Hemolytic Anemias

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Disclosures

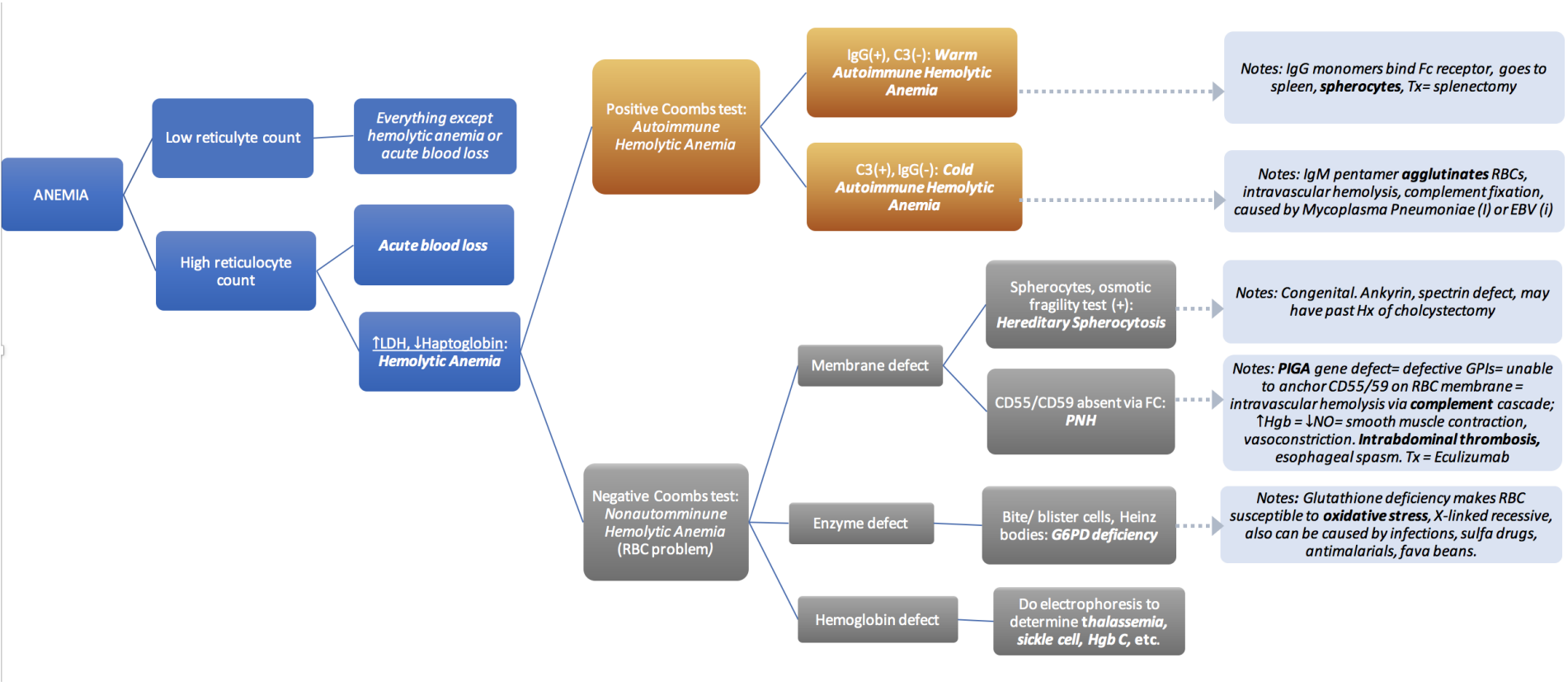
- Nagalla - Consultant honoraria and advisory board for Alexion and Sanofi

- Mehta – no disclosures

Objectives

- Recognize the clinical presentation, laboratory findings, pathophysiology hemolytic anemias
- Understand the evaluation and management of autoimmune hemolytic anemia

Approach to Hemolytic Anemia



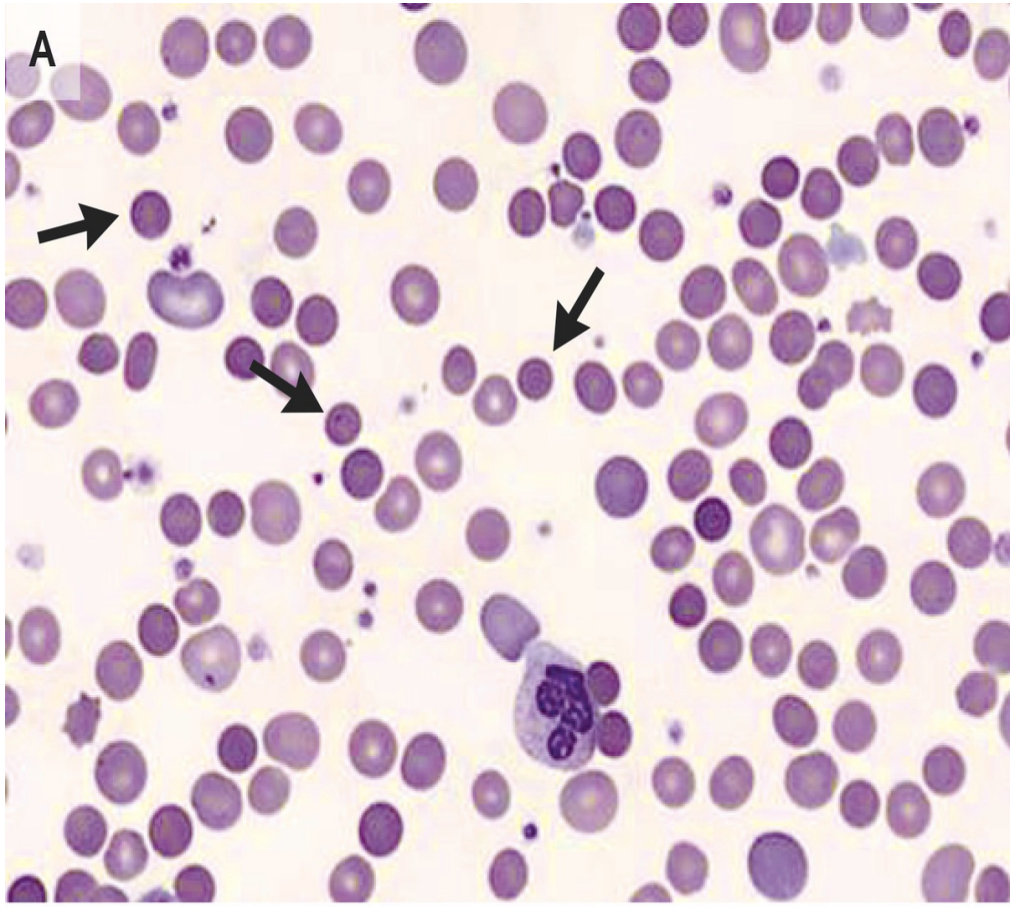
Case #1

- 18 y.o. female presents with fatigue. No PMH. No PICA symptoms. Her menses is light. No family history of anemia.
- Hgb – 8.0
- HCT – 24

Case #1

- Retic – 7.5%
- Absolute Retic count – 240k
- Haptoglobin <6
- MCV – 100
- Peripheral smear

Peripheral-Blood Specimen



RA Brodsky. N Engl J Med 2019;381:647-654.

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Case #1

- Retic – 7.5%
- Absolute Retic count – 240k
- Haptoglobin <6
- MCV – 100
- Peripheral smear
- Direct Coombs test - Positive

Different ways to classify hemolytic anemias

- Site of destruction - Intravascular vs. Extravascular
- Inheritance - Acquired vs. Inherited
- Origin of RBC destruction - Extrinsic vs. Intrinsic

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- Site of destruction - Intravascular vs. Extravascular
- Inheritance - Acquired vs. Inherited
- ***Origin of RBC destruction - Extrinsic vs. Intrinsic***

The Reticulocyte count

- Reticulocyte Production Index =

$$\frac{[\text{Reticulocytes (percent)} \times (\text{HCT} \div 45)]}{2}$$

  RPI > 2 suggest hemolysis

- Absolute Reticulocyte Count (ABR) =

  % retic count X RBC count/mm^3

  ABR > 125,000/µL = Usually Hemolysis

Hemolysis

- General lab evaluation for high retic
  - Low haptoglobin – plasma protein that binds free hgb to protect from loss of iron in the urine
  - Elevated LDH
  - Elevated indirect bilirubin

  all of the above can happen whether the hemolysis is intra- or extravascular
  - Urine hemosiderin present - occurs when destruction of the RBCs within the blood vessel(only seen intravascular hemolysis)

Extrinsic vs. Intrinsic

Extrinsic

- Immune
- Microangiopathic Hemolytic anemia
- Infection

Intrinsic

- Hemoglobinopathies
- RBC Enzyme disorders
- RBC Membrane disorders

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Immune Hemolysis

- Caused by the formation of antibodies against membrane proteins of one's own RBCs
- Antibody coated RBCs are removed in circulation by phagocytosis – usually by macrophages in the spleen
- Can be spontaneous or induced
- Warm vs. Cold antibodies
- Associated with an increased risk of thrombosis

Warm antibodies

- Antibodies attach better at 37˚C
- Antibodies typically IgG
- Phagocytosis of RBC(or part of membrane) – predominantly in spleen(but some in liver)
- Smear often has spherocytes
- Incidence 1-3 per 100,0000

RA Brodsky. N Engl J Med 2019;381:647-654.

Warm antibodies

- Most are Primary/Idiopathic
- Can be associated with other disorders
  - Autoimmune disorders
  - B-cell malignancies
  - Infections – eg, HIV
- Can be associated with Medications
  - Penicillin
  - Cephalosporins

Cold agglutinins

- Typically IgM
- Bind to RBC membranes better at lower temps
- Bound IgM will fix complement, which remains on RBC at higher temps(+DAT with C3)
- Both Intra- and Extravascular hemolysis

Cold agglutinins

- Commonly due to underlying lymphoproliferative disorder
- Can be associated with infections (eg, Mycoplasma)
- Often can see agglutination in the test tube

CAD vs CAS

- Primary cold agglutinin disease- Extravascular hemolysis and RBC agglutination without an identifiable underlying disorder

- Secondary cold agglutinin syndrome- secondary to viral infection, lymphoproliferative disorder, autoimmune diseases

Paroxysmal Cold Hemoglobinuria

- Cold antibody – that is IgG –> Donath-Landsteiner antibody
- Associated with viral infections in children
- Classic association with syphilis

Autoimmune Hemolytic Anemia (AIHA): Classification.

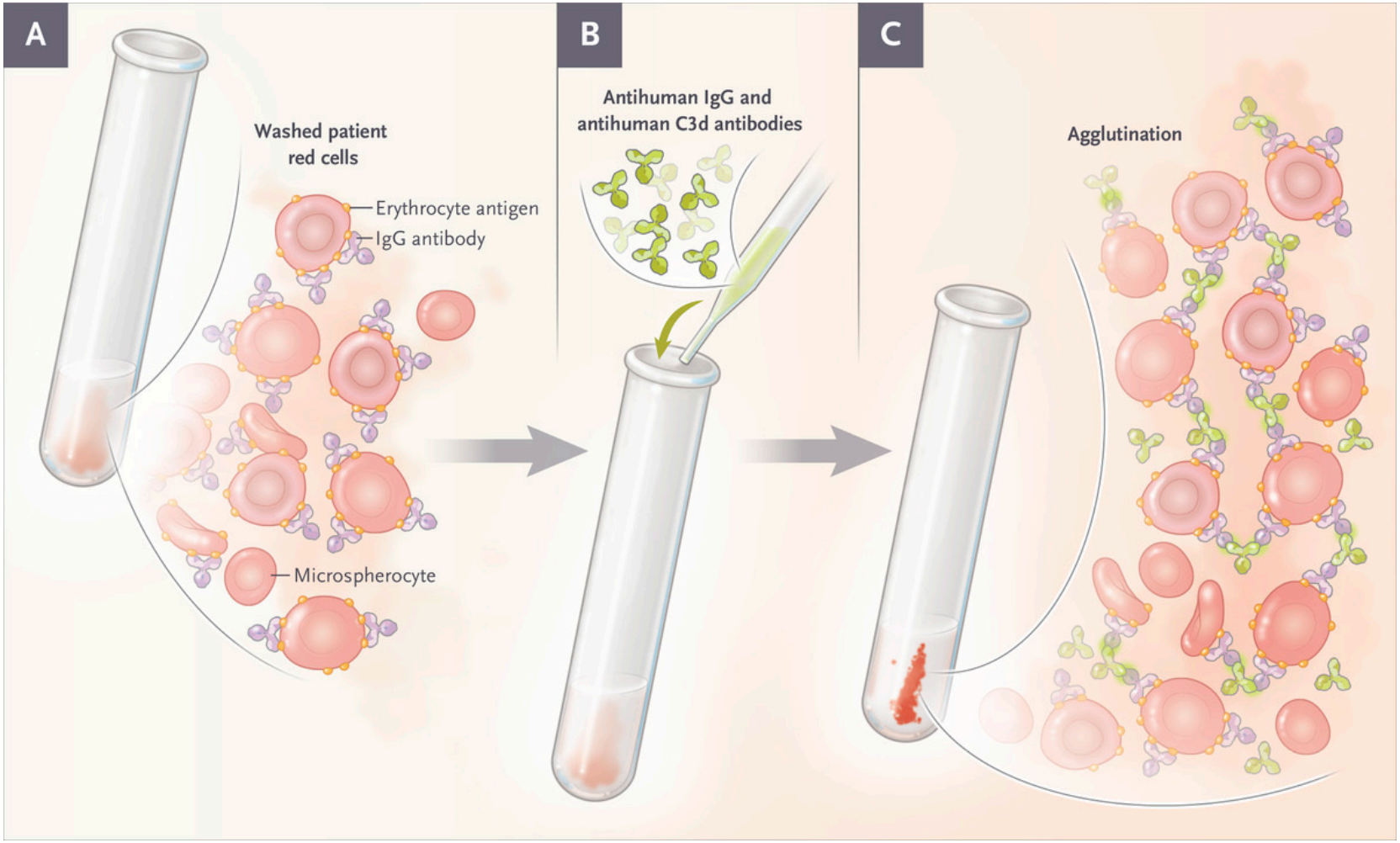
	Class	Optimal T of Reaction (Range)	Specificity	DAT Positivity
Warm AIHA (wAIHA)	IgG (possible Complement fixation)	37°C (0–40)	Rh system	IgG or IgG + C
Cold Agglutinin Disease (CAD)	IgM (common complement fixation)	4°C (4–34)	I/i system	C
Rare Disorders				
Mixed AIHA	Warm IgG and Cold IgM	4°C and 37°C		IgG + high titer cold IgM
Paroxysmal Cold Hemoglobinuria (PCH)	IgG (common complement fixation)	Reacts at 4°C and hemolyzes at 37°C	P or I Antigen	Positive Donath-Landsteiner Test

- Barcellini W, et al. J Clin Med. 2020 Nov 27;9(12):3859.

