BONE MARROW FAILURE DISORDERS

Aplastic Anemia

Etiology and Overview

- Idiopathic etiology in majority (65%) of cases; most common hereditary cause is Fanconi anemia.
- Aplastic anemia: Incidence unclear; based on death registry data from multiple countries. Equally common among males and females, all age groups. Small peaks in incidence seen in childhood, young adulthood (age 20–25 years). Possible causes include abnormality of marrow progenitors/immune-mediated suppression of hematopoietic stem cells (HSCs) and immunosuppressive effects of chemotherapy, radiation treatments; however, autoimmune damage to HSCs seen in majority of cases.[1,2]
  - Current research indicates acquired aplastic anemia is clonal disorder of HSCs, and advances in molecular and genomic sequencing techniques have shed new light on pathogenesis in terms of associated inflammatory processes, somatic mutations, and cytogenetic and telomerase abnormalities.[3]
- Fanconi anemia: Inheritance usually autosomal recessive but can be autosomal dominant or X-linked recessive. Equally common among males and females, occurs in all ethnic groups. Caused by variations in at least one of 22 genes (including *BRCA1* and *BRCA2*). Estimated 80% to 90% cases due to mutations in *FANCA*, *FANCC*, or *FANCG*. Incidence about 1 in 136,000 births. Equally common among males and females. More common among people of Ashkenazi Jewish descent, black South Africans, Roma population of Spain. Associated with pancytopenia (decreased production of RBCs, WBCs, platelets). Multiple specialists may be involved in patient care (hematologist, oncologist, endocrinologist, immunologist, nephrologist, orthopedist, cardiologist, ophthalmologist, medical geneticist).[4,5]

Onset and Symptoms

- Aplastic anemia: characterized by progressive weakness, pallor, dyspnea, frequent or long-lasting minor infections, sudden febrile illness, ecchymoses, mucosal bleeding, petechiae. No splenomegaly. Pancytopenia often present. Symptom severity variable; some individuals may experience mild symptoms lasting for years while others may have serious symptoms progressing to life-threatening complications.[1,2]
  - About 50% of patients diagnosed < 10 yrs; about 10% diagnosed as adults. Symptoms of bone marrow failure include anemia (often thrombocytopenia, leukopenia), infections, excessive bleeding.
  - Physical features seen in more than half of patients and may include shorter than normal stature; skin patches (café au lait spots); skeletal defects (extra, misshaped, or missing thumbs; incompletely developed or missing radii; anomalies of hips, spine, ribs); CNS, GI, GU, heart, ear, eye defects; endocrine abnormalities; low birth weight.
  - Adult patients at higher risk for solid tumors (especially H&N, skin, GI, GU) and hematologic malignancies, including myelodysplastic syndrome and acute myelogenous leukemia.

Diagnosis

- Aplastic anemia[1]
  - Bone marrow biopsy essential (low yield with aspirate); typically hypocellular and lacking marrow progenitors.
  - Moderate disease, < 30% bone marrow cellularity; severe disease, < 25% cellularity or < 50% cellularity containing < 30% hematopoietic cells; very severe disease, criteria for severe and neutropenia (< 200/μL).
  - Presence of neutropenia (< 500/μL), thrombocytopenia (< 20,000/μL), reticulopodia (< 1%, < 20,000/μL) but no cytologic abnormalities; telomerase mutation in 5% to 10% of adult-onset cases and shortened telomeres in half of patients.
  - Diagnostic criteria: marked marrow hypocellularity (with fat cells and fibrotic stroma replacing normal bone marrow tissue), 2 or more cytopenias.
  - Genetic testing with FISH excludes pancytopenia due to other hematologic malignancies.
- Fanconi anemia[6]
  - Laboratory findings: macrocytosis, increased fetal hemoglobin, cytopenia.
  - Cytogenetic testing of lymphocytes with diepoxybutane and mitomycin C shows increased chromosome breakage and radial forms. Diagnosis confirmed by biallelic pathogenic variants in 1 of 19 genes known to cause autosomal recessive form of disorder; or heterozygous pathogenic variant in *RAD51*, which causes autosomal dominant form; or hemizygous pathogenic variant in *FANCB*, which causes X-linked form.
  - Pathology findings: progressive bone marrow failure, adult-onset aplastic anemia; presence of hematologic malignancies (MDS, AML); early-onset solid tumors; excessive toxicities from radiation therapy, chemotherapy.

