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Benign Hematology Updates

Benign Hematology BASICS 101

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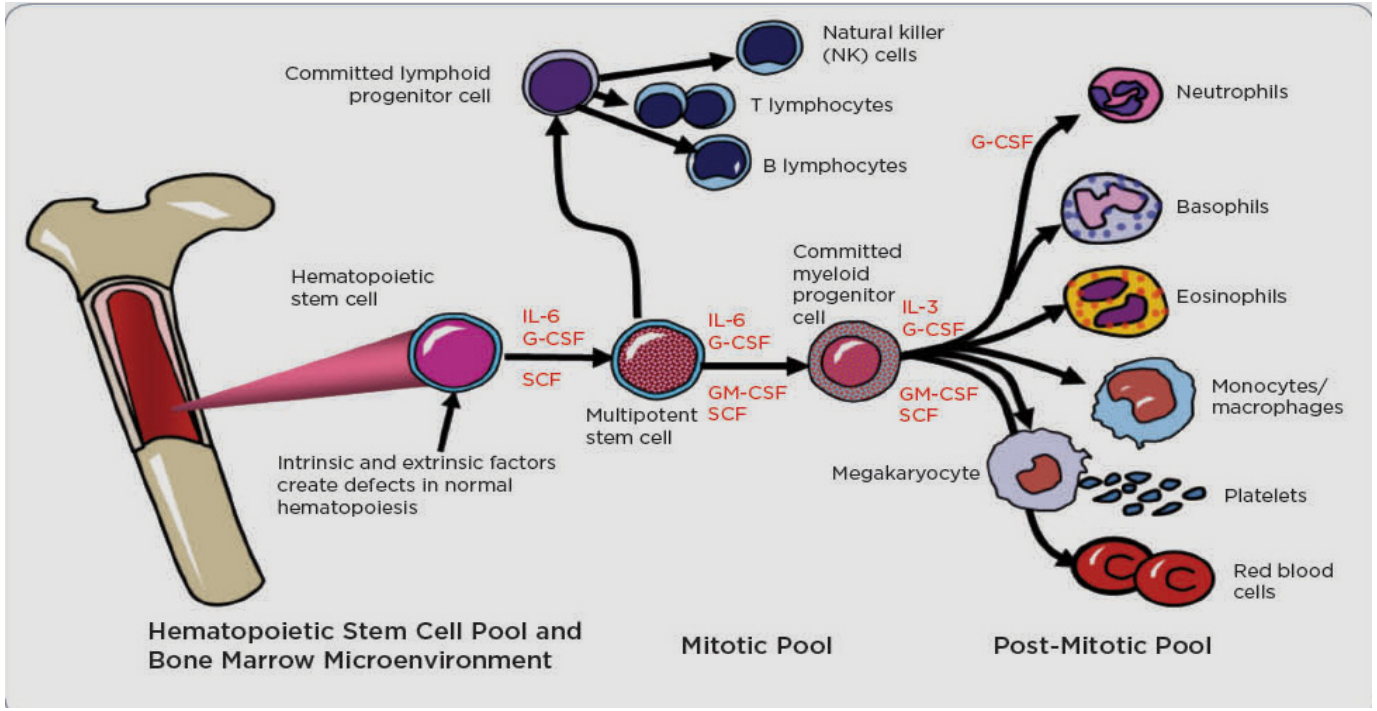
Hematopoiesis

Understanding normal hematopoiesis is essential to the differential diagnosis of abnormal blood counts



The bone marrow is the primary source for development of the components of blood (hematopoiesis), including myeloid and lymphoid progenitor cells (see figure). Hematopoiesis occurs primarily in the axial skeleton, with most production taking place in the pelvis (70%– 72%), the long bones such as the femurs, the skull, the sternum, the ribs, and vertebral bodies. Extramedullary hematopoiesis, or production of the elements of blood outside the bone marrow, may occur in the spleen and other accessory sites in selected disease states such as the myeloproliferative disorders and chronic leukemia.

Kurtin S. *J Adv Pract Oncol*. 2012;3(4):209-224.

Key Elements of the Myeloid Lineage
Bone marrow, mitotic pool: Intrinsic features

- Hematopoietic stem cells
  - Multipotent with self-renewal capacity, few in active division
  - Insensitive to standard chemotherapy or growth factors
  - Cytokine sensitivity: G-CSF, SCF, IL-6
- Myeloid progenitor cells
  - Committed to myeloid lineage, CFU-GEMM, differentiates into postmitotic pool: erythroid, granulocyte/macrophage, and megakaryocytic/platelet cell lines
  - CD34+ cells stimulated and collected for stem cell transplantation. Cytokine sensitivity: G-CSF, SCF, IL-6, EPO
- Cytogenetics and molecular attributes
  - Chromosomal and molecular attributes have prognostic significance in all hematologic malignancies and play a primary role in abnormal clonal evolution and ineffective hematopoiesis

CFU-GEMM = colony-forming unit–granulocyte, erythrocyte, monocyte, megakaryocyte; EPO = erythropoietin; G-CSF = granulocyte colony-stimulating factor; IL-6 = interleukin 6; SCF = stem cell factor

Kurtin S. *J Adv Pract Oncol*. 2012;3(4):209-224.

Key Elements of the Myeloid Lineage
Bone marrow microenvironment: Extrinsic features

- Elements form the bone marrow niche
- Trabecular bone
  - Rich in osteolineage cells (osteoblasts and osteoclasts), which play a role in regulation of HSC activity
  - Mediated by cytokines active in stroma and cytokine milieu (in particular, erythropoietin and IL-6) as well as parathyroid hormone and TNFα
  - Mesenchymal cells may play a role in nervous system regulation of hematopoiesis
  - Abnormal characteristics may contribute to tumorigenesis
- Stroma (bone marrow vascular niche)
  - Reticular perivascular cells, reticulin fibers, fibroblasts, adhesion molecules, adipocytes, iron stores
  - Rich in cytokines and hormones such as VEGF and TNFα, which play a role in regulating hematopoiesis
  - Sensitive to paracrine- and autocrine-mediated cytokines as well as exogenous exposure to cytokines and stress hormones
  - Abnormal characteristics may contribute to tumorigenesis, may serve as sanctuary site for leukemic stem cells
- Cytokine milieu
  - Glycoproteins that bind to cell surface receptors; includes IL-3, IL-6, SCF, G-CSF, EPO, TPO

EPO = erythropoietin; G-CSF = granulocyte colony-stimulating factor; HSC = hematopoietic stem cell; IL-3 = interleukin 3; IL-6 = interleukin 6; SCF = stem cell factor; TNFα = tumor necrosis factor alpha; TPO = thrombopoietin; VEGF = vascular endothelial growth factor

Kurtin S. *J Adv Pract Oncol*. 2012;3(4):209-224.

Key Elements of the Lymphoid Lineage

- Lymphocyte development requires the concerted action of a network of cytokines and transcription factors that positively and negatively regulate gene expression
- B lymphocytes (bursal or bone marrow–derived)
  - Express clonally diverse cell surface immunoglobulin (Ig) receptors recognizing specific antigenic epitopes required for antigen presentation
  - Involved in adaptive immunity through antibody production by terminally differentiated plasma cells
  - Play a role in wound healing, transplant rejection, tumor immunogenicity, dendritic cell regulation, lymphoid organ organogenesis, costimulation with T lymphocytes
  - Contribute substantially to multiple human autoimmune diseases
- T lymphocytes (thymus-derived)
  - Allow the immune system to recognize and fight intracellular pathogens
  - Express T-cell antigen receptor (TCR) on their cell surface that is encoded by a distinct set of genes
  - CD8-expressing effector T cells (CD8+ T cells) can induce death of infected or otherwise damaged/dysfunctional cells.
  - CD4-expressing effector T cells (CD4+ T cells) interact with antigen MHC class II complexes that are mostly expressed by immune cells during an immune response through secretion of wide collection of cytokines and can display both effector and regulatory properties

CD4 = cluster of differentiation 4; CD8 = cluster of differentiation 8; MHC = major histocompatibility complex

LeBien TW, et al. *Blood*. 2008;112(5):1570-1580; Moser M, et al. *Vaccine*. 2010(28s):C2-C13.

Basic Principles of Benign Hematology

- Patients referred for benign hematology consultation generally have blood counts that are out of range
  - Red blood cell: anemia, erythrocytosis
  - White blood cell: leukopenia, lymphopenia, neutropenia, lymphocytosis, neutrophilia, monocytosis, eosinophilia, basophilia
  - Platelets: thrombocytopenia, thrombocytosis
- Cytopenias or elevated elements of the CBC, differential, and platelet count may be a result of:
  - A bone marrow production problem (too few or too many)
  - A peripheral destruction process
  - A combination of both
- Underlying disorders may be:
  - Primary – either acquired or hereditary
  - Secondary – reactive to other underlying diseases or processes

CBC = complete blood count

The Role of Advanced Practitioner in the Diagnosis and Management of Benign Hematology Disorders

- Differential diagnosis should include
  - Review of past medical history
    - Possible hereditary disorders or comorbidities commonly associated with secondary processes
    - Medications that may contribute to acute processes
    - Any recent acute events/hospitalizations
  - Review of symptoms and H&P
    - Presenting signs and symptoms are related to the cell line(s) involved and/or mediating factors including growth factors, transcription factor signaling pathways, and coagulation pathways
    - Historic laboratory analysis to establish chronicity of changes
    - Physical exam should include focused skin examination, evaluation for presence of hepatosplenomegaly, adenopathy, or cardiac abnormalities
    - Review of any previous imaging for underlying processes: adenopathy, organomegaly, cirrhosis, aortic stenosis, hemosiderosis, etc.
- Diagnostic testing should be ordered based on the cell line(s) affected and presenting signs and symptoms

H&P = history and physical

Selected Benign Hematology Diagnoses With Recent Clinical and Therapeutic Developments

Hereditary/Acquired Bleeding Disorders	Autoimmune Cytopenias and Bone Marrow Disorders	Hemoglobinopathies	Bone Marrow Failure Disorders
Hemophilia	Autoimmune hemolytic anemia (AIHA)	Sickle cell disease	Aplastic anemia
von Willebrand disease (VWD)	Immune thrombocytopenia (ITP)	Beta-thalassemia	Paroxysmal hemoglobinuria (PNH)
	Hemophagocytic lymphohistiocytosis (HLH)		Pyruvate kinase deficiency (PKD)
	Castleman's disease		
	Mastocytosis		

Hereditary and Acquired Bleeding Disorders: Hemophilia

Hemophilia: Epidemiology and Pathophysiology

- Hemophilia is a rare inherited X-linked bleeding disorder characterized by lack of one of the proteins involved in blood clotting
- Ability to form a stable fibrin clot depends on a complex network of proteins and cells that comprise the clotting cascade
- FVIII and FIX are the only coagulation cascade proteins that are encoded by genes on the X chromosome
- Hemophilia is named according to the factor deficiency.
  - Hemophilia A
    - 1 in 5,000 male births
    - Lack functional copies of factor VIII (FVIII)
  - Hemophilia B
    - 1 in 25,000 male births
    - Lack functional Factor IX
- Spontaneous deep bruising, muscular hematomas, or bleeds into joints are related to level of factor deficiency
- Classified based on severity of deficiency
  - Severe: < 1% of normal factor activity levels; highest risk of spontaneous bleeding
  - Moderate: 1%–5% of normal factor levels; occasionally spontaneous, risk with minor trauma or surgery
  - Mild: 5%–50% of normal factor levels; risk with major trauma or surgery, rarely spontaneous

Pelland-Marcotte MC, et al. *Hematol Oncol Clin North Am*. 2019;33(3):409-423; Peters R, et al. *Nat Rev Drug Discov*. 2018;17(7):493-508.

Hemophilia: Collaborative Management

- Most patients with hemophilia are managed by comprehensive hemophilia centers (CHCs)
  - Birth through adulthood
  - Advanced practitioners (APs) may work as members of these interdisciplinary programs and assume a primary role in monitoring and management of hemophilia across the life span
- APs in hematology and oncology
  - For patients with access to regular factor replacement, life expectancy is now approaching that of the general male population
  - Patients with other forms of cancer or benign hematology disorders may be seen in a general practice
  - Co-management/collaboration with the CHC is recommended, particularly for APs in surgical oncology subspecialties

Mannucci PM, et al. *Blood*. 2009;114(26):5256-5263.

Hemophilia: General Principles of Treatment

- Recombinant and plasma-derived factors are available.
- Hemophilia A
  - Cryoprecipitate contains factor VIII (FVIII) but is not used commonly due to risk of blood-borne pathogens and high volume required.
  - FVIII dosing is calculated based on the desired FVIII level, the baseline level, and the patient's weight in kilograms.
  - The desired factor VIII (FVIII) level and frequency of dosing will vary based on the bleed severity/location, product being used, and other patient factors.
- Hemophilia B
  - Recombinant factor IX (FIX) or plasma-derived product replacements are available.
  - Factor VIII dosing is calculated based on the desired FVIII level, the baseline level, and the patient's weight in kilograms.
- Antifibrinolytic agents may be added to improve clot integrity and reduce early degradation.

Pelland-Marcotte MC, et al. *Hematol Oncol Clin North Am*. 2019;33(3):409-423; Peters R, et al. *Nat Rev Drug Discov.* 2018;17(7):493-508; Worden FP, et al. Hematology Board Review. 2018. Demos Medical, Springer Publishing.

Hemophilia: FDA-Approved Replacement Factors

Product	Brand Name	Half-life (h)	Cell Line	FDA Approval Year
Factor VIII (FVIII)				
rFVIIIFc	Eloctate/Elocta	19	HEK	June 2014
BAX 855	Adynovate/Adynovi	14–16	CHO	Dec 2016
BAY 94-9027	Jivi	19	CHO	Aug 2018
FVIII non-factor replacement product	Hemlibra	N/A	MoAb mimicking cofactor activity of FVIII	Nov 2017
Factor IX (FIX)				
rFIXFc	Alprolix	82	HEK	Mar 2014
rFIXFP	Idelvion	102	CHO	Mar 2016
N9-GP	Rebinyn/Refixia	93	CHO	May 2017

CHO = Chinese hamster ovary; Fc = fragment crystallizable [region]; FP = fusion protein; HEK = human embryonic kidney; MoAb = monoclonal antibody; N9-GP = nonacog beta pegol; r = recombinant

Pelland-Marcotte MC, et al. *Hematol Oncol Clin North Am*. 2019;33(3):409-423.

