genetic, blunted response to IV iron)

Iron Deficiency and IDA

- Impact beyond Anemia
  - Concern for potentially permanent behavioral and neurodevelopmental changes

Concern for IDA (low retic, Hgb and MCV) w/ no other affected cell lines

First add additional labs to include TIBC w/ iron, ferritin and retic count (if previously not obtained

The Children's Hospital at Saint Francis
Pediatric Hematology / Oncology
Gregory B. Kirkpatrick, MD
Martina C. Hum, MD
Shilpa Shukla, MD
Jill Salo, MD
Sara Mednansky, MD
Cori Lynn Ryan, CPNP-AC/PC

Noted Hgb value w/microcytosis, low ferritin and low iron studies

Yes

No

Macrocytic?

Consider folate/B12 deficiency

Hgb >7 g/dL and asymptomatic

- Start oral supplementation @ 4 mg/kg of elemental iron (ferrous sulfate or Novaferrum) & recheck labs in 3 months.
- Thorough dietary history (decrease cow's milk and increase iron rich foods)
- If having heavy menstrual cycles consider an OB/GYN consult

Hgb <7 g/dL and symptomatic

- Refer to ED for admit or direct admit for pRBCs +/- iron infusion and start of oral supplementation once stable Hgb is reached
- Call for PHO consult

Improved MCV/Hgb? Continue supplement x 2-3 months and switch to MVI to maintain iron stores

Unimproved MCV/Hgb despite compliance with oral supplement and remains asymptomatic. Consider GI consult and iron infusions

Unimproved MCV/Hgb d/t poor complaince? Try a different formulary (Novaferrum is much more tolerated)

cont. poor compliance with documented attempts at diet change/formulary change?

- Call for PHO consult to assist with PCP management
- Consider outpatient iron infusions

The Children's Hospital, Level A
6161 South Yale Avenue
Tulsa, Oklahoma 74136
918.502.6720
918.502.6725 fax
www.saintfrancis.com

Founded by The William K. Warren Foundatio

Case#3 15 yo F with fatigue for 3 months

- 15 yo F with history for progressively worsening fatigue and pallor 3 months; acutely comes to PCP for new onset dizziness with standing

- Symptomatic or Asymptomatic
- Acute or Chronic
- Degree of Severity?
- Next steps

