Bone Marrow Failure Disorders

Aplastic Anemia: Pathophysiology/Etiology

- Rare heterogeneous disorder characterized by bone marrow aplasia, failure of hematopoiesis, and pancytopenia
- Classification
  - Acquired (AAA): 80% of cases
    - 65% of the cases are considered idiopathic but largely as result of an immune-mediated destruction of hematopoietic cells where the T cells attack other cell types (eg, autoimmune disease)
    - Drugs/toxins or various infections have been known to induce bone marrow failure
      - Benzene, chloramphenicol, quinine
      - Hepatitis, Epstein-Barr virus, parvovirus, HIV
      - Radiation to marrow-producing regions
    - 10% to 20% of patients are found to have a premalignant disease following treatment with immunosuppressive therapy (PNH, MDS)
  - Constitutional/inherited (CAA) (rare): 20% of cases – includes Fanconi anemia, dyskeratosis congenita, and Shwachman-Diamond syndrome

HIV = human immunodeficiency virus; MDS = myelodysplastic syndrome; PNH = paroxysmal nocturnal hemoglobinuria

Jain D, et al. J Clin Lab Anal. 2012;26(6):452-458; Young NS. Hematology Am Soc Hematol Educ Program (2013). 2013(1):76-81.

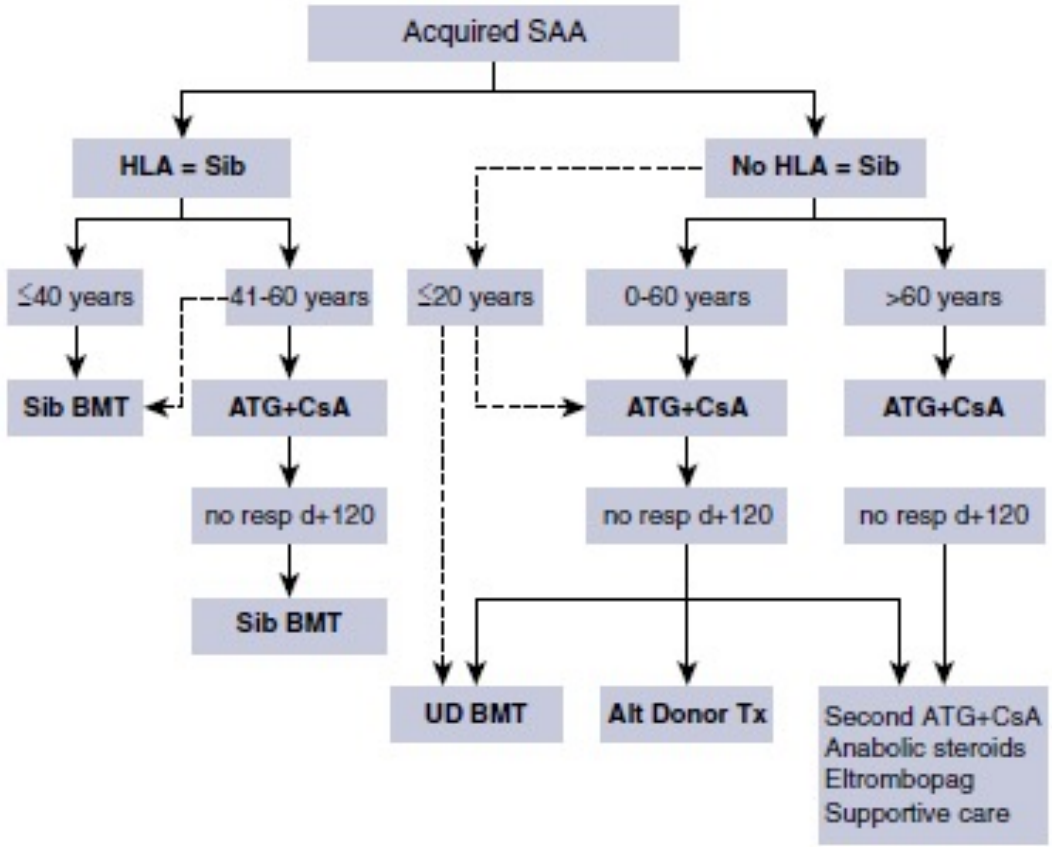
Aplastic Anemia: Presenting Signs and Symptoms/Differential Diagnosis of AAA