Hemophilia: Clinical Resources

- General Information from the Centers for Disease Control and Prevention (CDC): https://www.cdc.gov/ncbddd/hemophilia/facts.html
- Hemophilia Treatment Center (HTC) Directory, from the CDC: https://dbdgateway.cdc.gov/HTCDirSearch.aspx

Hereditary and Acquired Bleeding Disorders: von Willebrand Disorders

Pathophysiology and Classification

- von Willebrand factor (VWF) deficiencies may be inherited or acquired.
- VWF is a multimeric protein involved in platelet adhesion and blood coagulation by transporting factor VIII (FVIII) and preserving it from clearance.
- von Willebrand disease (VWD) is caused by the congenital deficiency of VWF.
  - Type 1: partial deficiency of VWF (75% of cases)
  - Type 2: impairment of VWF interactions with platelets or FVIII (second most common variant)
    - Further subdivided into 2A, 2B, 2M, 2N based on details of the phenotype
  - Type 3: severe deficiency of VWF (extremely rare, ~ 1 in 1 million)
- Acquired von Willebrand Syndrome (AVWS) is an acquired rare bleeding disorder associated with several underlying diseases and different pathogenic mechanisms.
  - Decreased synthesis of VWF: Hypothyroidism
  - Normal synthesis but increased clearance of VWF: Antibodies in autoimmune diseases, monoclonal gammopathies, myeloproliferative and lymphoproliferative malignancies
  - Proteolysis of VWF: Acute pancreatitis, liver cirrhosis, leukemia or high shear stress in the heart (aortic stenosis) or a device that unfolds VWF (LVAD), increasing susceptibility of VWF to proteolysis by ADAMTS-13
  - There is a high frequency of blood type O in the United States, and it is associated with “low” VWF.

LVAD = left ventricular assist device

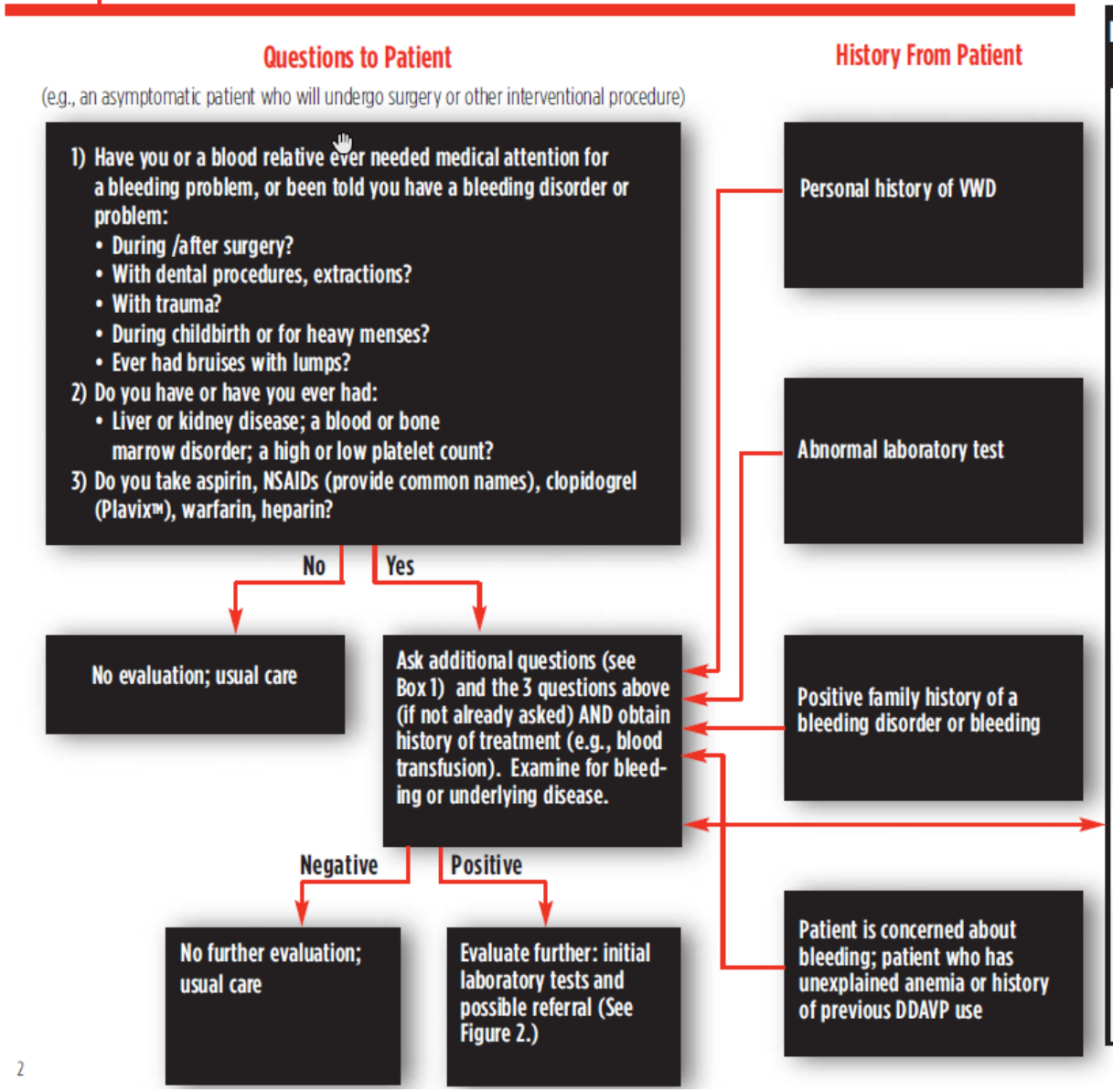
Mehta R, et al. *J Thromb Thrombolysis.* 2019;48(1):14-26.

von Willebrand Disease: Presenting Signs and Symptoms

- Bleeding and bruising are the most common presenting symptoms.
  - Mucosal bleeding symptoms such as easy bruising, epistaxis, gingival bleeding
  - Surgical bleeding
  - Heavy menstrual bleeding
  - Gastrointestinal bleeding (more common in type 2 AVWS)
  - Joint bleeds (more common in type 2N VWD and type 3 due to low factor VIII)
- Patients may be referred for surgical clearance or due to a recent bleeding episode or recurring bleeding episodes.
- Obtaining a detailed history to discern bleeding risk and any history of bleeding will be key to further work-up and possible treatment.

Sharma R, et al. *Blood*. 2017;130(22):2386-2391.

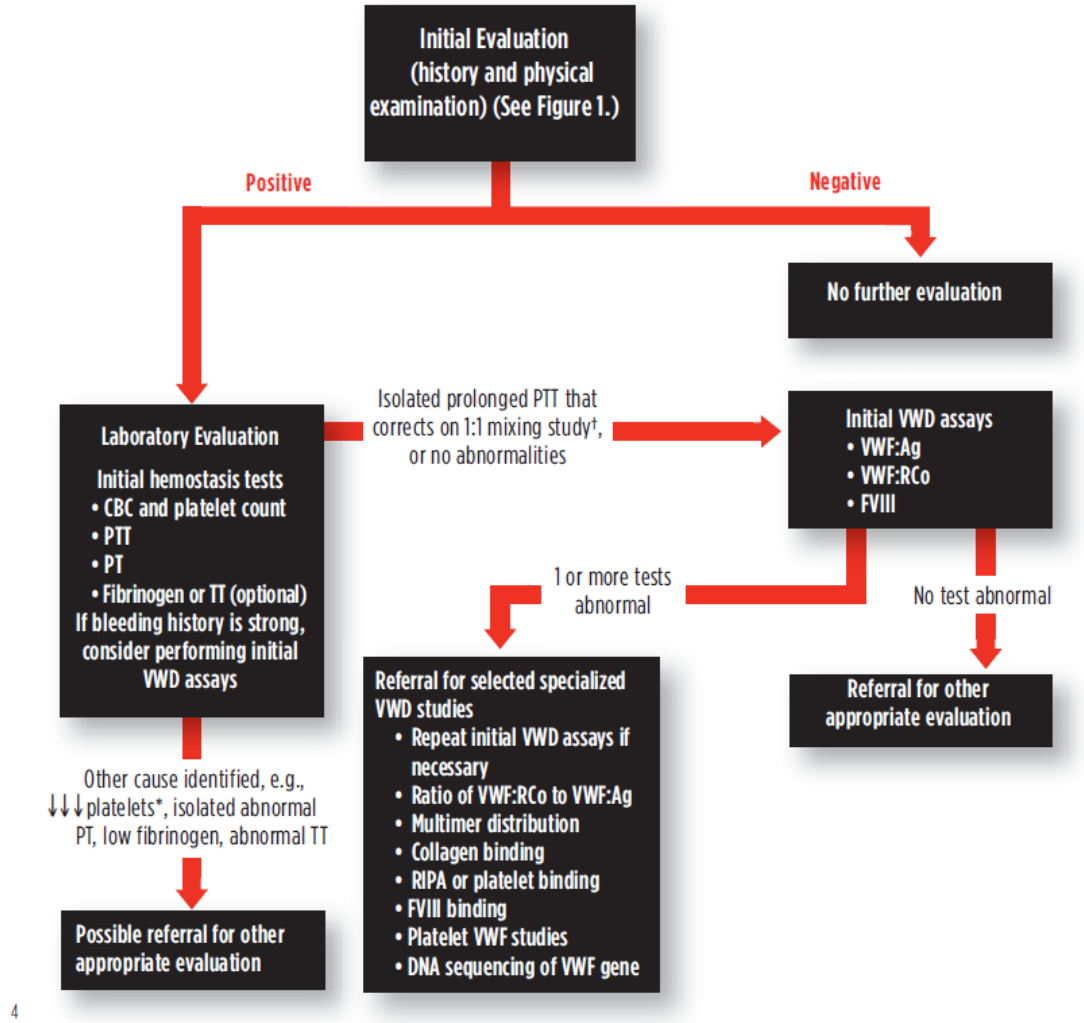
Figure 1: Initial Evaluation for VWD or other Bleeding Disorders



Box 1: Additional Questions To Screen for a Bleeding Disorder

1. Do you have a blood relative who has a bleeding disorder, such as von Willebrand disease or hemophilia?
2. Have you ever had prolonged bleeding from trivial wounds, lasting more than 15 minutes or recurring spontaneously during the 7 days after the wound?
3. Have you ever had heavy, prolonged, or recurrent bleeding after surgical procedures, such as tonsillectomy?
4. Have you ever had bruising, with minimal or no apparent trauma, especially if you could feel a lump under the bruise?
5. Have you ever had a spontaneous nose-bleed that required more than 10 minutes to stop or needed medical attention?
6. Have you ever had heavy, prolonged, or recurrent bleeding after dental extractions that required medical attention?
7. Have you ever had blood in your stool, unexplained by a specific anatomic lesion (such as an ulcer in the stomach, or a polyp in the colon), that required medical attention?
8. Have you ever had anemia requiring treatment or received a blood transfusion?
9. For women, have you ever had heavy menses, characterized by the presence of clots greater than an inch in diameter and/or changing a pad or tampon more than hourly, or resulting in anemia or low iron level?

Figure 2. | Laboratory Assessment for VWD or other Bleeding Disorders



* Isolated decreased platelets may occur in VWD type 2B.

\+ Correction in the PTT mixing study immediately and after 2-hour incubation removes a factor VIII (FVIII) inhibitor from consideration. Investigation of other intrinsic factors and lupus anticoagulant also may be indicated.

CBC = complete blood count; PT=prothrombin time; PTT = partial thromboplastin time; RIPA = Ristocetin-induced platelet aggregation; TT = thrombin time; WVF:Ag = VWF antigen; VWF:RCo = VWF Ristocetin cofactor activity. Referral to a hemostasis specialist is appropriate for help in interpretation, repeat testing, and specialized tests.

See full guidelines for levels of evidence for each recommendation www.nhlbi.nih.gov/guidelines/vwd

NIH Publication No. 08-5833 February 2008 http://www.nhlbi.nih.gov

Laboratory Values for von Willebrand Disease

Condition	Description	VWF:Rco (IU/dL)	VWF:Ag (IU/dL)	FVIII	VWF:Rco/ VWF:Ag
Type 1	Partial quantitative VWF deficiency (75% of symptomatic VWD patients)	< 30*	< 30*	↓ or Normal	> 0.5–0.7
Type 2A	↓ VWF-dependent platelet adhesion with selective deficiency of high-molecular-weight multimers	< 30*	< 30–200*#	↓ or Normal	< 0.5–0.7
Type 2B	Increased affinity for platelet GPIb	< 30*	< 30–200*#	↓ or Normal	< 0.5–0.7
Type 2M	↓ VWF-dependent platelet adhesion without selective deficiency of high-molecular-weight multimers	< 30*	< 30–200*#	↓ or Normal	< 0.5–0.7
Type 2N	Markedly decreased binding affinity for FVIII	30–200	30–200	↓↓	> 0.5–0.7
Type 3	Virtually complete deficiency of VWF (severe, rare)	< 3	< 3	↓↓↓↓ (< 10 IU/dL)	N/A
"Low VWF"**		30–50	30–50	Normal	> 0.5–0.7
Normal		50–200	50–200	Normal	> 0.5–0.7

*< 30 IU/dL is designated as the level for a definitive diagnosis of VWD; some patients with type 1 or type 2 VWD have levels of VWF:RCo and/or VWF:Ag of 30–50 IU/dL.
The VWF:Ag in the majority of individuals with type 2A, 2B, or 2M VWD is < 50 IU/dL.
** This does not preclude the diagnosis of VWD in patients with VWF:RCo of 30–50 IU/dL.

