NOTES
CONGENITAL ANEMIA

GENERALLY, WHAT IS IT?

PATHOLOGY & CAUSES

- Inherited macrocytic-normochromic anemias
  - Diamond–Blackfan anemia
  - Fanconi anemia

COMPLICATIONS

- Congenital anomalies, ↑ blood malignancy risk, solid tumor cancers

SIGNS & SYMPTOMS

- See individual disorders

DIAGNOSIS

- See individual disorders

TREATMENT

- See individual disorders

CONGENITAL ANEMIAS

	DIAMOND–BLACK ANEMIA	FANCONI ANEMIA
INHERITANCE PATTERN	Autosomal dominant	Autosomal recessive or X-linked
EFFECT OF GENETIC MUTATION	Ribosomopathy	Chromosome fragility
RBC CHARACTERISTICS	Macrocytic-normochromic	Macrocytic-normochromic
ANEMIA ONSET	Often apparent at birth	Diagnosis around age 8
ADDITIONAL CYTOPATHIES	No	Pancytopenia
CONGENITAL ANOMALIES	Present	Present
MALIGNANCY RISK	Increased	Increased
SPECIFIC TESTING	Elevated eADA	Chromosome breakage assay
TREATMENT	Corticosteroids, blood transfusions, stem cell transplant	Androgens, blood transfusions, stem cell transplant

DIAMOND–BLACKFAN ANEMIA (DBA)

osms.it/diamond-blackfan-anemia

PATHOLOGY & CAUSES

- Autosomal dominant ribosomopathy resulting in inherited bone-marrow failure syndrome, macrocytic-normochromic anemia, associated congenital anomalies
- Genetic mutation → ribosomopathy → impaired hematopoiesis → red blood cell aplasia → macrocytic-normochromic anemia
  - No other significant cytopathies evident
  - Sporadic, unpredictable penetrance → high degree of genotypic heterogeneity → variety of possible congenital anomalies

COMPLICATIONS

- Genetic predisposition to malignancies like myelogenous leukemia, myelodysplastic syndrome, solid tumors
- Congenital anomalies increase complication risk

SIGNS & SYMPTOMS

- Anemia often present at birth → signs and symptoms of impaired oxygen-carrying capacity (e.g. pallor, tachycardia, apnea, lethargy)
- Low birth weight, evidence of growth restriction usually present

Congenital anomalies

- *Craniofacial:* low-set ears, micrognathia, high-arched/cleft palate, broad nasal bridge
- *Neck:* short, may be webbed
- *Ophthalmological:* congenital glaucoma, cataracts, strabismus
- *Thumbs:* duplex/bifid; flat thenar eminence
- *Urogenital:* absent/horseshoe kidney
- *Cardiac:* ventricular/atrial septal defect, coarctation of the aorta

DIAGNOSIS

- DBA usually diagnosed within first month of life

DIAGNOSTIC IMAGING

Renal imaging/echocardiography

- Find internal congenital anomalies

LAB RESULTS

- Complete blood cell count (CBC) with red blood cell indices
  - ↓ red blood cell count, hemoglobin, hematocrit
  - Reticulocytopenia
  - ↑ mean corpuscular volume (MCV)
  - Normal mean corpuscular hemoglobin (MCH), white blood cell, platelet counts
- Bone marrow aspirate normal, except few/no erythroid precursors
- Serum erythropoietin, fetal hemoglobin (HbF) increased secondary to stress hematopoiesis
- Elevated erythrocyte adenosine deaminase (eADA)

OTHER DIAGNOSTICS

- Classical physical congenital anomalies associated with DBA
- Genetic testing, family history

TREATMENT

- 25% chance of spontaneous remission

MEDICATIONS

Corticosteroids

- Hemoglobin ↑ observed after steroid therapy initiation
- Weigh dose, duration of steroid treatment against adverse effects (e.g. growth disturbances, adrenal suppression, immunosuppression, pathological fractures)

SURGERY

Curative

- Allogeneic hematopoietic stem cell transplant

OTHER INTERVENTIONS

- Monitor for development of malignancies
- Specialist care (e.g. cardiology, nephrology, urology)
- Family support, genetic counseling

Transfusions

- Packed red blood cells
  - Maintain Hgb ≥ 8g/dL
  - Must be leukocyte poor to decrease transmission of cytomegalovirus
  - Monitor for iron overload, hemosiderosis

FANCONI ANEMIA (FA)

osms.it/fanconi-anemia

PATHOLOGY & CAUSES

- Autosomal recessive/X-linked disorder of chromosome fragility causing inherited bone marrow failure syndrome, macrocytic-normochromic anemia, pancytopenia

Physical abnormalities

- Short stature, malformations associated with the VACTERL-H (vertebral, anal, cardiac, tracheoesophageal, renal, limb and hydrocephalus) association
  - Microcephaly, congenital heart disease, imperforate anus, conductive deafness, hypogenitalia, cafe-au-lait spots

CAUSES

- Mutation of several genes responsible for DNA repair
  - Impaired cellular repair of DNA cross-links → impaired regulation of cell cycle, genomic instability → hematopoietic stem cell loss → macrocytic-normochromic anemia → bone marrow aplasia → pancytopenia
  - Predisposition for development of blood/solid tumor malignancies
- Bone marrow biopsy usually normocellular at birth
- Macrocytic-normochromic anemia and other cytopenias develop gradually → usually diagnosed within first eight years of life

COMPLICATIONS

- *Neutropenia:* life-threatening infections
- *Thrombocytopenia:* bleeding tendencies
- *Malignancies:* e.g. myelogenous leukemia, myelodysplastic syndrome, solid tumors
- *Endocrine derangements:* hypothalamic-pituitary axis disruption during fetal development
- Congenital anomalies

SIGNS & SYMPTOMS

- Cytopenias develop → clinical manifestations → increased bruising/bleeding, frequent infections
- Symptomatic anemia related to impaired oxygen-carrying capacity develops late in disease

DIAGNOSIS

- History, physical examination

LAB RESULTS

- CBC assessment, bone marrow examination

FA testing indicators

- Evidence of single-/multilineage cytopenias with no other identified cause
  - ↓ absolute neutrophil count, platelet count, absolute reticulocyte count, hemoglobin
- Hypocellular bone marrow (without evidence of malignancy/other known cause)
- Congenital anomalies
- *Family history:* people of Ashkenazi Jewish descent have ↑ carrier frequency

FA-specific testing

- Chromosome DEB assay
  - Laboratory test for chromosomal breakage performed on leukocytes (indicates chromosome instability syndrome; not FA-specific)
- Cytometric flow analysis
  - Examines cellular growth, division; cytometry following DNA crosslinking shows cells unable to repair DNA damage, cellular arrest in cell cycle G2 phase
- Chromosomal breakage test positive → FA gene sequencing recommended

TREATMENT

MEDICATIONS

Growth factors

- Granulocyte colony-stimulating factor (G-CSF)
- Granulocyte-macrophage-stimulating factor (GM-CSF)
- Thrombopoietin mimetics (e.g. romiplostim)

Androgen therapy

- (e.g. oxymetholone) sometimes ↑ blood cell count

SURGERY

Bone marrow failure

- Allogeneic hematopoietic stem cell transplant

OTHER INTERVENTIONS

- Screen, monitor for malignancies
- Specialist care (e.g. cardiology, nephrology, endocrinology)
- Family support, genetic counselling

Transfusions

- Leukoreduced, irradiated packed red blood cells
  - Symptomatic anemia
  - Hemodynamic instability
- Platelet transfusions
  - Platelet count < 10,000/microL
  - Evidence of severe bruising, bleeding