Brigham and Women's Hospital
Founding Member, Mass General Brigham

ANEMIA

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- Clinical focus: Non-malignant Hematology
- Research focus areas: Sickle Cell Disease
  Iron deficiency
  Duffy-null ANC (DANC)
  Health Equity

Commercial/Faculty Disclosures

Company	Role
Pfizer/Global Blood Therapeutics	Scientific Advisory Board
Pharmacosmos	Scientific Advisory Board
Shield Therapeutics	Scientific Advisory Board
Novo Nordisk/Forma Therapeutics	Scientific Advisory Board
Vertex pharmaceuticals	Scientific Advisory Board

Learning Objectives

Use case vignettes to:

- Review the work-up of anemia, in general.

- Highlight the presentation and management of specific causes of anemia.

Anemia

- Hemoglobin or hematocrit below the normal range for age and gender

- Anemia can be due to:
  - ↓ red cell production **(low retic count)**
  - ↑ red cell destruction **(high retic count)**
  - Red cell (blood) loss **(high retic count)**

Evaluation of Anemia

1. Size of RBCs – MCV
2. Reticulocyte count
3. Peripheral smear

Other Labs in Evaluation:

↑LDH
↑Indirect Bilirubin
↓/absent Haptoglobin

+ ↑ reticulocyte count ⟶ Hemolysis

+ ↓ reticulocyte count ⟶ Ineffective erythropoiesis

Evaluation of Anemia

RDW

Normal RDW	
	Anemia of inflammation
	Thalassemia trait
	Aplastic anemia
	Acute blood loss
	Renal disease
Elevated RDW	
	Iron deficiency
	Folate & vitamin B12 deficiency
	MDS
	Sickle cell disease

Evaluation of Anemia

Reticulocyte count

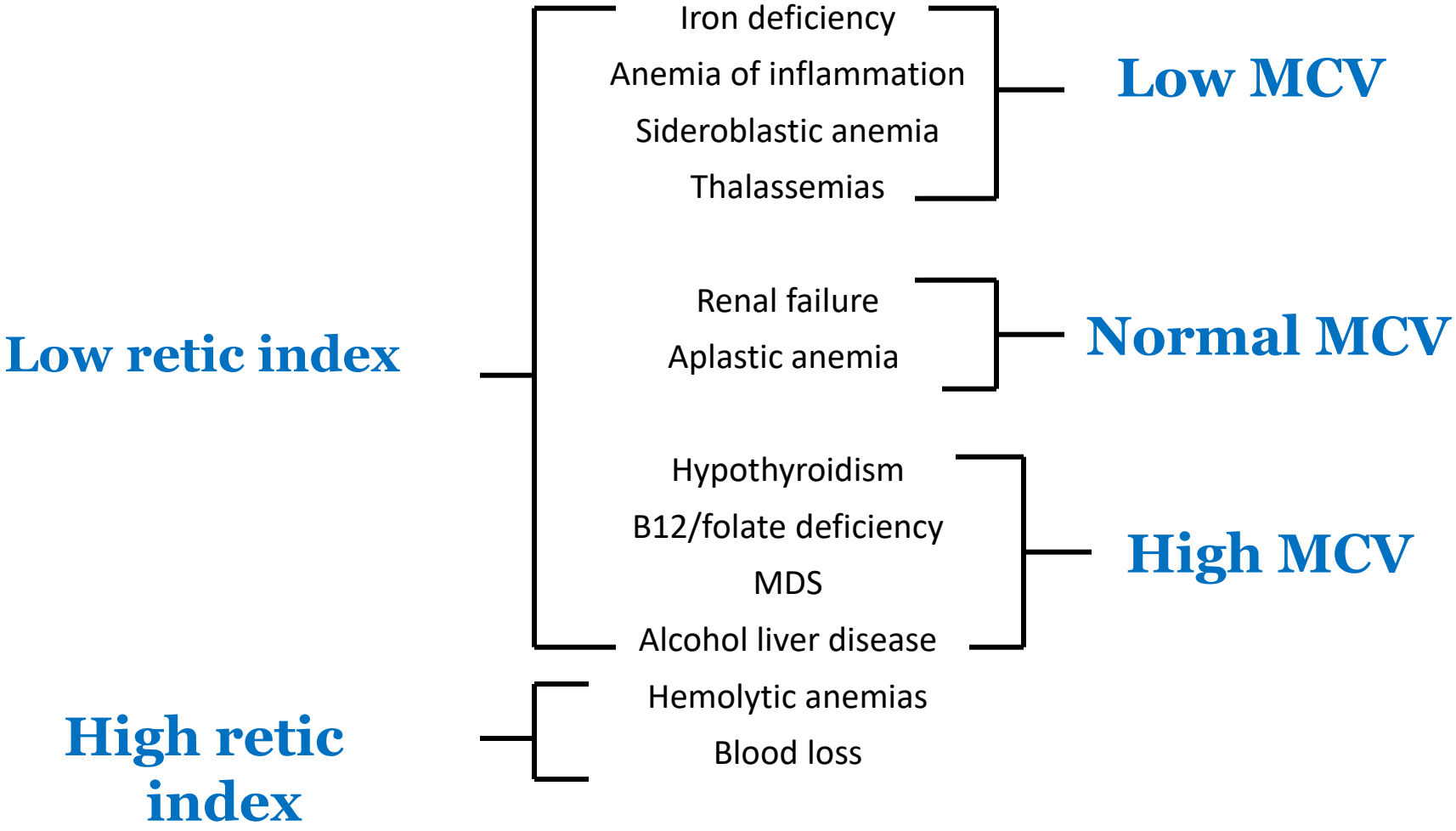
Corrected Reticulocyte Count/Reticulocyte Index

$$\text{Reticulocyte Index} = \text{Retic count} \times \frac{\text{Hematocrit}}{\text{normal Hct (45)}}$$

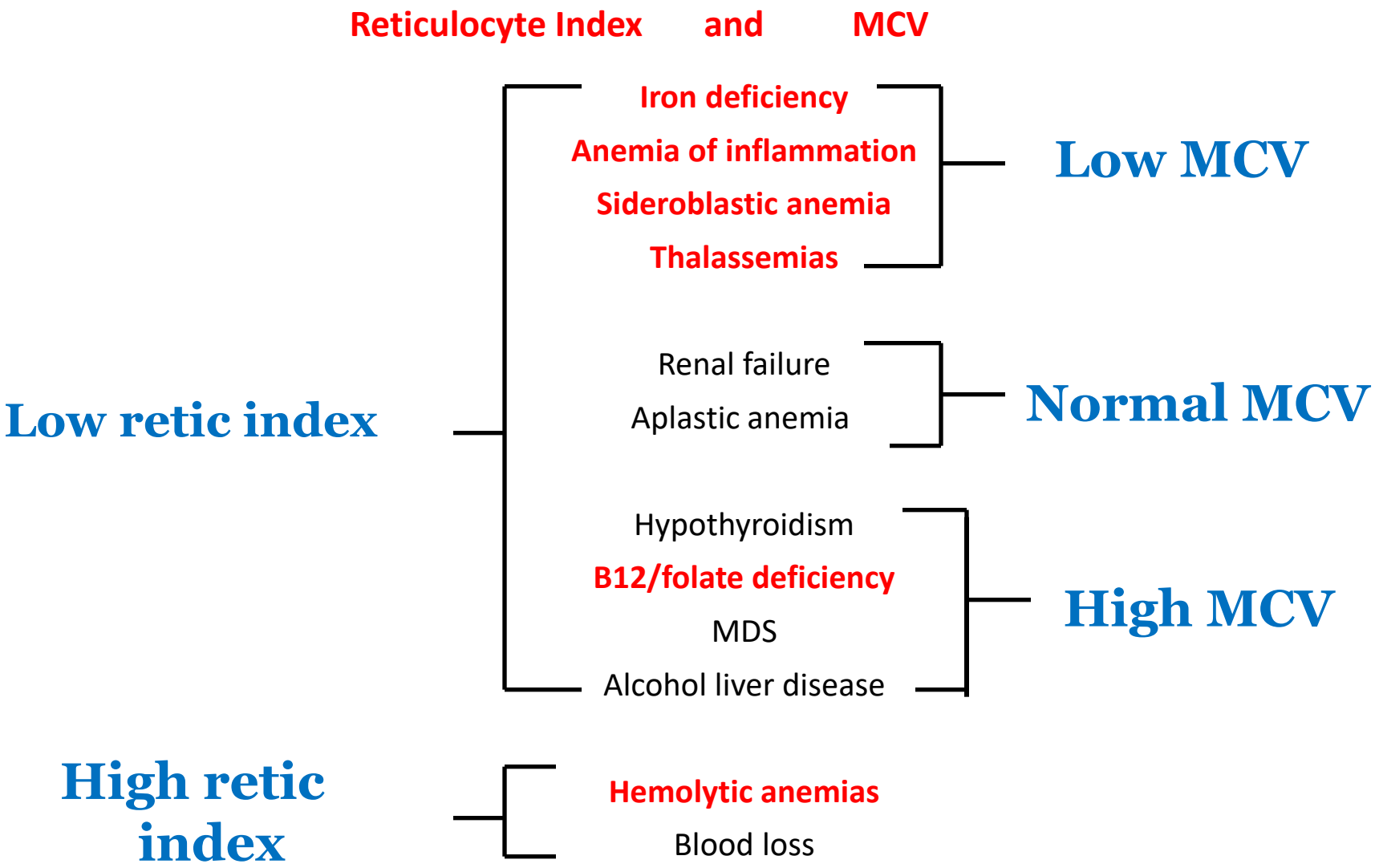
Retic. index in a normal healthy adult is between 1 - 2

Evaluation of Anemia

Reticulocyte Index and MCV



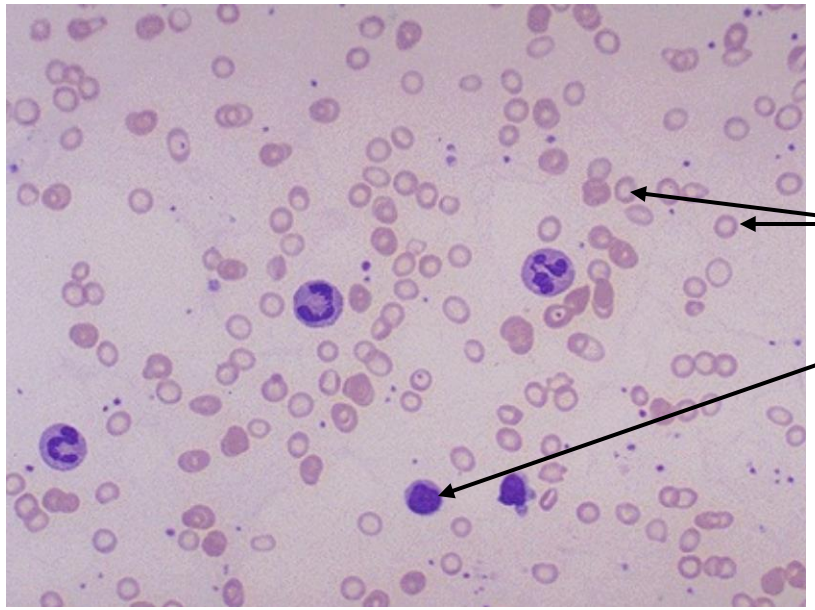
Evaluation of Anemia



Case 1

58 y o woman w/ SLE, HTN and GERD presents with intermittent headaches and fatigue.