Ag = antigen; FVIII = factor VIII; GPIb = glycoprotein Ib; Rco = ristocetin cofactor; VWD = von Willebrand disease; VWF = von Willebrand factor

NIH Publication No. 08-5833 February 2008; http://www.nhlbi.nih.gov

von Willebrand Disease: Clinical Management

- Treatment is aimed at cessation of bleeding or prophylaxis for surgical procedures
- Strategies include
  - Increasing plasma concentration of VWF by releasing endogenous VWF stores through stimulation of endothelial cells with desmopressin (DDAVP)
  - Replacing VWF by using human plasma-derived, viral-inactivated concentrates
  - Using agents that promote hemostasis and wound healing but do not substantially alter the plasma concentration of VWF

Treatment to Reduce or Prevent Bleeding in VWD

Desmopressin (DDAVP)

- Hormone that causes release of FVIII and VWF from storage sites within endothelial cells
- Can be given intranasally, subcutaneously, or intravenously
- Dosing varies by procedure/ bleeding risk
- Most common side effects
  - Vasomotor effects: facial flushing, headache, hypotension
  - Fluid retention: requires fluid restriction for first 24 hours after each dose to avoid hyponatremia and rare seizures

Antifibrinolytics

- Aminocaproic acid and tranexamic acid
- Help prevent clot degradation by inhibiting action of plasminogen
- Oral or intravenous
- Dosing varies by procedure/bleeding risk
- Most common adverse events: nausea, diarrhea (dose dependent)

VWF Replacement

- Generally reserved for patients with type 3 VWD, or patients refractory to other treatments
- May also be considered for procedures with a very high risk of bleeding, long duration, | high-risk location

FVIII = factor VIII; VWD = von Willebrand disease; VWF = von Willebrand factor

O'Brien SH, et al. *Hematol Oncol Clin North Am*. 2019;33(3):425-438.

von Willebrand Disease: Clinical Resources

- General resources from the Centers for Disease Control and Prevention (CDC): https://www.cdc.gov/ncbddd/vwd/index.html
- von Willebrand disease treatment guidelines from the CDC: https://www.cdc.gov/ncbddd/vwd/guidelines.html
- In January 2021, the American Society of Hematology (ASH) published updated international guidelines on VWD diagnosis (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7805340/) and management (https://pubmed.ncbi.nlm.nih.gov/33570647/)

Autoimmune Cytopenias

Warm Autoimmune Hemolytic Anemia (wAIHA): Pathophysiology

- Warm autoimmune hemolytic anemia (wAIHA) is the most prevalent form of autoimmune hemolytic anemia (AIHA), representing 60%–70% of all cases
  - Other less common subtypes include cold agglutinin disease (CAD), paroxysmal cold hemoglobinuria, mixed AIHA, and atypical AIHA
- Characterized by hemolysis of red blood cells
- Hemolysis is triggered by various underlying autoimmune or malignant diseases, infectious events, other factors (drugs, acute illness)
- Usually due to immunoglobulin G (IgG) autoantibody
  - May activate complement if present at high titer or if IgG1 and IgG3 subclasses are prevalent
- Recent studies indicate that involvement of T-cell and B-cell dysregulation, reduced CD4+ and CD25+ Tregs, increased clonal expansions of CD8+ T cells, and impaired lymphocyte apoptosis play a role

Tregs = regulatory T cells

Michalak SS, et al. *Immun Ageing*. 2020;17:38; Barcellini W, et al. *Blood*. 2021;137(10):1283-1294.

Most Common Secondary Conditions Associated With AIHA

- Warm AIHA
  - Hematologic disorders and lymphoproliferative diseases (CLL, Hodgkin and non-Hodgkin lymphoma)
  - Solid malignancy (thymoma, ovarian or prostate carcinoma)
  - Autoimmune diseases (SLE, Sjögren syndrome, systemic sclerosis, rheumatoid arthritis, colitis ulcerosa, PBC)
  - Viral infections (HCV, HIV, VZV, CMV, SARS-CoV-2)
  - Bacterial infections (tuberculosis, pneumococcal infections)
  - Leishmania parasites
  - Bone marrow or solid-organ transplantation
  - Primary immune deficiency syndromes (CVID, ALPS)
  - Sarcoidosis
- CAD
  - Lymphoproliferative diseases (Waldenström macroglobulinemia, non-Hodgkin lymphoma)
  - Solid malignancy
  - Infections (parvovirus B19, *Mycoplasma* sp., EBV, adenovirus, influenza virus, VZV infections and syphilis)
  - Autoimmune disease
  - Post-allogeneic HSCT
- PCH
  - Bacterial infections (*Mycoplasma pneumoniae*, *Haemophilus influenzae*, *Escherichia coli* infections and syphilis)
  - Viral infections (adenovirus, influenza A virus, VZV infection; mumps, measles)
  - Myeloproliferative disorders
- Mixed AIHA
  - Lymphoma
  - SLE
  - Infection
- DIIHA
  - Antibiotics (cephalosporins, beta-lactamase inhibitors, cotrimoxazole)
  - Antiviral drugs: HAART
  - Anti-PD-1 monoclonal antibodies (nivolumab, pembrolizumab)
  - Chemotherapy (carboplatin, oxaliplatin)
  - Nonsteroidal anti-inflammatory drugs (diclofenac)
  - Others: Methyldopa

ALPS = autoimmune lymphoproliferative syndrome; CLL = chronic lymphocytic leukemia; CMV = cytomegalovirus; CVID = common variable immunodeficiency; EBV = Epstein-Barr virus; HAART = highly active antiretroviral therapy; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HSCT = hematopoietic stem cell transplant; PBC = primary biliary cholangitis; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SLE = systemic lupus erythematosus; VZV = varicella zoster virus

Michalak SS, et al. *Immun Ageing*. 2020;17:38

AIHA Presentation and General Approach to Treatment

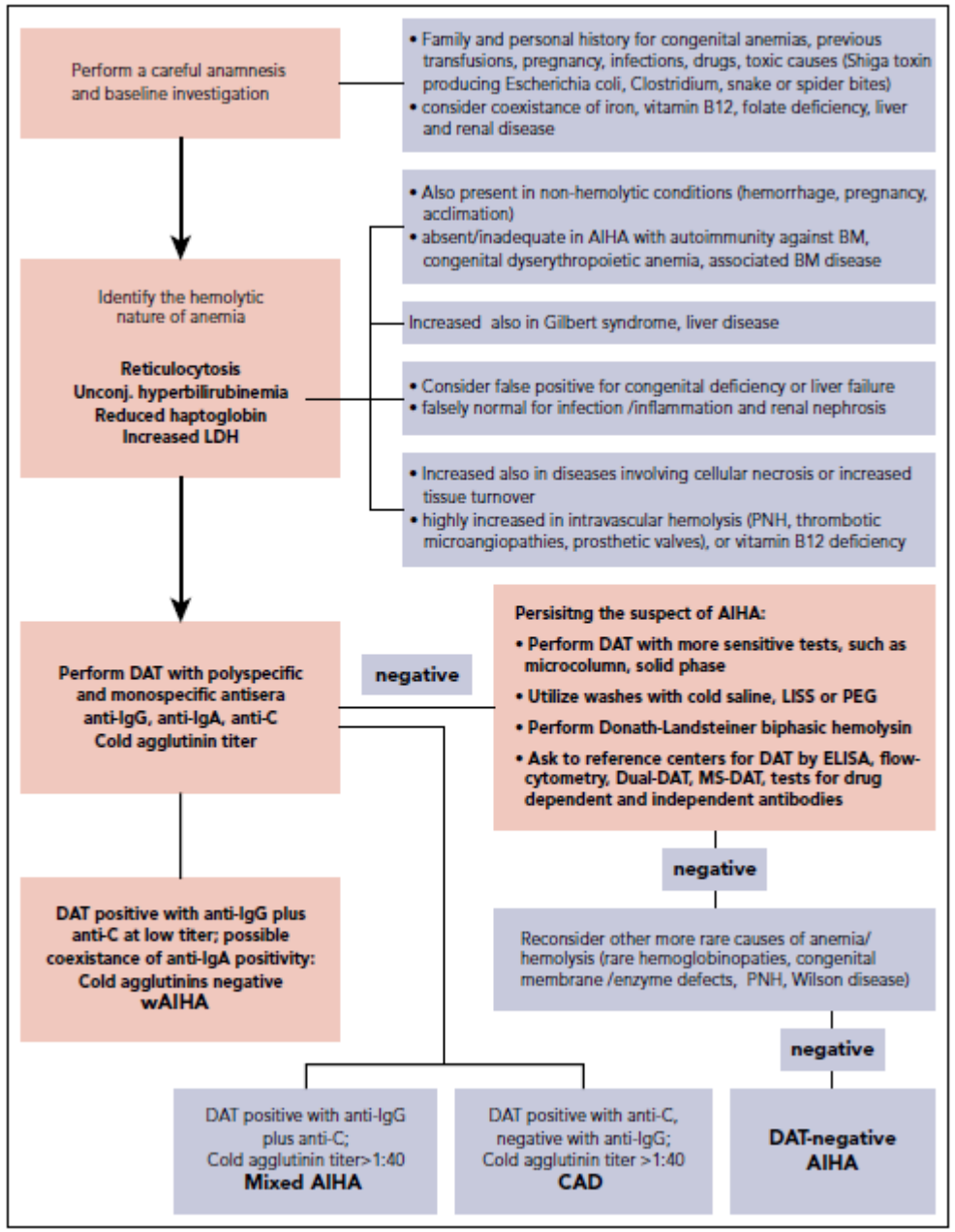
- Physical findings
  - Excessive fatigue, may be abrupt
  - Lightheadedness
  - Dark urine
  - Jaundice
  - Pallor
  - Palpitations
  - Symptoms associated with the underlying illness (may be undiagnosed in some cases)
- Laboratory findings
  - Normocytic anemia with spherocytes found on the peripheral smear
  - Reticulocytosis
  - Elevated indirect (unconjugated) bilirubin
  - Low or absent serum haptoglobin
  - Elevated lactate dehydrogenase
  - Increased urinary urobilirubin
  - Hemoglobinuria: indicates intravascular hemolysis
  - Positive DAT

AIHA = autoimmune hemolytic anemia; DAT = direct antiglobulin test

Michalak SS, et al. *Immun Ageing*. 2020;17:38

Diagnostic Algorithm for AIHA

- DAT or Coombs test is cornerstone of diagnosis.
  - Allows distinction of different forms of AIHA
- wAIHA
  - Most common: 60% to 70% of all cases
  - DAT is positive with anti-IgG antisera (70% of all wAIHA) or anti-IgG plus C at low titer.
- Cold agglutinin disease (CAD)
  - 20% to 25% of all AIHAs
  - DAT positivity with anti-C antisera and high titer of cold agglutinins
- Mixed AIHA
  - 5% to 10% of all AIHAs
  - DAT is positive for IgG plus C, and cold agglutinins are present at high titer.
- Atypical AIHA
  - 10% of all AIHAs
  - Include DAT2, IgA, and warm IgM-driven AIHAs
- Paroxysmal cold hemoglobinuria
  - Rare: 1% to 3% of all AIHAs
  - Sustained by the biphasic Donath-Landsteiner hemolysin



AIHA = autoimmune hemolytic anemia; DAT = direct antibody test; ELISA = enzyme-linked immunosorbent assay; LDH = lactate dehydrogenase; LISS = low-ionic salt solution; MS-DAT = mitogen-stimulated DAT; PEG = polyethylene glycol; PNH = paroxysmal nocturnal hemoglobinuria; wAIHA = warm autoimmune hemolytic anemia

AIHA: Clinical Management

- Treatment is aimed at suppressing the hyperactive immune response and treating the underlying disease

Treatment	Dose Schedule	Response Rate	Time to Response	Comments	Side Effects
Predniso(lo)ne	1–2 mg/kg daily for 3–4 wk	80% to 90% (estimated cure rate in 20% to 30% only)	7–25 d	Gradual tapering during a period no shorter than 4–6 mo Steroid boluses may be used for acute severe forms	Diabetes mellitus, hypertension, peptic ulcer, osteoporosis, adrenal suppression, myopathy, psychosis, delayed wound healing, insomnia, menstrual irregularity, weight gain
IVIG	0.4 g/kg daily for 5 days	30% to 40%	1–5 d	Responses usually last about 3 wk Advised in addition to steroids in critically ill patients, particularly during severe infections/sepsis	Infusion reactions particularly in patients with IgA deficiency, thromboembolic events, acute renal failure, increased serum viscosity

IVIG = intravenous immunoglobulin

Barcellini W, et al. *Blood*. 2021;137(10):1283-1294.

AIHA: Clinical Management (cont)

Treatment	Dose Schedule	Response Rate	Time to Response	Comments	Side Effects
Rituximab	375 mg/m^2 per wk for 4 wk	~ 80% (relapse-free survival of 60% at 3 y)	3–6 wk	Other schedules include: (a) low dose (100 mg wk for 4 wk) in patients with nonsevere hemolytic anemia, and in the elderly (b) 1 g days 1 and 15, particularly in wAIHA associated with other autoimmune diseases	• Infusion reactions, late-onset neutropenia, hypogammaglobulinemia, reactivation of underlying infections (HBV, HCV, HIV, tuberculosis, etc) • Regarding HBV reactivation, lamivudine prophylaxis up to 18 mo is recommended for anti-HBc Ab and/or anti-HBs Ab1 patients (if not vaccinated)
Splenectomy		~ 80% (curative rate 20% to 50%)	7–10 d	Discouraged for patients older than 65–70 y, and patients with cardiopulmonary disorders, thrombotic risk, immunodeficiencies, lymphoproliferative diseases, and systemic autoimmune conditions	Possible complications include serious infections (vaccinations warranted against *Neisseria meningitidis* ACWY and B type, Pneumococcal bacteria, and *Haemophilus influenzae* type b; annual flu vaccine; variable schedules for 5 yearly boosters) and thrombotic events

HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus

Barcellini W, et al. *Blood*. 2021;137(10):1283-1294.