Treatment and Pearls

- Aplastic anemia
  - Treatment of patients with no reversible cause (eg, AA due to specific medications, conditions) depends on age, disease severity, performance status, HCT donor availability.
  - Patients 50 y/o and older and young patients w/o HCT donor receive immunosuppressive therapy (eltrombopag, horse/rabbit ATG, cyclosporine A, prednisone) followed by HCT and administration of blood products.
  - Younger patients (< 50 y/o) in good health undergo HCT *before* receiving immunosuppressive therapy.
  - Monitor for common complications such as bleeding, infections, transformation to lymphoproliferative disorders; administer antibiotics, chemotherapy, transfusions as needed.
  - Monitor for secondary hemochromatosis, administer iron chelators as needed.
  - Advise patient to maintain careful personal hygiene (eg, brushing/flossing, regular dental visits) and follow neutropenic diet to protect against infection (ie, exclusion of dairy products, raw meat, most vegetables and fruits); avoid intense physical activities that increase risk of bleeding; start premenopausal patients on hormone treatment to reduce heavy menstrual bleeding common with aplastic anemia.
- Fanconi anemia[6]
  - HSCT is the only curative treatment but may not lower risk for solid tumors. GVHD risk reduced by T-cell depletion of donor graft. Secondary solid tumor risk reduced by conditioning regimen but no radiation prior to HSCT.
  - As with aplastic anemia, monitor for, caution patients about, and address common complications such as bleeding, infections, transformation to lymphoproliferative disorders; administer antibiotics, chemotherapy, transfusions as needed; genetic counseling as appropriate.

  - Oral androgens such as oxymetholone improve RBC, platelet count in about half of patients.
  - HPV vaccination to protect against associated cancers.
- Pearls
  - Bone marrow biopsy essential for diagnosis and to rule out other etiologies.
  - Flow cytometry, cytogenetics, molecular studies to detect for coexistent disorders such as PNH, MDS, or AML.
  - Differential diagnoses include megaloblastic anemia; bone marrow infiltrative disorders; transient bone marrow suppression from cytotoxic drugs, radiation, or viruses; hypoplastic MDS; large granular lymphocytic leukemia.

Prognosis/Outlook

- Aplastic anemia[1]
  - Improved understanding/diagnosis of aplastic anemia pathogenesis due to newer molecular, genomic techniques.
  - Risk of late clonal disease from immunosuppressive therapy, and GVHD/graft failure following HSCT.
  - Survival dependent on age, severity of disease, initial response to treatment. Prognosis significantly improved in past 30 years, due to advances in treatment and supportive care; currently 75% survive 5 years or longer following matched-donor bone marrow transplant. Recovery excellent when disease causes identified and eliminated.
  - Bleeding, infection still major causes of death from aplastic anemia.
- Fanconi anemia[5]
  - As noted, some individuals benefit from HSCT. Increased surveillance for cancer, and management of kidney and hormone problems, are important. Treatment is focused on symptom management.

References

1. Moore CA, Krishnan K. Aplastic Anemia. [Updated 2020 Nov 23]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-.
2. Acquired aplastic anemia. National Organization for Rare Disorders (NORD) Rare Disease Database.
3. Brzeźniakiewicz-Janus, K, Rupa-Matysek J, Gil L. Acquired aplastic anemia as a clonal disorder of hematopoietic stem cells. *Stem Cell Rev and Rep*. 2020;16:472–481.
4. Fanconi anemia. National Organization for Rare Disorders (NORD) Rare Disease Database.
5. Fanconi anemia. National Institutes of Health. National Center for Advancing Translational Sciences. Genetic and Rare Diseases Information Center (GARD).
6. Mehta PA, Tolar J. Fanconi Anemia. 2002 Feb 14 [Updated 2018 Mar 8]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021.