WBC 4.7, Hgb 8, Hct 25, MCV 74, platelets 544,000, retic count 1.5%, iron : 45, TIBC : 520, ferritin 20. Soluble transferrin receptor is 4.2 (0.8 – 3 mg/L).



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Which of the following would be of most benefit?

a) Epo stimulating agent therapy
b) Better control of SLE
c) 1 unit packed RBCs
d) Intravenous iron
e) Proton pump inhibitor therapy

Case 2

58 y o woman w/ SLE, HTN and GERD presents 2 years later with fatigue and dyspnea on exertion.

WBC 4.7, Hgb 7.8, Hct 23, MCV 76, platelets 267,000, retic count 1.5%, iron : 19, TIBC : 220, ferritin 209. Soluble transferin receptor is 0.9 (0.8 – 3 mg/L).

Case 2

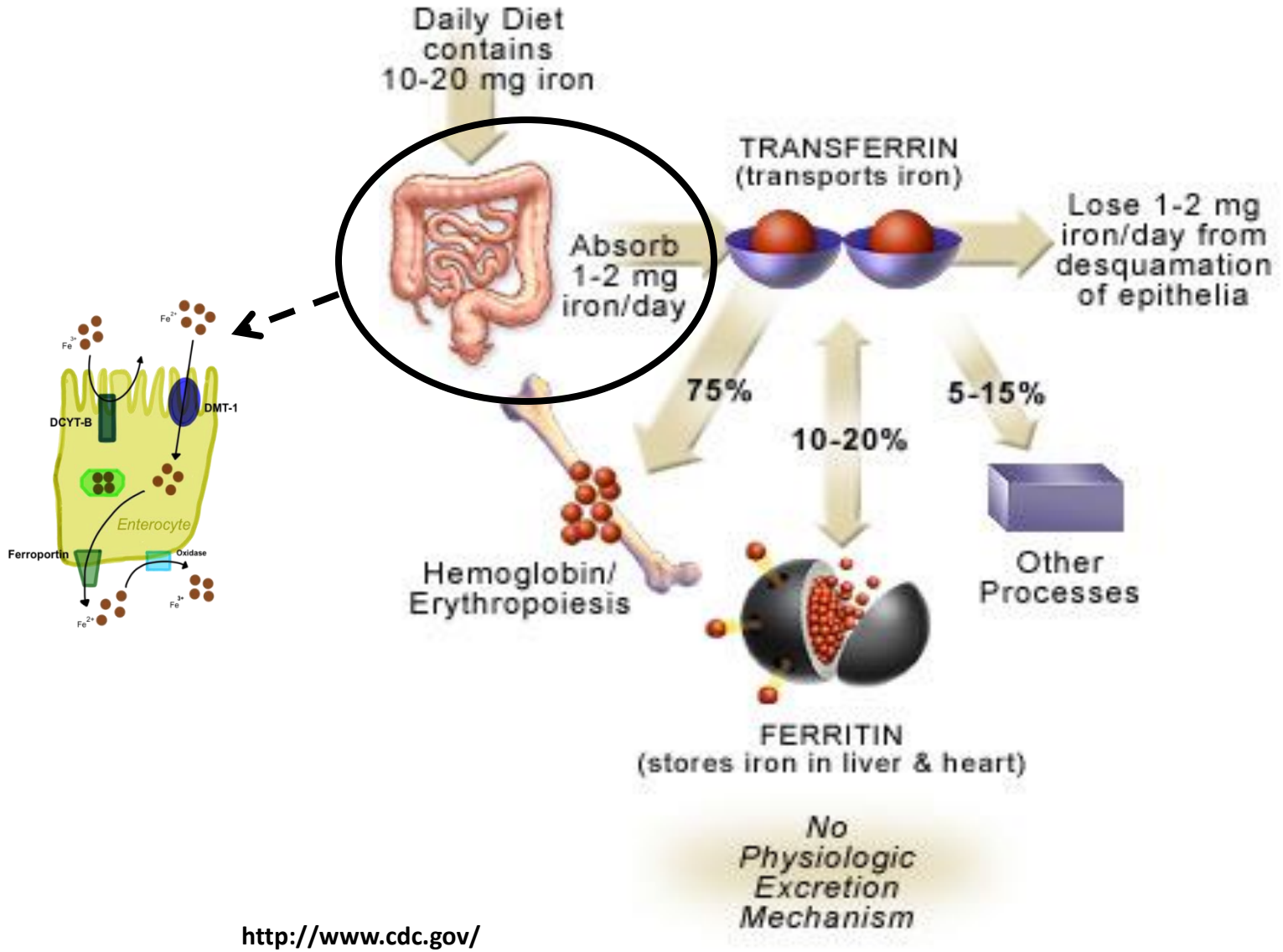
58 y o woman w/ SLE, HTN and GERD presents 2 years later with fatigue and dyspnea on exertion.

WBC 4.7, Hgb 7.8, Hct 23, MCV 76, platelets 267,000, retic count 1.5%, iron : 19, TIBC : 220, ferritin 209. Soluble transferrin receptor is 0.9 (0.8 – 3 mg/L).

What is the cause of her anemia:

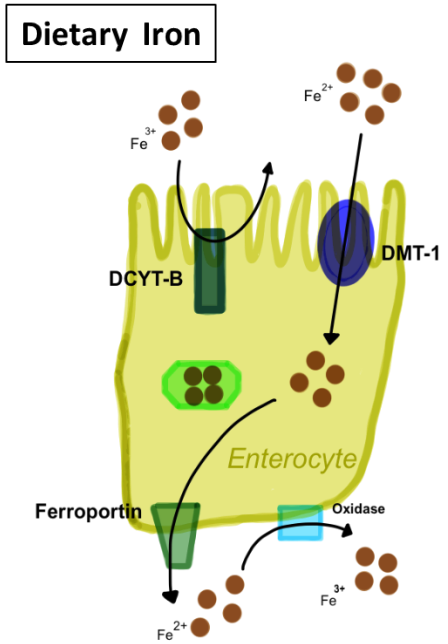
a) Iron deficiency
b) Anemia of inflammation
c) Iron deficiency and Anemia of inflammation
d) None of the above

