AUTOIMMUNE CYTOPENIAS

Autoimmune Hemolytic Anemia (AIHA)

Etiology and Overview[1,2]

- Nongenetic origin, but pathogenesis involves genetic, immunologic, and environmental factors, which cause increased, premature destruction of red blood cells (RBCs), with or without complement activation. Idiopathic in 50% of cases.
- When cause unknown, AIHA affects twice as many women as men; more common in women < 50 years old. Annual AIHA incidence is between 1 in 35,000 and 1 in 80,000 in North America and Western Europe.
- Can occur secondary to another medical condition or alone without apparent precipitating factor, and may develop gradually or occur suddenly.
  - Secondary causes include lupus, other autoimmune diseases; CLL, NHL, other hematologic malignancies; Epstein-Barr virus, CMV, HIV; mycoplasma pneumonia; hepatitis.
  - Can occur with certain medications (penicillin, quinine, methyldopa, sulfonamides) which can cause positive DAT (direct antiglobulin test)/Coombs but do not usually cause clinically significant hemolysis. Can also occur after blood and marrow stem cell transplant.
- Severity determined by RBC lifespan, rate of RBC replacement in bone marrow.
- Two main types: warm antibody hemolytic anemia (wAIHA), cold antibody hemolytic anemia (cAIHA).[3]
  - wAIHA: Autoantibody extravascular destruction of RBCs (mostly by IgG autoantibodies) primarily in spleen and occurring at temperatures above normal body temperature; affects people of all ages but median age of onset 52 years; may be idiopathic autoimmune or secondary to another disease (eg, lymphoid malignancy). Often severe and can be fatal.
  - cAIHA[3]: Autoantibody destruction of RBCs (mostly by IgM autoantibodies which are cold agglutinins) triggered by exposure to temperatures below normal body temperature (37°F to 39°F). More common in elderly.
- Two types of cAIHA
  - Cold agglutinin disease (CAD): usually IgM-mediated and characterized by RBC agglutination and complement binding, followed by extravascular hemolysis (mainly in liver, spleen) in absence of underlying disorder. Often associated with lymphoma. Can occur secondary to infectious disease (eg, *Mycoplasma pneumoniae*, mumps, CMV, infectious mononucleosis), immunoproliferative disorders (eg, non-Hodgkin lymphoma, CLL, MGUS), or connective tissue disorders (eg, RA, SLE). Prevalence, 16 per million; incidence, 1 person per million annually. Approximately 90% of cases associated with low-grade lymphoproliferative B-cell disorder; development of overt lymphoma rare.
  - Paroxysmal cold hemoglobinuria (PCH, also called Donath-Landsteiner syndrome): polyclonal IgG antibodies bind to RBCs in temperatures colder than normal body temperature and trigger complement-mediated intravascular hemolysis upon reheating. PCH very rare: 2% to 10% of AIHA cases and annual incidence 1 in 35,000 in North America.[4] Acute cases seen almost exclusively in children, typically induced by infection (mainly upper respiratory, with causative agent often not identified; has been associated with varicella zoster virus and mumps virus infections).

Onset and Symptoms[5]

- CAD: Typically develops between ages 40 and 80 years; median age of onset is 65. Many symptoms similar to other anemias, but variable and result from hemolysis and circulatory effects: hemolytic anemia, profound weakness and fatigue, dyspnea, acrocyanosis (bruising/redness of skin on distal parts of body), or Raynaud's sign under cold conditions, jaundice and/or splenomegaly, hemoglobinuria (dark brown urine), pallor, tachycardia, chills, fever, backache, headache. Jaundice (due to Hgb degradation into bilirubin) is primary clinical sign.
- PCH[4,6]: Sudden onset with severe intravascular hemolysis after exposure to cold temperatures (eg, from drinking or washing hands in cold water). Symptoms variable. Acute cases typically include high fever, chills, severe back and leg pain, hemoglobinuria (dark red to brown urine). Other symptoms: fatigue, dyspnea, pallor, temporary hepatomegaly and splenomegaly; less commonly, headache, nausea/vomiting, diarrhea. Chronic forms: repeated hemolytic episodes with cold exposure.

