Anemia	Classification	Etiology	Pathophysiology and Presentation	Lab Findings and Diagnosis	Treatment
HYPOPROLIFERATIVE ANEMIAS					
IRON DEFICIENCY ANEMIA	Normocytic anemia progressing to hypochromic microcytosis **THE MOST COMMON ANEMIA WORLDWIDE**	**Adult men** and **Post-menopausal women:** GI blood loss Gastric and duodenal ulcers, IBD, gastric or colonic carcinoma, hemorrhoids, aspirin. **Infants and peds:** normal negative iron balance during development **Other diseases:** celiac (sprue), gastric bypass, duodenal resection, GI parasites, secondary to intravascular hemolysis	**Decreased exercise capacity** **Cheilosis:** seen in severe deficiency **Koilonychia** **Delayed sensory, motor, and linguistic development in peds** **Pica** (e.g. pagophagia)	**SERUM** Decreased serum iron **Increased TIBC** Decreased transferrin saturation **Decreased serum ferritin** **PERIPHERAL SMEAR** NO RETICULOCYTOSIS Microcytosis (MCV > 80 fL) Hypochomism **MARROW ASPIRATE and Bx** **NML or increased G:E**	Oral iron therapy Parenteral iron
THE ANEMIA OF INFLAMMATION ANEMIA OF CHRONIC DISEASE	Normocytic anemia progressing to hypochromic microcytosis **THE MOST COMMON ANEMIA in HOSPITALIZED PATIENTS**	**Underlying Inflammatory Disease** Pneumonia, malignancy, autoimmune	Bacterial polysaccharides or IL-6 → increased hepatic hepcidin expression → inhibition of ferroportin →sequestration of iron in macrophages + enterocytes → increased storage iron and decreased transfer pool	**SERUM** Decreased serum iron **Decreased TIBC** Decreased transferrin saturation **Decreased serum ferritin** **PERIPHERAL SMEAR** Identical to iron-deficiency anemia	Tx underlying disease EPO therapy DOES NOT RESPOND TO EXOGENOUS IRON
LOW EPO ANEMIA ANEMIA OF CKD	Normocytic normochromic	**Chronic Kidney Disease (CKD)** **Endocrine:** Hypothyroidism, Hypopituitarism **Malnutrition** **Right Bohr Shift**	Predisposition towards infection Ecchymosis Epistaxis Anemic symptoms (fatigue, pallor)	**PERIPHERAL SMEAR** **NO RETICULOCYTOSIS** due to lack of EPO Replacement of medullary stroma by adipose CBC: pancytopenia	IM recombinant EPO

APLASTIC ANEMIA	Pancytopenic marrow failure	**Hereditary** Fanconi Anemia **Idiopathic:** currently thought to be autoimmune, involving cell-mediated attack on marrow precursors **Secondary:** radiation, benzene, DDT, myelosuppressive chemotherapy, EBV, Parvovirus B19		**SERUM** **INCREASED** serum iron due to aplasia of marrow stem cells **PERIPHERAL SMEAR** NO RETICULOCYTOSIS Microcytosis (MCV > 80 fL) Hypochomism **MARROW ASPIRATE and Bx** **NML or increased G:E**	ABx Transfuse RBCs Platelets ISD (cyclosporine, GCs, ATG) Allogenic bone marrow transplant
HEMORRHAGIC ANEMIAS					
BLOOD LOSS ANEMIA	Normocytic normochromic Hemodilution effect	**Hemeorrhage** The decreased Hct is due to hemodilution (due to transfusion with colloid or EXCF and ICF volume shifts)	**ACUTE:** no change in RBC count due to lack of ECV expansion **CHRONIC (> 7 d):** Increased erythrpoesis and marrow expansion	**PERIPHERAL SMEAR** NO RETICULOCYTOSIS until > 7 d. after blood loss anemia **MARROW ASPIRATE and Bx** **Decreased G:E** due to erythropoesis	Transfuse while blood or packed cells
MACROCYTIC ANEMIAS					
PERNICIOUS ANEMIA	Megaloblastic macrocytic Ineffective erythropoesis	**Autoimmune atrophic gastritis** Mediated by autoAbs to gastric parietal cells, and to IF Results in lack of absoption of B12 **Hereditary** AR inheritance. LOF mutation in IF.	Associated with: myxedema (hyperthyroidism), DM, gastritis Achlohydria, achylia, rugal atrophy Glossitis + atrophic papillae (smoot erythematous appearance) **Neurologic deficits**: diminished vibratory sense (dorsal columns), loss of proprioception (dorsal columns and DCST), spastic paralysis (LCST) Parasthesia	**Anti-parietal Abs**: high sensitivity and low specificity **Anti-IF Abs**: low sensitivity and high specificity Serum LDH and bilirubin are increased Peripheral smear shows canonical signs **Direct serum B12 levels (low specificity)** Should be considered in all	If treated with folate solely: leads to progression of neurological decline IM B12 Folate supplement