Iron Deficiency Anemia

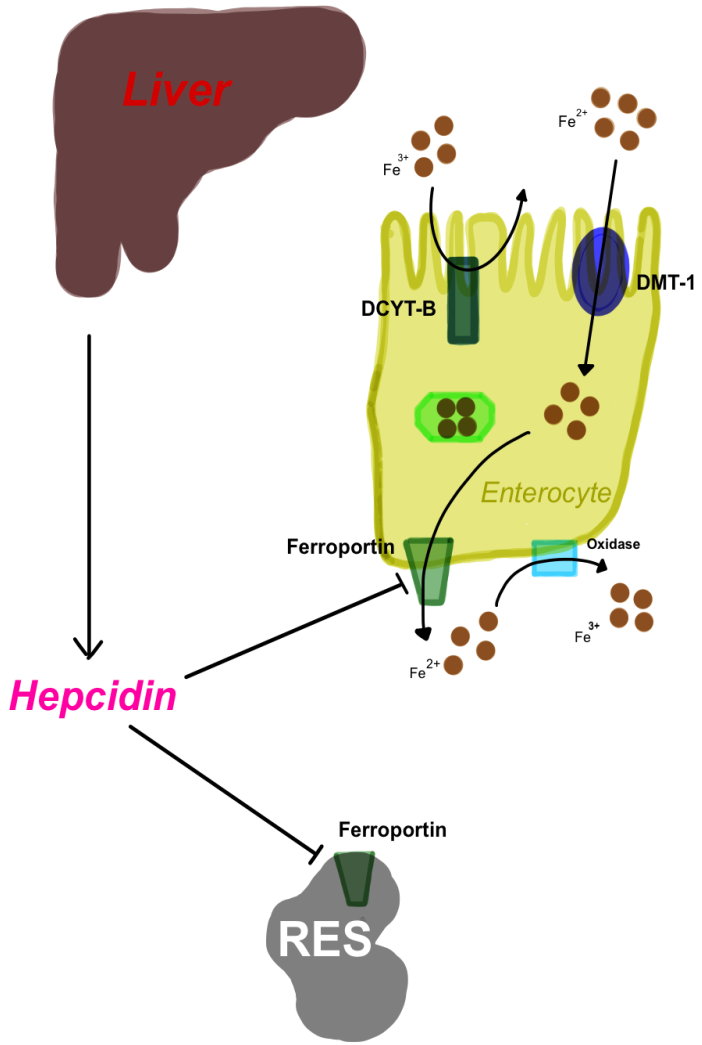


http://www.cdc.gov/

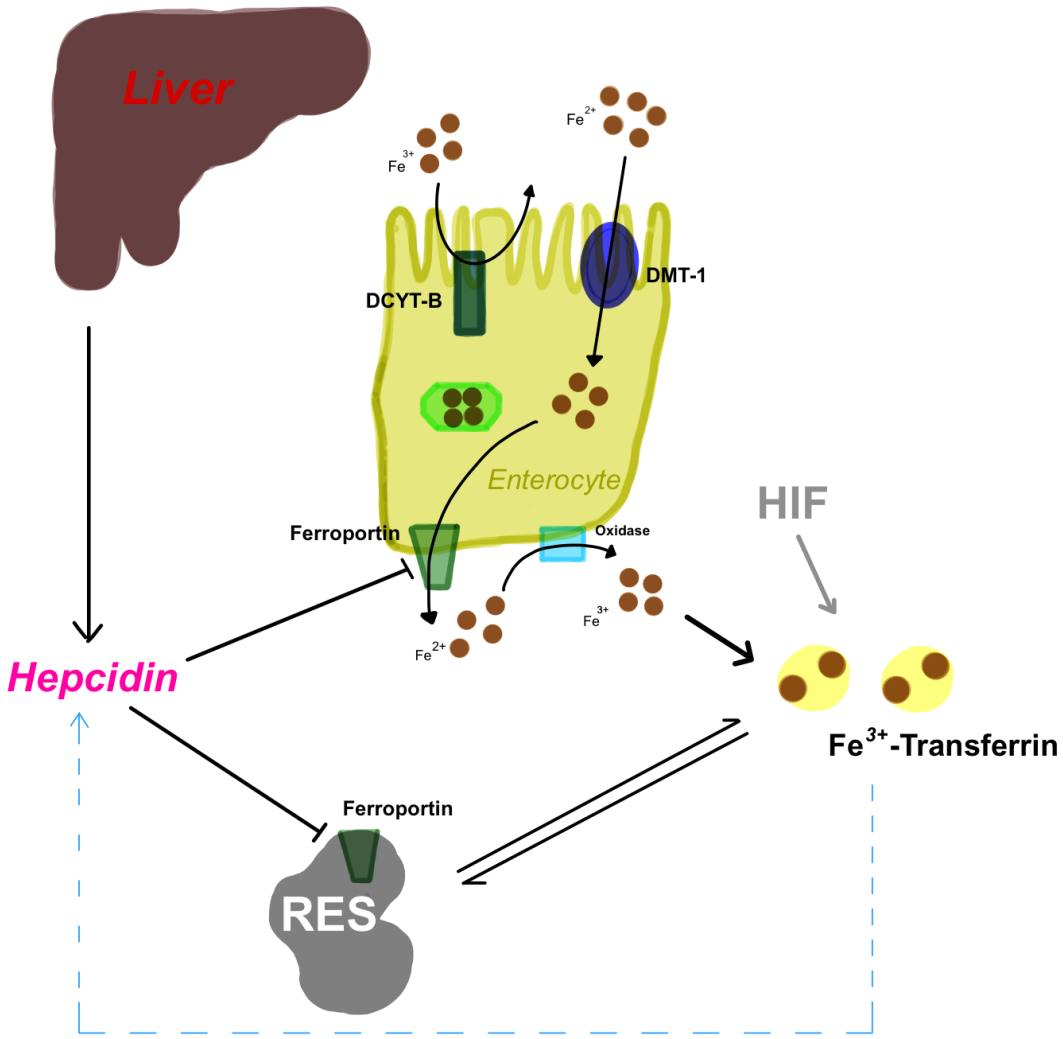
Iron Homeostasis



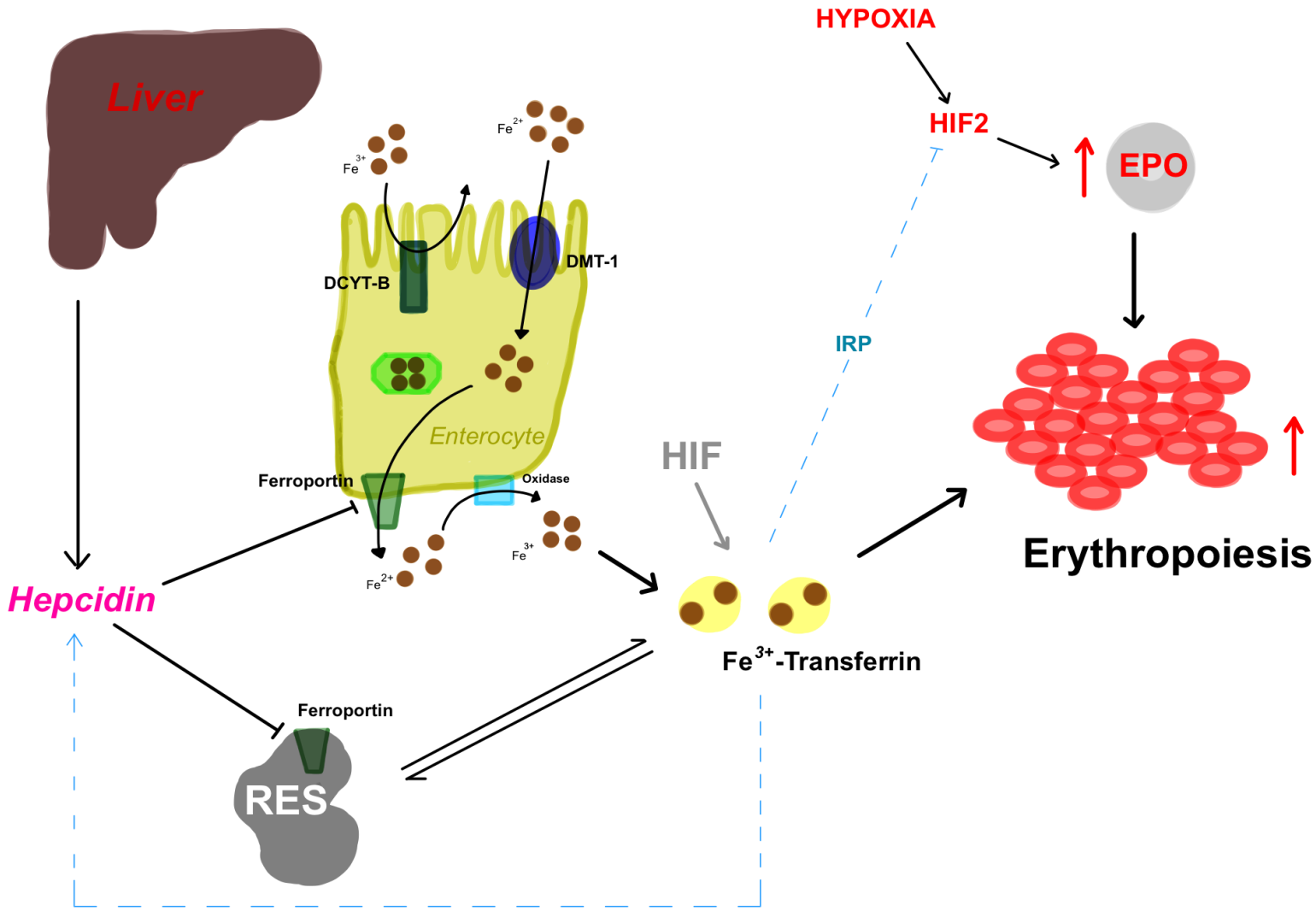
Iron Homeostasis



Iron Homeostasis

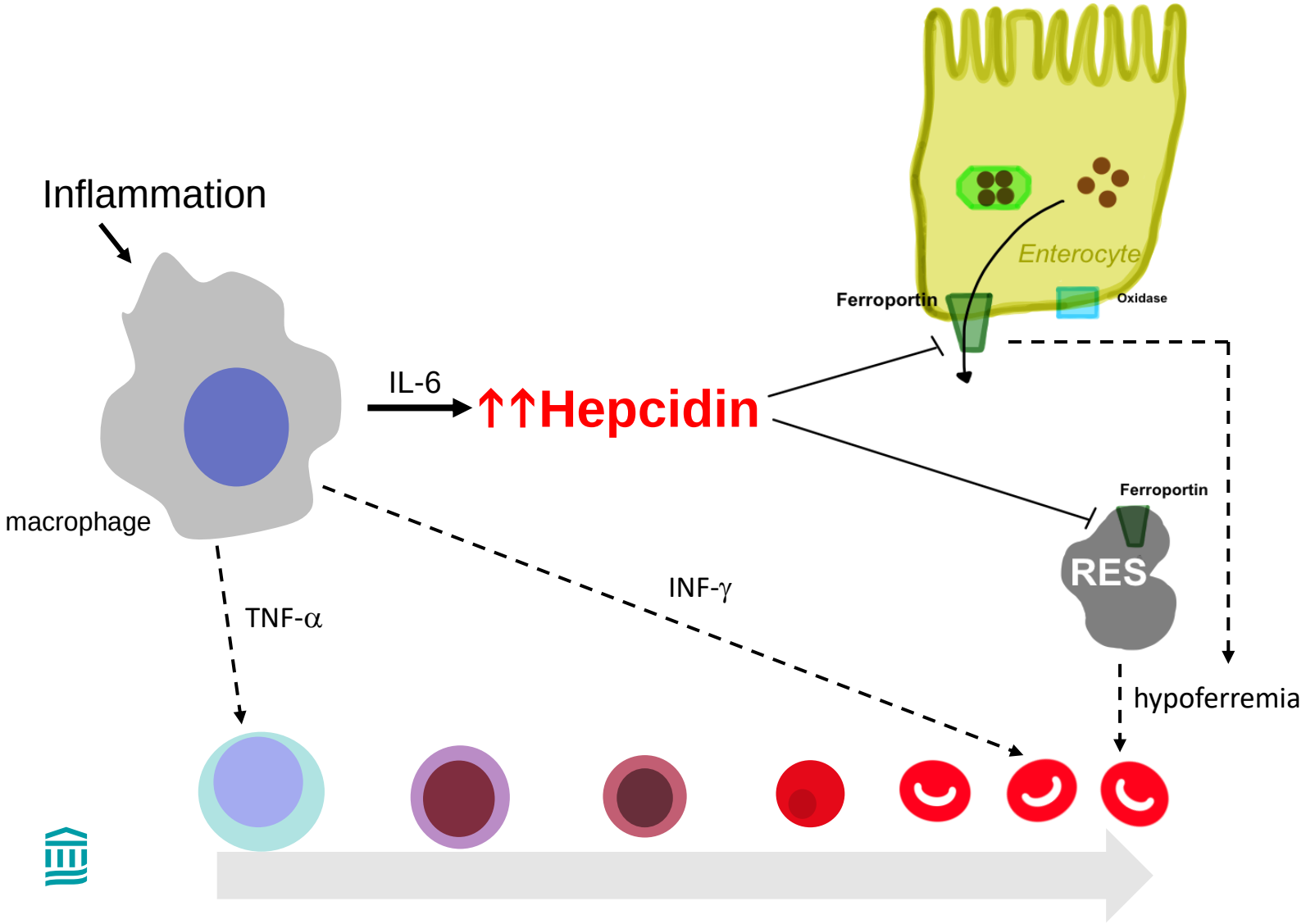


Iron Homeostasis



Anemia of Inflammation: Iron Sequestration Syndromes

Characterized by inappropriately high serum hepcidin



Anemia of Inflammation: Iron Sequestration Syndromes

Iron deficiency may exacerbate chronic diseases leading to accelerated clinical deterioration

- Inflammatory bowel disease
- CHF
- CKD
- Rheumatologic diseases: Rheumatoid arthritis, SLE
- Infections: HIV, TB
- Critical illness
- Malignancies: Hodgkin’s lymphoma, lung cancer

Difference in Biomarkers of Iron Deficiency and Anemia of Inflammation

Biomarker	Iron Deficiency	Anemia of Inflammation
MCV	Low	Normal
MCH	Low	Normal
Retic Hb	Low	Normal
* Serum transferrin (TIBC)	High	Low
Serum transferrin receptor	High	Normal
* Serum ferritin	Low	High
Serum hepcidin	Low	High

Ganz T. Anemia of Inflammation. N Engl J Med. 2019 Sep 19;381(12):1148-1157

Management of Iron Deficiency Anemia

Estimated to affect 2 billion people worldwide

Oral repletion - Ferrous sulfate/gluconate PO

Intravenous repletion

Expected Response to Fe Treatment

- Reticulocytosis – 5-7 days
- Increase in Hb – 2 weeks
- Ferritin repletion – 6 months

US FDA Approved Intravenous Iron Formulations

Drug	FDA Approval Date	Max Approved Dose	Indication for use in Iron Deficiency	Labile Iron release	Black Box Warning
LMW Iron Dextran	1991	100 mg	Dialysis-associated anemia	-	Yes
Ferric gluconate	1999	125 mg	CKD on HD receiving ESA	+++	No
Iron sucrose	2000	400 mg	All stages of CKD	+/-	No
Ferumoxytol	2009	510 mg	Adults with CKD	-	No
Ferric carboxy-maltose, FCM	2013	750 mg	Adults not tolerating/ responding to oral	-	No
Ferric derisomaltose	2020	1000 mg	Iron deficiency anemia	+	No

Table adapted from Bircher. 2014.