AIHA: Clinical Management (cont)

Treatment	Dose Schedule	Response Rate	Time to Response	Comments	Side Effects
Azathioprine	2–4 mg/kg daily	~ 60% (usually with steroids)	1–3 mo	Advised as steroid-sparing agent in AIHAs secondary to systemic autoimmune conditions, inflammatory bowel diseases, and autoimmune hepatitis	Myelotoxicity, particularly in case of thiopurine methyltransferase deficiency (start with 50 mg daily, and increase up to 150 mg in the absence of neutropenia), liver toxicity
Cyclosporine	2.5 mg/kg twice daily	~ 60%	1–3 mo	Advised as steroid-sparing agent, particularly in AIHAs secondary to autoimmune conditions, Evans syndrome, and in case of features of bone marrow failure	Kidney damage, hypertension, infections, nausea, excessive hair growth
Cyclophos-phamide	50–100 mg daily or 800 mg/m^2 IV monthly for 4–5 cycles	50% to 70%	2–6 wk	May be considered in cases of highly hemolytic disease, particularly if secondary to connective tissue disorders and lymphoproliferative diseases	Myelosuppression, infections, urotoxicity, secondary malignancy, teratogenicity, infertility

AIHA = autoimmune hemolytic anemia

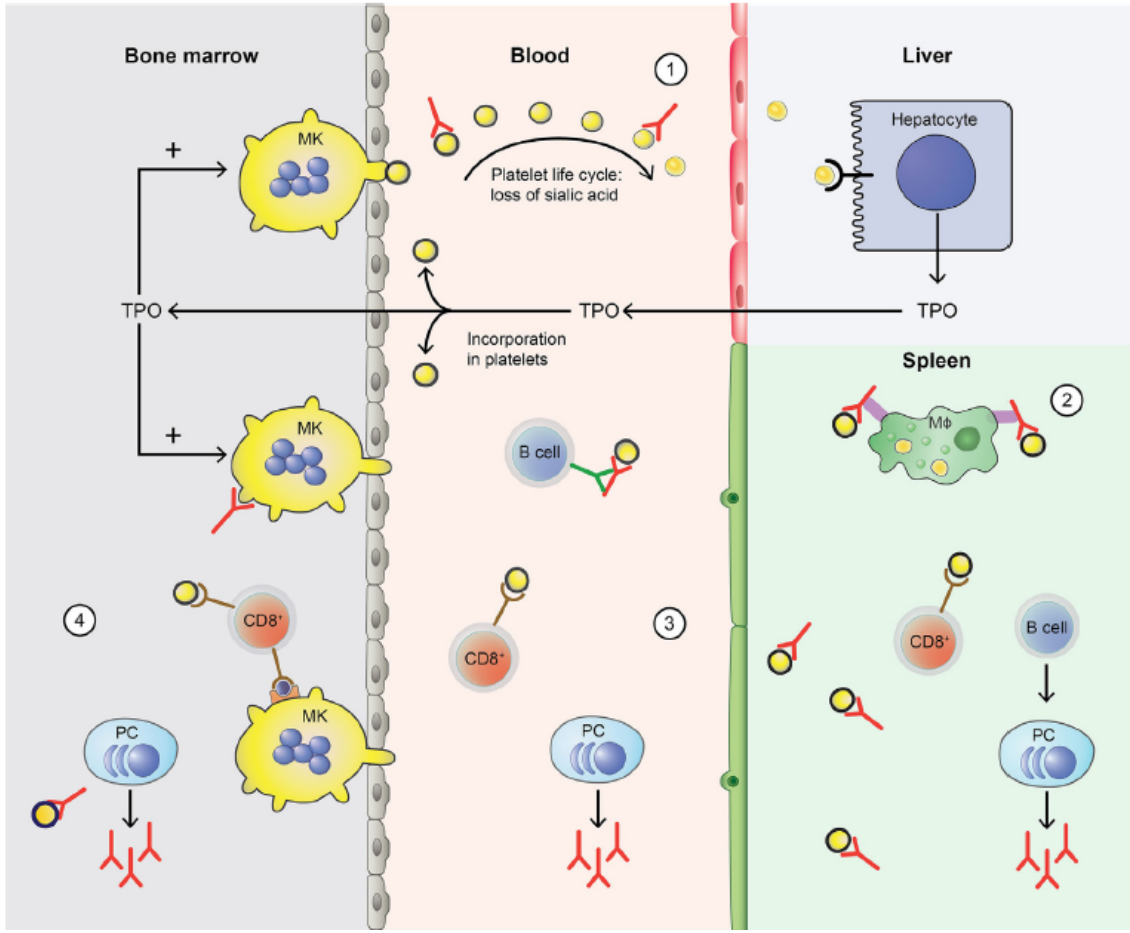
Barcellini W, et al. *Blood*. 2021;137(10):1283-1294.

AIHA: Clinical Resources

- National Organization for Rare Disorders https://rarediseases.org/rare-diseases/warm-autoimmune-hemolytic-anemia/
- American Autoimmune Related Diseases Association, Inc. http://www.aarda.org/
- Cold Agglutinin Disease Foundation https://coldagglutinindisease.org/

Immune Thrombocytopenia (ITP): Pathophysiology

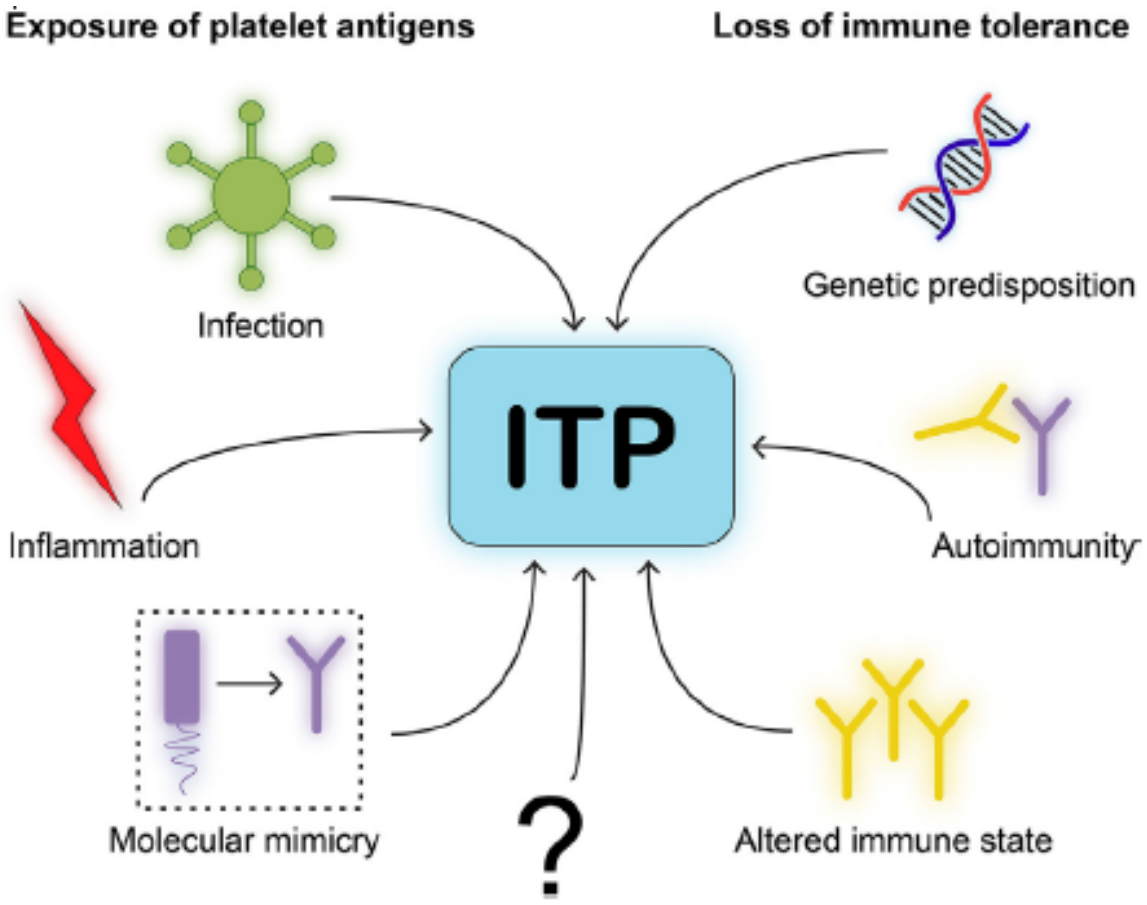
- Definition: unexplained low platelet count of < 100 × 10^9/L (platelet count < 100,000)
  - Previously known as idiopathic thrombocytopenia purpura
- Thrombocytopenia mediated by
  - Autoantibodies and autoreactive CD8+ cytotoxic T cells (Tc)
    - Directly lyse platelets
    - Inhibit megakaryocytes (MK)
- In the spleen, macrophages (MF) present platelet antigens to immune cells.
- B cells differentiate into platelet-reactive plasma cells (PC) that can secrete autoantibodies.
- Dysregulation of thrombopoietin (TPO) synthesis occurs in the liver.



Audia S, et al. *Autoimmun Rev*. 2017;16(6):620-632; Swinkels M, et al. *Front Immunol*. 2018;9:880.

Immune Thrombocytopenia (ITP): Pathophysiology

- Exposure of platelet antigens
  - An initiating event or trigger (eg, infection, inflammation)
  - Molecular mimicry of viral antigens to resemble platelet glycoproteins
- Self-reactivity and loss of immune tolerance
  - Genetic disposition in immune-related genes (rare)
  - Autoimmunity by comorbidities
  - Altered immune state, such as after organ transplantation



Immune Thrombocytopenia (ITP): Classification

- Incidence in adults: ~ 3.3–3.9 per 100,000 adults/year
- Classification
  - Primary: 80% of all cases, isolated or transient events
    - Newly diagnosed: Up to 3 months from time of diagnosis to resolution
    - Persistent: Extends 3 to 12 months from initial diagnosis to resolution
    - Chronic: Continuation of ITP after 12 months from initial diagnosis
  - Secondary: 20% of all cases, associated with other conditions
    - Systemic autoimmune disease
    - Pregnancy
    - Malignancies—particularly lymphoproliferative malignancies
    - Drugs: Prescription, recreational, over the counter
    - Chronic infections
    - *Helicobacter pylori*
    - HIV
    - Hep-C
    - Transplants (solid organ or stem cell)

Hep-C = hepatitis C; HIV = human immunodeficiency virus

Neunert CE. *Blood Adv.* 2017;1(24):2295-2301.

ITP: Presenting Signs and Symptoms and Differential Diagnosis

Signs and Symptoms

- ITP is a diagnosis of exclusion
- Presenting signs and symptoms are heterogeneous
- Most common physical findings
  - Purpura and or petechiae
  - Hemorrhagic episodes
    - Epistaxis, gum bleeding, hematuria, hematochezia, menorrhagia, etc.
    - Majority of patients do not experience severe bleeding episodes despite very low platelet counts
- Laboratory criteria: Unexplained low platelet count of < 100 × 10^9/L (platelet count < 100,000)

Diagnostic Evaluation

- Careful review of PMH and recent events that may identify a trigger
- Laboratory analysis is driven by suspected trigger(s)
  - CBC, differential, platelet count
  - Review of peripheral smear
  - Complete metabolic panel
  - Infectious evaluation
  - Serum immunoglobulins
- Bone marrow biopsy is only required if there is suspicion for an underlying bone marrow malignancy
- Imaging for splenomegaly or hepatic disease may be indicated for patients with known or suspected underlying malignancies

CBC = complete blood count; iTP = immune thrombocytopenia; PMH = past medical history

Neunert CE. *Blood Adv.* 2017;1(24):2295-2301.

American Society of Hematology Clinical Guidelines: Newly Diagnosed ITP

- Treatment is aimed at disrupting the autoimmune-mediated process
- Newly diagnosed ITP with a platelet count of ≥ 30 × 10^9/L
  - If patient is asymptomatic or has minor mucocutaneous bleeding: Observation
  - If symptomatic, comorbidities that predispose to bleeding, anticoagulant or antiplatelet medications, essential surgical procedure, or > 60 years old: Treatment with corticosteroids may be appropriate
- Newly diagnosed ITP with a platelet count < 30 × 10^9/L
  - Treat with corticosteroids
    - Prednisone 1–2 mg/kg with subsequent taper after response
    - Dexamethasone 40 mg × 4 days for 1–3 cycles
    - Selection of steroid is based on potential adverse events, ability to adhere to regimen, need for rapid response
    - If no initial improvement with one approach, alternative regimen may be effective
  - ***or*** Corticosteroids and IVIG
    - 1 g/kg as a 1-time dose (may be repeated if necessary)
    - IVIG can be used with corticosteroids when a more rapid increase in platelet count is required
    - IVIG can be used when corticosteroids are contraindicated

ITP = immune thrombocytopenia; IVIG = intravenous immunoglobulin

Neunert CE. *Blood Adv.* 2017;1(24):2295-2301.

American Society of Hematology Clinical Guidelines: Newly Diagnosed ITP (cont)

Treatment response

- Achieving a platelet count of 30,000/mL and doubling baseline platelet counts

Monitoring response to treatment

- Regular laboratory measure for platelet response
  - Should be review of peripheral smear – not automated
  - Frequency determined by risk of bleeding and potential side effects of treatment

Monitoring adverse events

- Steroids: Mood changes, hypertension, hyperglycemia, gastritis
- IVIG: Infusion reactions, headaches, rash, rare incidence of aseptic meningitis, thrombosis

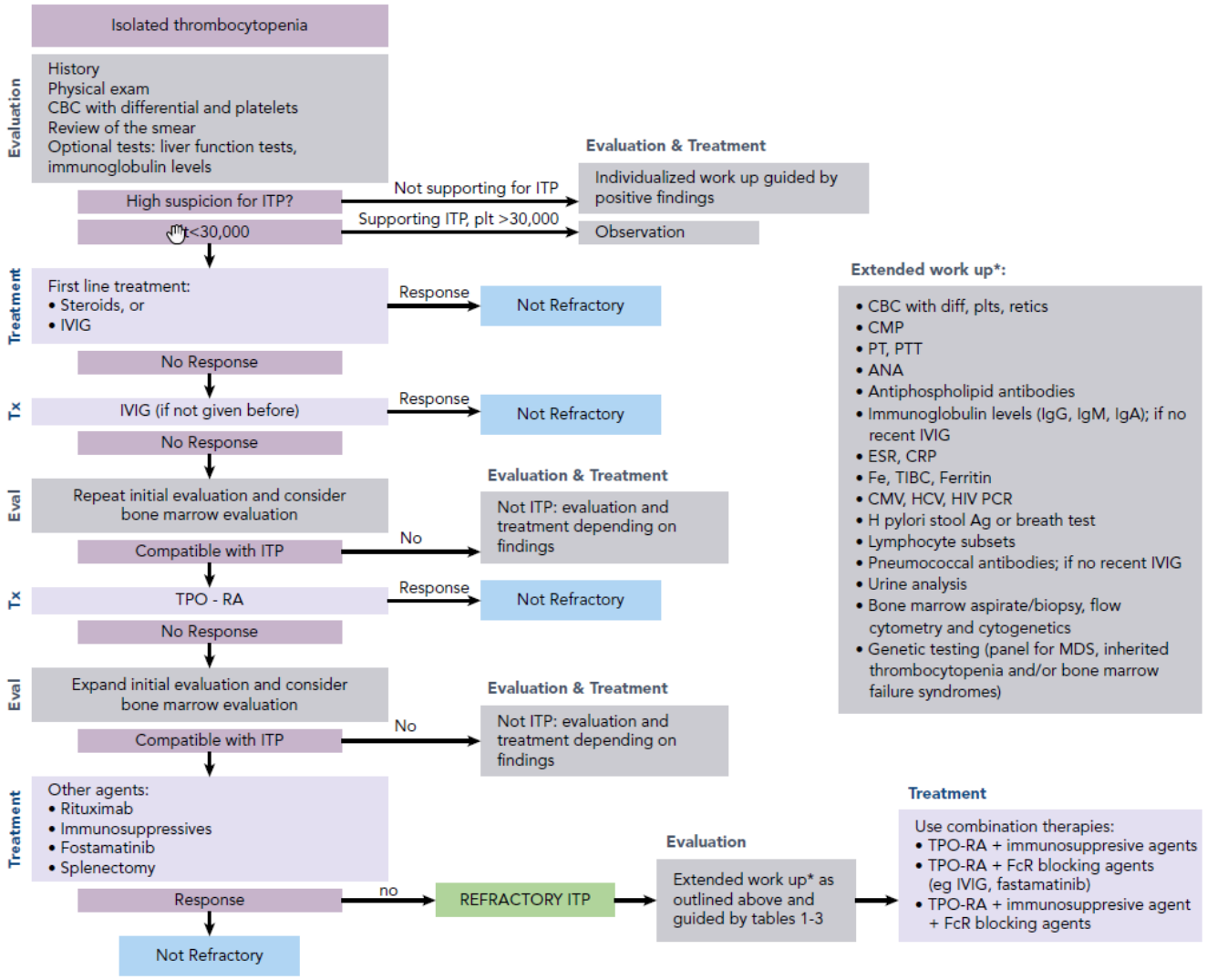
IVIG = intravenous immunoglobulin

Neunert CE. *Blood Adv*. 2017;1(24):2295-2301.