			Incoordinated nocturnal ambulation (due to loss of proprioception) *Megaloblastic Madness:* incontinence, dementia, spasticity of lower extremities	patients with unexplained dementia or neuropathy Schilling Test: can be used to measure absorption of B12 by quantifying urinary excretion of free radiolabled substrate	
B12 DEFICIENCY	Megaloblastic macrocytic with nutritional cause	Pernicious Anemia (leading cause) Blind Loop Syndrome (diverticula or surgical manipulation results in bacterial overgrowth) Dietary: strict veganism Chronic pancreatitis or CF Resected ileum Crohn's Disease (regional ileitis) Tapeworm infection Transcobalamin II deficiency	B12 is involved in two critical reactions **Conversion of methylmalonyl-CoA to succinyl-coA** Deficient mutase activity is the main cause of neurologic disease **Conversion of homocysteine to methionine** Met deficiency results in demylination of the DCs and LCST *but* neurologic disease is not seen in folate deficiency	**SERUM** Increased MMA Increased homocysteine Increased LDH Increased direct bilirubin due to medulalry hemolysis **PERIPHERAL SMEAR** CBC: pancytopenia is *severe deficiency* **Non-elevated reticulocyte count** (ineffective erythropoeisis) **Hypersegmented neutrophils** **Macrocytes** **Circulating megaloblasts** **MARROW ASPIRATE and Bx** Demonstrates evidence of **ineffective erythropoesis** due to apoptotic destruction of erythroid in the marrow **Megaloblastosis:** immaturity of nuclei in erythroid and myeloid precursors **Hypercellularity** in the erythroid and myeloid lines **Giant band cells** Macrocytosis and N:C dissociation in most mitotic	

				labile cells	
FOLATE DEFICIENCY		Dietary: lack of vegetables and dairy Malabsorption: celiac disease, deconjugase deficiency Pregnancy Hemolytic Anemia Alcoholism: decreased intake, decreased absorption, cirrhosis and decreased storage Phenytoin Medications: methotrexate, TMP-sulfa		All findings are identical to B12 deficiency BUT **MMA is not elevated**	

HEMOLYTIC ANEMIAS

General Features of Hemolysis

Anemia results with the RBC lifespan < 20 d.

Aplastic crisis may occur with chronic hemolytic anemia and infection with Parvovirus B19

- Results in a flu-like illness with transient erythrocyte aplasia

Results in folate deficiency due to increased erythropoeisis

Expanded medullary space may result in skeletal deformities (hereditary hemolytic anemias)

- Severe hereditary hemolysis results in extramedullary hematopoeisis and tumor-like lesions on the axial skeleton.

Kernicterus: hemolytic anemiain neonates results in deposition of direct bilirubin in the basal ganglia.

Gallstones: seen in chronic hemolysis

Iron overload: results from increased absorption (decreased hepcidin) and repeated transfusion

- **Seen in extravascualr hemolysis** since no iron is lost
- Hemosiderosis is rare in chonic hemolysis

Disseminated Intravascular Coagulation (DIC): seen in acute intravascular hemolysis due to liberation of RBC phospholipids