History and Physical

History

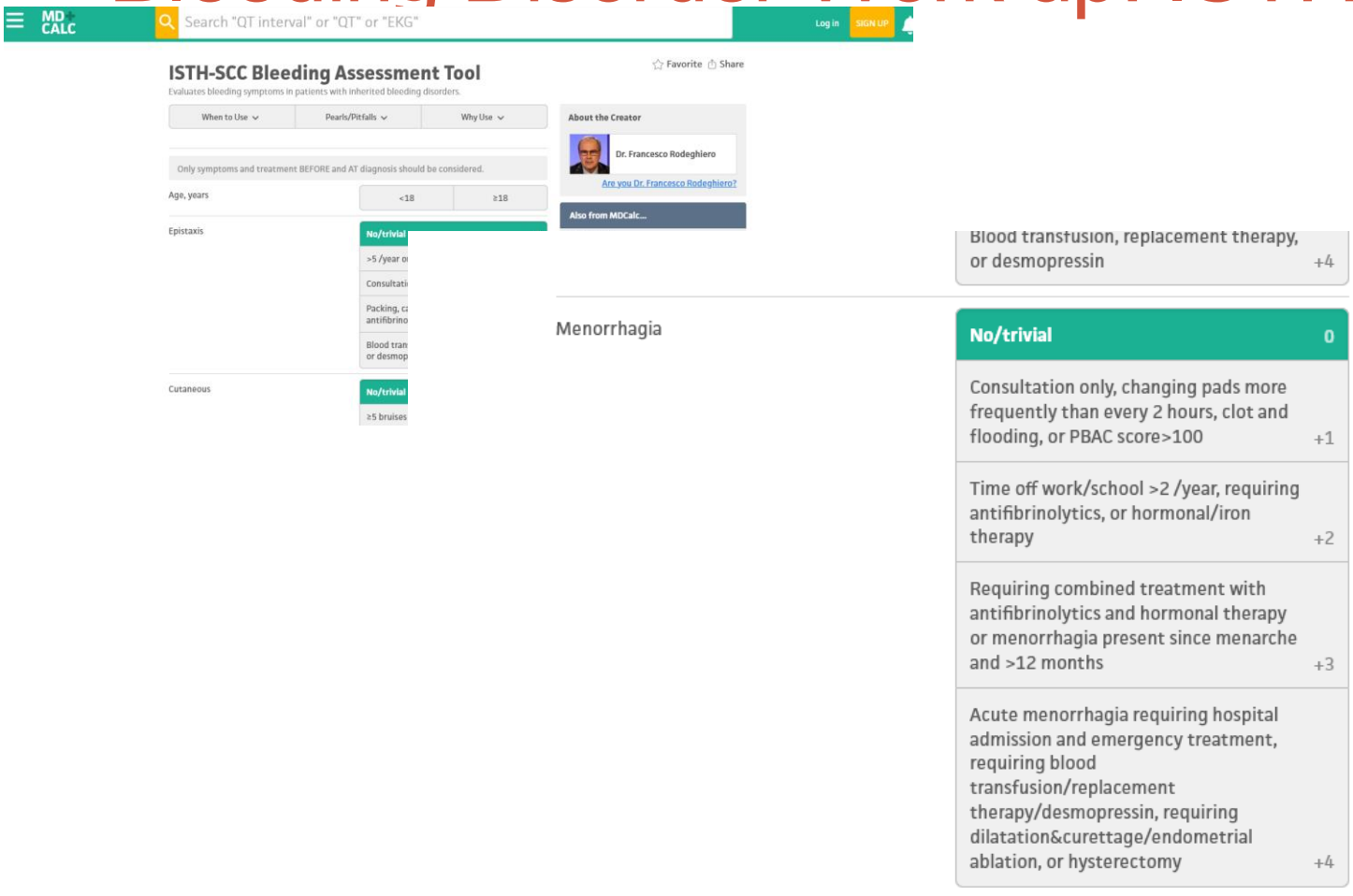
She has been more tired; in the past week taking naps after school
Exertional fatigue
With Standing transient dizziness that resolves with sitting/laying down
Eating Ice

What other History Elements would you obtain?

Menstrual history

- **Date of first period**
- **Assessment of frequency and duration**
- **Assessment of severity**
  - **Can use validated tools like**
    - Pictorial bleeding assessment chart (PBAC)
    - ISTH BAT
    - Menstrual Impact Score

Bleeding Disorder Work up: ISTH BAT



Family History

- What elements do you ask?

Exam

What would be considered as red flags in this case?

Labs

- CBCd: **Hgb 5.6 MCV 55 PLT 650K**
- Retic Count: 0.9%
  Peripheral Smear: Microcytic, Hypochromic Anemia
- Iron Studies
  - Iron Sat 3%, Ferritin 2, TIBC 650, Transferrin 500
- Prothrombin Time: WNL
- PTT: WNL
- Fibrinogen: WNL
- von Willebrand panel: Pending
- Comprehensive Metabolic panel: WNL
- Direct Antibody Test: Negative
- CMP: WNL
- UPT: NEG

Laboratory Evaluation

Hematologic work up

Prothrombin Time
PTT
Thrombin time
Fibrinogen
von Willebrand panel
Comprehensive Metabolic panel
Direct Antibody Test
LDH