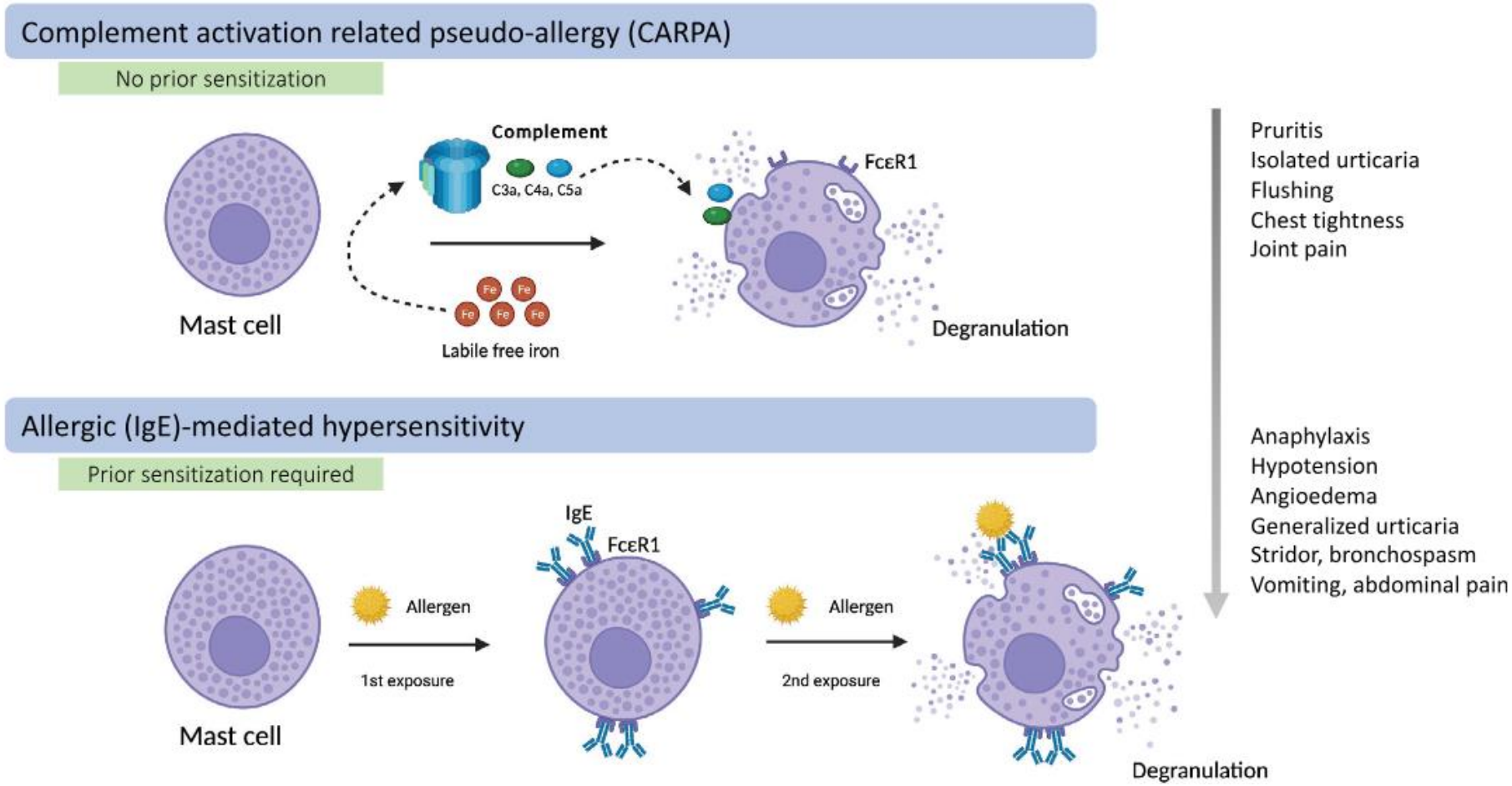
Comparative rates of adverse events with different formulations of intravenous iron

Maureen M. Okam,[1,2*] Elyse Mandell,[1,2] Nathanael Hevelone,[3] Rachel Wentz,[1] Ainsley Ross,[1] and Gregory A. Abel[4,5]

- Retrospective comparison of safety of IV irons used at our institution.
- 619 patients over 2 yrs : 32 adverse events (AEs), ranging from urticaria to chest pain.
- **No serious AEs or anaphylactic-type rxns.**
- AE rates between LMW Dextran and ferric gluconate were equivalent
- Iron sucrose had higher odds ratio of AEs (OR= 5.7; 95% CI 1.6–21.3).
- AE rates with IV iron are acceptable.

Am J Hematol. 2012 Nov;87(11):E123-4.

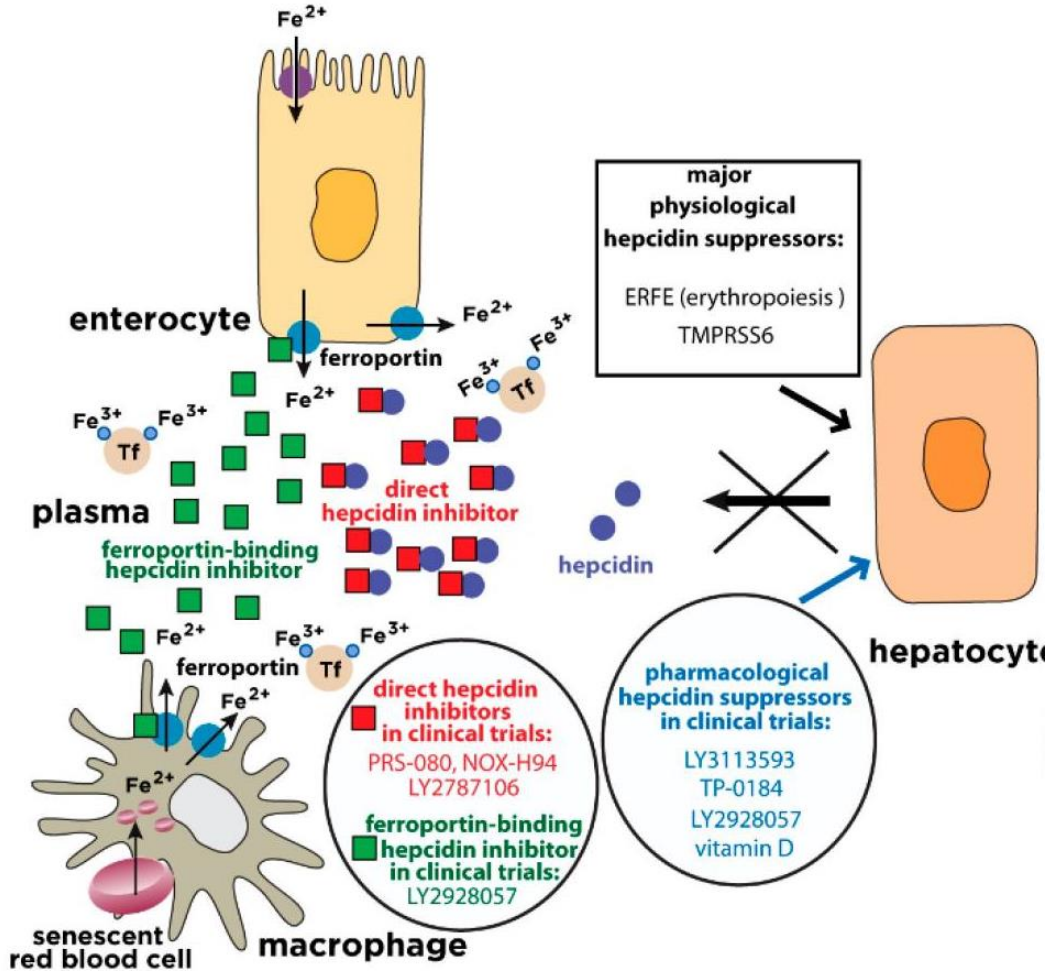
CARPA vs. Allergic (IgE)-mediated Hypersensitivity



Van Doren L, Steinheiser M, Boykin K, Taylor KJ, Menendez M, Auerbach M. Am J Hematol. 2024 Jul;99(7):1338-1348.

Management of Anemia of Inflammation

- Identify specific cause.
- Epo stimulating agents (ESA) are beneficial in pts with normal or elevated serum creatinine.[1,2,3]
- IV iron increases ESAs efficacy in select patient populations.[4]
- Goal Hgb 10 -11 g/dL.[5,6]
- New therapeutic strategies:
  - ❖ Target hepcidin-ferroportin axis



1. Littlewood et al. JCO 2001;19:2865-74.
2. Adamson, Hematol ASH Educ Prog 2008(1):159-165
3. Hertel et al. Am J Nephrol 2006;26:149-156
4. Coyne et al. J Am Soc Nephrol. 2007;18:975-84
5. Singh et al. N Engl J Med 2006; 255:2085-2098.
6. Pfeffer et al. N Engl J Med 2009;361:2019-2032

MOC Reflective Statements

Diagnosis and Treatment of Iron Def. & Anemia of Inflammation

Differentiating diagnosis:

- Fe deficiency – low iron, high TIBC, low ferritin
- Anemia of Inflammation – low iron, low TIBC, high ferritin

Bone marrow iron – normal in Anemia of Inflammation

Case 3

40 y o instructor at a firing range with no medical history presents with fatigue, irritability, dyspepsia & arthralgias. On exam: BP 145/90, pale, hearing loss and peripheral neuropathy.

Labs: WBC 6.2, Hgb 9.3, ↑RBC protoporphyrin level.

Smear: RBCs show basophilic stippling.

Which would expect to see?

a) BM aspirate with ringed sideroblasts

b) Peripheral smear with teardrops

c) Megaloblastic RBCs & elevated methylmalonic acid

d) Elevated hepcidin level

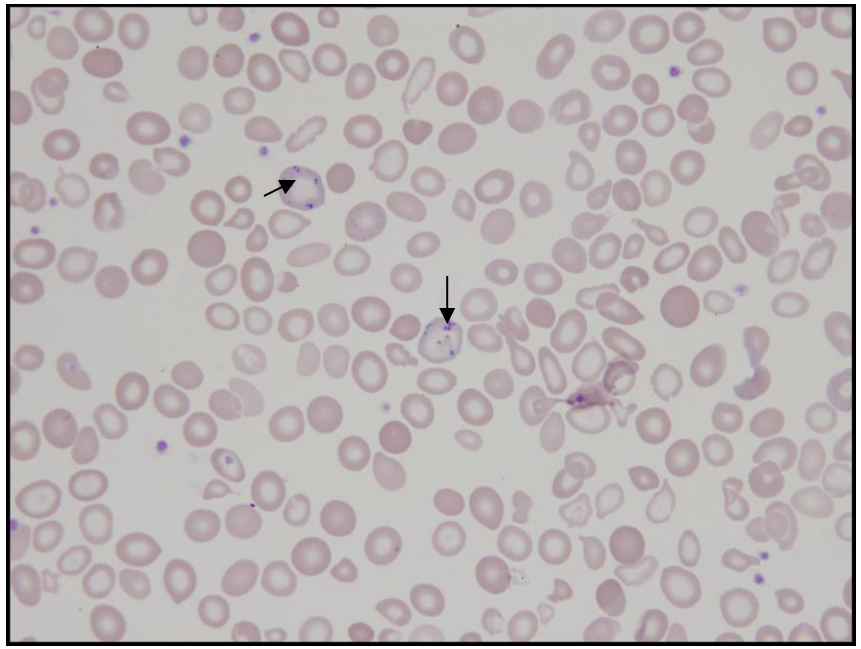
Sideroblastic Anemias

- Heterogenous group of anemias
- Characterized by Ineffective erythropoiesis

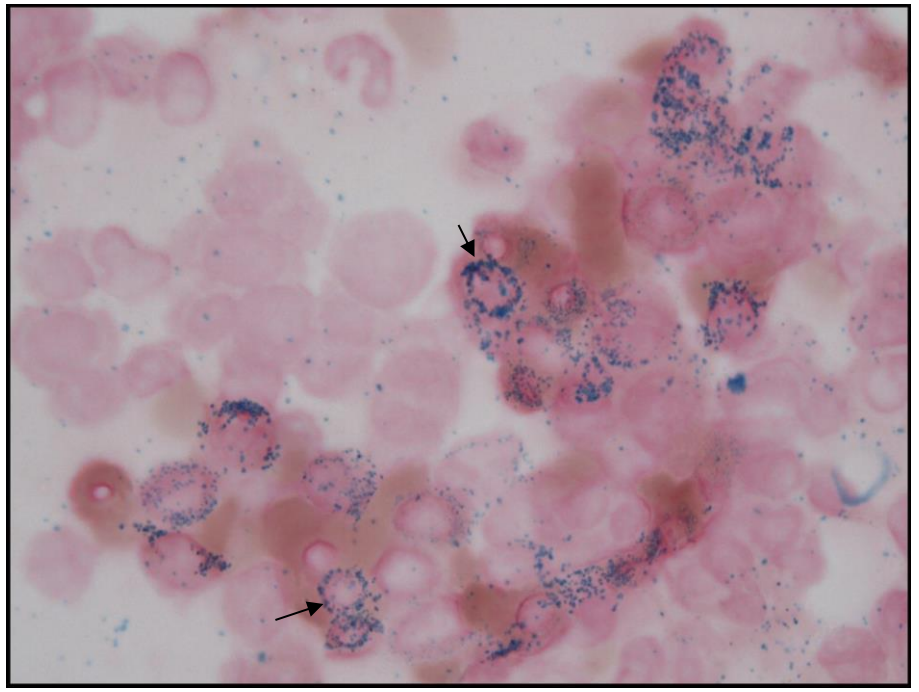
Causes	
CONGENITAL	
Non-syndromic	X-linked sideroblastic anemia etc.
Syndromic	Thiamine-responsive megaloblastic anemia etc.
ACQUIRED	
Clonal/neoplastic	MDS, RARS
	MDS/MPN
Metabolic/reversible	Excessive alcohol use
	Drugs (eg. isoniazid, linezolid, chloramphenicol)
	Copper deficiency (zinc toxicity), Pb poisoning
	Hypothermia