Diagnosis of Immune Hemolytic Anemia

- Elevated retic count with associated markers of hemolysis(eg, low haptoglobin, elevated indirect Bili, etc)
- Positive Direct Antiglobulin test(also called Direct Coombs Test)
- For Cold agglutinins – lab will often call to say blood has agglutinated in the test tube when at room temp (25˚C)

Direct Antiglobulin Test (Direct Coombs' Test).



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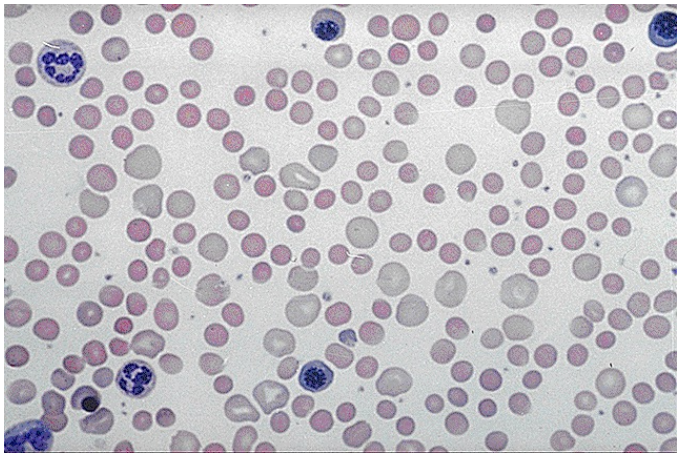
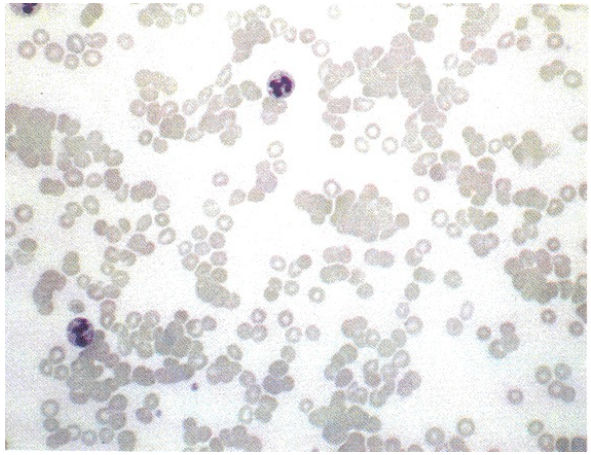
Warm (IgG) Autoimmune Hemolytic Anemia



- IgG autoantibodies bind to red cell surface.
- Leads to opsonization (removal by macrophages) of the red cells.
- Mostly extravascular hemolysis.

Cold (IgM) Agglutinin Disease



- IgM autoantibodies bind to the I antigen on erythrocytes when temperatures are at or below 37°C, resulting in agglutination.
- IgM fixes complement C3 on the red cells.
- IgM does not remain on cell surface.
- Mostly intravascular hemolysis.

Management of Warm Auto-Immune Hemolytic Anemias

Common Treatment Regimens for Warm Autoimmune Hemolytic Anemia.

Table 1. Common Treatment Regimens for Warm Autoimmune Hemolytic Anemia.

Treatment Option	Route	Dose	Serious Adverse Effects	Comments
First-line treatment				
Glucocorticoids (prednisone and methylprednisolone)	Oral or intravenous	Oral prednisone: 1–2 mg/kg of body weight/day; intravenous methylprednisolone: 500–1000 mg/day; begin slow taper (to be completed over 4–6 mo) if hemoglobin level >10 g per deciliter after 1–3 wk	Diabetes, osteoporosis, infections	
Second-line treatment*				
Rituximab	Intravenous	375 mg/m^2 of body-surface area weekly in 4 doses	Reactivation of hepatitis B virus infection; progressive multifocal leukoencephalopathy	All patients should be screened for hepatitis B surface antigen before initiation of drug.
Mycophenolate mofetil	Oral	500–1000 mg every 12 hr	Pancytopenia, lymphoma, infections	
Sirolimus	Oral	2 mg/m^2/day; trough goal, 5–15 ng/ml	Lymphoma, lung disease, opportunistic infections	Patients with the autoimmune lymphoproliferative syndrome have had a high response rate.
Immune globulin	Intravenous	500 mg/kg/day for 4 days or 1 g/kg/day for 2 days — most commonly as an adjunct to glucocorticoids or mycophenolate mofetil	Aseptic meningitis, renal insufficiency, hemolytic anemia	Responses are often transient, so immune globulin is not often used as a stand-alone drug.
Third-line treatment				
Azathioprine	Oral	1–2 mg/kg/day; maximum dose, 150 mg/day	Pancytopenia, infections, liver-function abnormalities	
Cyclosporine	Oral	5 mg/kg/day divided every 12 hr; target trough levels of >150 ng/ml and <300 ng/ml	Renal and hepatic dysfunction, lymphoma, hypertension	
Pulse-dose cyclophosphamide	Intravenous	500–1000 mg/m^2; 1–3 doses every 2–3 wk	Pancytopenia, infection, secondary cancer, infertility	
Fourth-line treatment				
High-dose cyclophosphamide or autologous bone marrow transplantation	Intravenous	50 mg/kg of ideal body weight/day for 4 consecutive days followed by granulocyte colony-stimulating factor	Pancytopenia, severe infection, hemorrhagic cystitis, secondary cancer, alopecia, hyponatremia, cardiac toxicity	

* Splenectomy is also considered to be a second-line treatment. Associated adverse effects are thrombosis and bacterial infections (encapsulated organisms). Vaccination against *Haemophilus influenzae*, meningococcus, and pneumococcus 8 to 10 weeks before splenectomy is strongly recommended.

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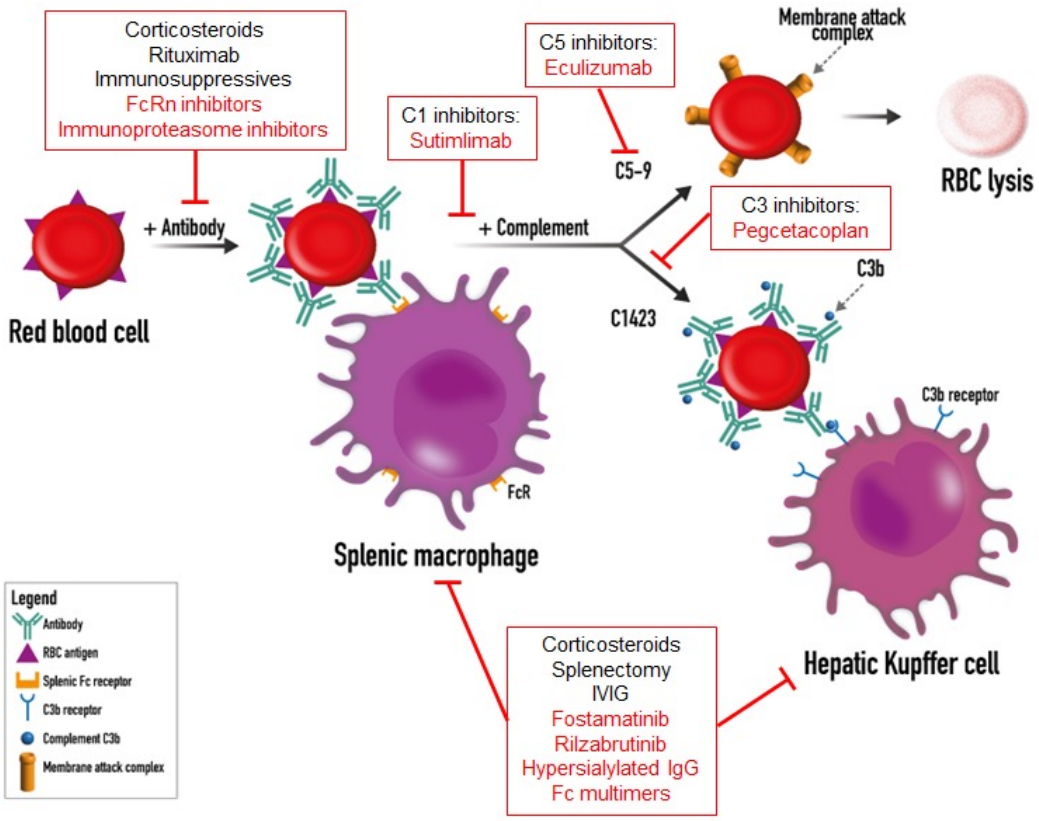
Warm autoimmune hemolytic anemia and the best treatment strategies



David J. Kuter, Warm autoimmune hemolytic anemia and the best treatment strategies, Hematology Am Soc Hematol Educ Program, 2022,

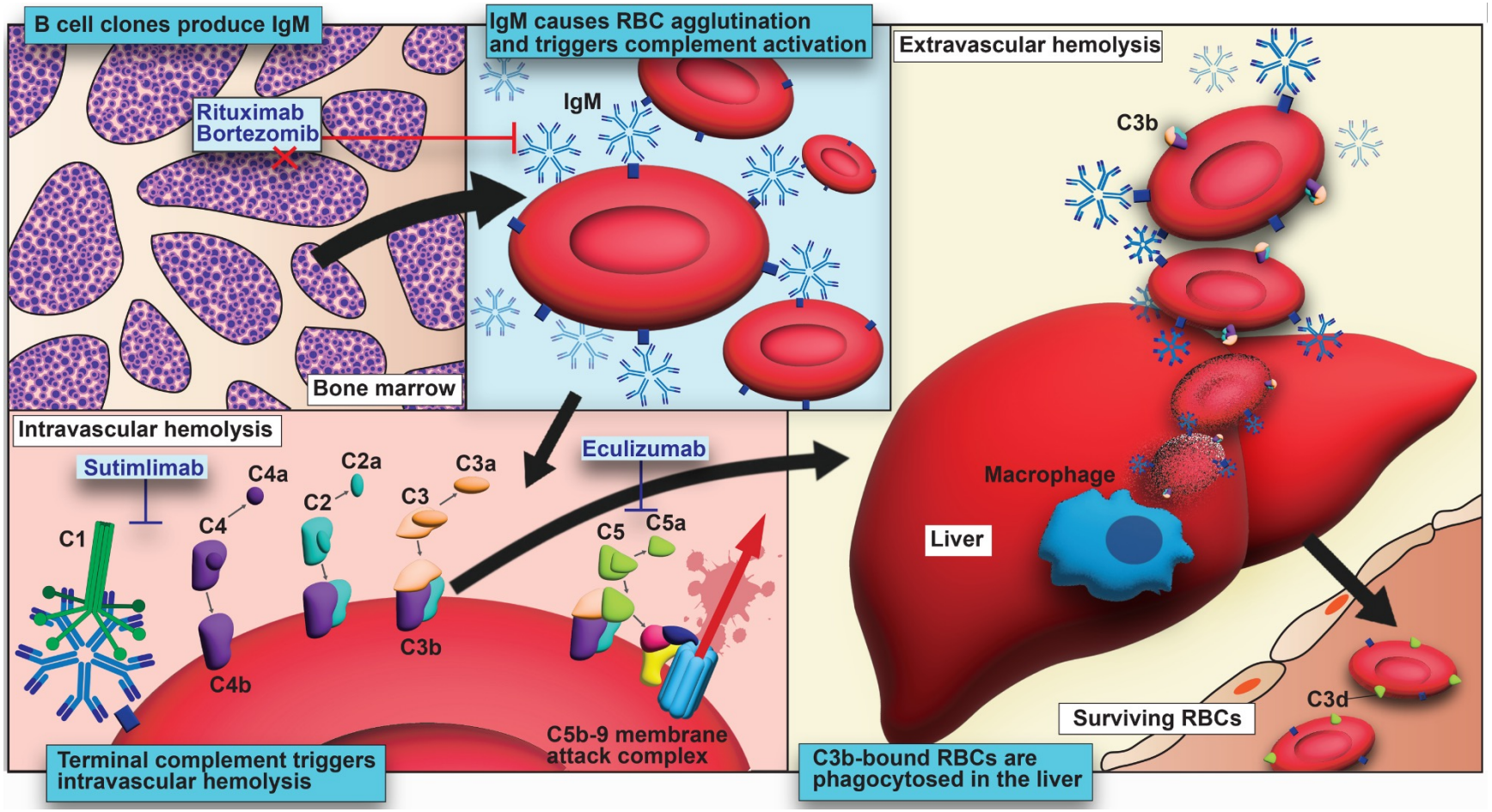
Management of Cold Agglutinin Disease

- If asymptomatic, do not need to treat(though some recent data at the ASH Annual meeting may suggest differently)
- Steroids and Splenectomy typically are not effective