- Presenting signs and symptoms are related to cytopenias
  - Macrocytosis
  - Blunted reticulocyte count
  - Petechiae, ecchymoses
  - Pallor
  - Infections
- Review of past medical history
  - Hepatic cirrhosis
  - Immunosuppression
  - Post-transplant
  - Infectious etiologies
  - Malignant bone marrow failure syndromes
  - Medications
  - Establish chronicity of cytopenias
- Diagnostic work-up:
  - CBC, differential and platelet count
  - Flow cytometry
  - Review of peripheral smear
  - Other labs based on history to rule out malignancy
- Bone marrow biopsy, aspirate, cytogenetics, FISH for possible malignant bone marrow failure states
- Diagnostic criteria: severe aplastic anemia (SAA)
  - Two of three peripheral cytopenias (ANC < 500/mm^3, platelet count < 20,000/mm^3)
  - ARC < 40,000/μL
  - Bone marrow cellularity of < 30% (requires bone marrow core biopsy)

ANC = absolute neutrophil count; ARC = absolute reticulocyte count; CBC = complete blood count; FISH = fluorescence in situ hybridization

Aplastic Anemia: Clinical Management

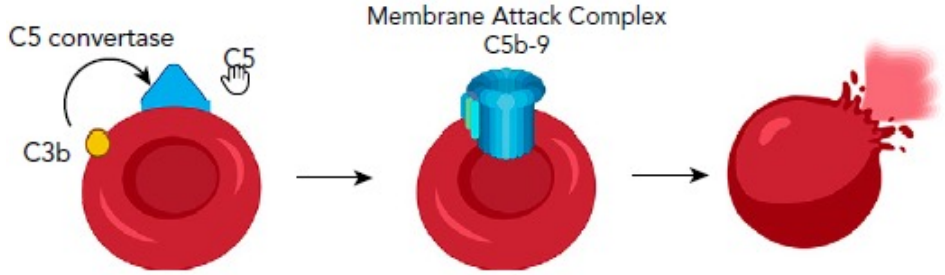
- The 2-year mortality of patients with SAA without immunosuppressive therapy exceeds 80%
  - Severe infections are the most common cause of death
- Supportive care is essential concurrently with immunosuppressive therapy
  - Transfusion support
  - Anti-infective prophylaxis
  - Other supportive care
- HLA testing for allogeneic hematopoietic stem cell transplantation (HSCT) should be obtained and patients eligible for transplant who have a suitable donor should be considered for HCST
- Anti-thymocyte globulin (ATG), cyclosporine, prednisone, and thrombopoietin-stimulating agents (eltrombopag) remain the standard regimen for eligible patients



Bacigalupo A. Blood. 2017;129(11):1428-1436.

Paroxysmal Hemoglobinuria (PNH): Pathophysiology

PNH is a rare complement-driven nonimmune hemolytic anemia



- Incidence is ~ 1–1.5 cases per million individuals worldwide
  - Most patients present between the ages of 30 and 59 years
- Frequently accompanied by bone marrow failure
- Associated with a high risk of thrombosis (leading cause of death)
- High mortality if not diagnosed and treated promptly
- Caused by germline (rare) or somatic (acquired) mutations in the phosphatidylinositol glycan anchor biosynthesis class A gene (*PIGA*).
- *PIGA* gene encodes for the glycosyl-phosphatidylinositol (GPI) anchor expressed on cell surfaces
- GPI anchor is required for the binding of surface proteins to the cell, including complement inhibitors CD55 and CD59
- CD55 and CD59 are specifically responsible for protecting red blood cells from complement-mediated lysis
- GPI-deficient cells lack these proteins on their surface and render PNH erythrocytes susceptible to hemolysis
- Promoting event(s) that suppresses the normal stem cells allow the PNH clone to become dominant, leading to clinical disease

Brodsky RA. Blood. 2021;137(10):1304-1309; Luzzatto L, et al. Brit J Haematol. 2020;191(4):579-586.