Sideroblastic Anemias

RBCs containing Pappenheimer bodies



Ringed sideroblasts in Bone Marrow



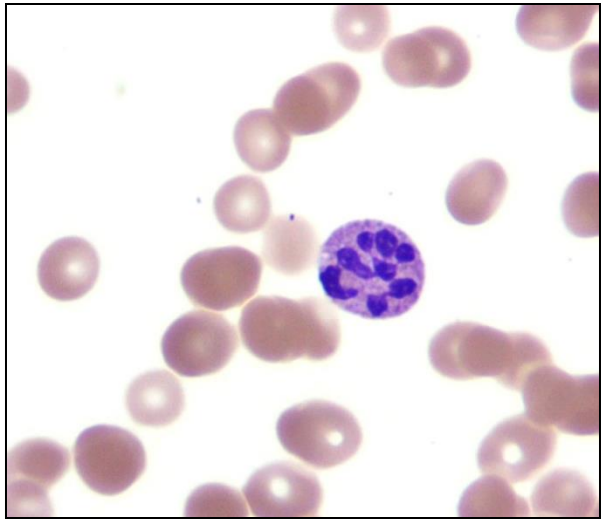
Courtesy Arthur Skarin, MD.

Case 4

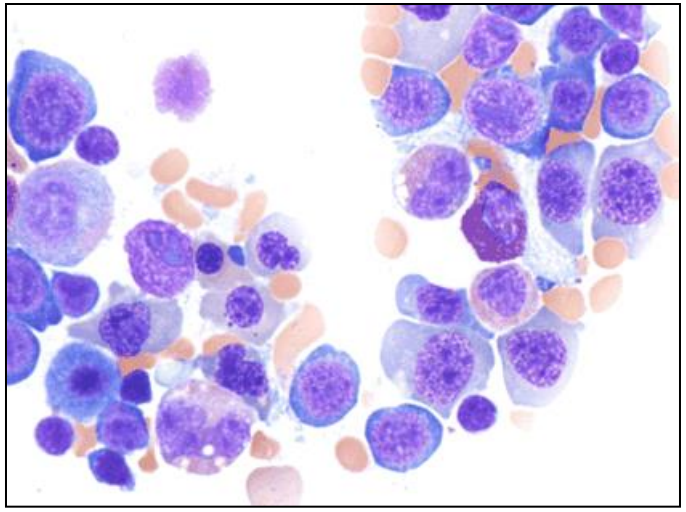
70 y o woman with diabetes is brought to PCP by her family for progressive dementia. Labs are reported as normal. Donepezil (Aricept) started. Six months f/u, no improvement. Gait is unsteady. WBC 2.9, hgb 8.3, platelets 85,000, retic ct 0.9%.

She is diagnosed with vitamin B12 deficiency.

Peripheral blood smear



Bone marrow aspirate



Nuclear-cytoplamic asynchrony

Case 4

70 y o woman with diabetes diagnosed with vitamin B12 deficiency

Which of the following would you expect to find?

a) ↑ folate, ↓ B12, normal MMA,↓ homocysteine

b) normal folate, ↓ B12, ↑ MMA,↓ homocysteine

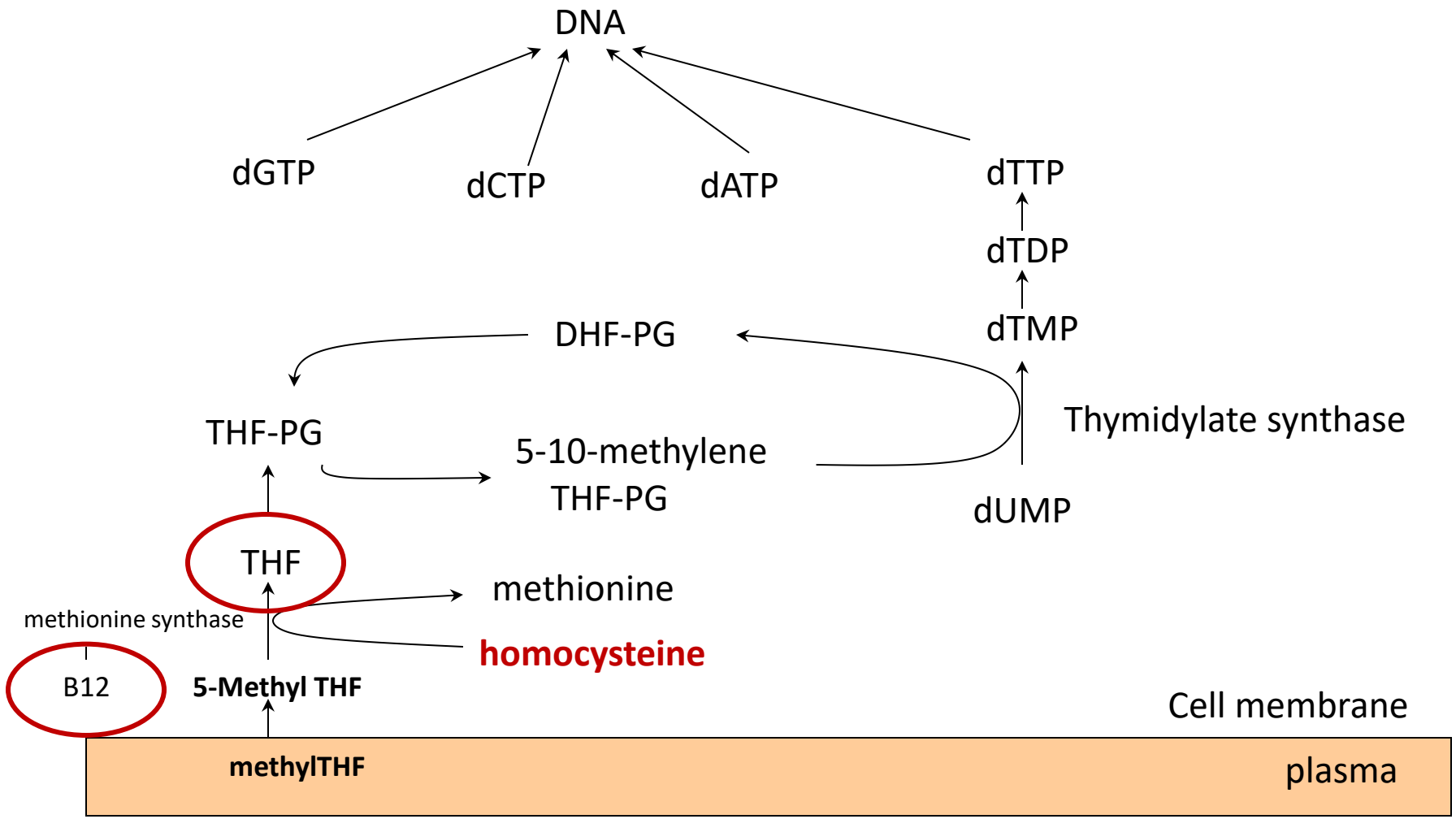
c) normal folate, ↓ B12, normal MMA, ↑ homocysteine

d) normal folate, low normal B12, ↑ MMA, ↑ homocysteine

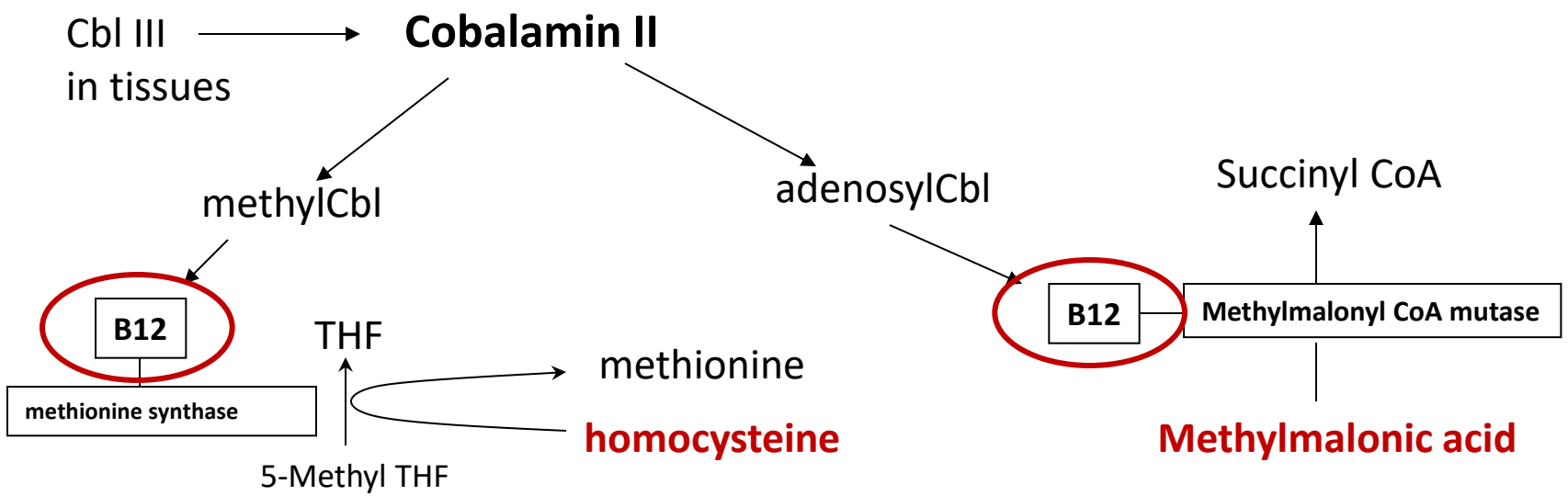
e) ↑ folate, normal B12, ↓ MMA, ↑ homocysteine

Biochemistry of Megaloblastic Anemia

- Impaired DNA Synthesis -



Physiology of Vitamin B12



DNA Synthesis

Lipid metabolism

Folate vs B_{12} Deficiency

	Folic acid def	**Vit. B_{12} deficiency**
History	EtOH pregnancy poor overall intake	vegan pernicious anemia PPI use
Neurological deficits	No	paresthesias, dementia, madness
Homocysteine	High	High
Methylmalonic acid	Normal	High