- In ABO reactions, complement activation results in shock

HEREDITARY SPHEROCYTOSIS (HS)	AD inheritance Extravascular Hemolysis	Mutations within the ankyrin gene (chromosome 8) → deficit in spectrin → progressive membrane loss	In newborns: kernicterus Throughout NH: bilirubin gallstones Cholecystitis is an early indicator of HS	**SERUM** Increased indirect bilirubin Increased LDH **PERIPHERAL SMEAR** **Spherocytes > 20%:** round cells	Splenectomy if > 5 yrs Pneumococcal vaccine

				without central pallor May not be apparent **Reticulocytosis** A rapid screening test for relatives of HS index case **Increased osmotic fragility:** lysis occurs at 0.65% saline **MARROW ASPIRATE and Bx** Hypercellularity	
TRAUMATIC HEMOLYTIC ANEMIA	Intravascular Hemolysis	**Microvascular endothelial damage**: vasculitis, malignant HTN **Cardiac**: valve prostheses (aortic, mitral) with fibrin deposition, aortic valve dissection **Microangiopathic Hemolytic Anemia**: deposition of fibrin and platelet plugs in small vessels **TTP**: microthrombi result in renal failure, neurological deficits, fever, thrombocytopenia, and MHA **HUS**: in peds, occurign after viral URIs and EHEC DIC, disseminated carcinoma, pre-eclampsia	Cardiac valve hemolysis is typically asymptomatic and compensatesd	**SERUM** Increased indirect bilirubin Increased LDH Decreased TIBS and saturation (iron depletion) **PERIPHERAL SMEAR** **Schistocytes:** diagnostic of traumatic hemolysis. These are RBC fragments. **MARROW ASPIRATE and Bx** Hypercellularity **URINE** Hemosiderinuria Hemoglobinuria Methemoglobinuria	
PYRUVATE KINASE DEFICIENCY	AR inheritance Extravascular Hemolysis MOST COMMION GLYCOLYTIC DEFECT Affects Northern Europeans	PK deficiency → increased intracellular 2,3 DPG due to flux through the Rapaport-Luebering pathway → increased peripheral O2 delivery → anemic tolerance	Chronic hemolytic anemia Infancy and peds: anemia and jaundice		
G6PD DEFICIENCY	X-linked inheritance	Deficient G6PD → depletion of NADPH → depletion of GSH pools and catalase → oxidation of HgB	**GDPD B:** normal WT variant **GDPD A:** variant with normal function. Used to verify that tumor	Direct assay of RBC G6PD activity	

	Mixed intravascular and extravascular hemolysis MOST COMMON RBC METABOLIC DEFECT Affects Africans, Med basin, Middle East	and membrane SH → formation of disulfide bridges between globin and RBC membrane → Heinz bodies → non-deformability → extravascular hemolysis With severe oxidative stress: oxidation of membrane SH results in perforation and intravascular hemolysis Drugs may trigger hemolysis in the oxidative variants of G6PD deficiency: Sulfamethoxizole Nitrofurantoin Primaquine Dapsone	cells are monoclonal. **Chronic congentical hemolytic anemia variants**: mutation occurs at NADP binding site **Oxidative variants**: result in acute episodes of hemolysis during stress (e.g. infection) *G6PD A⁻:* African variant. Mutation results in shorted half-life. Only older cells hemolyze upon stress, so anemia is self-limiting in the face of oxidation. *G6PD Med*: the half-life is drastically reduced. Stress results in severe intravascular hemolysis with anemia, hemoglobinuria, and jaundice. Most patients with oxidative variants are asymptomatic!	In *G6PD A⁻*, test must be delayed for several weeks after hemolysis to allow for repopulation of sensescent cells In *G6PD Med*, the assay may be done at any time	
ANEMIAS OF DISORDERD GLOBIN SYNTHESIS					
SICKLE CELL DISEASE (SCD)	Chronic Extravascular Hemolysis **Most common genotypes:** $B^{S}\beta^{S}$, $\beta^{S}\beta^{0}$, $\beta^{S}\beta^{C}$ **Sickle Trait:** HbAS Typically asymptomatic Polyuria due to medulalry gradient collapse Painless hematuria Sickling with severe dehydration or altitidue	**Glu6 → Val** substitution in the β subunit of HbA. Results in polymerization of the deoxegenated form of HbS. Repeated sickling and expansion results in permanent cellular deformity. Vasoocclusive episodes are provoked by: Acidosis Increased 2,3 DPG Hypoxemia Low HbF	**Hemolytic Anemia** **Vaso-occlusive crises** Sickled cells are prone to conglomeration in the small vessels Hemolysis liberates heme, depleting NO and arginine (via release of arginase). Vasoconstriction Platelet aggregation Endothelial activation *Recurrent painful crises* (typically dactylitis) Requires hospitalization and transfusion if vasoocclusive *Acute Chest Syndrome*: tachypnea, hypoxia, pain, fever, cough, infiltrates.	**PERIPHERAL SMEAR** Sickled Cells HJ Inclusions Targetoid cells Anisocytosis, Poikilocytosis Reticulocytosis **ELECTROPHORESIS** HbSS, HbS + HbA2, HbSC Charge variation allows for good separation of various Hb.	**Management of painful crises**: Analgesics (narcotics), hydration, NSAIDs, supplemental O2, exchange transfusion **Prophylactic PCN** **Pneumovax** **Hydroxyurea** (increases HbF) **Iron chelation** Allogenic bone marrow