Management of Cold Agglutinin Disease

- B-Cell directed therapy - Anti-CD20 therapy is one of the mainstays of therapy
- Sutimlimab (antibody against C1s) approved for CAD
    - Achieves a rapid response from the hemolysis standpoint
    - Vaccination needed against encapsulated bacteria

Cold AIHA and the best treatment strategies



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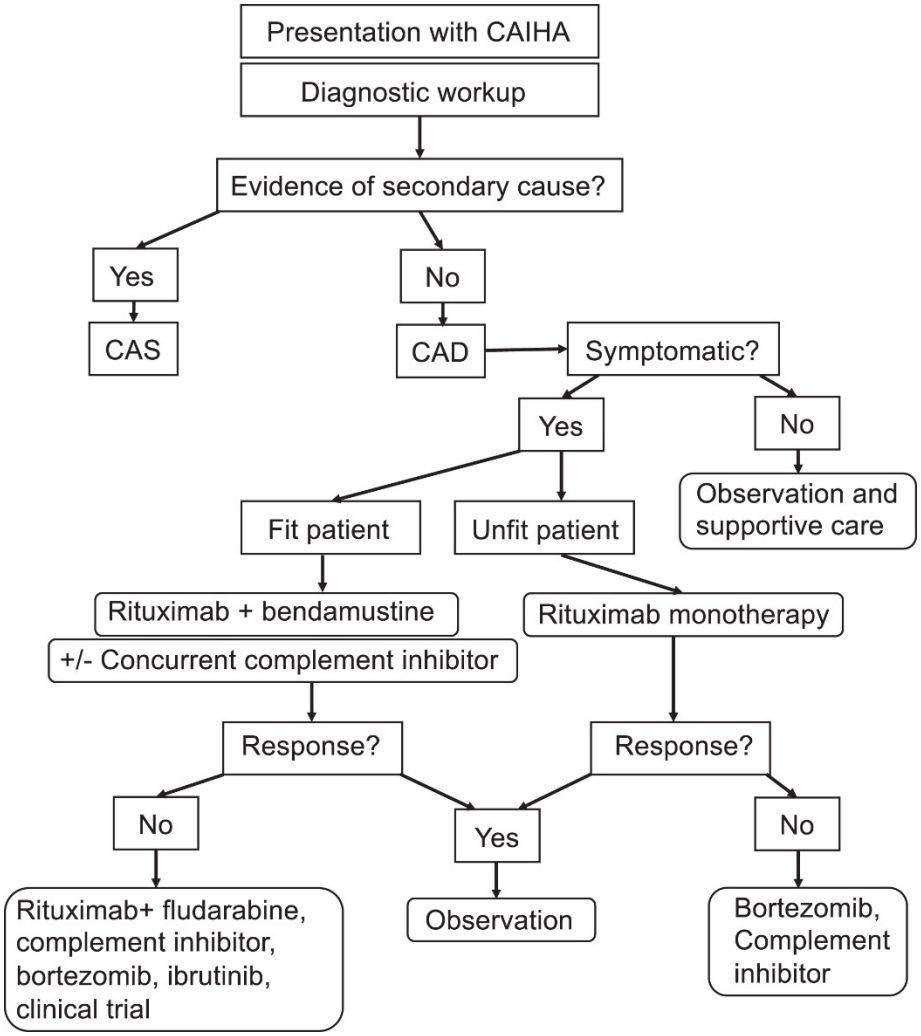

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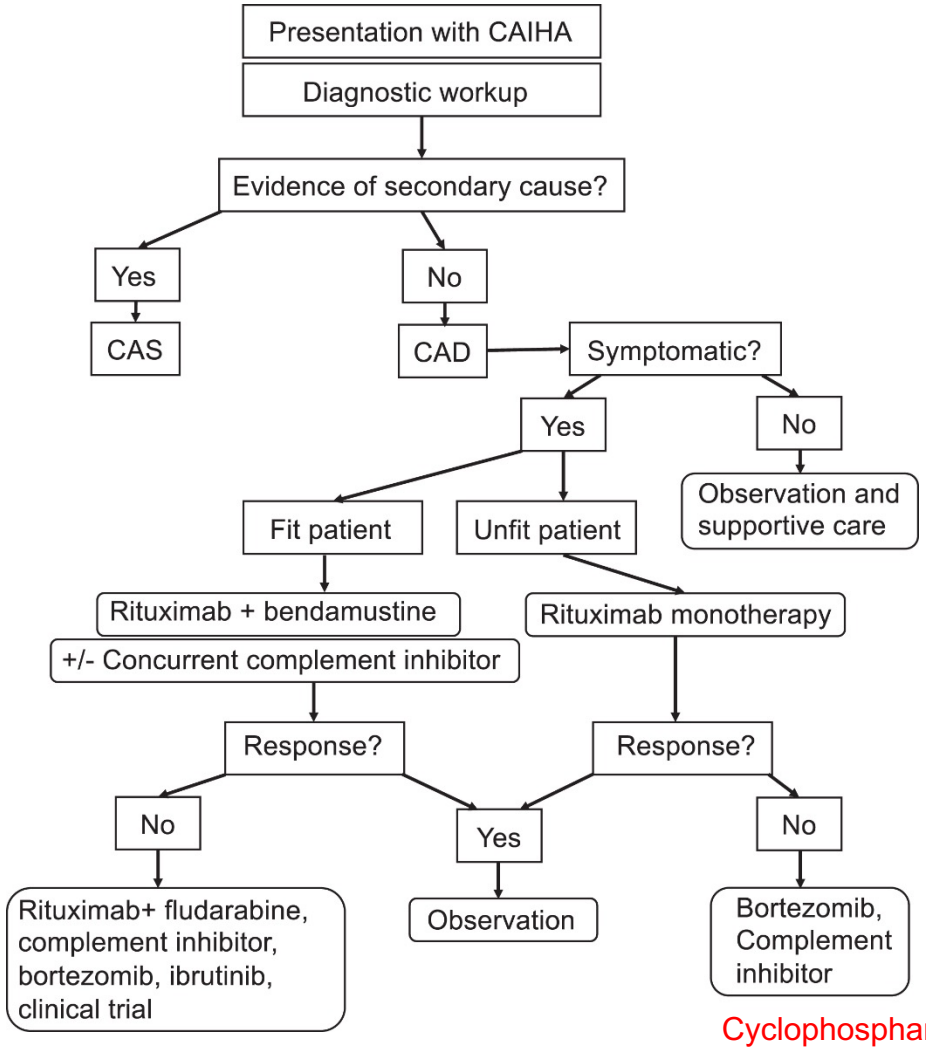

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Extrinsic vs. Intrinsic

Extrinsic

- Immune
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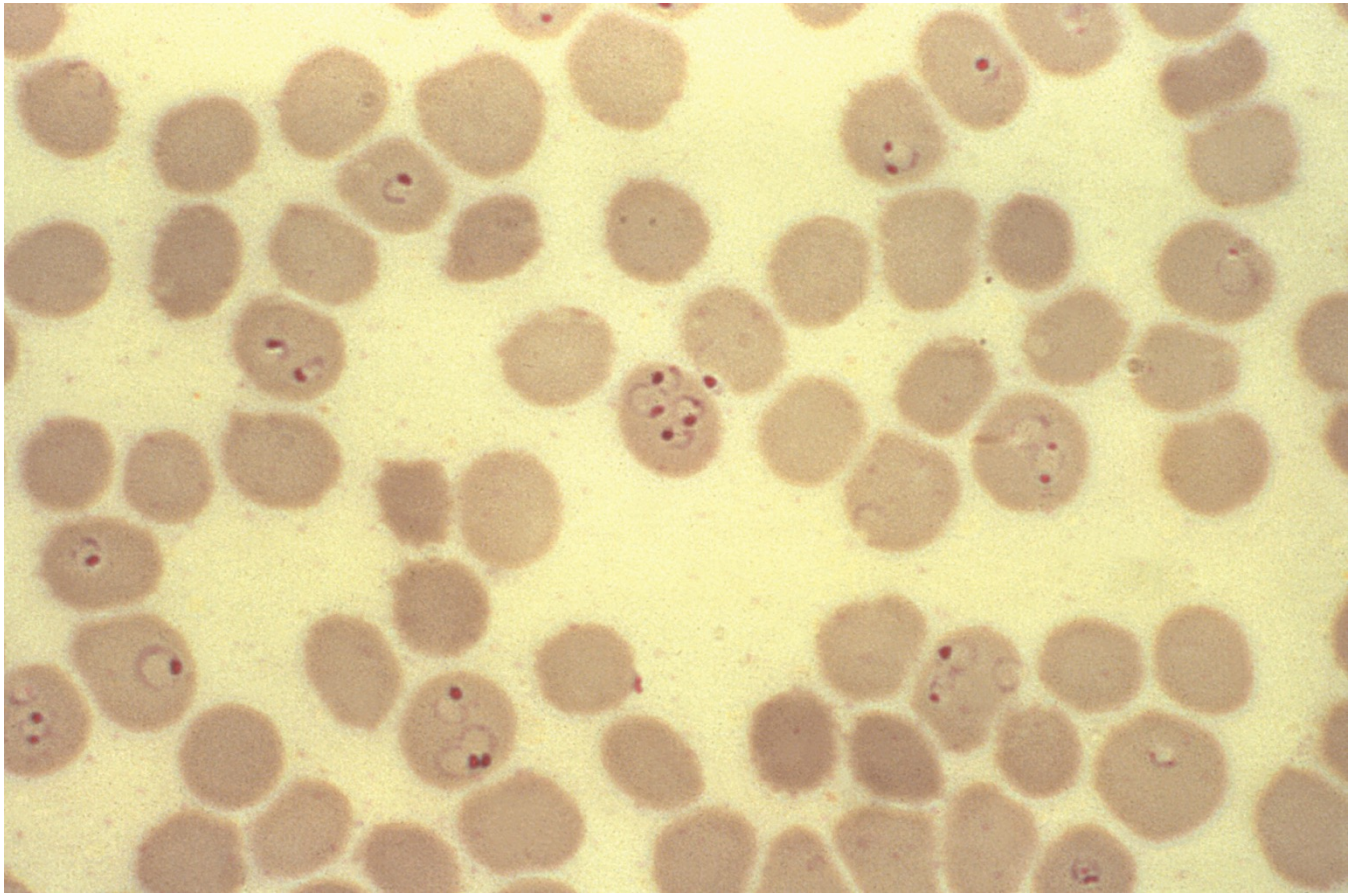
- ***Infection***

Intrinsic

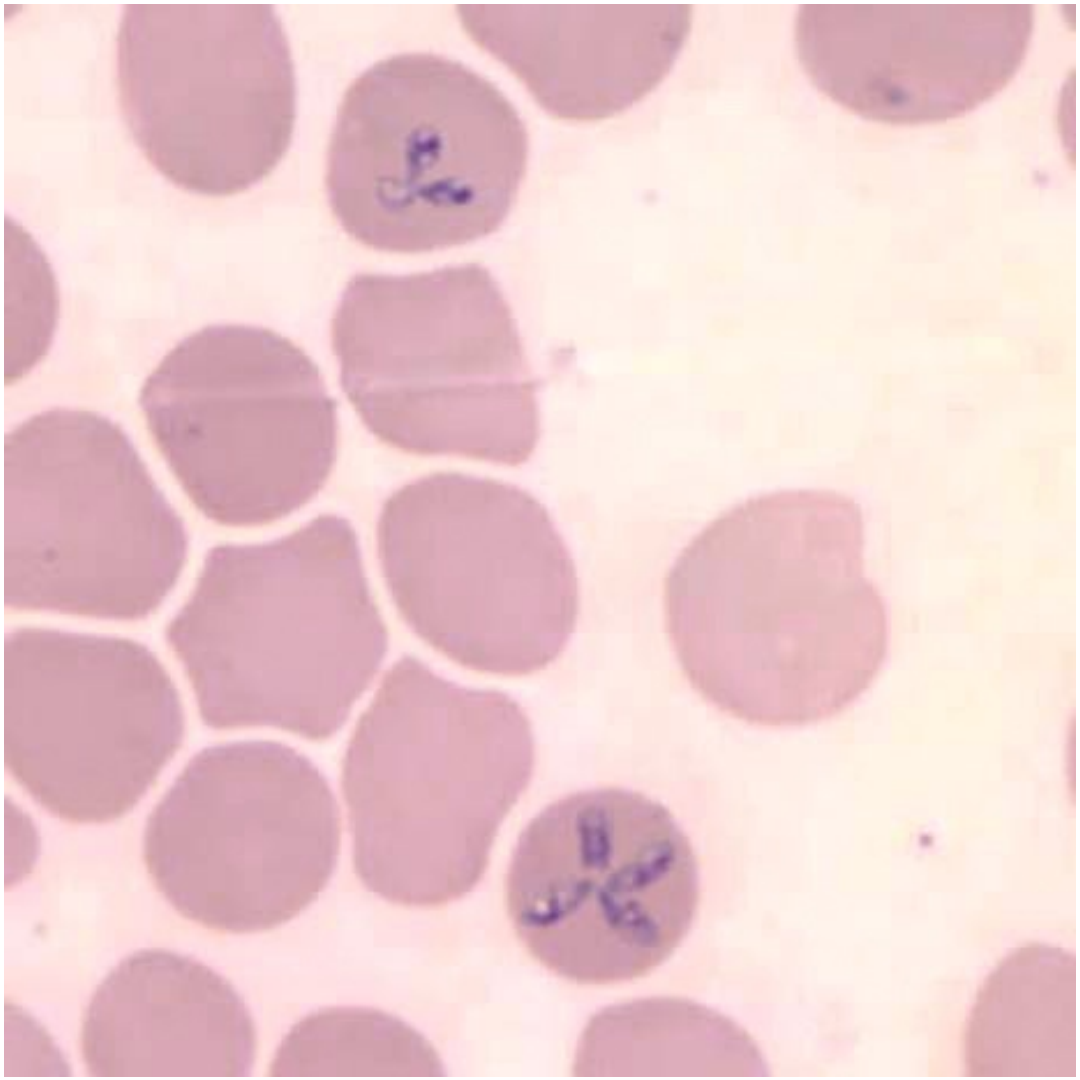
- Hemoglobinopathies
- RBC Membrane disorders
- RBC Enzyme disorders