MOC Reflective Statements

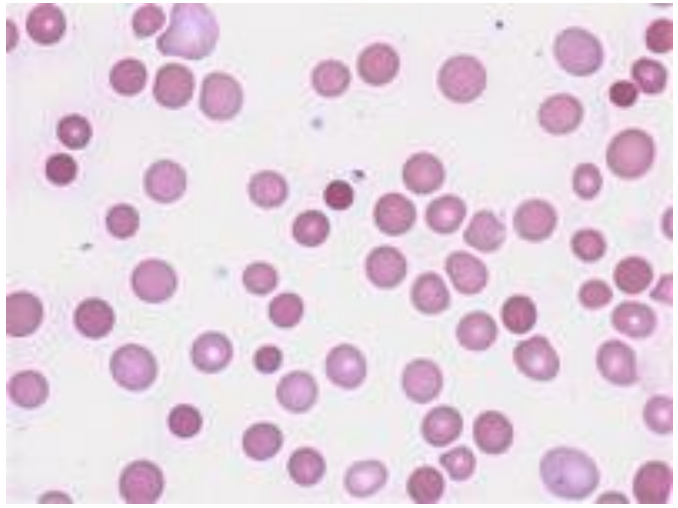
Differentiating folate vs vitamin B12 deficiency

- ↑ Methylmalonic acid & neurological deficits in vitamin B12 deficiency.
- Intrinsic factor Ab - ~99% specificity for pernicious anemia
- Parietal cell Ab – 85-90% sensitivity, but **low specificity**

Case 5

60 y o woman with Rheumatoid Arthritis presents with joint swelling and a 2 wk history of worsening weakness and dizziness.

Labs: WBC 4.7, Hgb 7.3, Hct 25%, MCV 92, MCHC 39 platelet count 177,000. T bil 3.1, retic 23%, LDH 636, direct Coombs (+) for IgG and complement.



Smear shows spherocytes

Case 5

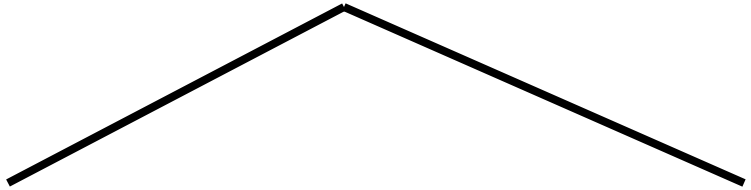
60 y o woman with Rheumatoid Arthritis presents with joint swelling and a 2 wk history of worsening weakness and dizziness.

Labs: WBC 4.7, Hgb 7.3, Hct 25%, MCV 92, MCHC 39 platelet count 177,000. T bil 3.1, retic 23%, LDH 636, direct Coombs (+) for IgG and complement.

What would you expect?

a) Eosin-5-maleimide to be abnormal
b) Treatment with steroids to be beneficial
c) Sputum culture positive for Mycoplasma pneumonia
d) Osmotic fragility to be normal
e) Splenomegaly

Hemolytic Anemias



Hereditary

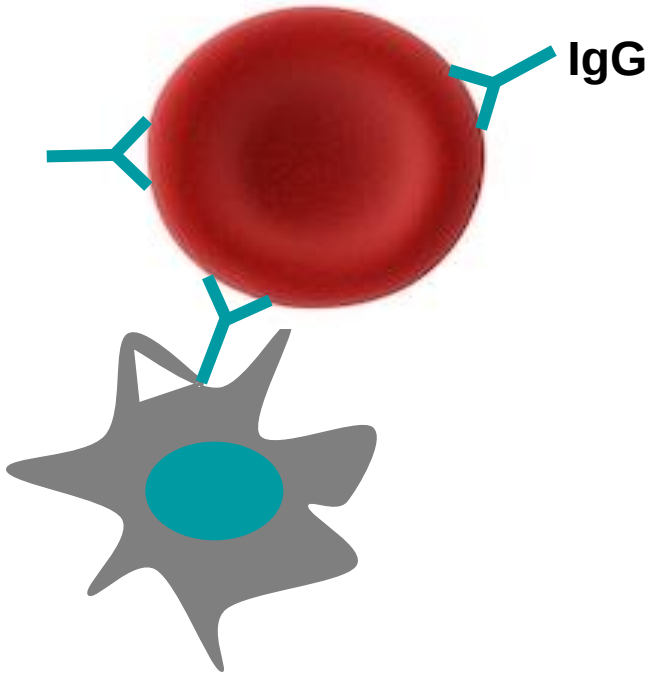
1. Defects in RBC membrane
2. Defects in RBC metabolism (enzymopathies)
3. Defects in Hemoglobin (hemoglobinopathies)

Acquired

1. Immune HA
2. Non-immune HA

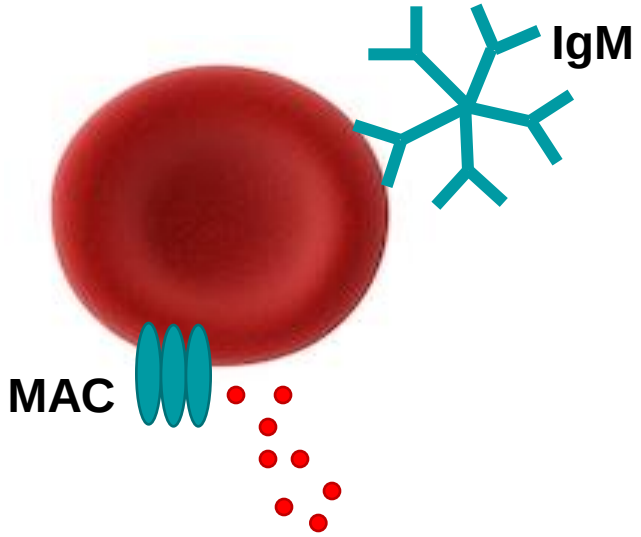
Autoimmune Hemolytic Anemia

Warm AIHA



Splenic macrophages

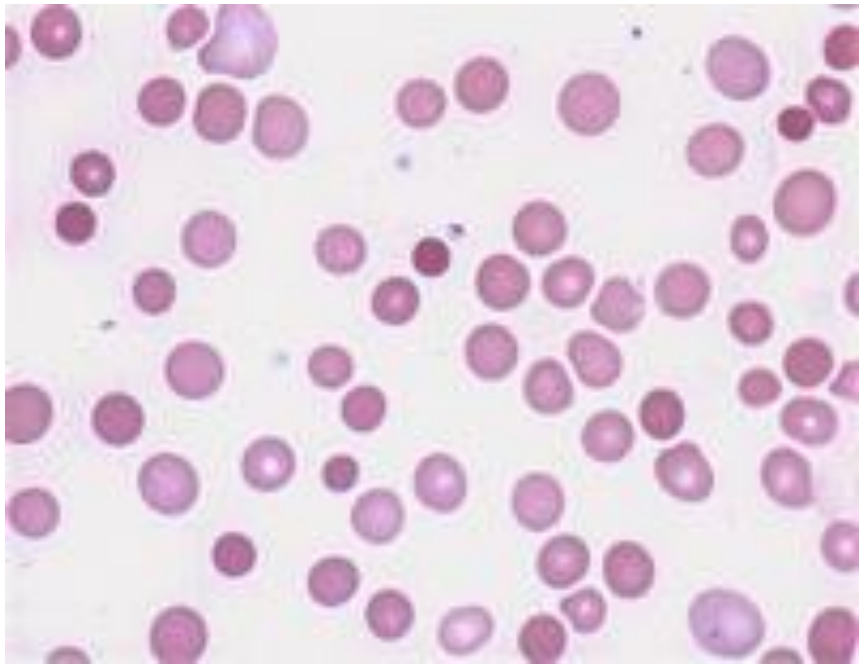
Cold AIHA



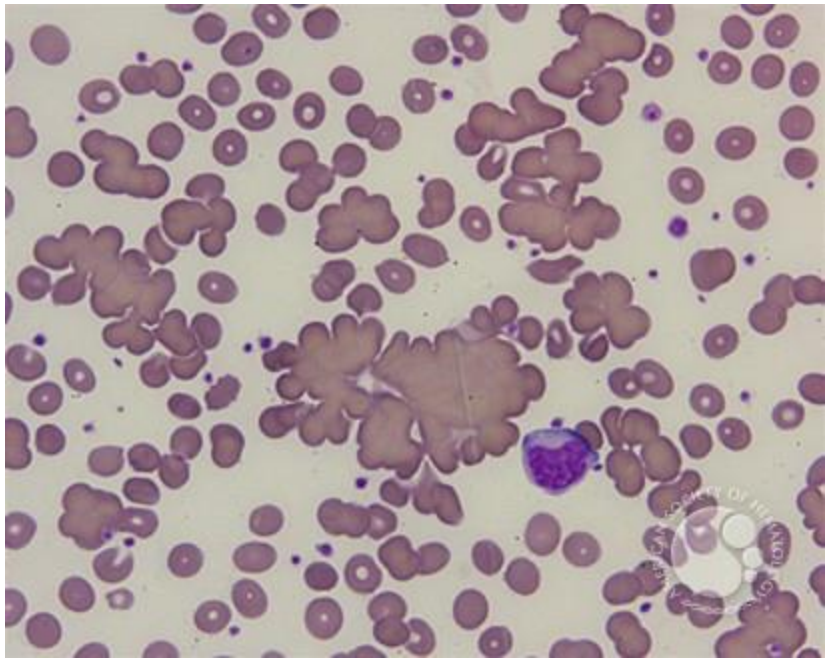
Intravascular hemolysis

Autoimmune Hemolytic Anemia

Warm AIHA



Cold AIHA



Courtesy ASH Image bank

Autoimmune Hemolytic Anemia

	Warm AIHA	**Cold AIHA**
Direct Coombs	IgG or IgG & C3	C3 only
Antibody	IgG	IgM
Etiology	1. Drugs: Methyldopa, PCN, sulfa 2. Malignancy: CLL, NHL 3. Infection	1. Drugs: Quinidine 2. Malignancy: NHL 3. Infection: Mycoplasma 4. Paroxysmal cold hgb'inuria
Treatment	Steroids Rituximab Splenectomy Treat underlying disease	No role for steroids Warm pt Rituximab +/- benda; fludarabine Treat underlying disease

Treatment of Warm AIHA

First line therapy –

➢Corticosteroids.[1,2] No specific dose. Prednisone 1 mg/kg/day

Second line

➢Rituximab 375 mg/m2 wkly for 4 wks – CR in 29-55% pts, PR in 50% pts[3,4,5]

➢Splenectomy - some response in 59-100% pts.[6]

Supportive Care

RBC transfusions – Cross-matching is difficult because of pan-agglutinating Abs. Use closest match possible

1. Allgood et al. Am J Med 1967;43(2):254-273
2. Zupanska at al. Haematologia 1981;14(4):425-433.
3. Dierickx et al. J Intern Med **2009**;**266**(**5**):**484-491**
4. Bussone. Am J Hematol 2009;84(3):153-157
5. D'Arena. Eur J Haematol 2007;79(1):53-58
6.Crowther et al. Blood 2011;118 (15) 4036-4040

MOC Reflective Statements

Hemolytic anemias - ↑LDH, ↑ retic count, low haptoglobin

- Spherocytes – AIHA or hereditary spherocytosis
  - Diagnosis AIHA – direct Coomb's test
  - Hereditary spherocytosis – life-long history, family history

Case 6

32 y o woman presents with 3 day history of colicky abdominal pain and fatigue.