	Renal papillary necrosis $\beta^S\beta^0$ results in severe anemia Heterozygosity with α thalessemia trait decreases HbS concentrations		Resembles ARDS. Associated with local or remote infection. *Stroke:* subclinical infarction *Chronic ischemic damage:* Aseptic osteonecrosis of the femoral head, Pulmonary HTN CKD, Retinopathy **Functional Asplenia** Predisposition to infection and sepsis Splenic autoinfarction leads to stabilization of acute anemia (decreased sequestration) The disease typically becomes symptomatic > 6 mo. due to conversion to β chain synthesis.	**SERUM** Increased indirect bilirubin Increased LDH	transplantation
αTHALASSEMIA SYNDROMES	Hypochromic microcytic Ineffective erythropoeisis Chronic extravascular hemolysis	Typically involve deletion of α globin alleles (chromosome 16).	**α thalassemia carrier** αα/α- Asymptomatic without anemia Elevated Bart's hemoglobin (γ_4) **α thalassemia trait** α-/α-: prevalent in Med and Africa Increased incidence of thalessemia trait and silent carriers α-/α- and αα/-- : prevalent in East Asia Increased incidence of HbH disease and hydrops fetalis Hypochromic microcytosis Negligible anemia **HbH disease** α-/-- Chronic extravascualar hemolytic anemia due to HbH (β_4) inclusions	**α thalassemia syndromes** All hemoglobins are affected May detect Bart's hemoglobin	**HbH disease** Transfusion if necessary Folci acid supplement Splenectomy

			Hypochromic microcytosis Hemolysis is typically compensated Targetoid cells Oxidant drugs provoke hemolysis **Hydrops Fetalis** **--/--** Most Hb is Bart's (high O2 affinity and low delivery) Mortality is due to hepatic failure (ischemia and extramedullary hemaptopoeisis)		
β THALASSEMIA SYNDROMES	Hypochromic microcytic Ineffective Erythropoesis Chronic extrvascualr hemolysis	Various mutations within the β globin coding region of chromosome 11 → decreased synthesis (Typically not a deletion)	**β thalessemia minor** (Hb > 9 d/dL) Typically β/β+ Asymptomatic with negligible anemia DESPITE microcytosis (r/o iron deficiency and inflammation) **β thalessemia intermedia** (Hg 6 -9 g/dL) Typically β+/β+, β+/β^0, β/β^0 Microcytic anemia with several aberrant RBC morphologies (targetoid, nucleated blasts) **β thalessemia major** (Hb < 6 g/dL) β^0/β^0 α_4 hemoglobin precipitates, resulting in Ineffective erythropoeisis Extravascualr hemolysis Severe microcytic anemia Hepatospenomegaly Marrow expansion and bone deformity Increased GI iron absorption and transfusion hemochromatosis	**β thalessemia minor** Increased HbA2 (> 3%) Increased HbF Most hemoglobin is HbA **β thalessemia intermedia** HbF 10 – 90% and HbA2 > 3% Decreased HbA **β thalessemia major** Absence of HbA Only detect HbF + HbA2	Screen maternal MCV and ferritin **Suspect thalessemia with microcytosis and NML ferritin** **β thalessemia intermedia** Transfusion if necessary Folci acid supplement Splenectomy **β thalessemia major** Transfusion Iron chelation Allogenic stem cell transplant Splenectomy