PNH: Differential Diagnosis of High-Risk Groups

- As a rare disease, PNH is often undiagnosed, despite its considerable morbidity and mortality
- Testing for PNH should be implemented in high-risk groups

Patient Characteristics	Examples
Patients with evidence of hemolysis without obvious cause	• Coombs-negative hemolytic anemia • Hemoglobinuria or hemosiderinuria • Cytopenia due to bone marrow dysfunction • Hemolysis with signs of renal dysfunction
Patients with evidence of bone marrow dysfunction	• Patients with aplastic anemia • Patients with myelodysplastic syndromes (MDS) with evidence of hemolysis, hypoplasia, or refractory cytopenia • Patients with unexplained cytopenia

Patients with unexplained thrombosis	• And evidence of hemolysis without obvious cause
	• Venous and arterial thrombosis
	  • In unusual sites (eg, intra-abdominal veins, cerebral veins, dermal veins)
	  • With any cytopenia
	  • Nonresponsive to anticoagulant
	  • In young patients

Devos T, et al. Eur J Haematol. 2018;101(6):737-749.

PNH: Presenting Clinical Manifestations

Clinical Manifestation	Comments
Thromboembolic events (TE)	• Present in 40% of PNH patients • 85% are venous • Often atypical sites (intra-abdominal veins, cerebral veins, dermal veins) • 50% of TE occur during anticoagulation therapy
Cytopenias	• 50% to 60% of aplastic anemia cases have a PNH subclone • 15% to 20% of MDS cases have a PNH subclone • Treatment of the primary bone marrow failure (BF) syndrome is recommended
Pulmonary hypertension (PHT)	• Elevated levels of NT-proBNP due to increased pulmonary artery resistance • Echocardiogram evidence of elevated systemic-pulmonary arterial pressure (36% of PNH patients) • Subclinical small pulmonary emboli (PE) may contribute to PHT • Cardiac MRI shows subclinical PE in 60% of cases
Renal insufficiency	• Present in 14% of subclinical PNH patients, 44% of classic PNH patients, and 10% of PNH/BF patients • Caused by hemosiderin deposition in the proximal tubules of renal cortex

NT-proBNP = N-terminal pro-hormone B-type natriuretic peptide; MDS = myelodysplastic syndrome; MRI = magnetic resonance imaging

Brodsky RA. Blood. 2021;137(10):1304-1309; Wong EKS, et al. Semin Immunopathol. 2018;40(1):49-64; Devos T, et al. Eur J Hematol. 2018;101(6):737-749.

PNH: Presenting Clinical Manifestations (cont)

Clinical Manifestation	Comments
Erectile dysfunction	• 53% of the male classic PNH patients • 6% of patients with PNH and a bone marrow failure disorder
Abdominal pain	• Present in 33% of PNH patients • Associated with a higher risk of TE • May be due to vascular dysfunction and microthrombosis • May also be due to major visceral thrombosis (eg, Budd-Chiari syndrome)
Laboratory Findings	• Cytopenias: anemia most common; normochromic, normocytic anemia with polychromasia (unless active bleeding, may see microcytosis) • Thrombophilia: complement-dependent • Elevated reticulocyte count, except in the case of concurrent bone marrow failure • Direct antibody test (DAT) negative • Elevated total and direct bilirubin • Flow cytometry of peripheral blood: absence of specific GPI-linked proteins (CD55, CD59), or of the GPI anchor itself, will establish the diagnosis • Elevated D-dimer • Hemoglobinuria
Diagnostic imaging	• May be ordered to evaluate symptoms or confirm presence of TEs

Brodsky RA. Blood. 2021;137(10):1304-1309; Wong EKS, et al. Semin Immunopathol. 2018;40(1):49-64; Devos T, et al. Eur J Hematol. 2018;101(6):737-749.

PNH: Clinical Management Overview

- Treatment of any underlying bone marrow failure disorder
  - Aplastic anemia
  - Myelodysplastic syndromes
- Treatment of the sequalae of PNH
  - Anticoagulation for thromboembolism
  - Symptomatic treatment for pain, fatigue
  - Interdisciplinary management of pulmonary hypertension, renal insufficiency
- Treatment of the PNH clone using complement inhibitors (CI)
  - Anti-C5 therapy in the form of the humanized monoclonal antibodies
  - Anti-C3 therapy
- Allogeneic hematopoietic stem cell transplant
  - Reserved CI refractory patients or inaccessible CI treatment
- Care coordination
  - Anti-complement agents are not readily available and require planning and coordination to ensure they are available at the prescribed intervals.
  - In episodes of acute hemolysis, emergency rooms will not likely have access to these drugs
  - Patients should wear a medical ID bracelet and should discuss any travel plans with their clinical team

PNH Clinical Management: C5 - Complement Inhibitors

Eculizumab

Dosing

- 600 mg weekly for the first 4 weeks, followed by
- 900 mg for the fifth dose 1 week later, then
- 900 mg every 2 weeks thereafter
- 1200 mg every 2 weeks for any breakthrough hemolysis