Persistent or Refractory ITP

Definition

- Platelet counts do not respond to ≥ 2 treatments
- There is no single medication to which they respond
- Platelet counts are very low and accompanied by bleeding



Ag = antigen; ANA = anti-nuclear antibodies; CMP = comprehensive metabolic panel; CMV = cytomegalovirus; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; Eval = evaluation; HCV = hepatitis C virus; H pylori = *Helicobacter pylori*; plt/Plt = platelets; PT = prothrombin time; PTT = partial thromboplastin time; TIBC = total iron binding capacity; Tx = treatment

Miltiadous O, et al. Blood. 2020;135(7):472-490.

Treatments for Persistent or Refractory ITP in Adults

Drug	Class	FDA-Approved Indication(s)	Route	Common Adverse Events
Eltrombopag	TPO-RA	Treatment of ITP with insufficient response to corticosteroids, immunoglobulins, or splenectomy	Oral – once daily without food or with a meal low in calcium (≤ 50 mg)	**Serious**: Hepatotoxicity, increased risk of death and progression from MDS or AML, Thromboembolic **Common**: Anemia, nausea, pyrexia, ALT increased, cough, fatigue, headache, and diarrhea
Romiplostim	TPO-RA	Treatment of ITP with insufficient response to corticosteroids, immunoglobulins, or splenectomy	Subcutaneous, 1 mcg/kg based on actual body weight – titrated to response. Use the lowest dose to achieve and maintain a platelet count ≥ 50 × 10^9/L as necessary to reduce the risk for bleeding	**Serious**: Hepatotoxicity, increased risk of death and progression from MDS or AML, thromboembolic **Common**: anemia, nausea, pyrexia, ALT increased, cough, fatigue, headache, and diarrhea
Avatrombopag	TPO-RA	Treatment of ITP with insufficient response to prior therapy	20 mg oral daily (do not exceed 40 mg daily)	**Serious:** Thrombotic/thromboembolic complications **Common: H**eadache, fatigue, contusion, epistaxis, upper respiratory tract infection, arthralgia, gingival bleeding, petechiae, and nasopharyngitis
Fostamatinib	SYK-inhibitor (blocks Fc receptor)	Treatment of ITP with insufficient response to a previous treatment	100 mg orally twice daily with or without food	**Serious:** Hypertension, hepatotoxicity, diarrhea, neutropenia, embryo-fetal toxicity **Common:** diarrhea, hypertension, nausea, respiratory infection, dizziness, ALT/AST increased, rash, abdominal pain, fatigue, chest pain, and neutropenia
Rituximab	Anti-CD20 MoAb		Intravenous weekly × 4 (100 mg/m^2)	**Serious:** hypersensitivity reactions, hepatitis B reactivation **Common:** flu-like symptoms

AML = acute myeloid leukemia; ALT = alanine aminotransferase; AST = aspartate transaminase; ITP = immune thrombocytopenia; MDS = myelodysplastic syndrome; MoAb = monoclonal antibody; SYK = spleen tyrosine kinase inhibitor; TPO-RA = thrombopoietin receptor antagonist;

ITP: Clinical Resources

- American Society of Hematology (ASH) Guidelines for ITP https://www.hematology.org/education/clinicians/guidelines-and-quality-care/clinical-practice-guidelines/immune-thrombocytopenia-guidelines
- Platelet Disorder Support Association (PDSA) https://www.pdsa.org/what-is-itp.html
- ITP Natural History Study Registry https://itpstudy.iamrare.org/

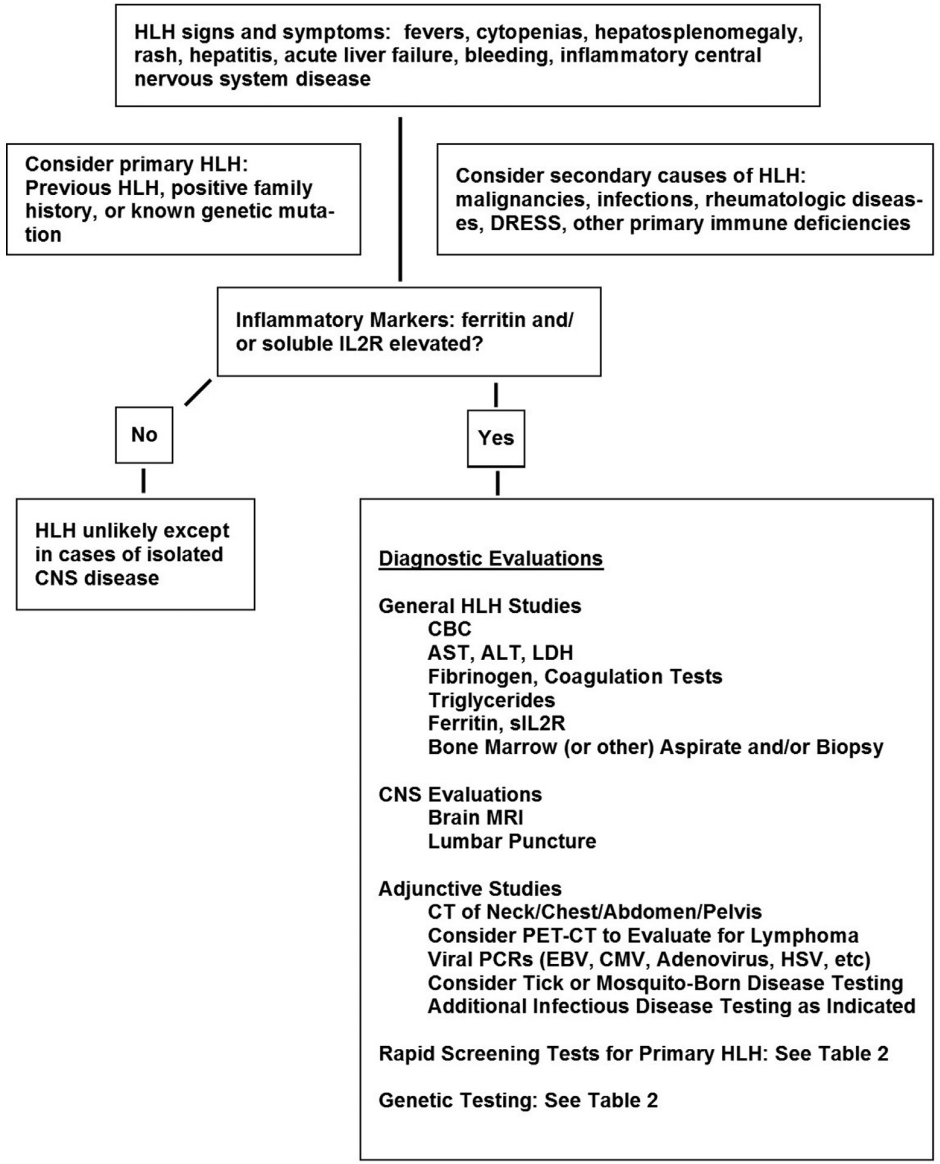
Bone Marrow Disorders

Hemophagocytic Lymphohistiocytosis (HLH): Pathophysiology

- Hemophagocytic lymphohistiocytosis (HLH) is an overwhelming clinical syndrome associated with extreme immune activation.
- Activated lymphocytes and macrophages infiltrate organs causing secondary clinical manifestations.
  - Bone marrow (cytopenias, fevers); liver (hepatic dysfunction); skin (rash); lymph nodes (lymphadenopathy); spleen (splenomegaly); central nervous system (seizures and/or focal deficits to encephalopathy)
- HLH is life-threatening due to rapid progression to multisystem organ failure if the diagnosis is not considered and immunosuppression confidently initiated.
- Primary HLH is a genetic disease found in children.
  - Primary HLH is almost universally fatal without treatment.
- Secondary HLH is associated with various underlying immunodeficiency, autoimmune, infections or malignant disorders and is more common in adults.
  - Case series of adults treated with a variety of regimens report a 30-day mortality of 20% to 44% and overall mortality of 50% to 75%.
  - Patients with HLH associated with malignancy suffer a worse prognosis.

Risma KA, et al. *J Allergy Clin Immunol Pract*. 2019;7(3):824-832; Schram AM, et al. *Blood*. 2015;125(19):2908-2914.

Suggested Diagnostic Strategy for the Syndrome of HLH



ALT = alanine aminotransferase; AST = aspartate aminotransferase; CBC = complete blood cell count; CNS = central nervous system; CMV = cytomegalovirus; CT = computed tomography; EBV = Epstein-Barr virus; DRESS = Drug Reaction with Eosinophilia and Systemic Symptoms; HSV = herpes simplex virus; LDL = lactate dehydrogenase; MRI = magnetic resonance imaging; PET-CT = positron emission tomography-computed tomography; sILR2 = soluble IL-2 receptor.

Risma KA, et al. *J Allergy Clin Immunol Pract*. 2019;7(3):824-832.

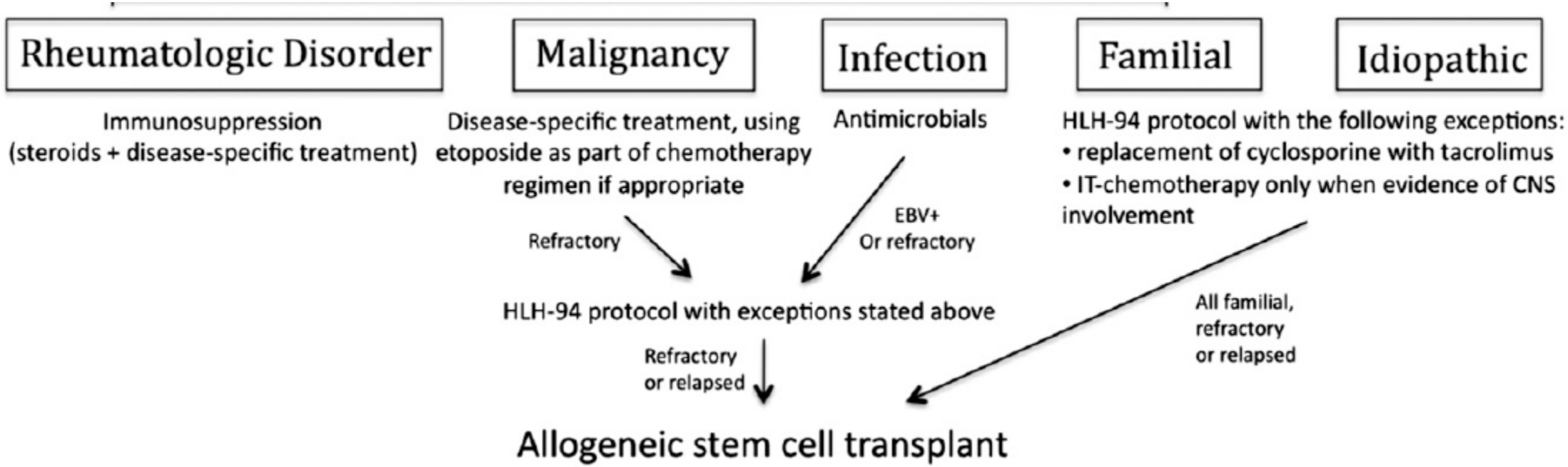
HLH: Diagnostic Guidelines for HLH

Diagnosis of HLH requires a molecular diagnosis consistent with HLH or 5 of 8 of the following criteria:

1. Fever
2. Splenomegaly
3. Cytopenias affecting ≥ 2 lineages
    a. Hemoglobin < 9 g/dL
    b. Platelets < 100×10^9/L
    c. Neutrophils < 1.0×10^9/L
4. Hypertriglyceridemia and/or hypofibrinogenemia
    a. Triglycerides ≥ 265 mg/dL
    b. Fibrinogen ≤150 mg/dL
5. Hemophagocytosis in bone marrow, spleen, or lymph nodes
6. Low or absent NK cell activity
7. Ferritin ≥ 500 mg/L
8. sCD25 (ie, sIL2R) ≥ 2400 U/mL

Schram AM, et al. *Blood*. 2015;125(19):2908-2914.