Paroxysmal Nocturnal Hemoglobinuria (PNH)

Etiology and Overview[1-3]

- Acquired clonal disorder previously known as Marchiafava-Micheli disease. Prevalence 0.5–1.5 per million in general population. Males and females equally affected. Can occur at all ages but often affects young adults.
- Caused by somatic mutation of X-linked *PIGA* (phosphatidylinositol glycan class A) gene in hematopoietic stem cells.
- *PIGA* mutation leads to deficiency of production of GPI membrane anchoring proteins CD55 and CD59 on blood cell surfaces, making them more sensitive to complement destruction (due to lack of GPI anchor)[4]
- Pancytopenia. Characterized by premature complement-mediated hemolysis of RBCs (hemolytic anemia; because RBCs lack GPI anchor to anchor on protective proteins CD55 and CD59, they are more sensitive to complement and undergo hemolysis) as well as low levels of WBCs, platelets.
- Blood clots common, hemorrhage less common. Some normal blood production (from normal hematopoietic stem cells) occurs.[5]
- Chronic hemolysis underlies symptoms, which range from mild to life-threatening depending on degree of hemolysis and degree that clots block blood flow to major organs (mainly stomach, liver, brain).
- 15% to 30% develop venous thrombosis, possibly due to defective platelets and chronic hemolysis; continued thrombosis may lead to renal disease (acute, chronic).[6]
- Immune-mediated bone marrow failure rather than hemolysis may be predominant clinical characteristic in some patients.
- Increased risk of infection and (rarely) leukemia, due to effect on leukocytes.
- Repeated testing for PNH recommended for patients with aplastic anemia (with or without bone marrow transplantation) and myelodysplastic syndrome (MDS).

Onset and Symptoms[2]

- Red or dark brown urine often (but not always) noticeable in morning after passing (nocturnal) urine accumulated in bladder during night.
- Clinical manifestations of hemolytic anemia, thrombophilia, bone marrow failure.
- Hemolytic anemia due to reduced RBCs; exacerbated by underlying dysfunction of bone marrow.
- Mild hemolysis: fatigue, headache, cognitive effects, tachycardia, exercise-induced chest pain/dyspnea.
- Severe hemolysis: disabling fatigue; dysphagia; esophageal, abdominal, penile spasms (with latter causing erectile dysfunction); pallor, jaundice.
- Patients may present with visceral thrombosis prior to PNH diagnosis.[5,7,8]

Diagnosis[6,9]

- Patients present with direct antiglobulin (Coombs) test negative, hemolysis, or thrombosis.
  - Hemoglobinuria often a less common presenting symptom.
- Flow cytometric analysis of peripheral blood RBCs, granulocytes, monocytes[10,11]
  - Shows population of cells deficient in glycosylphosphatidylinositol (GPI) anchor protein.
  - Presence of CD59 and/or CD55 on peripheral RBCs useful to determine degree of GPI anchor deficiency.
  - CD59, CD24, CD16 or any other GPI-linked proteins expressed on peripheral blood granulocytes: Deficiency of 2 or more GPI-linked proteins is sensitive and specific for diagnosis of PNH.
  - FLAER (fluorescently labeled inactive toxin aerolysin) binding of peripheral blood granulocytes: Since FLAER binds GPI anchor, lack of FLAER binding sufficient for diagnosis of PNH.
- CBC and reticulocyte count, to evaluate effects on production of leukocytes, platelets.
- Other laboratory abnormalities: cytopenias; signs of intravascular hemolysis (elevated LDH and indirect bilirubin, low haptoglobin), iron deficiency, hemosiderinuria.
- International PNH Interest Group classifies PNH as subclinical (< 10% GPI-AP–deficient PMNs), PNH in bone marrow failure syndrome (< 50% GPI-AP–deficient PMNs), and classic (> 50% GPI-AP–deficient PMNs).

Treatment and Pearls[6,12]

- Eculizumab (long-acting humanized monoclonal antibody targeting complement C5) approved March 2007, to reduce hemolysis; used to treat classic PNH; if inadequate response, adjust dose/frequency, consider BMT in patients who do not respond or who are intolerable to standard treatment, supportive care. Patients with large PNH clones may benefit from eculizumab. International PNH Interest Group notes patients with subclinical PNH do not benefit from eculizumab.
- Ravulizumab-cwvz (long-acting complement inhibitor, prevents hemolysis) approved December 2018 for adults with PNH.
- Pearls
  - Consider workup for PNH in younger patients who present with Coombs-negative hemolytic anemia and/or unprovoked thrombosis.
  - PNH can occur secondary to another bone marrow disorder, including aplastic anemia and MDS.
  - PNH can affect all blood cell lines. Evaluate white cell and red cell lines via flow cytometry.
  - All patients must be vaccinated with meningococcal vaccine before starting complement inhibitor therapy. If unable, begin prophylactic antibiotics.