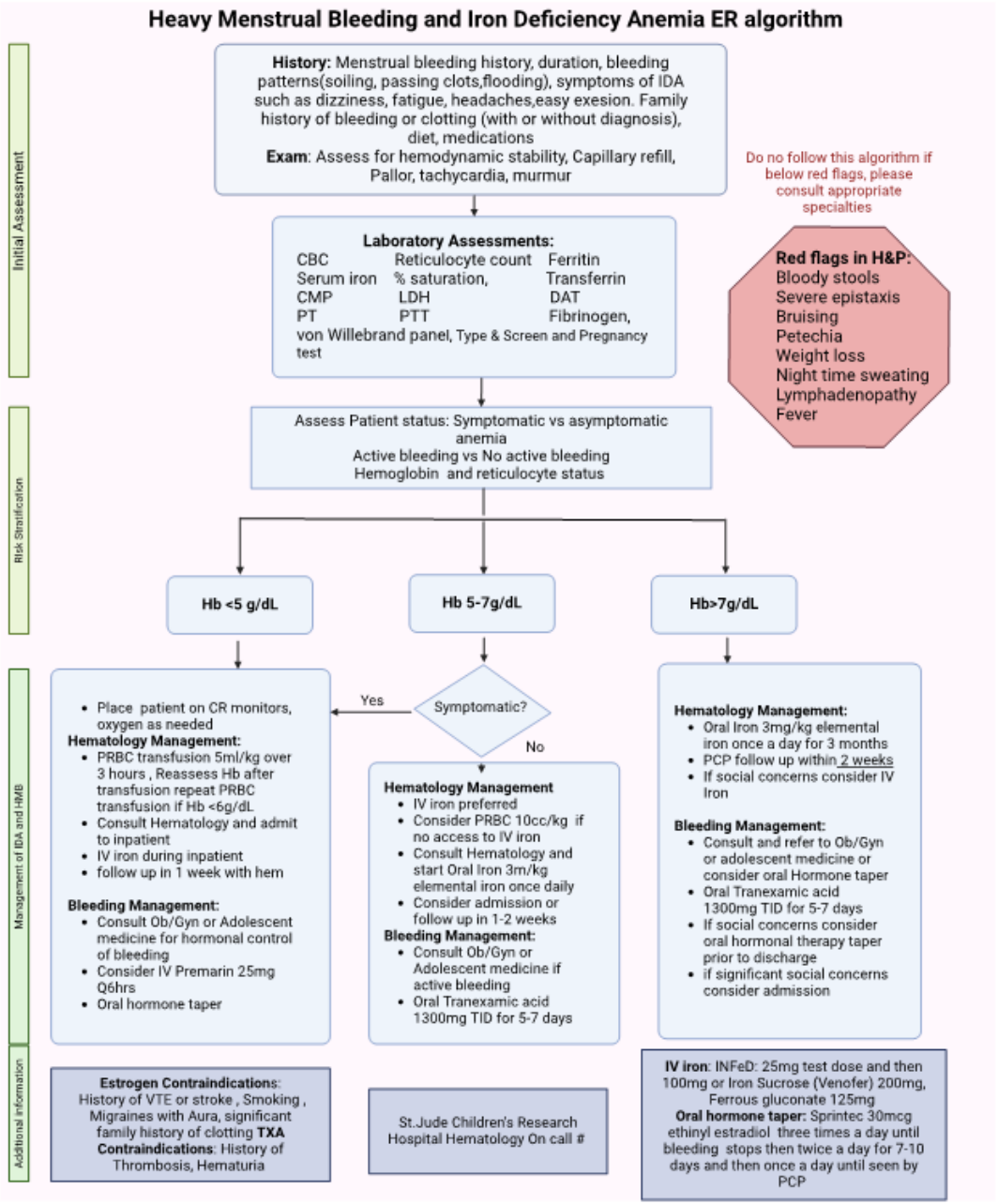
Non-Hematologic Work up

TSH
T4
Pelvic Ultrasound

Consult
Hematology
Ob/Gyn or Adolescent Medicine

Create a Treatment Plan

Heavy Menstrual Bleeding and Iron Deficiency Anemia ER algorithm



HMB IDA

- IMPORTANCE of follow-up

- Severe IDA with HMB (Hb <7g/dl)
  - Follow up in 1 week to assure trends are improving
  - After that 1 month and 3 month follow up
  - Patient may need more than 3 months therapeutic iron supplements
- Non-severe IDA with HMB (Hb>7g/dl)
  - 1 month and then 3 month follow up
  - May need longer than 3 months