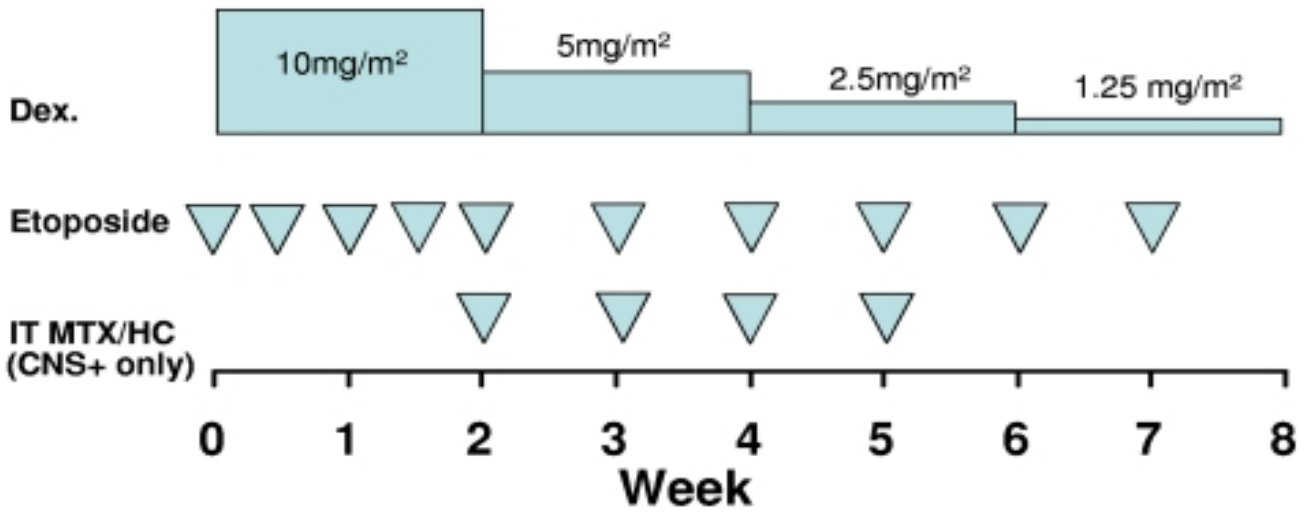
HLH: Clinical Management



CNS = central nervous system; EBV = Epstein-Barr virus; HLH = hemophagocytic lymphohistiocytosis; IT = immunotherapy

Jordan MB, et al. *Blood*. 2011;118:4041-4052; Schram AM, et al. *Blood*. 2015;125(19):2908-2914.

HLH-94 Protocol



Induction therapy for HLH in adults

- Etoposide is dosed as 150 mg/m^2 per dose
- Dexamethasone (Dex.) is dosed as indicated and may be given orally or intravenously, although the latter is preferred at therapy initiation
- Intrathecal methotrexate and hydrocortisone (IT MTX/HC) should be given to patients with evidence of CNS involvement, as early as LP may be safely performed (which may vary from the diagram) and dosed > 3 years, 12/15 mg
- Weekly intrathecal therapy is generally continued until at least 1 week after resolution of CNS involvement (both clinical and CSF indices)

CNS = central nervous system; CSF = cerebrospinal fluid; LP = lumbar puncture

Jordan MB, et al. *Blood*. 2011;118:4041-4052; Schram AM, et al. *Blood*. 2015;125(19):2908-2914.

HLH Resources

- National Organization for Rare Disorders https://rarediseases.org/rare-diseases/hemophagocytic-lymphohistiocytosis/

Castleman's Disease: Epidemiology and Pathophysiology

- Castleman disease(s) (CD) represent lymphoproliferative disorders
  - Encompasses several distinct clinicopathological disorders at the intersection of hematology, immunology, oncology, rheumatology, and virology
  - Have a wide range of etiologies, presentations, treatments, and outcomes
- Unicentric CD (UCD): One single lymph node station
  - Likely a clonal neoplastic process
  - Most likely cell of origin is stromal, specifically the follicular dendritic cell
- Clinically multicentric CD (MCD): Disseminated disease
  - POEMS-MCD: polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, skin changes (POEMS)-associated MCD
  - Idiopathic MCD (iMCD)
    - iMCD-TAFRO: thrombocytopenia, ascites, reticulin fibrosis, renal dysfunction, organomegaly
    - iMCD-NOS: iMCD not otherwise specified
  - Human herpesvirus-8–associated MCD (HHV-8+ MCD)
    - Uncontrolled HHV8 infection is the etiological driver in HHV8-MCD

Dispenzieri A, et al. *Blood*. 2020;135(16):1353-1364.

Clinical Features of Castleman's Disease

Feature	UCD	iMCD-NOS	iMCD-TAFRO	POEMS-Associated MCD	HHV-8+-MCD
Age	Fourth decade	Fifth to sixth decade	Fifth decade	Fifth decade	Fifth decade HIV positive; seventh decade HIV negative
Systemic symptoms	±	++ Occasional PN	+++ Anasarca	++	+++ Kaposi sarcoma
Lymphadenopathy	Central most common; often bulky	Peripheral plus central; often small volume	Peripheral plus central; often small volume	Peripheral plus central	Peripheral plus central; often small volume
Organomegaly	±	++	+++	+++	+++
Abnormal inflammatory markers	±	++	+++ Increased prolactin	++	+++
Anemia, thrombocytopenia, abnormal LFTs	±	++ Sometimes thrombocytosis	+++	±	+++ HHV8 DNA detectable in plasma

+ sometimes present; ++ often present; +++ very often present; - rarely present

HHV8 = human herpesvirus-8; HIV = human immunodeficiency virus; iMCD = idiopathic MCD; LFTs = liver function tests; MCD = multicentric disease; NOS = not otherwise specified; PN = peripheral neuropathy; POEMS = polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes; TAFRO = thrombocytopenia, ascites, reticulin fibrosis, renal dysfunction, organomegaly; UCD = unicentric disease

Dispenzieri A, et al. *Blood*. 2020;135(16):1353-1364.

Clinical Features of Castleman's Disease (cont)

Feature	UCD	iMCD-NOS	iMCD-TAFRO	POEMS-Associated MCD	HHV-8+-MCD
Hypergammaglobulin-emia	±	+++	±	+	+++
Renal dysfunction	-	+	++ Invasive coagulation and fibrinolysis	+	++
Autoimmune phenomena	Rare, but PNP can be seen	++ AIHA, PNP, ITP, ILD	±	±	Positive DAT in 46%, MG in 28%
Pathological features	Usually, HV variant	Usually, PC variant	Usually mixed or hypervascular	Usually mixed or PC type	Usually, PC variant and often plasmablastic

+ sometimes present; ++ often present; +++ very often present; - rarely present

AIHA = autoimmune hemolytic anemia; DAT = direct antiglobulin test; HV = hyaline vascular; ILD = interstitial lung disease; ITP = immune thrombocytopenic purpura; MG = monoclonal gammopathy; PNP = paraneoplastic pemphi; PC = plasma cell

Dispenzieri A, et al. *Blood*. 2020;135(16):1353-1364.

Clinical Features of Castleman's Disease (cont)

Feature	UCD	iMCD-NOS	iMCD-TAFRO	POEMS-Associated MCD	HHV-8+-MCD
Therapy	Surgery	IL-6 targeted therapy, rituximab, systemic therapies	Same as iMCD but also calcineurin inhibitors	Local radiation Myeloma type therapy, including ASCT	Rituximab, etoposide
Clinical course	Benign	Variable	Very Aggressive	Aggressive	Aggressive
Risk for lymphoma	+	+	±	±	++

+, sometimes present; ++, often present; +++, very often present; -, rarely present;
ASCT = autologous stem cell transplant
*Fever, sweats, weight loss, malaise, effusions, autoimmune, and respiratory symptoms

Dispenzieri A, et al. Blood. 2020;135(16):1353-1364.

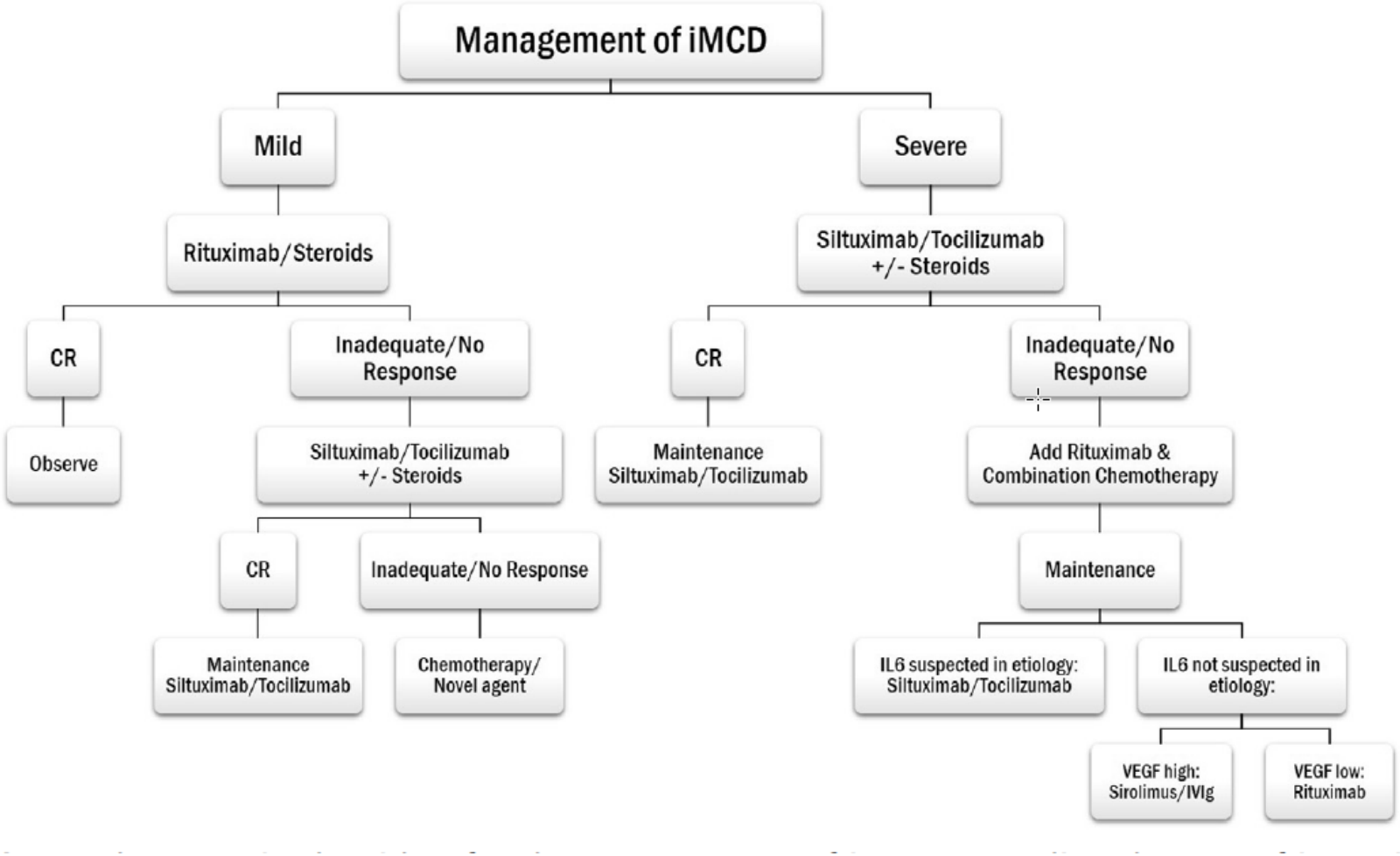
Treatment Options for Castleman's Disease

iMCD-NOS and iMCD-TAFRO	POEMS-Associated	HHV-8+-MCD
First-Line Therapy		
• Siltuximab • Tocilizumab • Corticosteroids	• If no bone lesions, iMCD-like therapy • If bone lesions, myeloma type therapy including ASCT	• If HIV-positive, combination antiretroviral therapy • Rituximab
Second-Line and Beyond Options		
• Rituximab • Cyclosporin • Sirolimus • IVIG • Thalidomide • Lenalidomide • Bortezomib • R-CVP, R-CHOP • ASCT† †Increased ESR, CRP, cholinesterase, ferritin, and low albumin	• As above	• Etoposide • Liposomal doxorubicin • Interferon • Antiviral therapy

ASCT = autologous stem cell transplant; HIV = human immunodeficiency virus; IVIG = intravenous immunoglobulin; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-CVP = rituximab, cyclophosphamide, vincristine, prednisone

Dispenzieri A, et al. Blood. 2020;135(16):1353-1364

Management of iMCD



van Rhee F, et al. *Hematol Oncol Clin North Am.* 2018;32:89-106.

Castleman's Disease: Clinical Resources

- All patients with a diagnosis of CD should be encouraged to register for the Castleman Disease Collaborative Network (CDCN) ACCELERATE natural history registry (#NCT02817997, www.CDCN.org/ACCELERATE) and be informed of opportunities to contribute blood samples to research (www.CDCN.org/samples)
- National Organization for Rare Disorders https://rarediseases.org/rare-diseases/castlemans-disease/

Mastocytosis: Pathophysiology

- Mastocytosis comprises a heterogeneous group of disorders characterized by expansion and accumulation of neoplastic mast cells in 1 or more organ systems.
- Subvariants of mastocytosis include
  - Cutaneous mastocytosis (CM), in which no systemic involvement is found
  - Systemic variants (SM)
    - SM may be aggressive (ASM) or more indolent (ISM)
- Organ involvement may include
  - Spleen, liver, gastrointestinal tract
  - Bone marrow is involved in virtually all patients regardless of the type of SM
  - Skin involvement is usually found in patients with indolent SM (ISM)
- More than 90% of patients with systemic mastocytosis (SM) have a gain-of-function mutation in codon 816 of the receptor tyrosine kinase (*KIT* D816V)

Valent P, et al. Blood 2017;129(11):1420-1427.