Prognosis/Outlook

- Improved understanding of molecular basis of PNH has led to development of targeted therapy that has improved prognosis. Better understanding needed of thrombophilia pathobiology in PNH.
- Updated analysis from the International PNH Registry published in 2020 reported on clone size trends and data on disease activity, adverse vascular events, RBC transfusions, bone marrow failure, and symptoms related to PNH.[13]

References

1. Paroxysmal nocturnal hemoglobinuria. National Institutes of Health. US National Library of Medicine. MedlinePlus.gov.
2. Paroxysmal nocturnal hemoglobinuria. National Institutes of Health. National Center for Advancing Translational Sciences. Genetic and Rare Diseases Information Center (GARD).
3. Paroxysmal nocturnal hemoglobinuria. National Organization for Rare Disorders (NORD) Rare Disease Database. Retrieved from Paroxysmal Nocturnal Hemoglobinuria - NORD (National Organization for Rare Disorders) (rarediseases.org)
4. Dal MS, Karakuş A, Ekmen MÖ, et al. Presentation and management of paroxysmal nocturnal hemoglobinuria: A single-center experience. *Hematol Rep*. 2016;8(1):6409.
5. Griffin M, Munir T. Management of thrombosis in paroxysmal nocturnal hemoglobinuria: A clinician's guide. *Ther Adv Hematol*. 2017;8(3):119-126.
6. Parker CJ. Update on the diagnosis and management of paroxysmal nocturnal hemoglobinuria. *Hematology Am Soc Hematol Educ Program*. 2016(1):208-216.
7. Hill A, Kelly RJ, Hillmen P. Thrombosis in paroxysmal nocturnal hemoglobinuria. *Blood*. 2013;121(25):4985-4996.
8. Griffin M, Hillmen P, Munir T, et al. Significant hemolysis is not required for thrombosis in paroxysmal nocturnal hemoglobinuria. *Haematologica*. 2019;104(3).
9. Bessler M, Hiken J. The pathophysiology of disease in patients with paroxysmal nocturnal hemoglobinuria. *Hematology Am Soc Hematol Educ Program*. 2008(1):104-110.
10. Fletcher M, Sutherland DR, Whitby L, et al. Standardizing leucocyte PNH clone detection: An international study. *Cytometry B Clin Cytom*. 2014;86(5):311-318.
11. Richards SJ, Dickinson AJ, Cullen MJ, et al. Presentation clinical, haematological and immunophenotypic features of 1081 patients with GPI-deficient (paroxysmal nocturnal haemoglobinuria) cells detected by flow cytometry. Br J Haematol. 2020;189(5):954-966.
12. Shah N, Bhatt H. Paroxysmal Nocturnal Hemoglobinuria. [Updated 2020 Dec 1]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan.
13. Schrezenmeier H, Röth A, Araten DJ, et al. Baseline clinical characteristics and disease burden in patients with paroxysmal nocturnal hemoglobinuria (PNH): Updated analysis from the International PNH Registry. *Ann Hematol*. 2020;99(7):1505-1514.

Pyruvate Kinase Deficiency (PKD)

Etiology and Overview[1-3]

- Rare autosomal recessive chronic disorder of unknown frequency caused by mutations in *PKLR* resulting in pyruvate kinase deficiency and impaired glycolysis, leading to alteration and premature destruction of RBCs (hemolytic anemia). Affects males and females. RBCs with PKD last weeks or several days, whereas normal RBCs last about 120 days.
- Fetal hydrops, from fluid buildup in fetal tissues and organs, occurs; heart must pump higher blood volume than normal to deliver sufficient oxygen to tissues.
- Kernicturis in infants, neurologic condition due to toxic levels of bilirubin.
- Jaundice (due to high bilirubin levels) common in newborns.
- Life-long risk of gallstones due to increased levels of unconjugated bilirubin; other complications include pulmonary hypertension, osteoporosis, extramedullary hematopoiesis, iron overload.
- Anemia common finding in children and adults.