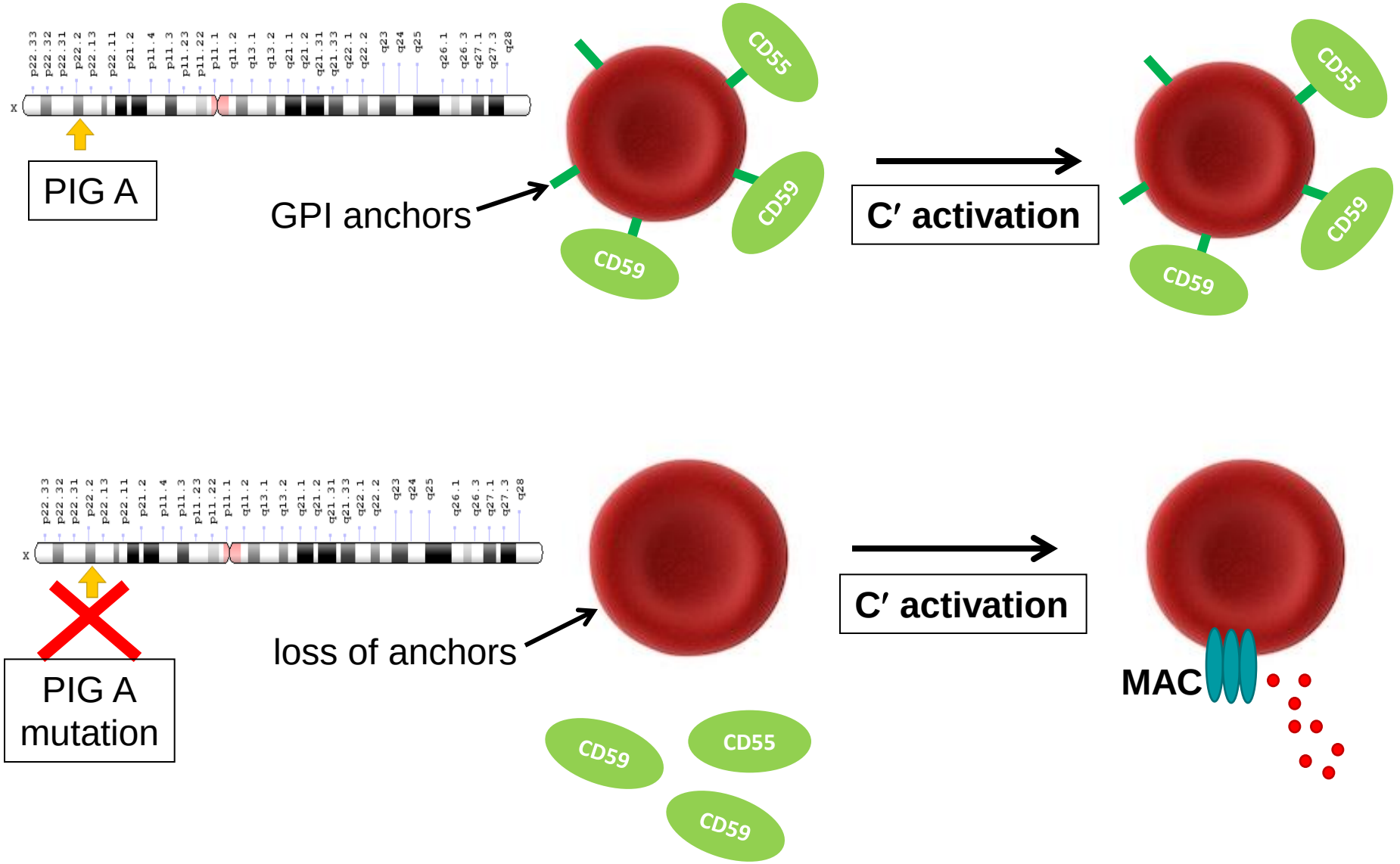
Labs: WBC 2.9, Hct 22% MCV 78, platelets 60,000, retic count 9%, direct and indirect Coombs (-), ferritin 10. Abdominal USS shows portal vein thrombosis.

U/A – hemosiderin (+).

The most likely diagnosis is:

A) Factor V Leidin mutation
B) Paroxysmal cold hemoglobinuria
C) Warm autoimmune hemolytic anemia
D) Aplastic anemia
E) Paroxysmal nocturnal hemoglobinuria

Paroxysmal Nocturnal Hemoglobinuria



Paroxysmal Nocturnal Hemoglobinuria

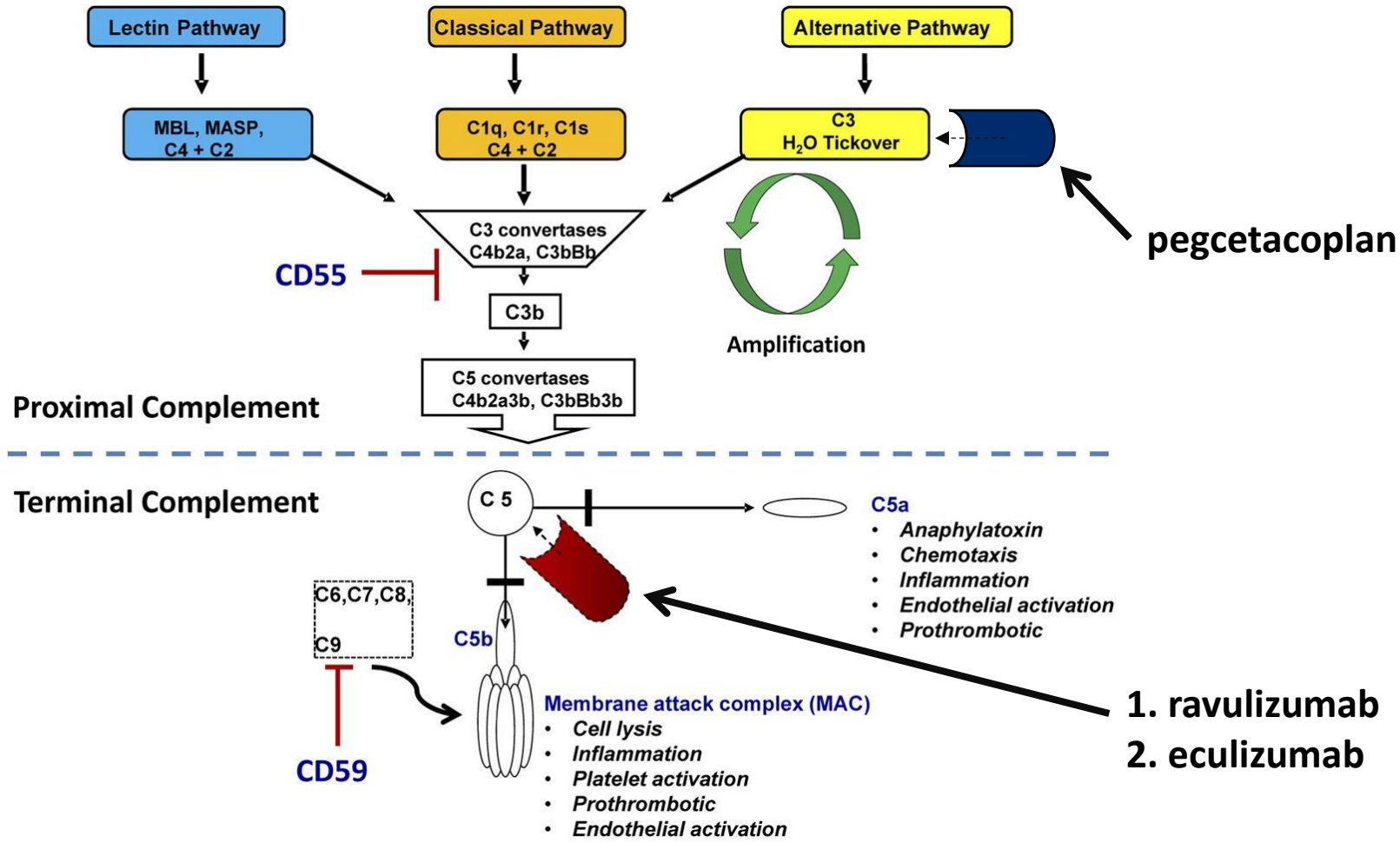
Epidemiology: 1-10 cases per million

Clinical Manifestations:

- Chronic hemolysis →urine hemosiderin→ Fe def.
- Bone marrow dysfunction: Thrombocytopenia
- Thrombosis: hepatic, mesenteric, cerebral veins.
- Smooth muscle dystonia: pulm HTN, CKD.

Diagnosis: flow cytometry for absence of CD55 & CD59

PNH Therapies

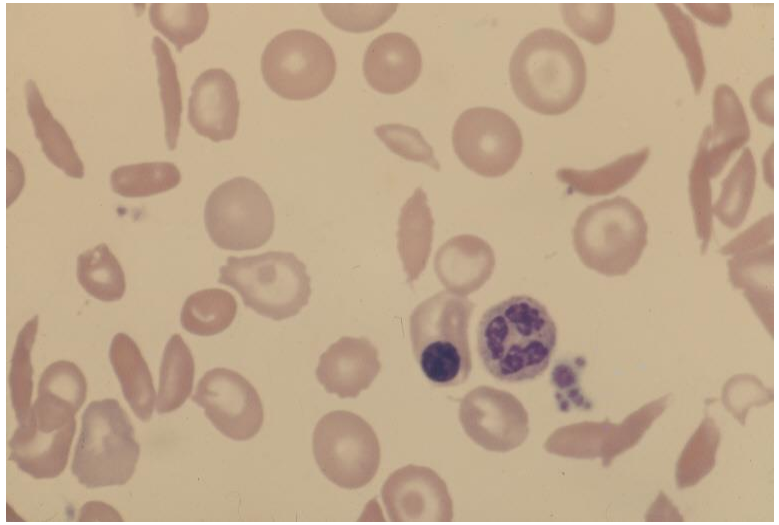


- Allogeneic stem cell transplant in refractory cytopenias.

Modified from Brodsky. Blood 2014;124:2804-2811

Case 7

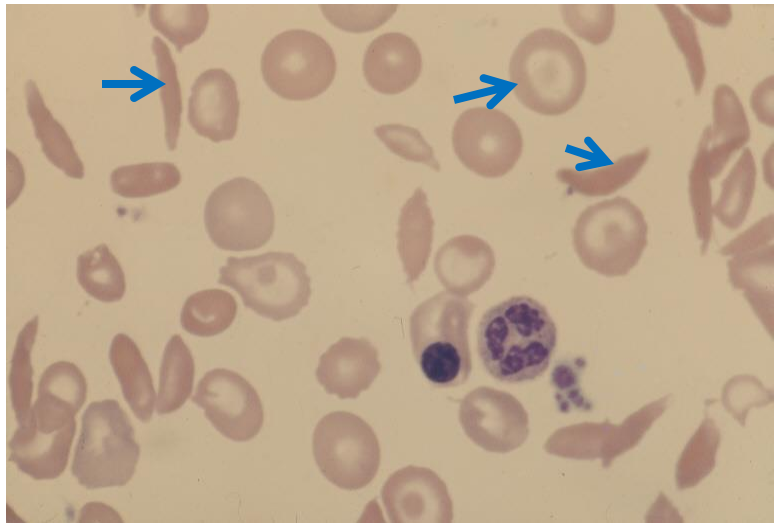
34 yr old Hispanic woman who is 20 weeks pregnant presents with generalized aches and fatigue. She's had an episode once in her life before. Her pulse is 102, temp 101, BP 120/80. She's jaundiced. Her labs show: Hct 22, WBC 14, platelets 420,000. LDH 574, retics 15%



What diagnostic test is most appropriate?