Infection

- Chronic hemolytic anemia of varying degrees
- Associated with Splenomegaly
- Peripheral Smear findings often lead to the diagnosis



Ronald S. Go, Kevin H. M. Kuo, 2019, Hemolytic anemias excluding hemoglobinopathies, American Society of Hematology Self-Assessment Program, Seventh Edition, Figure 8-10

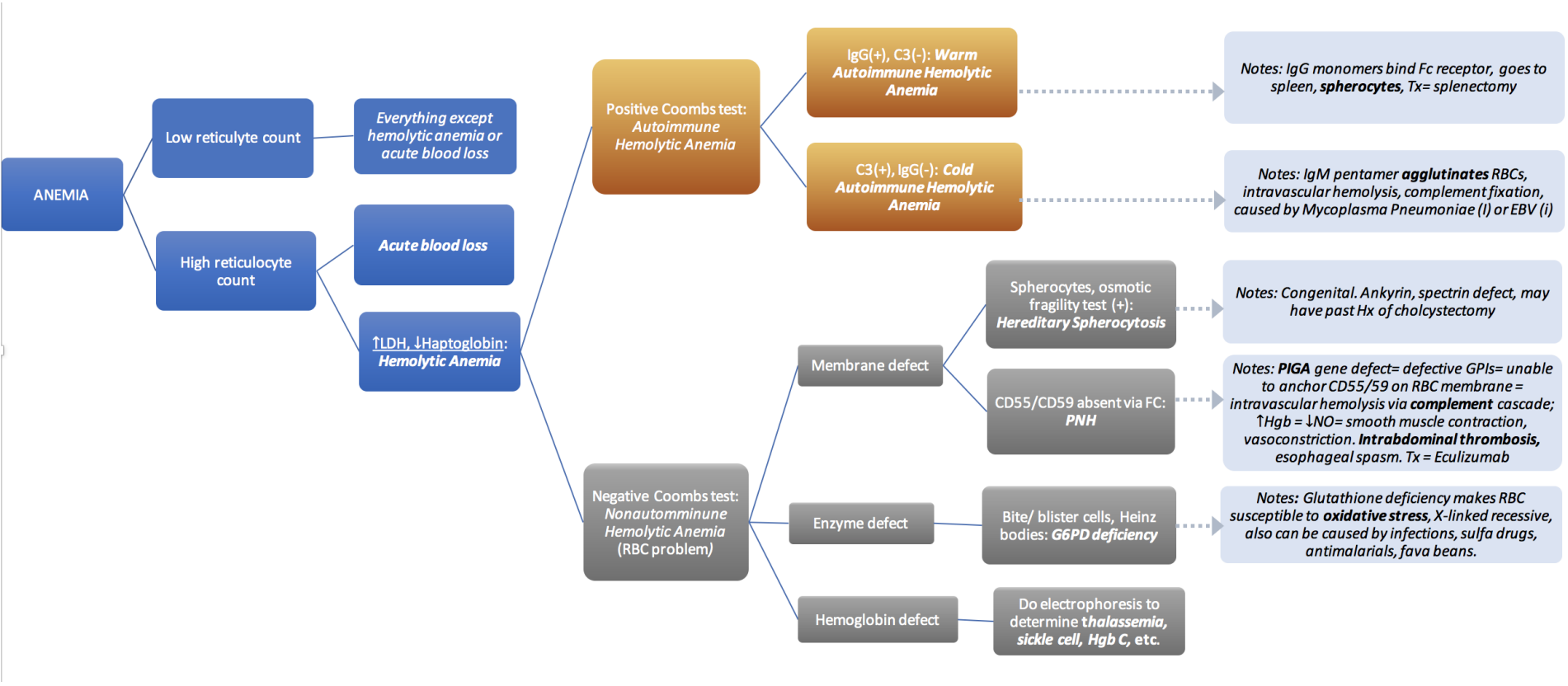


Ronald S. Go, Kevin H. M. Kuo, 2019, Hemolytic anemias excluding hemoglobinopathies, American Society of Hematology Self-Assessment Program, Seventh Edition, Figure 8-12

Intrinsic Hemolytic conditions

- Hemoglobinopathies – discussed in separate lecture
- Membrane defects
- Enzyme deficiencies

Approach to Hemolytic Anemia



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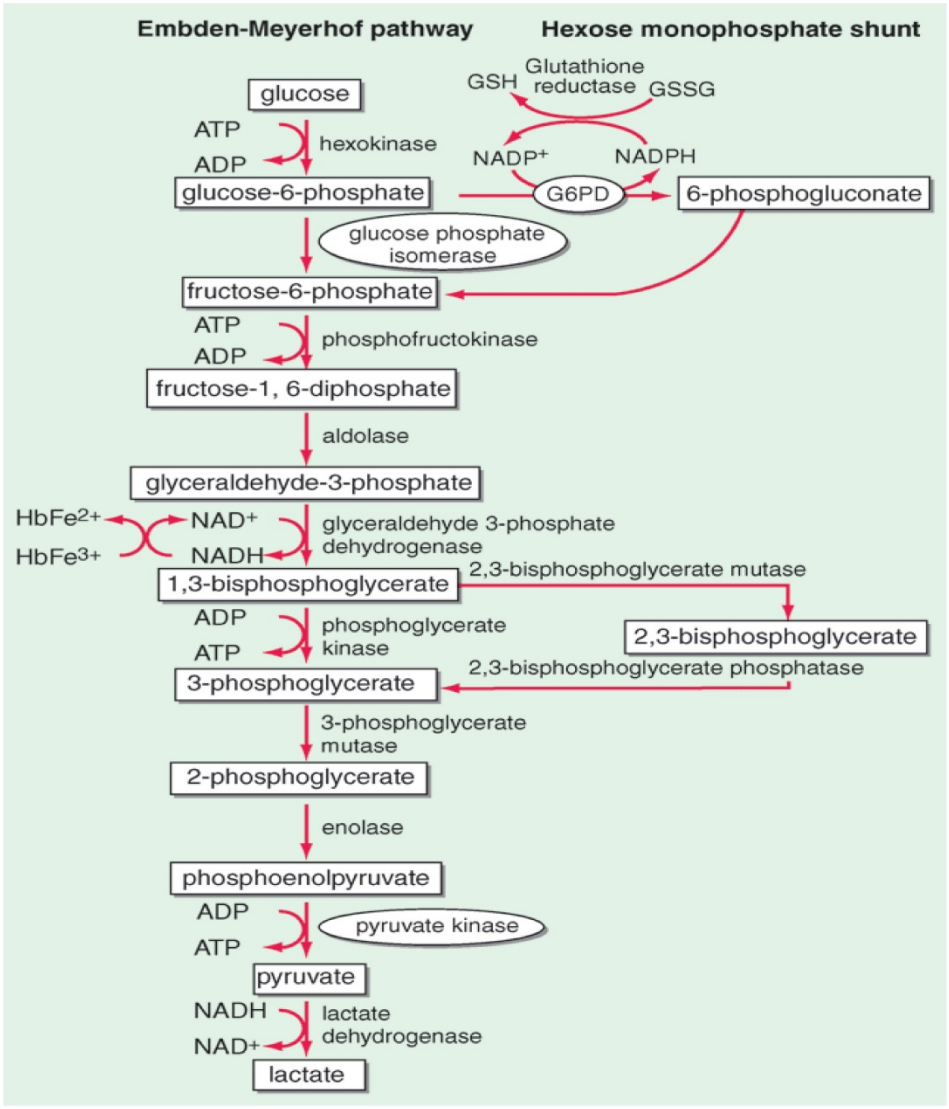
Diagnosis and clinical management of enzymopathies

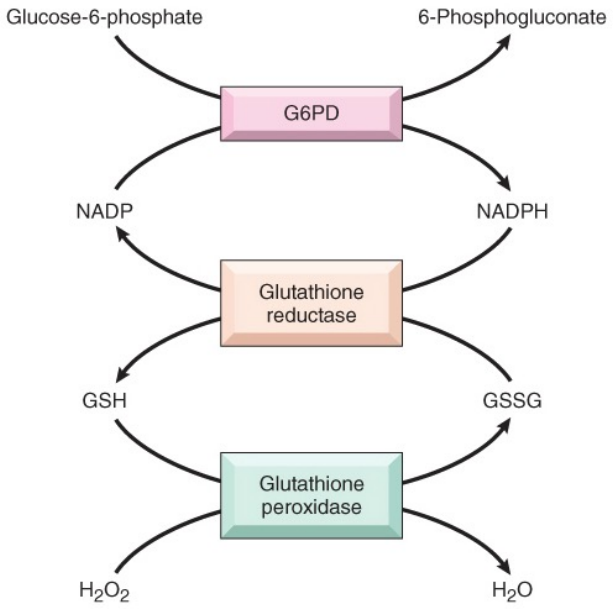


Lucio Luzzatto, Diagnosis and clinical management of enzymopathies, Hematology Am Soc Hematol Educ Program, 2021, Figure 1.

Glucose-6-phosphate dehydrogenase deficiency

- Most common red cell enzyme deficiency
- > 100 million people have it
- G6PD enzyme gene on X-chromosome
- Potentially protects against malaria
- Presentation variable – severe, moderate, mild, none

Mechanism of Hemolysis



- Free radicals need to be reduced
- Lack of NADPH allows for free radicals to bind hemoglobin
- Hemoglobin denatures (Heinz bodies)

G6PD Deficiency: Subtypes

G6PD Enzyme Subtype	Common Demographic Features	Severity
G6PD B	Most common	WT enzyme
G6PD A+	20-30% of African Black individuals	Normal, no hemolyisis
G6PD A-	10-15% of African American and African Black individuals	Mild to moderate hemolysis
G6PD Kaiping	Asian individuals	Mild to moderate hemolysis
G6PD Mahidol	SE Asian individuals	Mild to moderate hemolysis
G6PD Mediterranean	Mediterranean, Middle East, India	Severe hemolysis
G6PD Canton	Asian individuals	Severe hemolysis
G6PD Gaohe	Asian individuals	Severe hemolysis

Pediatr Clin North Am. 2018 Jun;65(3):579-595.

G6PD deficiency syndromes

- Drug-induced hemolysis
- Infection-induced hemolysis
- Favism
- Neonatal jaundice
- Chronic non-spherocytic hemolytic anemia

G6PD Oxidant Stressors

Drugs
Chlorpropamide
Dapsone
Dabrafenib
Methylene Blue
Nitrofurantoin
Nitrofurazone
Phenazopyridine
Primaquine
Rasburicase
Pegloticase
Tafenoquine

Infections
Hepatitis A/B/E
CMV
Enterovirus
Dengue
Coronavirus
Bacterial infections

Chemicals/Foods
Henna compounds
Naphthalene (mothballs)
Phenylhydrazine
Amyl nitrate
Fava beans

Fava beans

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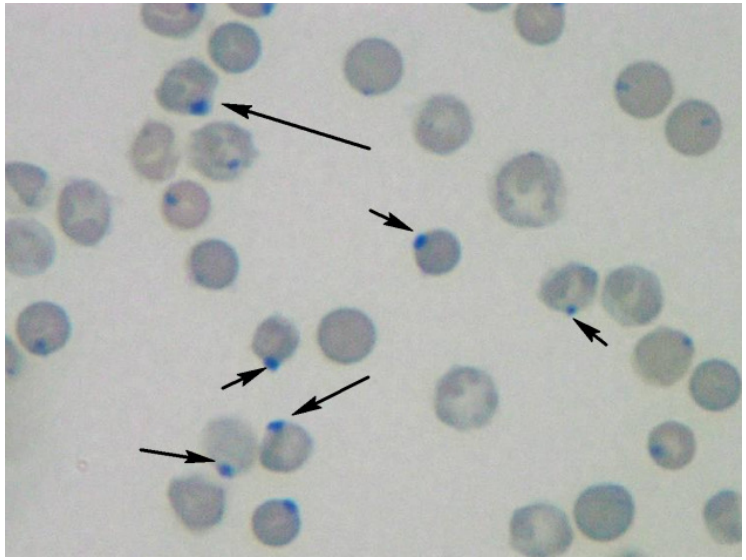
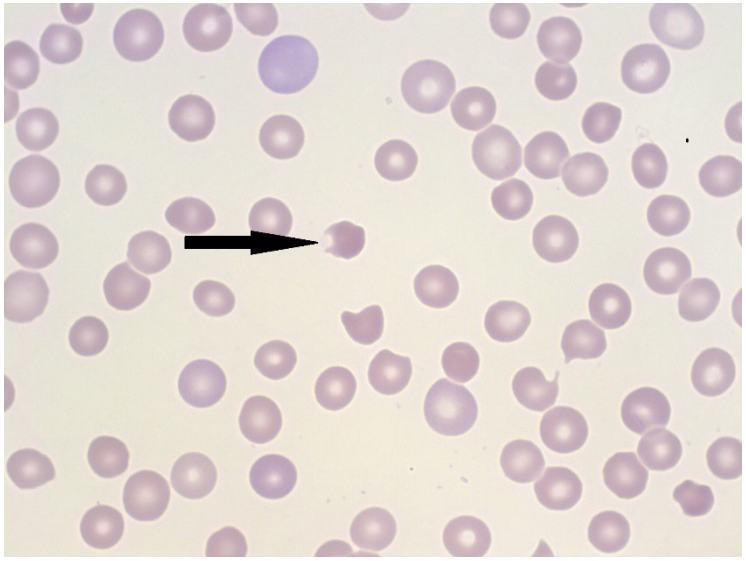
G6PD Deficiency: Heinz Bodies

Supravital stain



http://www.medical-labs.net/summary-of-abnormal-red-blood-cell-morphologies-and-disease-states-3023/.