Symptoms of Other Illnesses Mimicking Systemic Mastocytosis

- **Inflammatory bowel disease:** Patients may experience weight loss, abdominal cramping and pain, nausea and vomiting, fatigue, and irregular bowel movements
- **Irritable bowel syndrome:** Patients may experience heartburn, nausea and vomiting, presence of clear or white mucus, abdominal pain, and presence of constipation or diarrhea
- **Malabsorption:** Patients may experience diarrhea and weight loss; however, more characteristic symptoms are often based on the specific cause
- **Myeloproliferative neoplasms:** Patients can experience fatigue, weight loss, abdominal discomfort, easy bruising or bleeding, infections, and other symptoms.
- **Other symptoms:** Urticaria, flushing

Systemic Mastocytosis: Diagnostic Criteria

Major Systemic Mastocytosis (SM) Criterion	Multifocal dense infiltrates of MCs (≥ 15 MCs in aggregates) in BM biopsies and/or in sections of other extracutaneous organ(s)
Minor SM Criterion	a. >25% of all MCs are atypical cells (type I or type II) on BM smears or are spindle-shaped in MC infiltrates detected on sections of visceral organs
	b. KIT point mutation at codon 816 in the BM or another extracutaneous organ
	c. MCs in BM or blood or another extracutaneous organ exhibit CD2 and/or CD25
	d. Baseline serum tryptase level > 20 ng/mL (in case of an unrelated myeloid neoplasm, item d is not valid as an SM criterion)
If at least 1 major SM criterion and 1 minor SM criterion or 3 minor SM criteria are fulfilled, the diagnosis of SM can be established	

Mastocytosis: Clinical Management

- Currently, there is no curative treatment for mastocytosis
- Treatment of mastocytosis is primarily directed at controlling the symptoms caused by the release of mast cell mediators
  - H1 and H2 antihistamines are therefore cornerstones of the treatment to relieve symptoms
  - Cromolyn sodium can be especially effective for the treatment of some gastrointestinal symptoms, decreasing bone pain, treating headaches and some of the skin manifestations.
  - Mast-cell stabilizers such as ketotifen can be used to treat some of the skin involvement
  - Leukotriene antagonists can also be used to improve symptoms in patients
  - Proton-pump inhibitors can be used to treat the increased acid production in the stomach
  - Steroids may be necessary in patients unresponsive to other therapy or with more advanced disease

Mastocytosis: Clinical Management (cont)

- *KIT* D816V, a primary oncogenic driver of MC differentiation, proliferation, and survival, is an attractive target because of its high frequency in systemic mastocytosis (SM)
  - In 2017, midostaurin (Rydapt) was approved by the FDA for the treatment of adults with aggressive SM, with SM with associated hematological neoplasm, or with mast cell leukemia
  - National Comprehensive Cancer Network guidelines are now available to guide treatment approaches to SM, including the use of midostaurin and enrollment in clinical trials using KIT inhibitors or other agents
  - Allogeneic stem cell transplantation remains a preferred option for eligible patients with SM

Mastocytosis: Clinical Resources

- National Organization for Rare Disorders
  https://rarediseases.org/rare-diseases/mastocytosis/
- The Mast Cell Disease Society, Inc.
  http://www.tmsforacure.org/

Hemoglobinopathies

Hemoglobinopathies: Pathophysiology

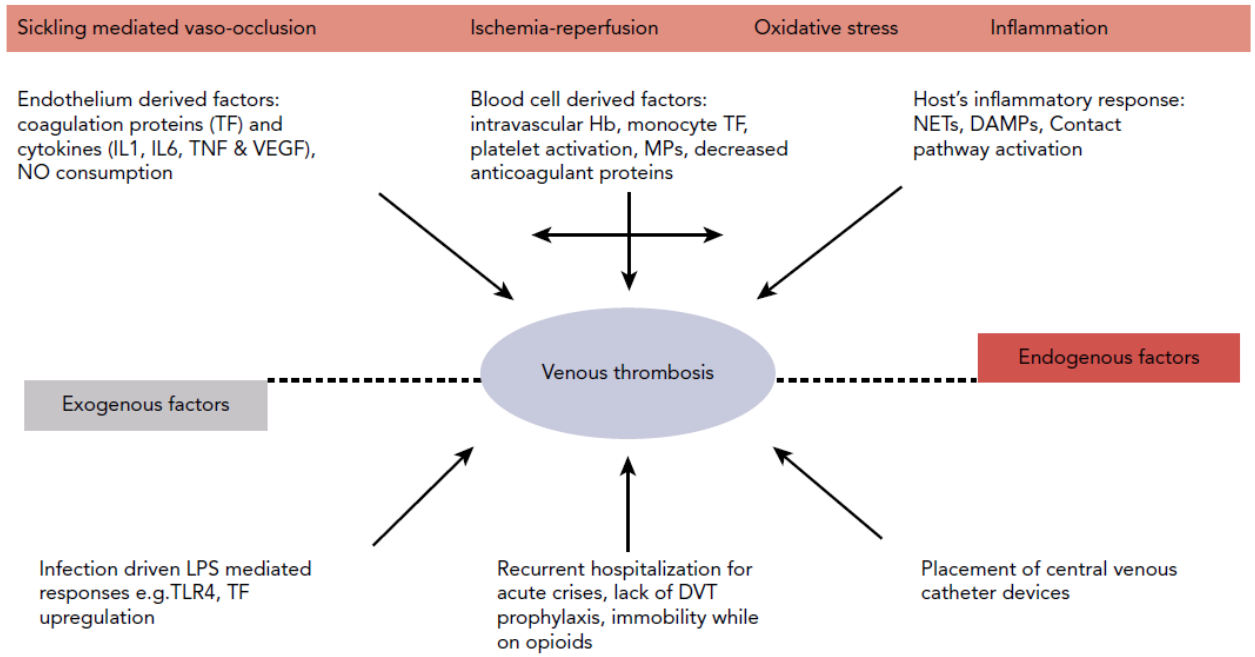
- The inherited disorders of hemoglobin (Hb) production are the most common human monogenic disorders affecting the adult β globin gene (HBB)
  - An estimated 7% of the world's population carries a mutation for a monogenetic disorder of hemoglobin
    - 250 000 individuals born each year with clinically significant sickle cell disease
    - 300 000 born each year with thalassemia
- β globin is encoded by a structural gene found in a cluster with the other β-like genes on chromosome 11 (11p 15.15)
  - Each expressed at distinct stages of development through a process referred to as hemoglobin switching (embryonic → fetal → adult)
- β thalassemia and sickle cell disease (SCD) are the most clinically significant inherited disorders of hemoglobin (Hb) production
  - Sickle Cell Disease
    - A homozygous hemoglobin [Hb] SS, or compound heterozygous HbS/b-thalassemia or HbS/HbC is the most common inherited blood disorder in the United States
    - Characterized by abnormal polymerization of Hb tetramers upon deoxygenation resulting in acute and chronic end-organ damage
  - Sickle Cell Trait (SCT)
    - Heterozygous form HbAS
    - Sickle cell hemoglobin C disease, hemoglobin S/beta thalassemia (Sβthal) have a milder course compared with HbSS
    - SCT is highest in Africans and is seen mostly in people of African descent in other parts of the world
  - β thalassemia
    - Results from a relative excess of a chains due to reduced production of β globin chains and, in some instances, increased dosage of a globin

Sickle Cell Disease (SCD): Signs and Symptoms

- **Sickle cell crisis**
  - Intermittent painful episodes
  - Hemolytic anemia
  - Vascular inflammation
  - Vaso-occlusion

Eventual end organ damage

- **Hypercoagulability** due to activation of prothrombotic factors or decreased antithrombotic proteins
  - Cerebrovascular disease: strokes, transient ischemic attacks, thromboembolic events
- **Cardiopulmonary disease**
- **Renal disease**
  - Hyposthenuria, proteinuria, episodic hematuria and papillary necrosis, renal tubular disorders, glomerulonephropathy, acute renal injury segmental glomerulosclerosis, chronic kidney disease, and chronic renal failure
- Sickle hepatopathy
- Bone infarcts and eventual osteonecrosis
- Sickle retinopathy



DAMP, damage-associated molecular pattern; IL, interleukin; LPS, lipopolysaccharide; MP, microparticle; NET, neutrophil extracellular trap; TF, tissue factor; TLR, Toll-like receptor; TNF, tumor necrosis factor a; VEGF, vascular endothelial growth factor.

Shet AS, et al. *Blood*. 2018;132(17):1761-1769; Thein SL, et al. *Blood*. 2018;132(17):1750-1760.

Sickle Cell Disease (SCD): Cardiopulmonary Disease

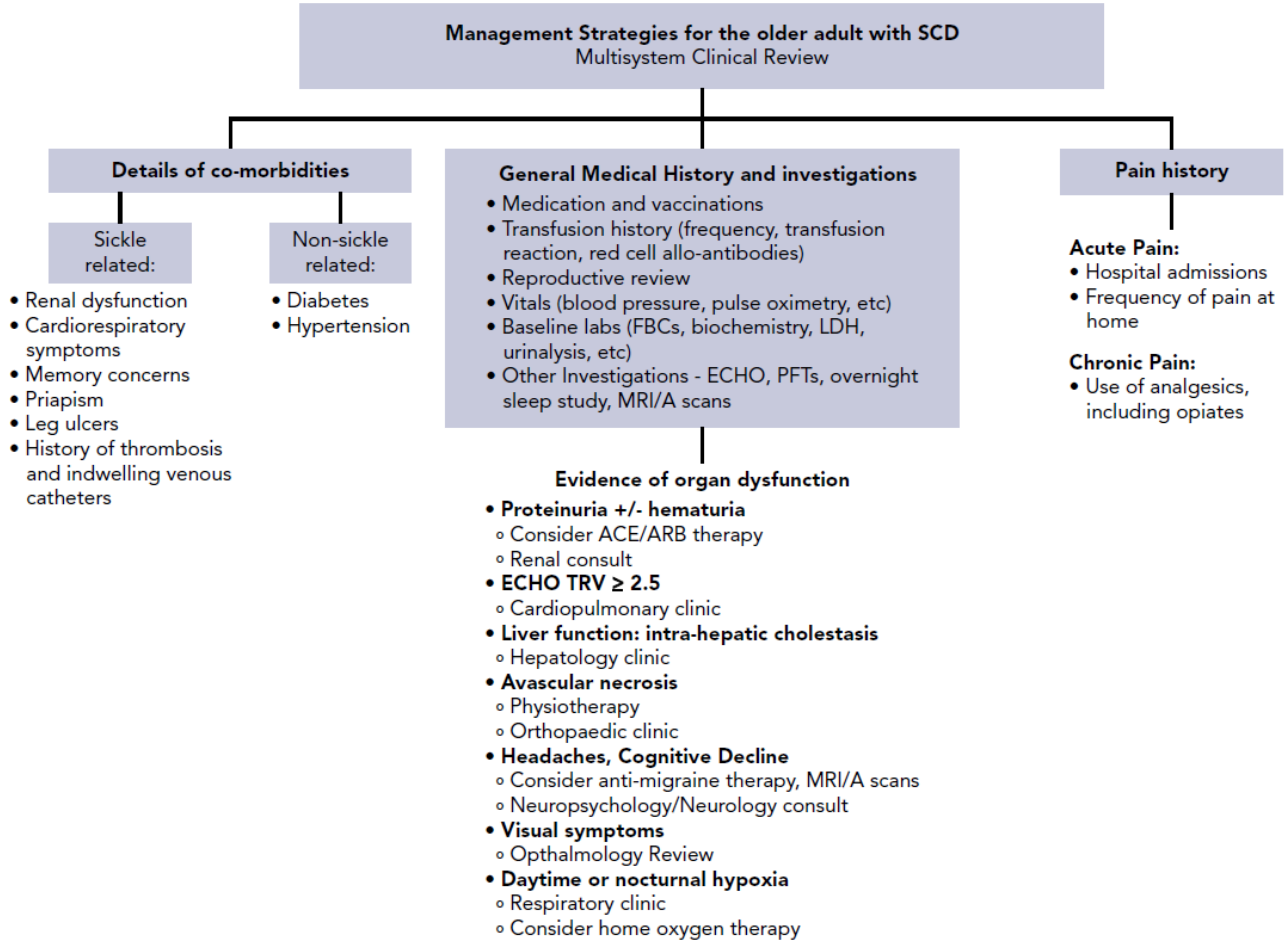
- Asthma
- Acute chest syndrome (ACS)
  - Acute illness characterized by fever and/or respiratory symptoms, accompanied by a new pulmonary infiltrate on chest x-ray
  - Severe hypoxia is useful predictor of severity and outcome
  - Signs and symptoms in adults
    - Fever
    - Cough
    - Chest pain
    - Dyspnea
    - Tachypnea
    - Wheezing
    - Skeletal pain
    - Hypoxia
    - Hemoptysis
- Pulmonary hypertension
- Left ventricular hypertrophy

Diagnostics

- Chest radiograph
- Full blood count
- Complete metabolic panel
- Blood group and screen (or crossmatch)
- Blood cultures
- ABG measurement on room air in adults (if SpO2 ≤ 94% on room air). This should not be done on room air if patient is in obvious respiratory distress or if SpO2 saturations fall to < 85% if oxygen is stopped briefly.
- Serology for atypical respiratory organisms and urine for pneumococcal and *Legionella* antigen
- Sputum for bacterial culture and sputum and nasopharyngeal aspirate for immunofluorescence or polymerase chain reaction (PCR) for viruses in patients with coryzal symptoms

Howard J, et al. *Br J Haematol*. 2015;169:492-505.

Management Strategies for the Older Adult With Sickle Cell Disease



Thein SL, et al. *Blood*. 2018;132(17):1750-1760.

Comprehensive Health Maintenance at Specialized Centers That Provide Multidisciplinary Care Using Standard Guidelines

Preventive measures

- Regular monitoring and periodic comprehensive evaluations for common complications
- Frequency of visits and laboratory monitoring depends on the genotype, medication, and disease severity
  - Folic acid supplementation if diet inadequate
  - Genetic counseling
  - Immunization according to the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices
  - Education about complications of sickle cell disease

Comprehensive Health Maintenance at Specialized Centers That Provide Multidisciplinary Care Using Standard Guidelines (cont)

- Monthly complete blood count, reticulocyte count, percent hemoglobin S, CMP, and ferritin for patients on chronic transfusion and chelation
- Monitor vitamin D levels and supplement if < 30 IU
- Blood pressure measurement each visit
- Neurocognitive testing if imaging abnormalities, or school or work performance difficulties
- Ophthalmology evaluation for retinopathy biannually if normal, more frequent if abnormal
- Echocardiogram to evaluate pulmonary hypertension and diastolic dysfunction; brain natriuretic peptide if any symptoms of pulmonary hypertension
- Pulmonary function studies if history, signs, or symptoms of asthma or other respiratory disease
- Sleep study if history of snoring or other symptoms of obstructive sleep apnea
- Evaluate bone density if abnormal
- Radiographic evaluation of hips to assess femoral avascular necrosis if pain in hips, knees or low back. Avascular necrosis also seen in shoulder and knees.