You must treat the underlying loss to fully address IDA

SOP

- Looking for stakeholders to work with our team to review and develop anemia SOP for both inpatient and outpatient populations

Case #4

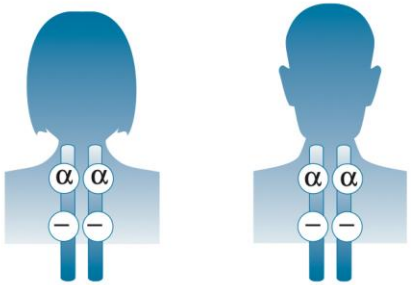
- 5 yo F admitted for WCC; prior history of microcytic anemia treated with 3 months of oral iron. Did not come back for follow-up labs to assess iron response. Clinically generally well. Exam is non-focal. CBCd obtain in office.

- WBC 7.0
- PLT 457
- Hgb 11.7
- MCV 60
- Diff: WNL

Put back on oral iron 4 mg/kg elemental for 1 month with no change in Hgb

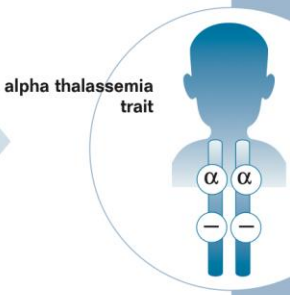
Ferritin: 100

Thalassemia



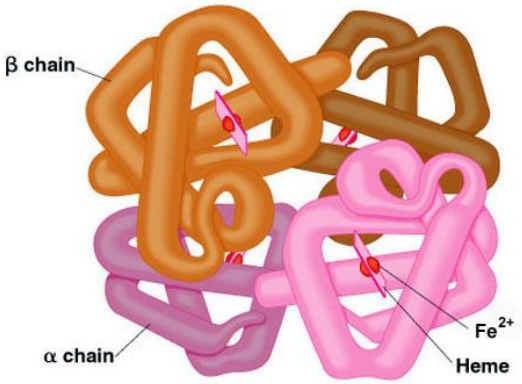
If **both parents** carry **alpha thalassemia trait** in which the two abnormal genes of each parent are on opposite chromosomes, their children will inherit **alpha thalassemia trait.**

An individual with two abnormal alpha globin genes is said to have **alpha thalassemia trait**. The two abnormal genes can be on the same chromosome or on each chromosome in the pair.



Alpha Thalassemia Trait.
In this condition, in which two of the four alpha globin genes are missing or defective, the lack of alpha globin protein is somewhat greater. Both abnormal alpha globin genes may be on the same chromosome (cis position) or one may be on each chromosome in the pair (trans position).

Physicians often mistake alpha thalassemia trait for iron deficiency anemia and incorrectly prescribe iron supplements that have no effect on the anemia. Patients with this condition have smaller red blood cells and a mild anemia, although they do not experience symptoms.



Structure of hemoglobin

Cooley's Anemia
FOUNDATION
Leading the Fight Against Thalassemia
(800) 522-7222 or info@cooleysanemia.org
www.cooleysanemia.org

Thalassemia

- Thalassemias are inherited hemoglobinopathies that arise from the unbalanced synthesis of globin chains, which results in abnormal hemoglobin (Hb)
- Alpha and Beta Thalassemia
- Mild anemia →incompatible with life (hydrops fetalis)
- How to discriminate IDA vs Thalassemia
  - NBS
  - Iron studies/Response to oral iron trial
  - Hgb Electrophoresis
  - Family history
  - Mentzer index (>13 IDA, <13 c/f thalassemia)
  - Genetic testing

MCV (fl) / RBC (millions per microliter)