Bite Cells/Blister Cells

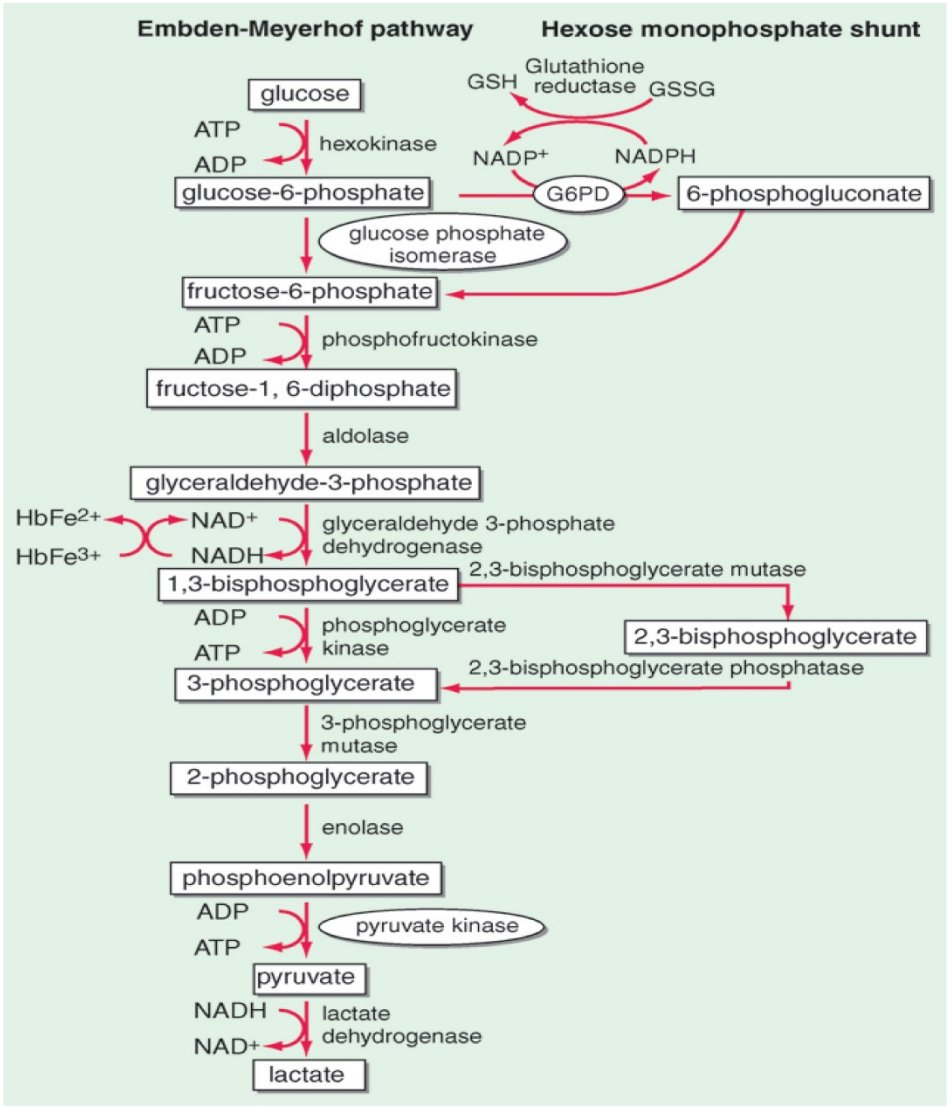


- Heinz bodies (also referred to as "Heinz-Ehrlich bodies") are inclusions within red blood cells composed of denatured hemoglobin.
- Enzyme activity – but ***should not*** check during an acute episode

G6PD Deficiency: Management

- Prevention!!!
  - Avoiding Oxidative Stressors (drugs, fava beans)
- Fortunately, acute hemolysis in G6PD patients is usually short lived.
  - Rarely requires transfusions
- Neonatal jaundice is treated in same way as neonatal jaundice from other etiologies
  - Phototherapy
  - Exchange transfusion
- Folate supplementation

Diagnosis and clinical management of enzymopathies



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Glycolytic enzymes

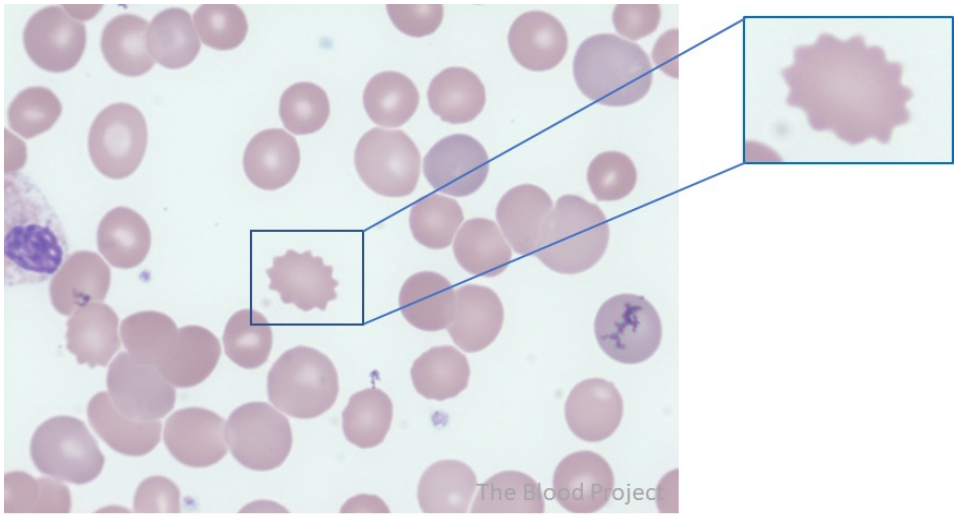
- Decreased activity leads to decreased ATP production
- Diminished ability to maintain Sodium and Potassium balance
- Causes increased 2,3 DPG – which improves O_2 delivery

Glycolytic enzymes – Pyruvate Kinase deficiency

- 2nd most common enzyme deficiency
- Result from mutations in PKLR gene
- Autosomal recessive trait
- Found in all ethnic groups
- Treatment – Historically
  - Splenectomy
  - Red cell transfusions

Manifestations of PK Deficiency

- Depletion of ATP: Disturbs cation gradient.
- Loss of H_2O and K+: Cell dehydration leading to Echinocytes.
- Premature removal of red blood cell from the circulation.



Echinocytes
(Burr Cell, Crenated cell)

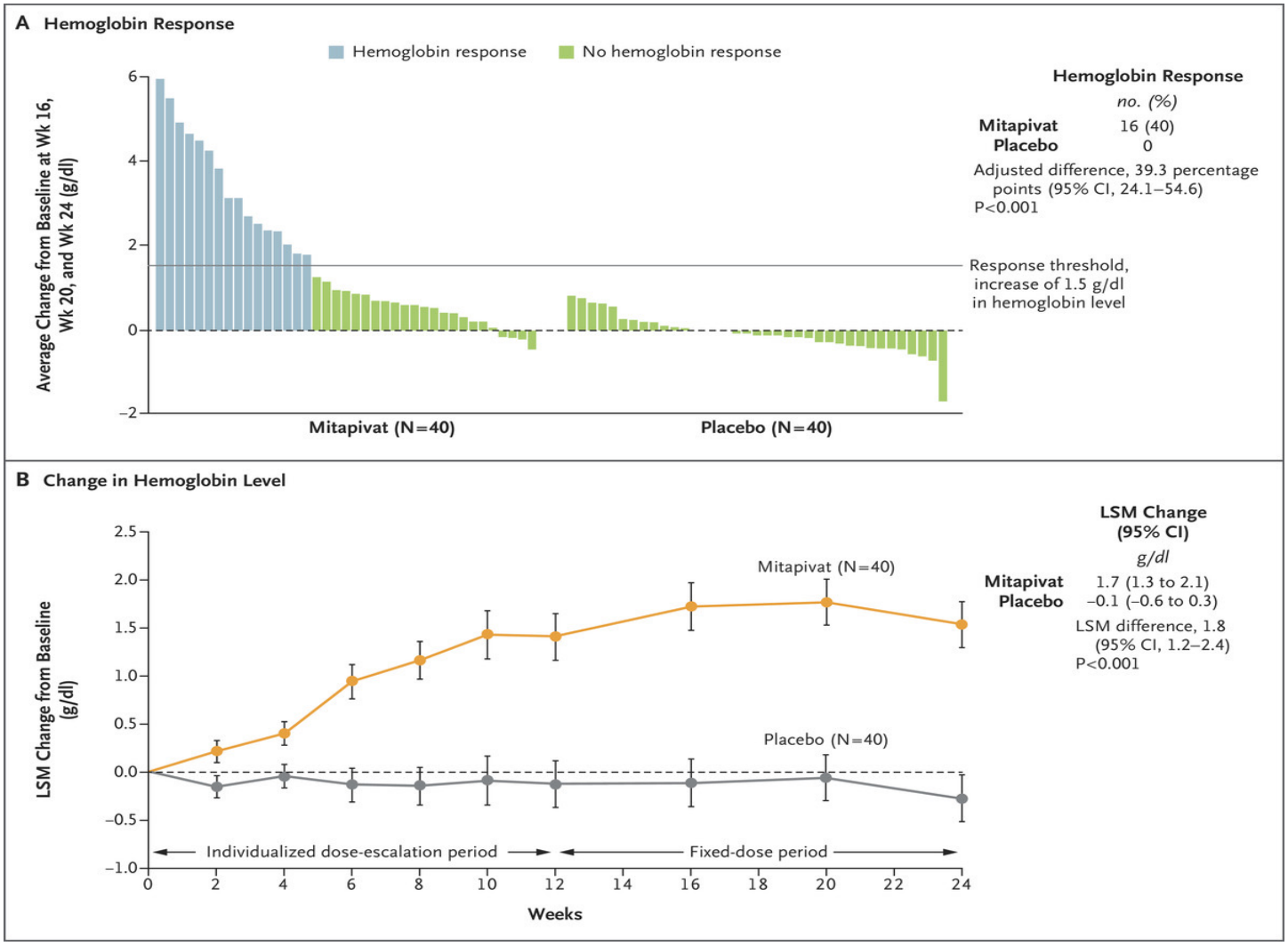
https://www.thebloodproject.com/burr-cell/#:~:text=Definition,blood%20cells%20retain%20central%20pallor.

PK Deficiency Treatment - Mitapivat

- First oral activator of red cell pyruvate kinase
- FDA approved for treatment of PK deficiency
- Phase III study – ACTIVATE – demonstrated efficacy of the agent.

Al-Samkari et al. N Engl J Med 2022;386:1432-1442.

Changes from Baseline in the Hemoglobin Level.



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Membrane Defects

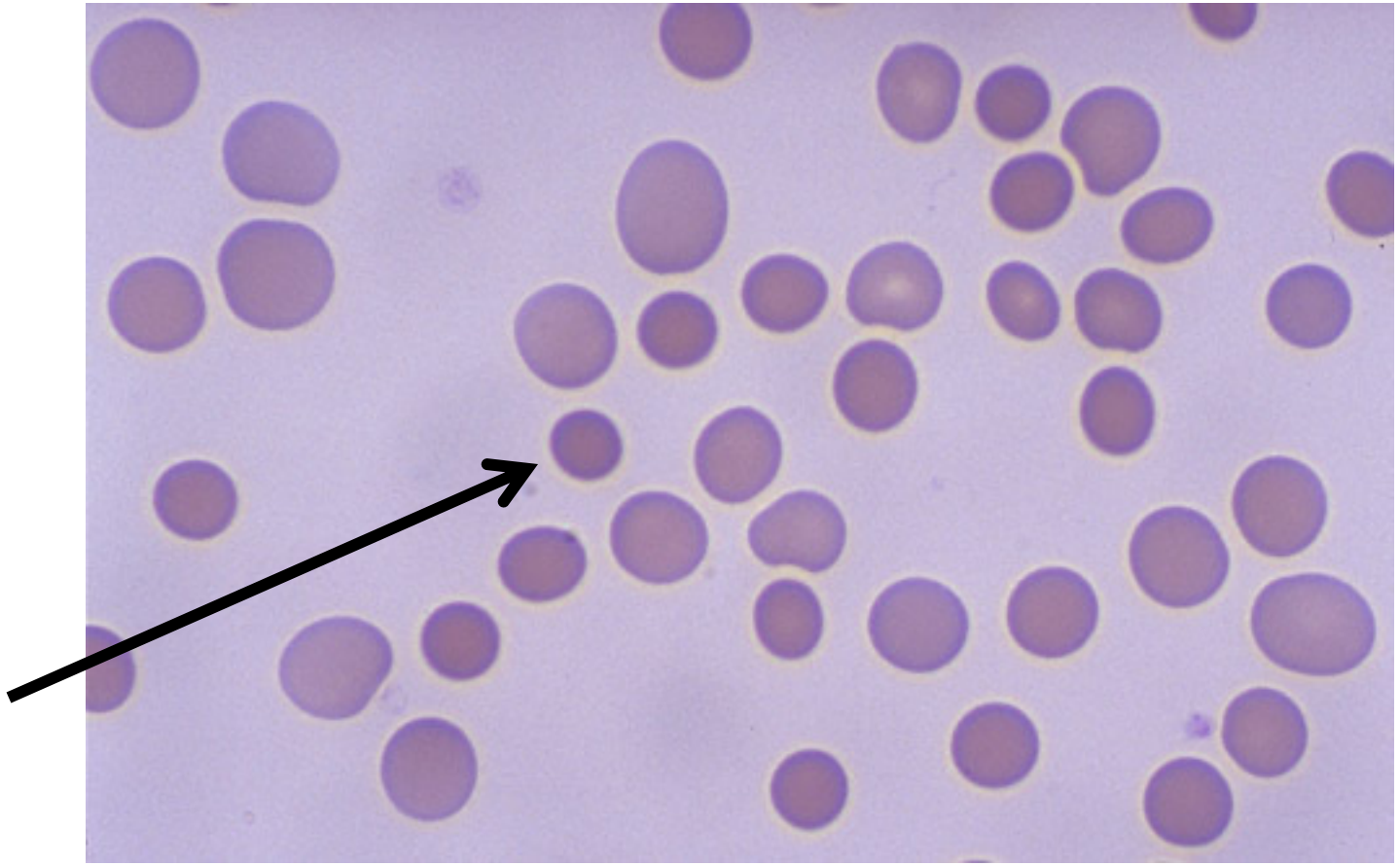
- Congenital
  - Hereditary Spherocytosis
  - Hereditary Elliptocytosis
- Acquired
  - Spur cell anemia
  - PNH