Ravulizumab

- After binding to C5, inhibits FcRn-mediated recycling, leading to its lysosomal degradation along with C5

Dosing

- Weight-based dosing regimen with loading dose followed by every 8-week maintenance dosing

Body Weight	Loading Dose	Maintenance Dose
40 to < 60 kg	2400 mg	3000 mg
60 to < 100 kg	2700 mg	3300 mg
≥ 100 kg	3000 mg	3600 mg

Serious Adverse Events (AEs)

- The main risk of terminal complement blockade by eculizumab is life-threatening *Neisseria* infections (0.42 infections per 100 patient-years)
- All patients treated with eculizumab MUST be vaccinated against *Neisseria meningitidis*, at least 2 weeks before starting eculizumab. In severe PNH, where eculizumab treatment cannot be postponed, 2 weeks of prophylactic therapy with ciprofloxacin is recommended after vaccination

Common AEs

- Headache, nasopharyngitis, back pain, and nausea

PNH: Clinical Management

- Treatment of any underlying bone marrow failure disorder
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- Treatment of the sequalae of PNH
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  - Symptomatic treatment for pain, fatigue
  - Interdisciplinary management of pulmonary hypertension, renal insufficiency
- Treatment of the PNH clone using complement inhibitors
  - Anti-C5 therapy in the form of the humanized monoclonal antibodies
    - Eculizumab
    - Ravulizumab
  - Anti-C3 pathway - investigational

Brodsky RA. Blood. 2021;137(10):1304-1309; Devos T, et al. Eur J Haematol. 2018;101(6):737-749; Luzzatto L, et al. Br J Haematol. 2020;191(4):579-586.

PNH: Clinical Resources

- This is PNH
  https://thisispnh.com
- PNH*Source* for clinicians
  https://pnhsource.com
- National Organization for Rare Disorders
  https://rarediseases.org/rare-diseases/paroxysmal-nocturnal-hemoglobinuria/

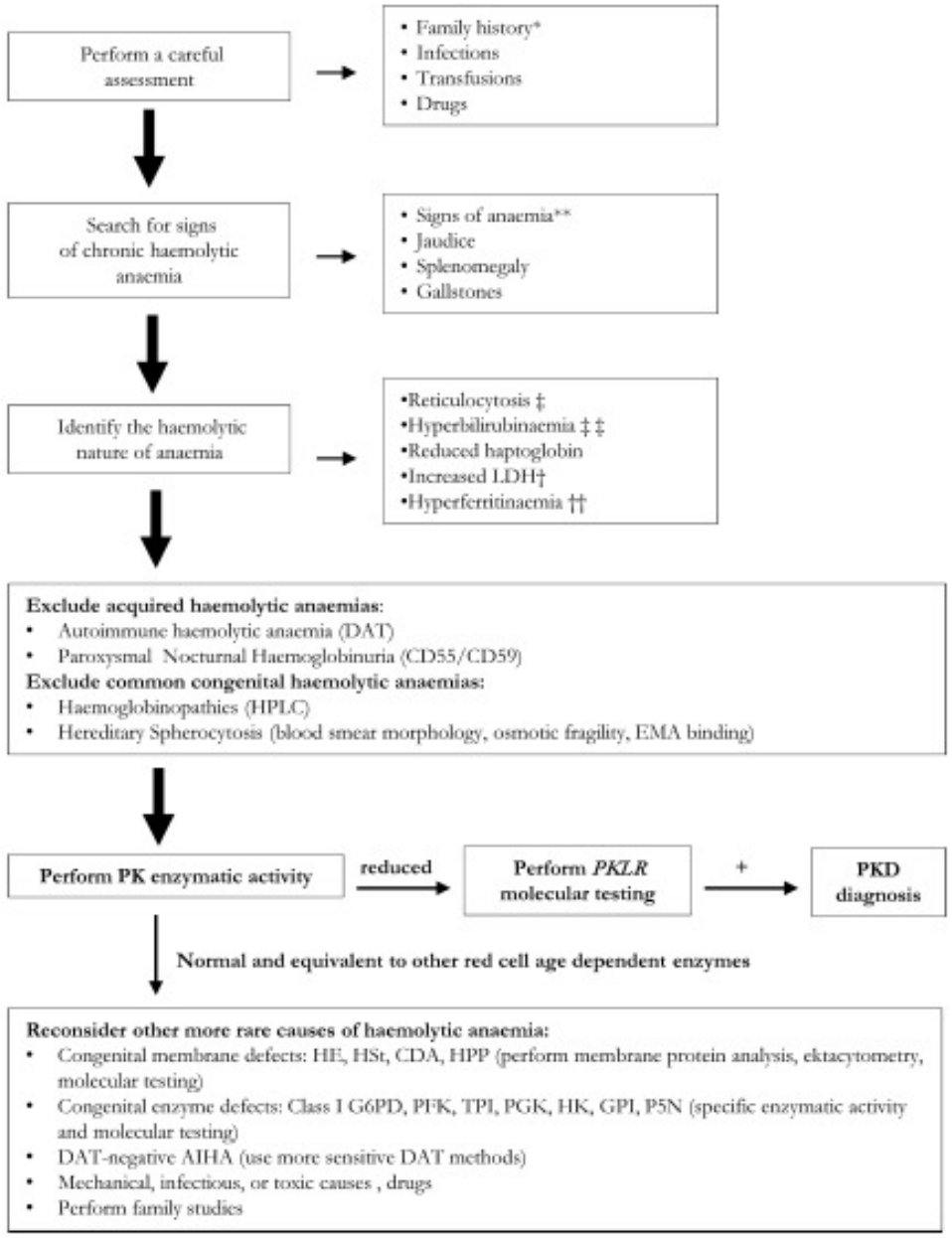
Red Cell Pyruvate Kinase (PK) Deficiency (PKD): Pathophysiology