Case #5

- 6 yo M with fatigue, vague abdominal pain, constipation and pallor; worsened performance at school; presented ~5 months and worsening

- Exam: Mild generalized abdominal pain; Non-focal otherwise, except now in the 30th%tile for H/W and previously in the 40th. He has mild tenderness elicited by abdominal palpation

- Famhx: Brother with similar behavioral concerns
- Social: Lives with mom and dad; Home built in 1930s

Labs

- CBC
- WBC 6.0 appropriate diff
- Hgb 8 g/dL
- Hct 28%
- MCV 60
- +Hypochromic/Basophilic stippling

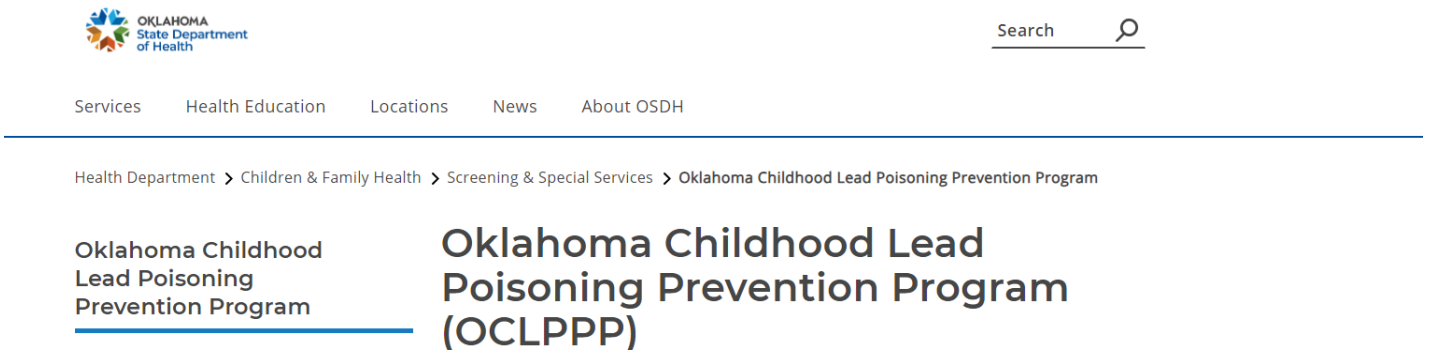
Retic Count – Normal but not elevated in the setting of anemia

Iron studies: Appropriate

What are is on our differential?