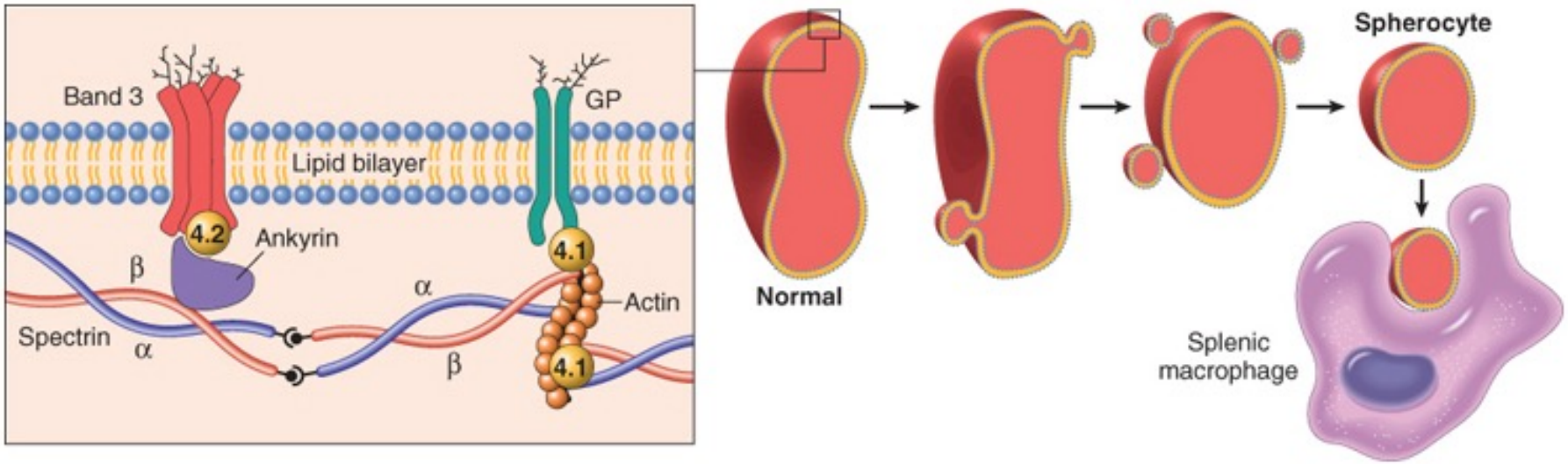
Testing for Hereditary Anemias

- Anemia ID (Agios and PerkinElmer) is a genetic test panel for CDA, DBA, Enzymopathies, Membranopathies and Hyperbilirubinemias
  - Blood or saliva test kits are available
- Invitae does RBC membrane disorders and Enzymopathies genetic panel or hereditary hemolytic anemia panel

Hereditary Spherocytosis

- Incidence – 1 in 5000 in U.S.
- Dominant, recessive, or de novo mutations in genes encoding RBC membrane proteins (ankyrin, band 3, spectrin, and protein 4.2) results in HS
- Clinical picture
  - Anemia – varying severity
  - Splenomegaly
  - Gallstones
  - Spherocytes on the smear

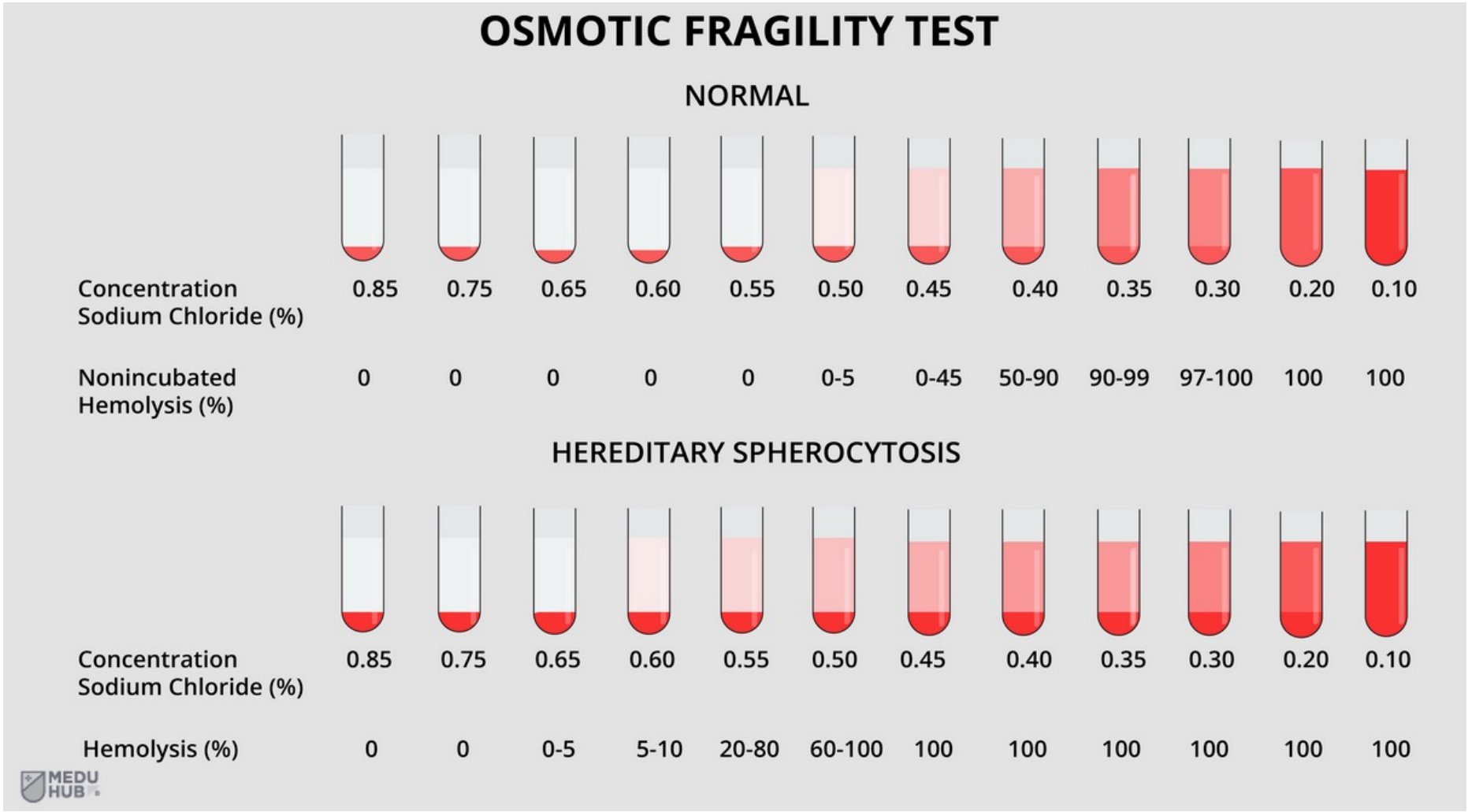




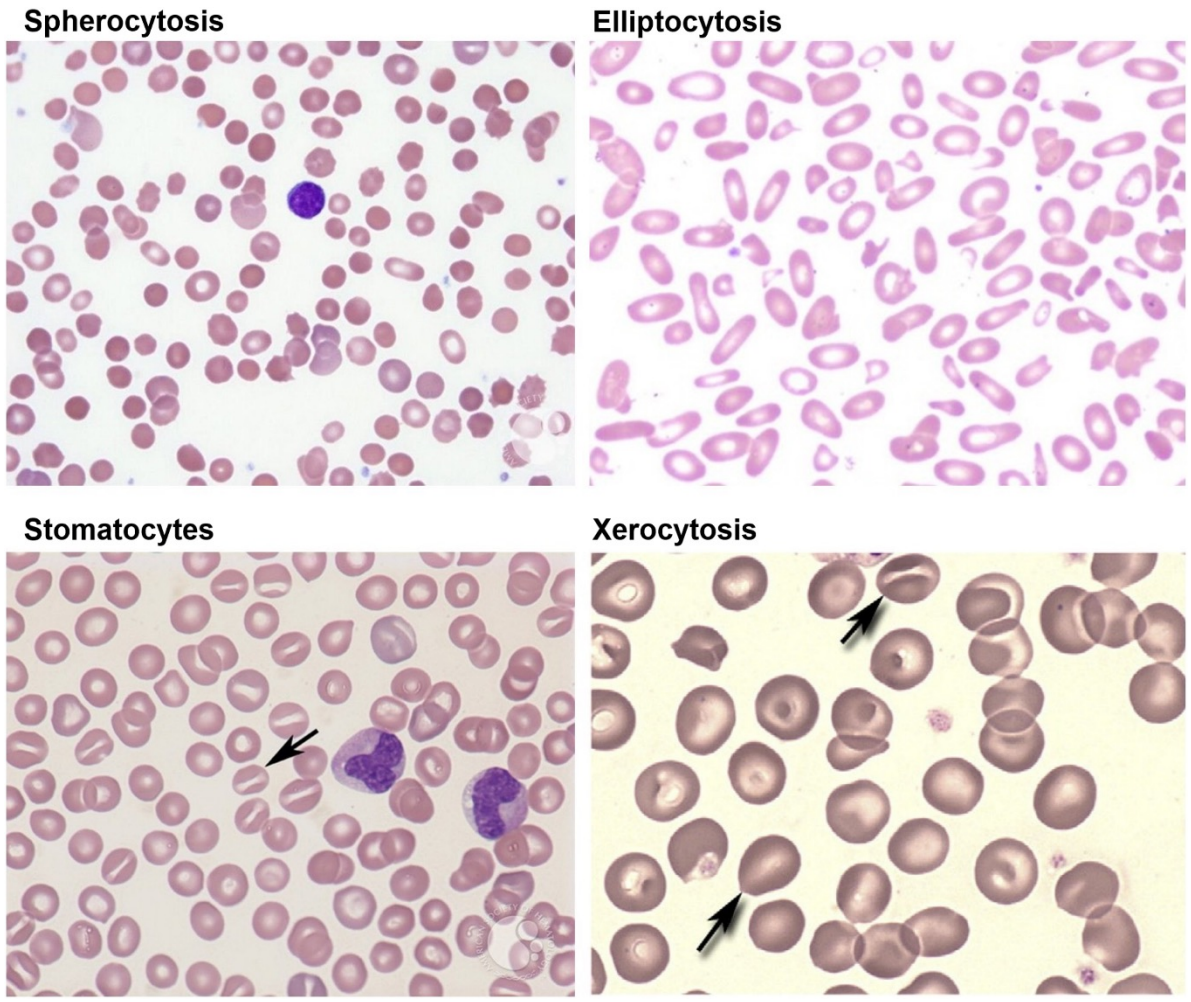
HS - Diagnosis

- Family history
- Spherocytes on the smear
- MCV – normal (usually)
- MCHC – increased
- Increased Osmotic Fragility
- eosin-5’-maleimide binding test
- DNA testing panels
- Treatment- Total vs Subtotal splenectomy

Osmotic Fragility



Inherited Membrane Defects



Narla Mohandas, Inherited hemolytic anemia: a possessive beginner's guide, Hematology Am Soc Hematol Educ Program, 2018,

Table 2. Red cell membrane disorders

Disorder	Severity	Inheritance	Molecular defects	Morphology	Osmotic fragility	Splenectomy
HS	Mild to severe	AD, AR, de novo	Ankyrin-1, band 3, α-spectrin, β-spectrin, protein 4.2	Varying degree of spherocytes	Mild to marked decrease	Beneficial
HE	Nonhemolytic to severe	AD	α-spectrin, β-spectrin, protein 4.1	Elliptocytes and fragmented red cells	Normal to marked decrease	Beneficial
OHS	Mild to moderate	AD	RhAG	Stomatocytosis	Increased	Not recommended
HX	Nonhemolytic to moderate	AD	Piezo-1, Gardos channnel	Some target cells	Decreased	Not recommended

AD, autosomal dominant; AR, autosomal recessive.