- Rare congenital, nonspherocytic hemolytic anemia
- Caused by glycolytic defect due to compound heterozygous or homozygous mutations in *PKLR* gene on chromosome 1q21
- *PKLR* gene mutations lead to PK deficiency
- PK deficiency leads to a reduction in ATP, shortened reticulocyte and red cell lifespan
  - Inability to maintain the red cell electrochemical gradient and membrane integrity
  - Red cell damage and clearance in the spleen

Risitano AM, et al. *Front Immunol*. 2019;10:1157.

PKD: Presenting Signs and Symptoms, Differential Diagnosis

- History and physical examination
  - Facial jaundice (32%)
  - Scleral icterus (58%)
  - Bone deformities (9%)
  - Bone fractures (17%)
  - Hyperpigmentation (6%)
  - Splenomegaly (35%)
  - Gallstones (45%)
- Laboratory findings
  - Vitamin D deficiency
  - Endocrine dysfunction
  - + hemolysis screen
    - Elevated reticulocyte count
    - Elevated lactate dehydrogenase
    - Elevated direct and indirect bilirubin
    - Low hemoglobin



Grace RF, et al. *Blood*. 2018;131(20):2183-2192.

PKD: Clinical Management in Adults

Supportive Management	Recommendations
Folic acid supplementation	Daily folic acid supplementation may be appropriate for any patient with reticulocytosis >15% and evidence of hemolysis OR patients with mild hemolysis but a limited diet
Red cell transfusions	Individualized based on underlying comorbidities and symptoms Balance risk of iron overload and resolution of symptoms after transfusion Monitor serum ferritin Iron chelation therapy is indicated for treatment of hemosiderosis
Full splenectomy	**Indications** • Transfusion dependence • Massive splenomegaly at risk of spleen rupture due to lifestyle choices **Pre-post splenectomy immunizations are required** **Post-splenectomy thromboprophylaxis** • Prophylactic anticoagulation can be considered, once safe from a bleeding perspective, immediately post-splenectomy, in those with other thrombotic risk factors. • Low-dose aspirin could be considered until the platelet count is < 500 × 10^9/L in adults with advanced age, a history of thrombosis, hypercholesterolemia and cigarette smoking.
Management in pregnancy	Multidisciplinary care with a hematologist and high-risk obstetrician with close attention to fetal growth and transfusions to the pregnant woman on the basis of both her symptoms and fetal ultrasounds/monitoring

Grace RF, et al. Brit *J Haematol*. 2019;184(5):721-734.

PKD: Clinical Resources

- National Organization for Rare Disorders https://rarediseases.org/rare-diseases/pyruvate-kinase-deficiency/
- Genetic and Rare Diseases (GARD) Information Center http://rarediseases.info.nih.gov/GARD/

Thank you!