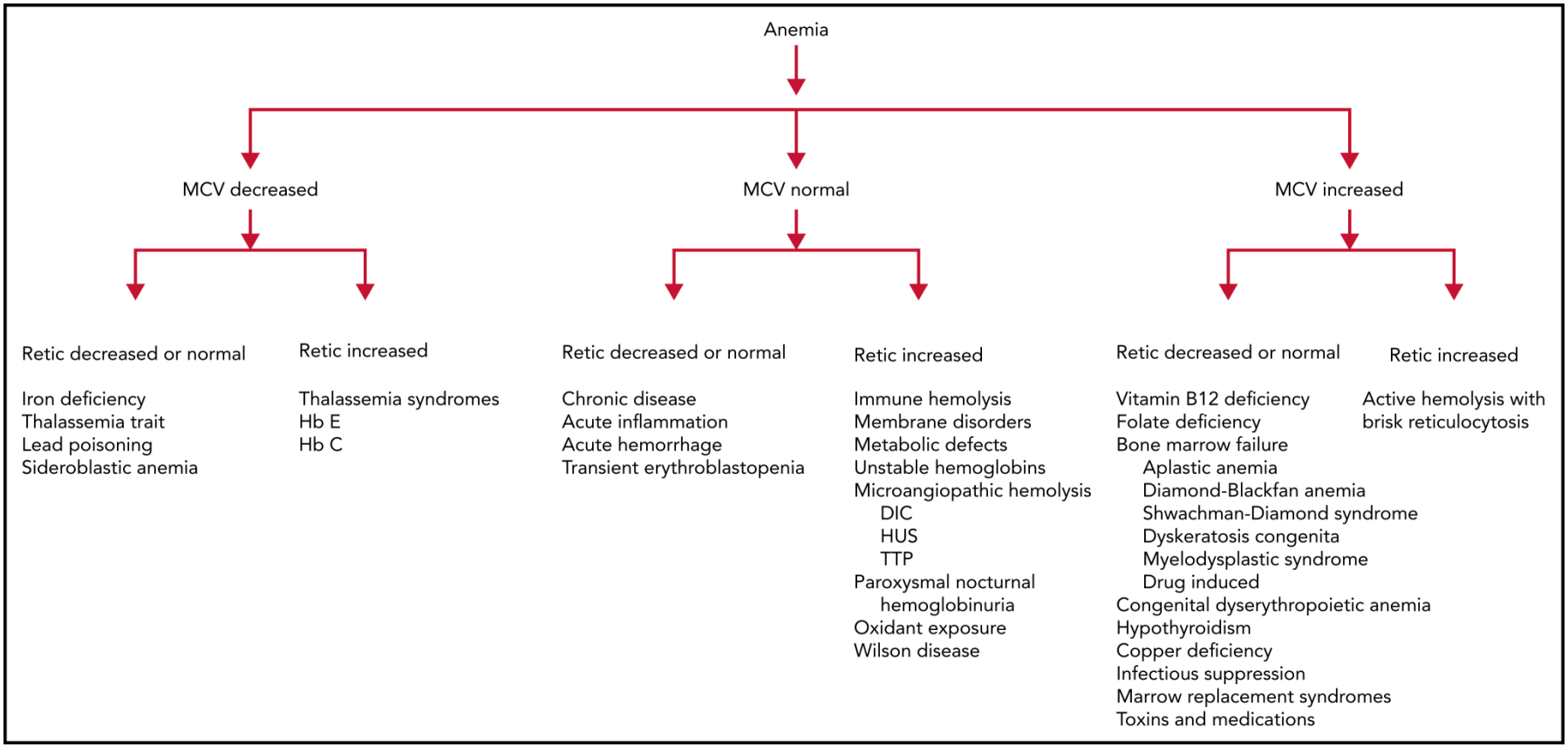
Lead Toxicity

- Shorted RBC cell survival; Alters heme biosynthesis
  - Also acts at the level of the bone marrow
- Rule out co-occurring IDA
- Lead absorption increased by deficiencies in other minerals; PICA



Normocytic anemia

Anemia in the pediatric patient



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CASE #6

- 18 month old seen for fatigue and pallor
  - Not a picky eater; appropriate cow milk intake
  - NBS normal, Term infant, no concerns at time of birth
  - No history of easy bruising or bleeding; Denies Jaundice/icterus/dark urine
  - Viral illness ~1 month prior to presentation
  - No prior transfusion history and Hgb at 12 month WCC appropriate
  - Exam: Non-focal; crawling around your office; no concern for congenital anomalies
  - Famhx: No family history of anemia (IDA, thalassemia, ect..)

Case #6

- CBCd
  - WBC 6.0
  - PLT 400K
  - Hgb 5.0
  - MCV 80
- Retic
  - 0.81%; Retic Hgb 43 (wnl)
- Ferritin 33 mg/dl
- Path review: Normocytic anemia; no abnormal RBC forms
- TIBC/Transferrin/Iron/Iron Sat: appropriate

What are potential considerations from hypoproliferative normocytic anemia?