Onset and Symptoms[3]

- Highly variable; symptoms may be severe and apparent at birth in some patients but milder and manifest later (during childhood, adulthood) in others.
- Hemolytic episodes caused by stressors (such as pregnancy) and infections; common parvovirus B19 infection (also known as “fifth disease”) can trigger aplastic crisis by sharply reducing hemoglobin level, often requiring blood transfusion.
- Splenomegaly
- Iron overload in liver, heart, endocrine organs can cause symptoms once significant iron deposits have occurred.
- Other complications: bone fragility, skin ulcers (especially around ankles); less commonly, pulmonary hypertension and extramedullary hematopoiesis.

Diagnosis[3]

- Clinical testing to determine patient has anemia due to hemolysis (low Hb level, elevated level of conjugated bilirubin; elevated reticulocyte count, low haptoglobin level).
- Standard test for PKD (performed at specialized laboratories): measurement of pyruvate kinase activity in RBCs; low activity indicates PKD.
- Molecular genetic testing (performed at specialized laboratories) indicating *PKLR* mutation known to cause PKD.

Treatment and Patient Education[2,3]

- Allogeneic hematopoietic stem cell transplant (HSCT) curative; however, given high mortality risk associated with HSCT, splenectomy preferred.
- Individualized treatment plans recommended due to high symptom variability.
- Phototherapy for infants with bilirubinemia; facilitates faster bilirubin metabolism and excretion.
- Splenectomy (to help reduce RBC destruction) for patients (5 years and older) who require frequent blood transfusions or have frequent symptoms of anemia; cholescystectomy may be considered at time of splenectomy and in patients with symptomatic gallstones.
- Splenectomy patients should receive pneumococcal vaccine at recommended intervals.
- Mitapivat (pyruvate kinase-R activator) carries orphan drug designation for treatment of PKD.
- Supportive care: gallbladder monitoring for gallstones; folic acid supplementation to support RBC production; vitamin D, calcium, exercise to support bone health.
- Genetic counseling recommended for patients and families.

Prognosis/Outlook

- Treatment remains supportive rather than curative.
- Because current knowledge of HSCT in PKD is derived predominately from animal studies, and guidelines are lacking, HSCT should be considered investigational treatment. Worldwide study of HSCT in PKD found strong decline in survival of treated PKD patients treated with HSCT over age of 10 years. Authors conclude this "suggests the need to evaluate HSCT as a treatment option early in life," but note transfusion dependency alone should not be indication for performing HSCT in PKD.[4]
- Mitapivat in phase 3 ACTIVATE-T trial in 27 regularly transfused adults with PKD met primary endpoint of statistically significant and clinically meaningful 33% reduction in predefined transfusion burden. Results announced January 2021. ACTIVATE, a global, randomized, double-blind, placebo-controlled phase 3 trial of mitapivat in adults with PKD who do not receive regular transfusions also met its primary endpoint; 40% percent of patients randomized to mitapivat achieved Hb response, defined as a ≥1.5 g/dL sustained increase in Hb concentration from baseline, compared with 0 patients randomized to placebo. Results announced December 2020. Manufacturer (Agios) anticipates filing for regulatory approval based on ACTIVATE and ACTIVATE-T data in the US and Europe in Q2 2021 and mid 2021, respectively.[5]

References

1. Pyruvate kinase deficiency. National Institutes of Health. US National Library of Medicine. MedlinePlus.gov.
2. Pyruvate kinase deficiency. National Institutes of Health. National Center for Advancing Translational Sciences. Genetic and Rare Diseases Information Center (GARD).
3. Pyruvate kinase deficiency. National Organization for Rare Disorders (NORD) Rare Disease Database.
4. van Straaten S, Bierings M, Bianchi P, et al. Worldwide study of hematopoietic allogeneic stem cell transplantation in pyruvate kinase deficiency. *Haematologica*. 2018 Feb;103(2):e82-e86.
5. Agios reports data from phase 3 ACTIVATE-T trial of mitapivat in regularly transfused adults with PK deficiency. [written by TrialSite staff, January 29, 2021] TrialSiteNews,com.