CMP = comprehensive metabolic panel

Sickle Cell Disease: Therapeutic Landscape

Hydroxyurea

- Baseline: CBC/differential (ANC), reticulocyte count, hemoglobin electrophoresis (HPLC), creatinine, LFTs (ALT, bilirubin)
- Monthly toxicity laboratory tests: CBC with differential
  - Hold if ANC < 1 × 10^9/L or platelet count is < 100,000; reduce dose if ANC is 1 to 1.5 × 10^9/L or platelet count is < 150,000
  - Restart at lower dose once recovered
- Once maximum tolerated dose is reached, follow every 2–3 months and assess for compliance and toxicity (CBC with differential, mean corpuscular volume, creatinine, ALT, reticulocyte count)
- Monitor for leg ulcers

Voxelotor

- Allosteric modulation of Hb S shifts oxyHbC. Voxelotor prevents RBCs from forming sickle shape and binding together
- Approved by FDA in 2019 to treat SSD in adults and children 12 years and older
- How administered: 1500 mg once daily with or without food
  - Dose modification required for concurrent CYP3A4 inducers, strong CYP3A4 inhibitors, or in moderate to severe hepatic impairment
- Possible side effects include headache, diarrhea, abdominal pain, nausea, fatigue, and fever. Rarely, allergic reactions may occur, causing rashes, hives, or mild shortness of breath. Patients should talk to their doctors about other medicines they take.

Crizanlizumab-tmca

- Indicated to reduce the frequency of vaso-occlusive crises (VOCs) in adults and pediatric patients, aged 16 years and older, with sickle cell disease
- Helps prevent blood cells from sticking to blood vessel walls and causing blood flow blockage, inflammation, and pain crises
- How administered: 5 mg/kg by IV infusion over a period of 30 minutes at weeks 0 and 2, then every 4 weeks
- Possible side effects: nausea, joint pain, back pain, fever

ANC = absolute neutrophil count; ALT = alanine aminotransferase; FDA = US Food and Drug Administration; Hb = hemoglobin; LFTs = liver function tests; oxyHbC = oxyhemoglobin C; RBCs = red blood cells; SSD = sickle cell disease

Characterization of Beta Thalassemia

β-Thalassemia Minor	β-Thalassemia Intermedia	β-Thalassemia Major (Cooley's anemia)
Patients typically have 1 normal functioning β-globin	Patients usually have partial β-globin function	Patients typically have no β-globin gene function
Patients have mild or no anemia (typically asymptomatic)	Patients may have mild-to-moderate anemia not dependent on transfusions	Patients have the most severe type of anemia
Patients usually do not require regular transfusions	May require regular RBC transfusions if anemia becomes severe	Patients require regular lifelong RBC transfusions

RBC = red blood cell

Ben Salah N, et al. *Hematology*. 2017;22(10):607-616; Cappellini MD, et al. *Blood Rev*. 2018;32(4):300-311; Rachmilewitz EA, et al. *Blood*. 2011;118(13):3479-3488; Rund D, et al. *N Engl J Med*. 2005;353(11):1135-1146.

Beta Thalassemia Complications

- Complications of beta thalassemia are numerous and include:
  - Growth failure
  - Bone disease
  - Cardiac abnormalities (pulmonary hypertension, heart failure, arrhythmias)
  - Predisposition to thrombosis
  - Extramedullary hematopoiesis (splenomegaly, masses with compression)
  - Endocrinopathies

Beta Thalassemia: Routine Monitoring in Adults

Test	Frequency of Monitoring
Alpha and beta globin genotyping	Once at diagnosis
High-resolution HLA typing	At diagnosis, when transplant is being considered
Pain assessment	Every 3–6 months
CBC with differential	Every 6 months if no transfusions
Comprehensive metabolic panel	Every 6 months
Iron panel	Every 6 months
Ferritin	Every 3 months or more often in transfusion-dependent disease
RBC genotype/phenotype	Once at start of transfusions
Liver iron concentration by MRI	When ferritin reaches 500 ng/mL in transfusion-dependent patient, then annually
Cardiac T2 MRI	Annually in transfusion-dependent patients

CBC = complete blood count; HLA = human leukocyte antigen; MRI = magnetic resonance imaging; RBC = red blood cell

Khandros E, et al. Hematol Oncol Clin North Am. 2019;33(3):339-353.

Beta Thalassemia: Routine Monitoring in Adults (cont)

Test	Frequency of Monitoring
Hepatitis A, B, C serology (PCR as indicated), HIV testing	Annually
Echocardiogram and EKG	Annually
TSH and free T4	Annually
FSH, LH, estradiol, prolactin (women), testosterone (men)	Annually
Vitamin D	Annually
Parathyroid hormone	Annually
Bone density by DEXA scan	Annually
Visual acuity and dilated ophthalmology examination	Annually for patients on iron chelation therapy
Audiology examination	Annually for patients on iron chelation therapy
Vitamin C level	Annually for patients on iron chelation therapy
Zinc level	Annually for patients on iron chelation therapy

DEXA = dual-energy x-ray absorptiometry; EKG = electrocardiogram; HIV = human immunodeficiency virus; FSH = follicle-stimulating hormone; LH = luteinizing hormone; PCR = polymerase chain reaction; TSH = thyroid-stimulating hormone

Khandros E, et al. Hematol Oncol Clin North Am. 2019;33(3):339-353.

Beta Thalassemia: Clinical Management

- Regular blood transfusions
- Chelation therapy for hemosiderosis
- Daily doses of folic acid
- Possible surgical removal of gallbladder
- No iron supplements
- Erythropoietin-stimulating agents
- Bone marrow transplantation

- Luspatercept
  - Trap-ligand: Binds to TGFβ ligands to suppress SMAD2/3 signaling; restores erythropoiesis by increasing the number and improving the quality of mature RBCs
- How administered
  - Once every 3 weeks by subcutaneous injection; titrated dosing
- Serious AEs included cerebrovascular accident and DVT
- Most common AEs: headache (26% vs 24%), bone pain (20% vs 8%), arthralgia (19% vs 12%), fatigue (14% vs 13%), cough (14% vs 11%), abdominal pain (14% vs 12%), diarrhea (12% vs 10%) and dizziness (11% vs 5%)

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.

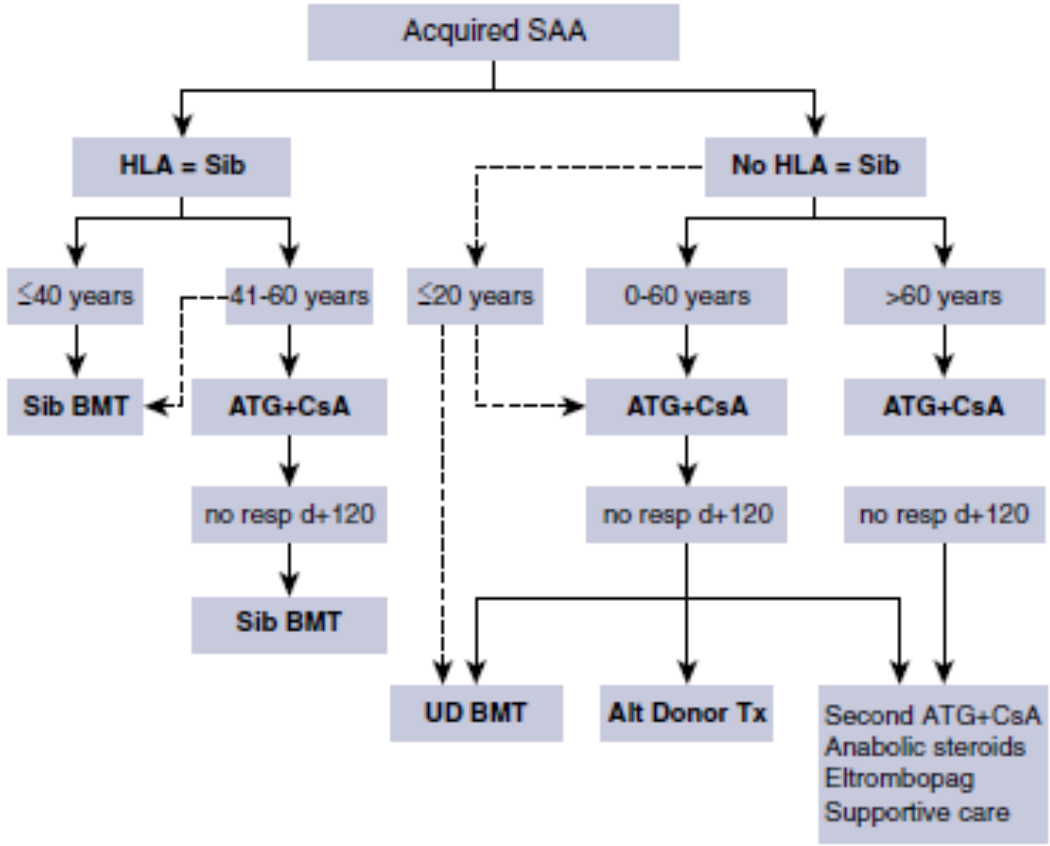
Aplastic Anemia: Presenting Signs and Symptoms/Differential Diagnosis of AAA

- 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

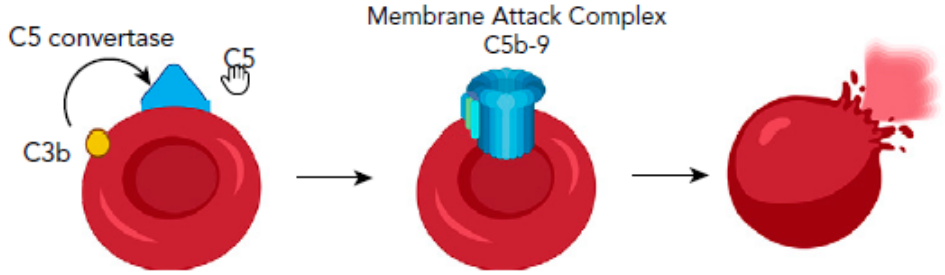
- The 2-year mortality of patients with SAA without immunosuppressive therapy exceeds 80%
  - Severe infections are the most common cause of death
- Supportive care is essential concurrently with immunosuppressive therapy
  - Transfusion support
  - Anti-infective prophylaxis
  - Other supportive care
- 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
  - 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
  - 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/

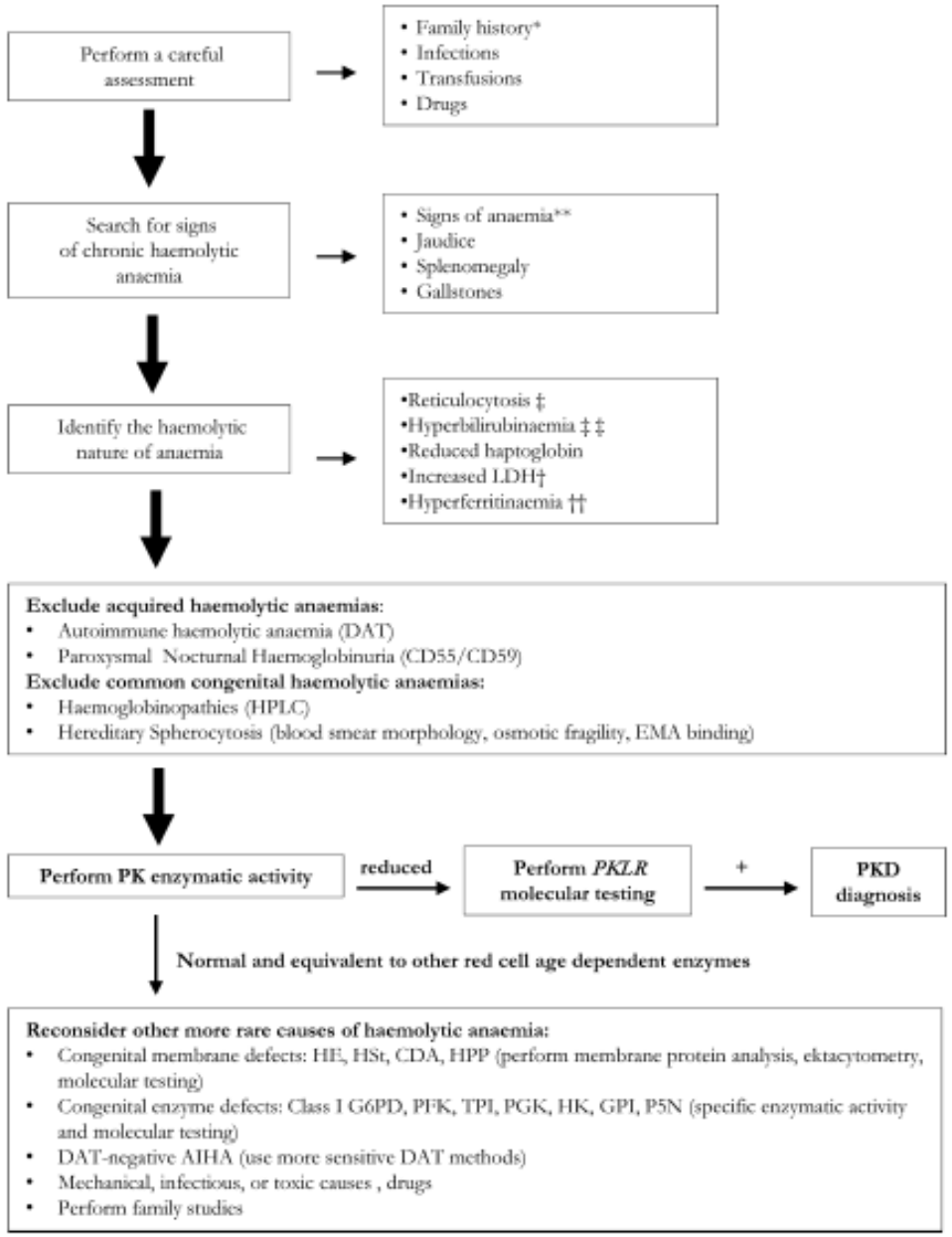
Red Cell Pyruvate Kinase (PK) Deficiency (PKD): Pathophysiology

- 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!