Transient Erythroblastopenia of Childhood

Aplastic Anemia

Infectious suppression

Drug induced aplasia: AED

DBA (Most often marcocytic)

TEC

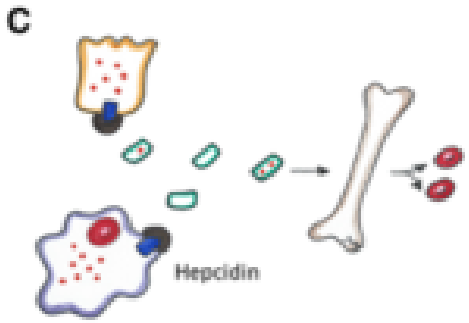
- Most common cause of pure red cell aplasia in pediatric patients
- Still relatively uncommon
- Toddlers– median ~26 months of age
- Self-limited
- Potentially viral-triggered
- Hallmarks: Normal MCV, low Retic count
  - In recovery can have robust reticulocytosis that can be confused with other etiologies such as hemolysis

Diamond Blackfan Anemia

- Presents in infancy; 90% diagnosed by 1 year of age
- Pure red cell aplasia
  - Classically macrocytic
  - High EPO; ineffective erythropoiesis
  - Progressive normocytic anemia and reticulocytopenia
  - BM- absent or low erythroid precursors
- Endocrine d/o
- Congenital anomalies
  - Craniofacial
  - Thumb/extremity
  - Short Stature
  - Renal
  - Cardiac
- Elevated Hgb F and eADA
- Predisposition to malignancy → AML
- Steroid responsive; pRBC transfusion; HSCT

Anemia of Inflammation/Anemia of Chronic disease

- A form of iron restricted erythropoiesis
- Excessive hepcidin production
  - Block at small bowel and release from macrophages "hemosiderin laden macrophages"
- Iron is typically normal– but just can't be used
- Limited absorption from the GI tract



Anemia of inflammation

- Treat the underlying cause
- IV iron may be helpful

Normocytic anemia

- Clinical history for acute loss, source of inflammation, hypothyroidism, renal disease
  - Growth
  - Hx of recent or recurrent infection/inflammation

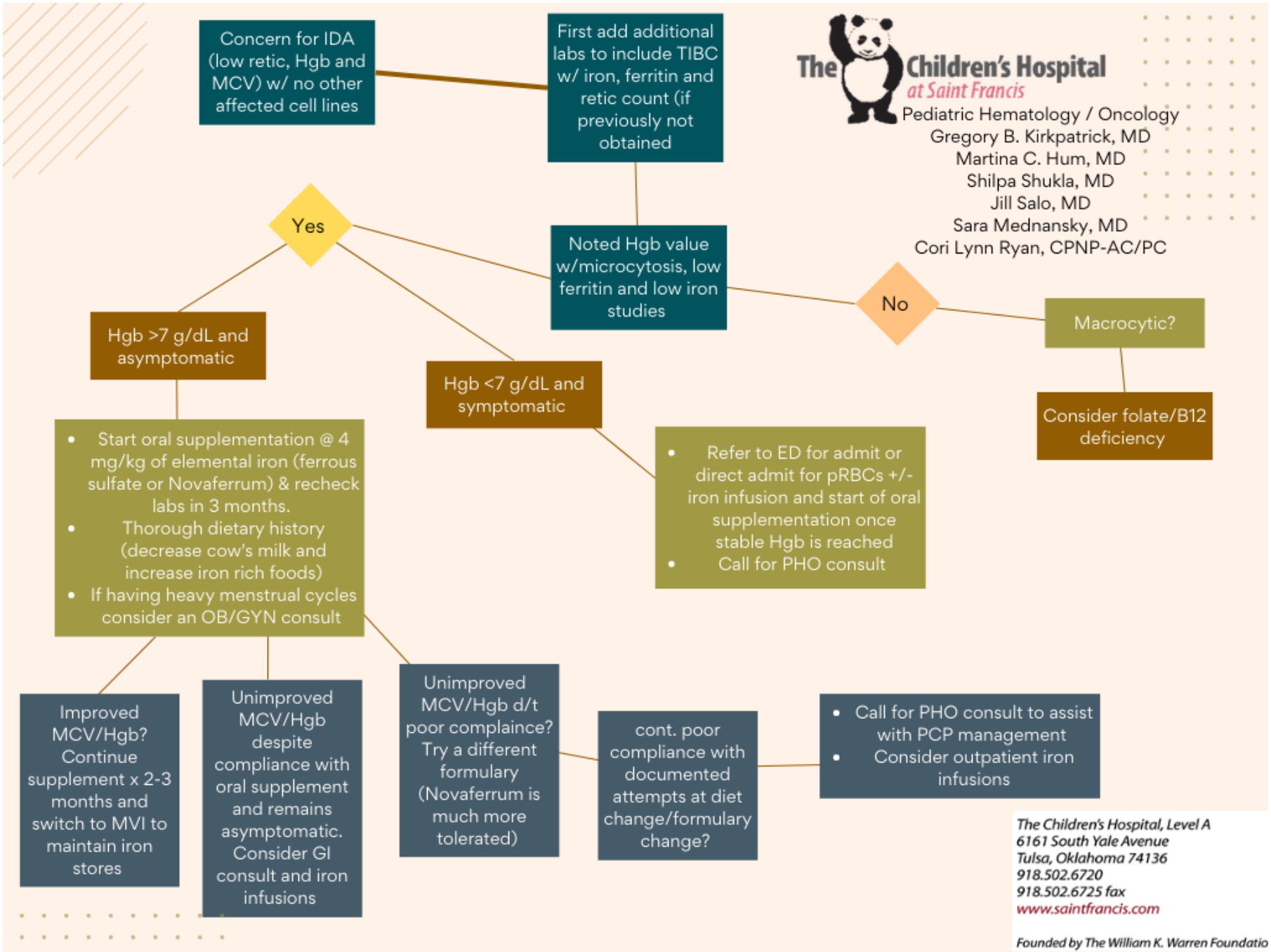
- Work-up
  - CBC, retic, smear
  - CMP
  - TSH, free T4
  - CRP/ESR