Narla Mohandas, Inherited hemolytic anemia: a possessive beginner's guide, Hematology Am Soc Hematol Educ Program, 2018,

Acquired Membrane Defects

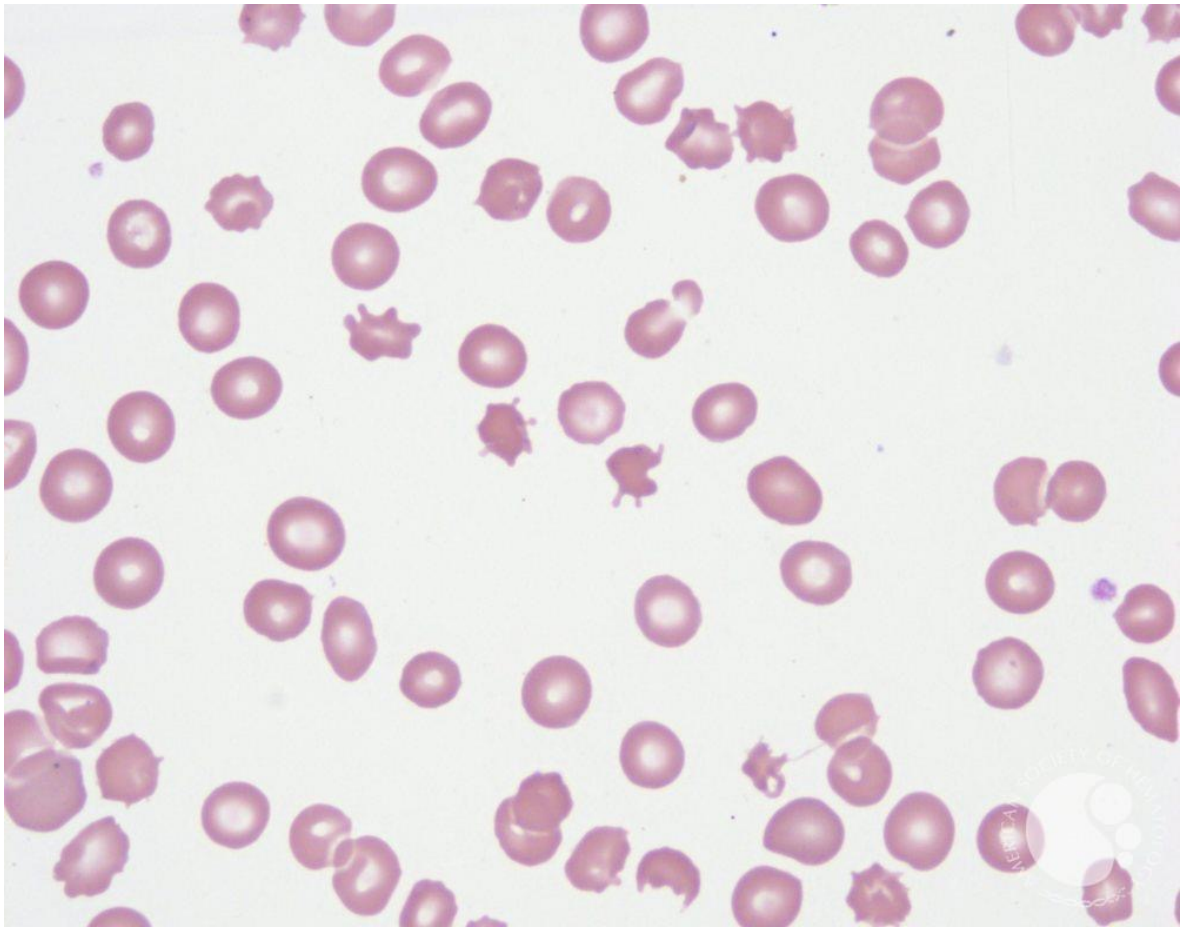
- Spur cell anemia – RBC membrane accumulates cholesterol leading to the spiculated appearance
- Found in end stage liver disease

Acanthocyte (spur cell)

Image ID: 60518

Authors: Teresa Scordino

Category: Morphologic variants of Red Blood Cells > Normal Red blood cell morphology with resting lymphocyte for comparison > Poikilocytosis > Acanthocytes

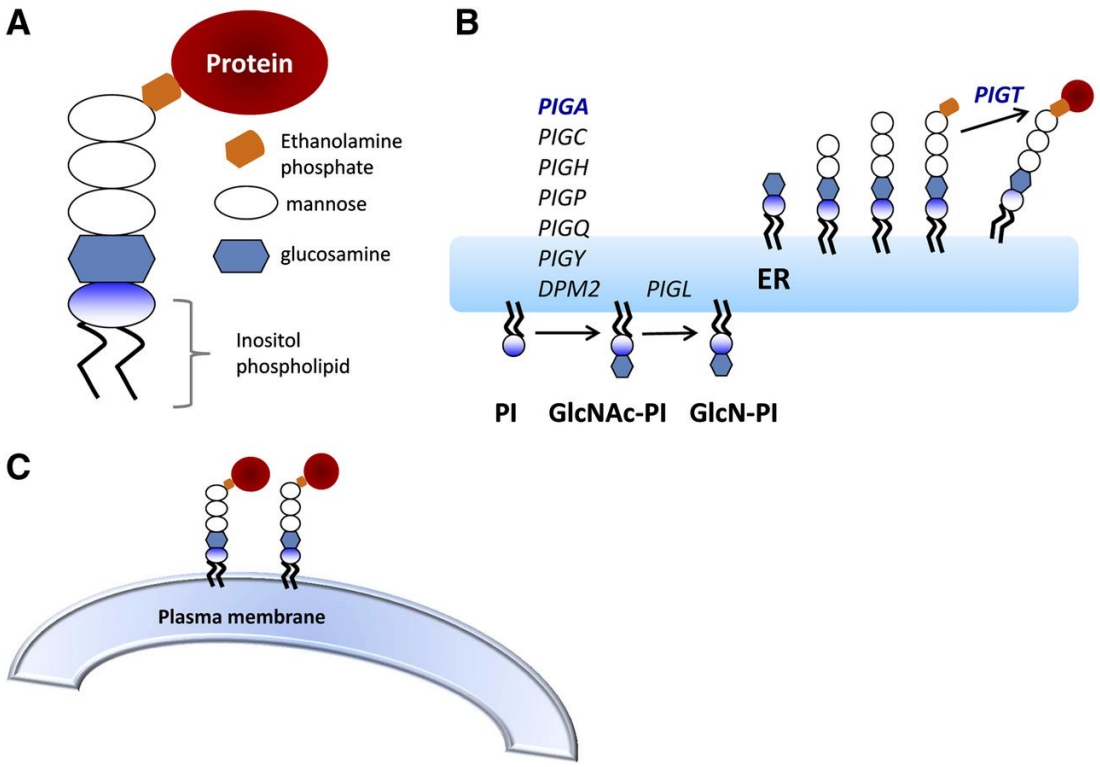


Paroxysmal Nocturnal Hemoglobinuria

Pathogenesis of PNH

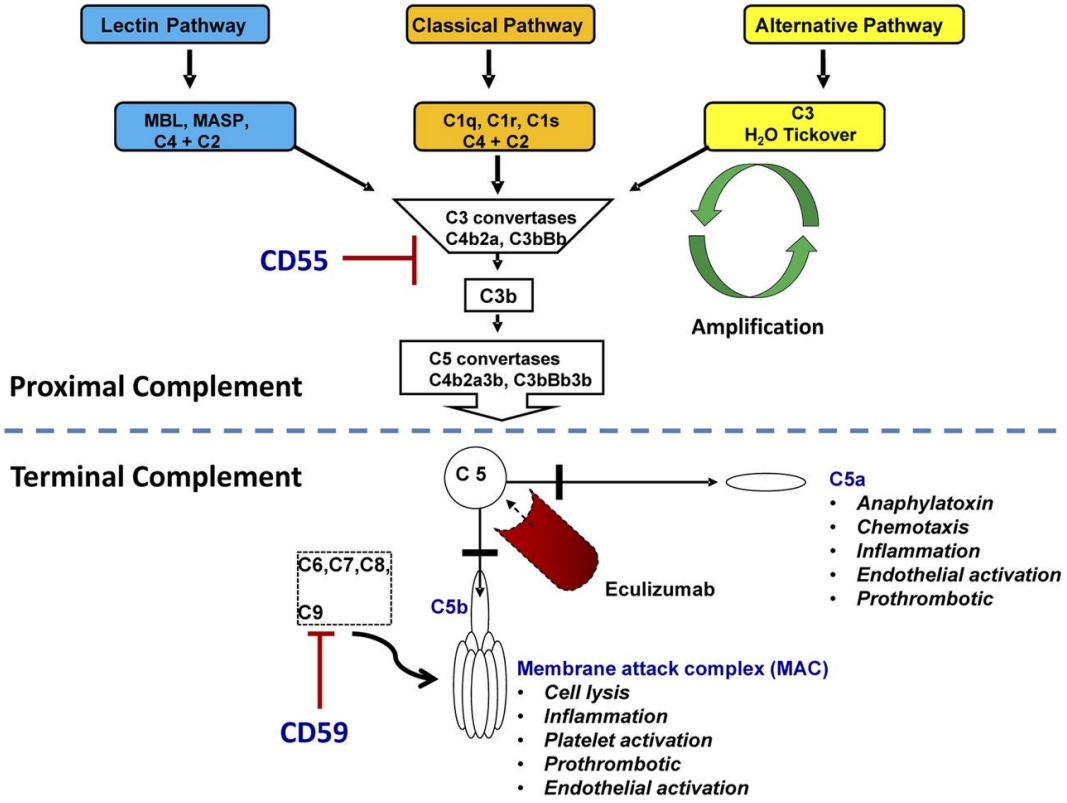
- PNH is the result of an acquired mutation in the *PIGA* gene ((phosphatidylinositol glycan anchor biosynthesis, class A)
- *PIGA*- involved in initial synthesis of the glycosylphosphatidylinositol (GPI) anchor
- More than 150 human proteins are GPI-anchored proteins
- *PIGA* mutations protect cells from immune mediated destruction
- Small PNH clones seen in majority of patients with BMF
- Some BMF can be seen in patients with de novo PNH

GPI anchor biosynthesis



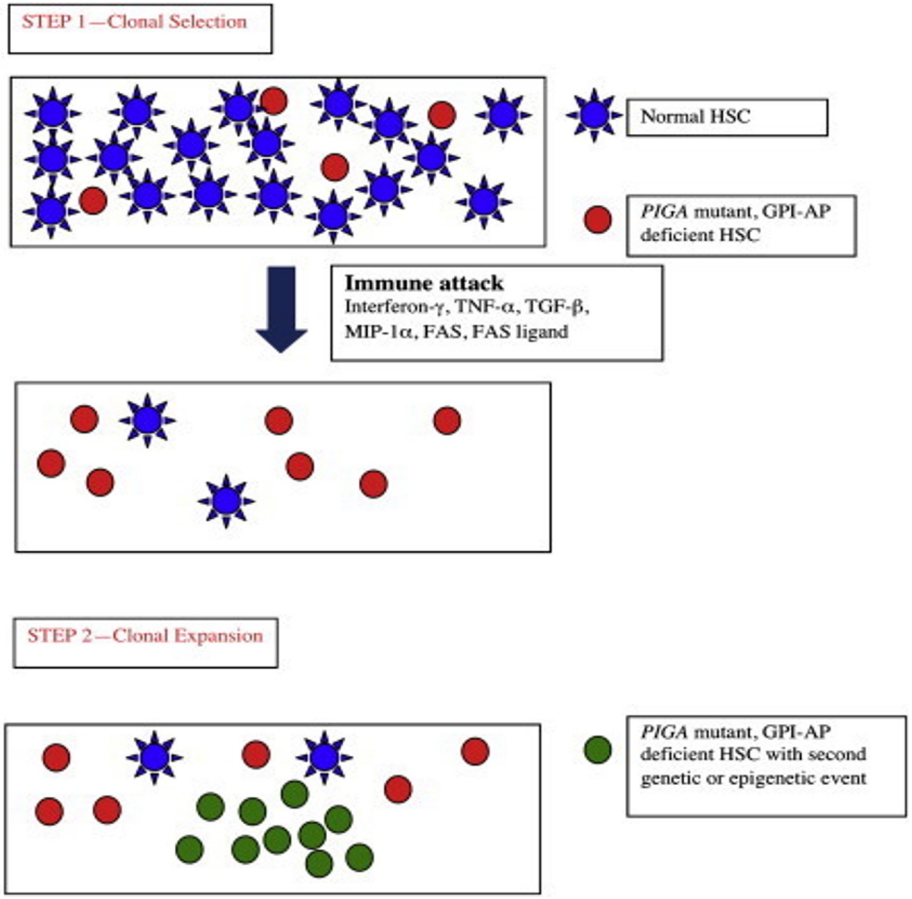
Robert A. Brodsky, Paroxysmal nocturnal hemoglobinuria, Blood, 2014, Figure 1