34 yr old Hispanic woman who is 20 weeks pregnant presents with generalized aches and fatigue. She's had an episode once in her life before. Her pulse is 102, temp 101, BP 120/80. She's jaundiced. Her labs show: Hct 22, WBC 14, platelets 420,000. LDH 374, retics 15%

A) Full liver function tests
B) Hemoglobin electrophoresis
C) Bone marrow biopsy
D) Rapid strep test
E) Osmotic fragility



Case 7 continues

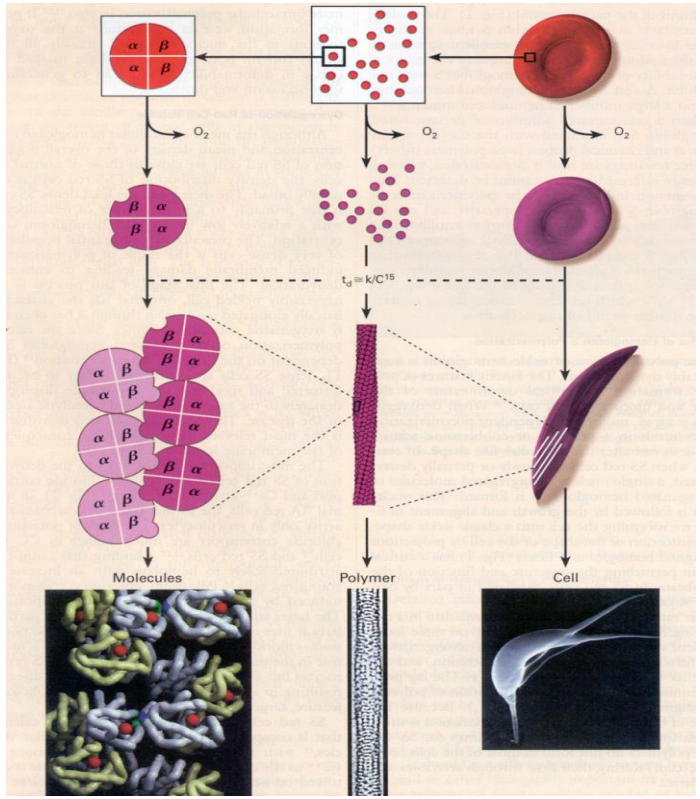
8 hrs later, patient is SOB, chest pain, tachycardic, diaphoretic, Rm air O2 sat is 83%. CXR shows bilateral lower lobe infiltrates.

What is the most appropriate next step?

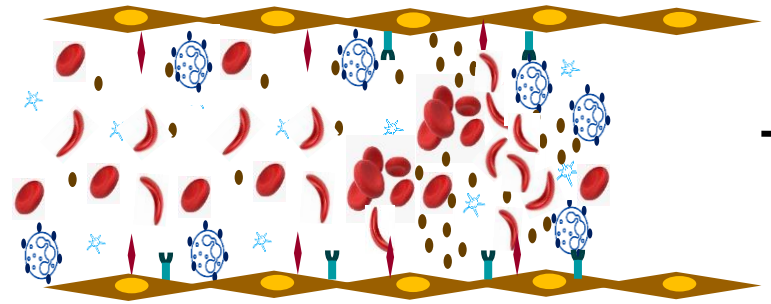
A) Continue current antibiotics and exchange RBC transfusion, send sputum cultures
B) Continue current antibiotic, IV pain medication and deliver baby as soon as possible
C) Continue current antibiotics, send for V/Q scan, initiate anticoagulation
D) Expand antibiotic coverage for atypicals and monitor patient closely
E) Expand antibiotic coverage for atypicals, exchange RBC transfusion immediately.

Sickle Cell Syndromes **(Qualitative Defect)**

- Due to a point mutation in β-globin chain : **β_6 Glu→Val**



Bunn, NEJM 1997;337:762

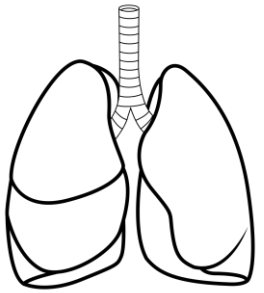


Sickle vasculopathy

Acute vaso-occlusive Episodes (VOE)

pain

Acute chest syndrome

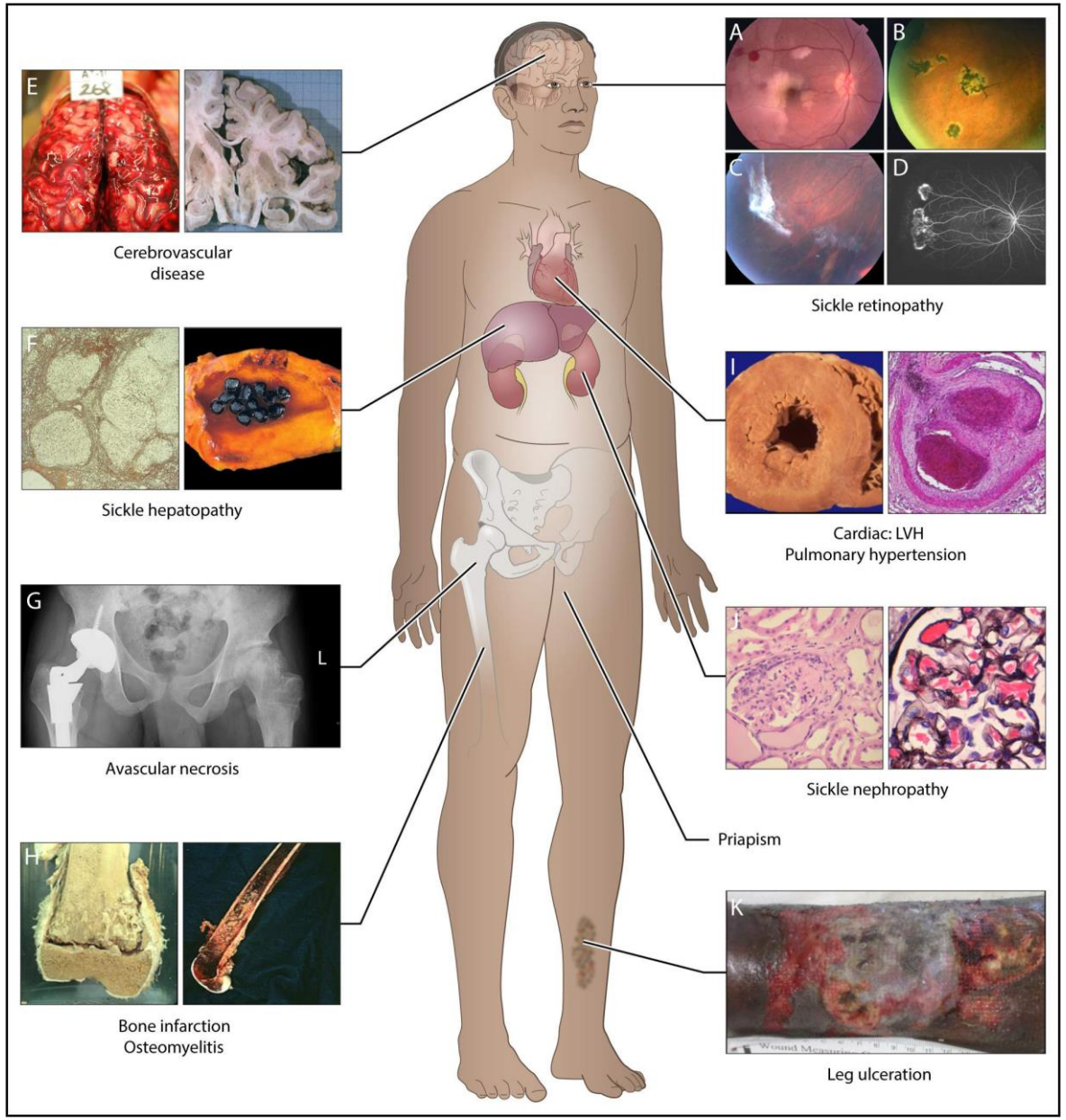


Modified from Dutra, FF and Bozza, MT. Front Pharmacol 2014;5:15

Sickle Cell Disease is a Multisystemic Disease

Homozygous inheritance of S β-globin
Hb electrophoresis (**Sickle Cell Anemia**):

- **HbS -75-95%,**
- HbF 2-20%,
- HbA_2<4%



Akinsheye, Idowu, et al. *Blood,* 118.1 (2011): 19-27.
Swee Lay Thein and Jo Howard. Blood (2018) 132:17, 1750-60.

Acute Chest Syndrome (ACS)

Acute chest syndrome is characterized by fever, chest pain, shortness of breath, hypoxia and a new infiltrate(s) on CXR.

TABLE 4. CAUSES OF THE ACUTE CHEST SYNDROME.*

CAUSE	ALL EPISODES (N=670)	AGE AT EPISODE OF ACUTE CHEST SYNDROME		
		0–9 YR (N=329)	10–19 YR (N=188)	≥20 YR (N=153)
	no. of episodes (%)			
Fat embolism, with or without infection†	59 (8.8)	24	16	19
Chlamydia‡	48 (7.2)	19	15	14
Mycoplasma§	44 (6.6)	29	7	8
Virus	43 (6.4)	36	5	2
Bacteria	30 (4.5)	13	5	12
Mixed infections	25 (3.7)	16	6	3
Legionella	4 (0.6)	3	0	1
Miscellaneous infections¶	3 (0.4)	0	3	0
Infarction‖	108 (16.1)	50	43	15
Unknown**	306 (45.7)	139	88	79

Vichinsky et al. NEJM 2000; 342:1855-1865

Acute Chest Syndrome (ACS)

Treatment for acute chest syndrome includes:

- antibiotic coverage for typical and atypical orgs.
- RBC exchange transfusion to a goal HbS <30%
- Aggressive supportive care

Vichinsky et al. N Eng J M 2000; 342:1855-1865

Sickle Cell Disease Treatments

- There are NO disease-modifying agents for acute VOE
- There are FDA-approved agents for chronic management

Drug	Mechanism of Action	Approval Status
Hydroxyurea	Induces Fetal Hemoglobin	FDA approval 1998
L-glutamine	Improves RBC Redox balance	FDA approval 2017
Adakveo (crizanlizumab)	P-selectin monoclonal Ab	Nov 2019
Stem cell transplant	Allogeneic transplant	Approved
Gene therapy	Autologous transplantation of modified gene	Approved in Dec 2023

MOC Reflective Statements

Sickle Cell Disease

- Urgent exchange RBC transfusion for Acute chest syndrome
- Target HbS<30%

Diagnosis and Treatment of PNH

- Gold standard for diagnosis : Flow cytometry for absence of **CD55 &CD59**

Treatment : anti C5 mAbs **Ravulizumab or Eculizumab**
C3 inhibitor, **Pegcetacoplan**

Commercial/Faculty Disclosures

Company	Role
Pfizer/Global Blood Therapeutics	Scientific Advisory Board
Pharmacosmos	Scientific Advisory Board
Shield Therapeutics	Scientific Advisory Board
Novo Nordisk/Forma Therapeutics	Scientific Advisory Board
Vertex Pharmaceuticals	Scientific Advisory Board

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