If anemia is mild and work-up reassuring: statistical anemia – 2.5% population will fall below normal
Routine f/u or PHO consult to ensure stability

Wrap Up

- Interested in working on anemia SOP?

- Please Contact:
  - smednansky@saintfrancis.com


Concern for IDA (low retic, Hgb and MCV) w/ no other affected cell lines
First add additional labs to include TIBC w/ iron, ferritin and retic count (if previously not obtained
The Children's Hospital at Saint Francis
Pediatric Hematology / Oncology
Gregory B. Kirkpatrick, MD
Martina C. Hum, MD
Shilpa Shukla, MD
Jill Salo, MD
Sara Mednansky, MD
Cori Lynn Ryan, CPNP-AC/PC
Yes
Noted Hgb value w/microcytosis, low ferritin and low iron studies
No
Macrocytic?
Consider folate/B12 deficiency
Hgb >7 g/dL and asymptomatic
Hgb <7 g/dL and symptomatic
Start oral supplementation @ 4 mg/kg of elemental iron (ferrous sulfate or Novaferrum) & recheck labs in 3 months.
Thorough dietary history (decrease cow's milk and increase iron rich foods)
If having heavy menstrual cycles consider an OB/GYN consult
Refer to ED for admit or direct admit for pRBCs +/- iron infusion and start of oral supplementation once stable Hgb is reached
Call for PHO consult
Improved MCV/Hgb? Continue supplement x 2-3 months and switch to MVI to maintain iron stores
Unimproved MCV/Hgb despite compliance with oral supplement and remains asymptomatic. Consider GI consult and iron infusions
Unimproved MCV/Hgb d/t poor complaince? Try a different formulary (Novaferrum is much more tolerated)
cont. poor compliance with documented attempts at diet change/formulary change?
Call for PHO consult to assist with PCP management
Consider outpatient iron infusions
The Children's Hospital, Level A
6161 South Yale Avenue
Tulsa, Oklahoma 74136
918.502.6720
918.502.6725 fax
www.saintfrancis.com
Founded by The William K. Warren Foundatio

Questions?