Complement regulation and C5 inhibitor



Robert A. Brodsky, Paroxysmal nocturnal hemoglobinuria, Blood, 2014, Figure 2

Clonal selection and expansion

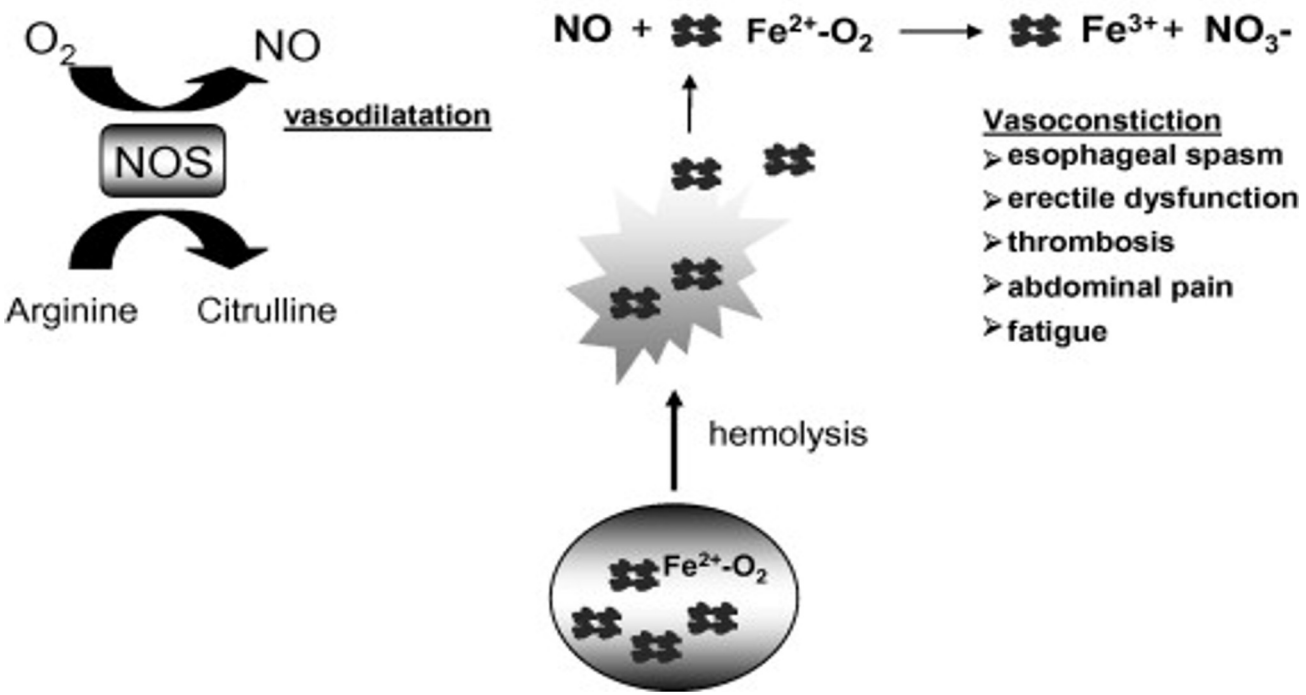


Hematol Oncol Clin North Am. 2009 Apr;23(2):333-46

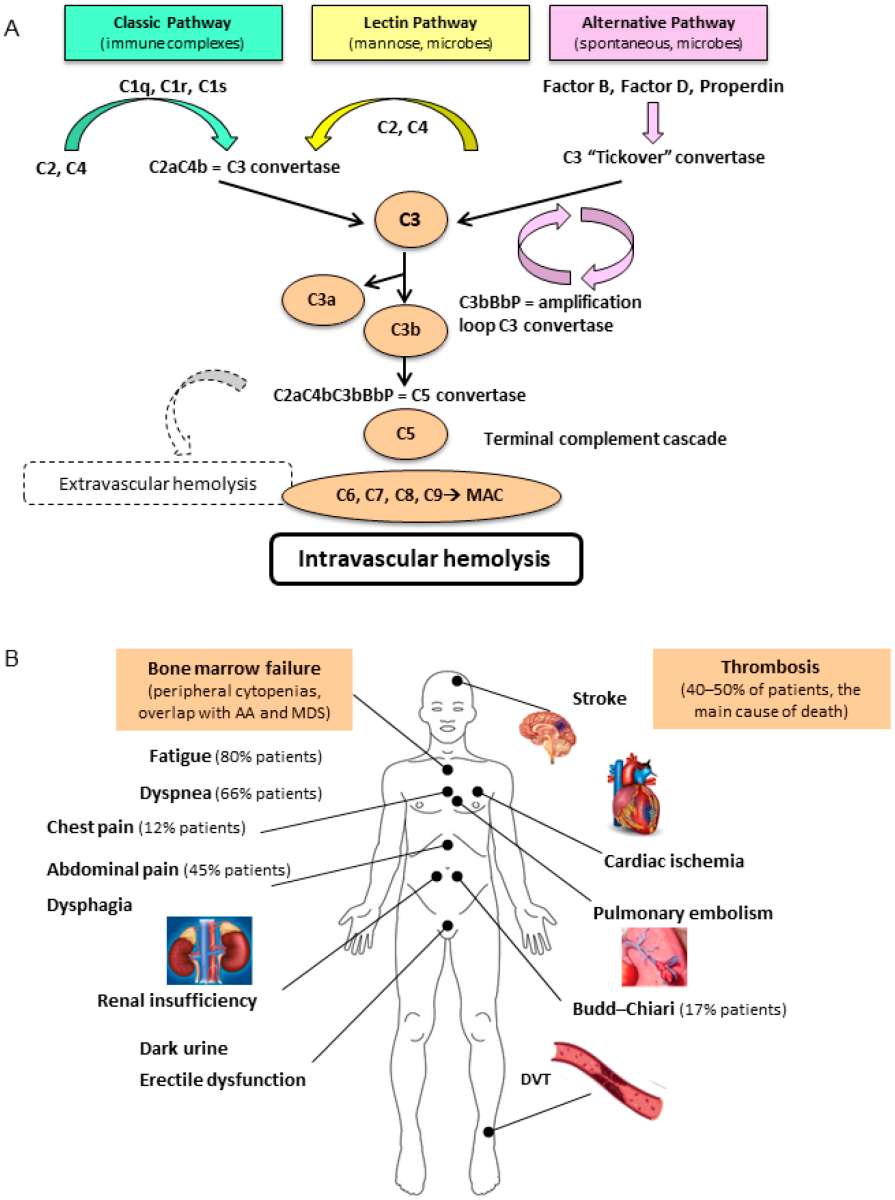
Clinical presentation in PNH

- Anemia
  - Multiple causes
  - Intravascular & Extravascular hemolysis, BMF, IDA, Anemia of CKD
- Thrombosis
  - Venous>>>arterial
  - Unusual locations
  - ↓NO, procoagulant microparticles, ↓fibrinolytic proteins, ↑cytokines
- Smooth muscle dystonia
  - ↓NO

Role of Nitric oxide



Blood Rev. 2008 Mar;22(2):65-74



Fattizzo B, Serpenti F, Giannotta JA, Barcellini W. Difficult Cases of Paroxysmal Nocturnal Hemoglobinuria: Diagnosis and Therapeutic Novelties. J Clin Med. 2021 Mar 1;10(5):948. doi: 10.3390/jcm10050948. PMID: 33804461; PMCID: PMC7957780.

Urinalysis in PNH

Blood +++

RBC <2 RBC/HPF

Blood on dipstick with negative microscopy

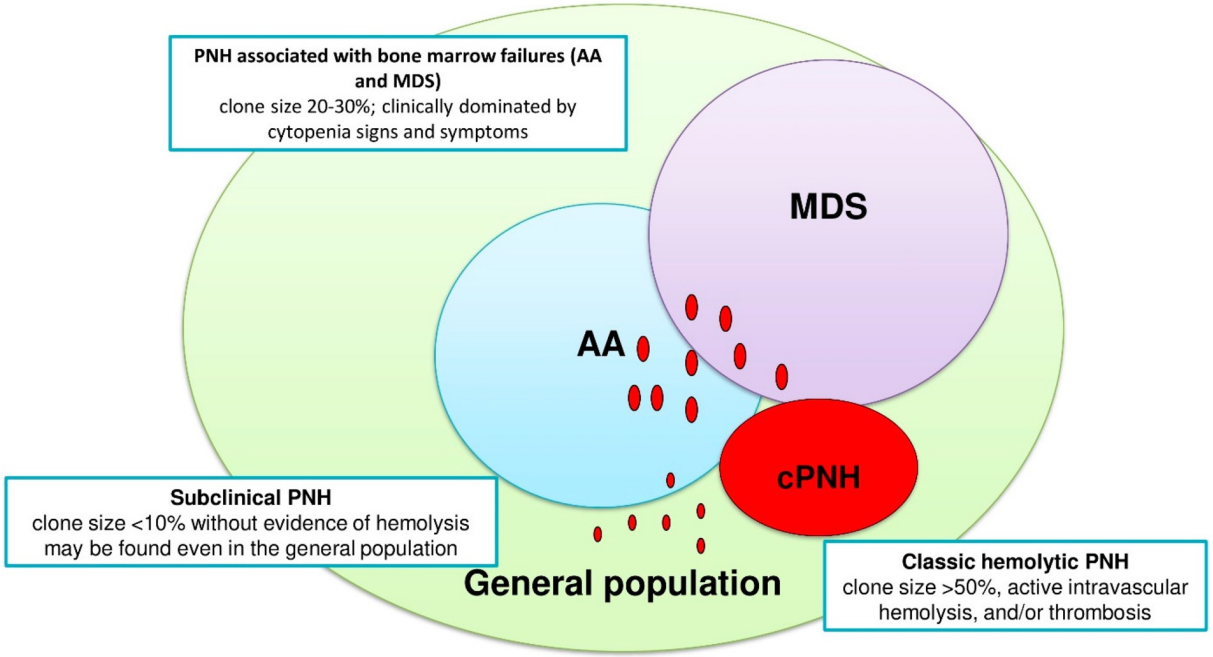
- Hemoglobinuria and not hematuria
- Myoglobinuria

The best test to assess for hemoglobinuria or hematuria is urine hemosiderin

Diagnosis of PNH

- Flow cytometry for granulocytes and RBCs deficient in GPI-anchored proteins like CD55and CD59
- Antibodies directed against CD45, glycophorin A, CD59, CD24, CD14, CD15, CD64, as well as FLAER
- FLAER - FLuorescent AERolysin : bacterial toxin aerolysin binding GPI anchor
- Studying the RBC population alone can underestimate clone size

Classification of PNH

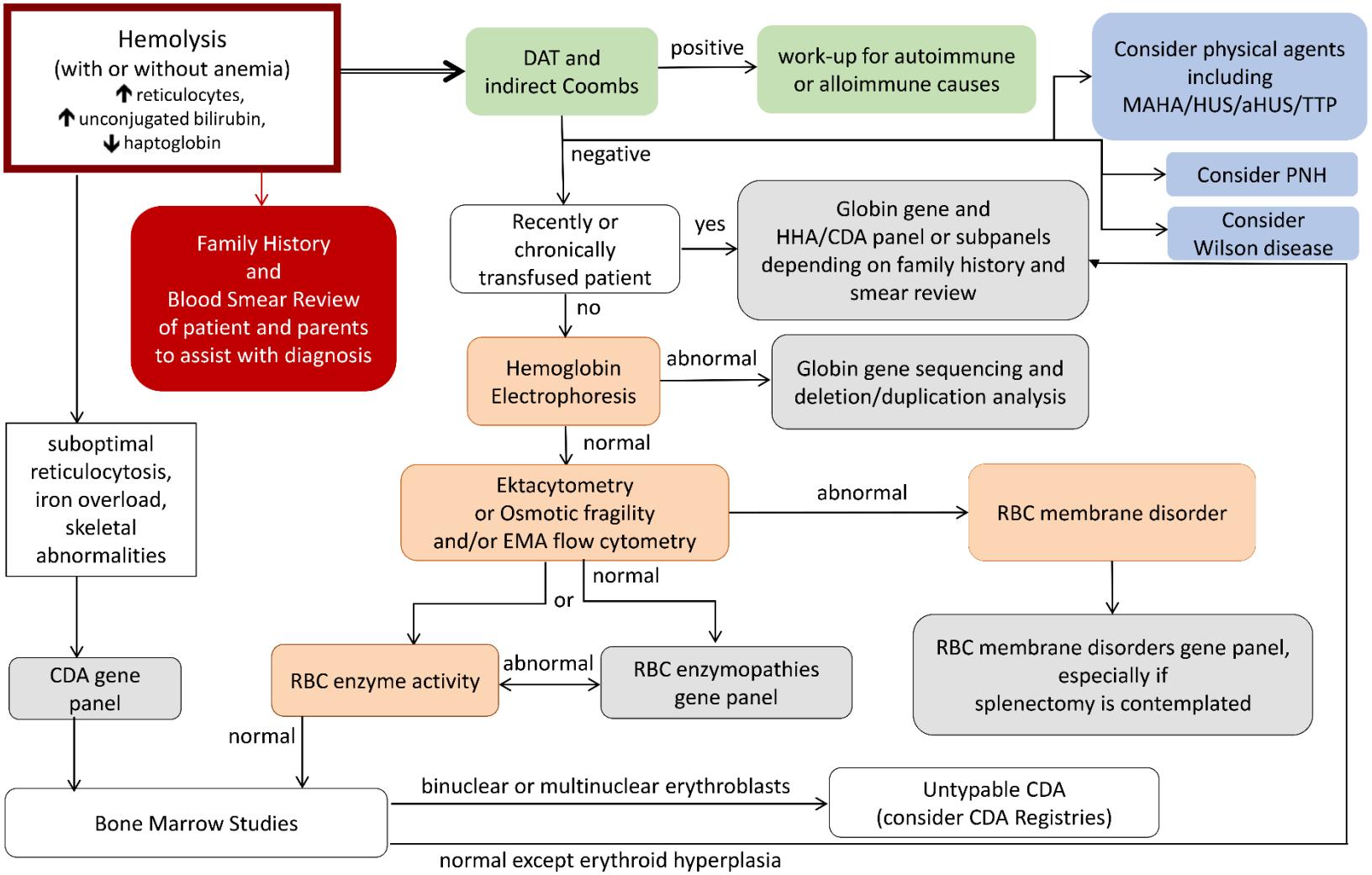


Fattizzo B, Serpenti F, Giannotta JA, Barcellini W. Difficult Cases of Paroxysmal Nocturnal Hemoglobinuria: Diagnosis and Therapeutic Novelties. J Clin Med. 2021 Mar 1;10(5):948. doi: 10.3390/jcm10050948. PMID: 33804461; PMCID: PMC7957780.

Complement inhibitors

- C5 inhibitors (Ravulizumab, Eculizumab)-intravenous
- C3 inhibitors (Pegcetocoplan)-subcutaneous
- Factor D inhibitor (Danicopan)-oral
- Factor B inhibitor (Iptacopan)-oral

Diagnosis and clinical management of red cell membrane disorders



Theodosia A. Kalfa, Diagnosis and clinical management of red cell membrane disorders, Hematology Am Soc Hematol Educ Program, 2021,

Thank you!