Diagnosis

- CAD[7]
  - Evidence of anemia (CBC), plus evidence of hemolysis (high reticulocyte count, high LDH, high indirect bilirubin, low haptoglobin)
  - Positive Coombs (direct antiglobulin) test for C3 (complement component 3) with or without IgG on RBCs; clumping of RBCs in presence of reagent establishes diagnosis, may suggest cause
  - Cold agglutinin titer of ≥ 64 at 4°C
  - (Evaluation for secondary causes of CAD)
- PCH[4]
  - Evidence of hemoglobin in urine and anemia linked to hemolysis (CBC), plus high LDH and high bilirubin in blood, urine
  - Negative Coombs test
  - Positive Donath-Landsteiner test
  - Anti-P specificity of IgG autoantibodies
- wAIHA[8]
  - Evidence of anemia caused by hemolysis, plus high reticulocyte count, high LDH, high indirect bilirubin, low haptoglobin
  - Positive Coombs text
  - (Evaluation for secondary causes of wAIHA)

Treatment and Patient Education

Individualized treatment based on specific patient factors and type and severity of AIHA. Supportive care for symptomatic patients should include folic acid and (if needed) vitamin supplements. Patients with severe anemia (Hgb < 6 g/dL) or hemodynamic instability should receive blood transfusions. In patients with secondary AIHA, treatment of any underlying autoimmune disease(s) essential.[9]

- CAD diagnosis[5]
  - Evaluate for underlying conditions (lymphoma, infection, autoimmune disease, separate underlying blood disorder).
  - Advise patient on avoidance of cold exposure (esp. to head, face, extremities).
  - Take measures to reduce hemolysis, circulatory symptoms (eg, if hospitalized, prewarm IV infusions).
  - Mild or slowing RBC destruction: treatment not required.
  - Accelerating RBC destruction: Rituximab is first-line treatment, in combination with fludarabine, bendamustine, or prednisone (although typically doesn't respond to steroids); rituximab also used to treat relapses.

  - Cases secondary to other medical conditions: treatment of underlying disorder (eg, lymphoma) often improves symptoms.
  - Treatment resistance may require total splenectomy plus immune suppression with oral azathioprine or cyclophosphamide and (in severe cases) blood transfusion.
- PCH[4]: Most cases self-limited, with treatment not needed if mild clinical symptoms. Treatment is symptomatic (avoidance of cold triggers, warm RBC transfusion as appropriate); lasting effectiveness not seen with rituximab, corticosteroids, splenectomy. Temporary reduction of hemolysis with plasmapheresis.
  - wAIHA[8]: Supportive care, including corticosteroids, rituximab. Typically requires long courses of steroids. In severe cases, immunosuppressive therapy, blood transfusions, or splenectomy.

Prognosis/Outlook

- Death from AIHA is rare; outlook depends on timely identification and management of underlying cause(s).
- Promising research into agents targeting B and T cells, macrophages and plasma, as well as therapies inhibiting different points along complement pathways.[9]
- CAD not associated with significantly reduced life expectancy, but CAD may increase risk of thromboembolism; further clinical studies needed.[5]
- PCH generally resolves when symptoms treated, with patients asymptomatic between episodes. Complications of continued attacks include severe anemia and (rarely) kidney failure.[6]
- wAIHA associated with increased risk of venous thromboembolism, notably posing increased risk of pulmonary embolism (due to DVT) in legs; more rarely, arterial clots increase risk of myocardial infarction and stroke.[8]
- In May 2020, First International Consensus Group published guidelines on AIHA aimed at standardizing diagnosis and treatment of AIHA subtypes, plus overview of current novel therapies.[10]

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Immune Thrombocytopenia (ITP)

Etiology and Overview[1-4]

- Previously known as idiopathic thrombocytopenic purpura. An acquired, not inherited, thrombocytopenia that can be primary or secondary (due to other medical conditions) with < 200,000 cases in the US per year. Thought to be caused by antibody-mediated destruction of platelets due to B-cell production of immunoglobulin G autoantibodies against platelet antigen and resulting in low platelet count via platelet destruction and/or decreased production of platelets. The etiology is not entirely understood but there are key differences between childhood and adult ITP. There is a much higher likelihood of spontaneous remission in children than adults and treatment guidelines favor observation in children vs treatment in adults. Some investigators believe condition may be triggered in children by viral infection such as hepatitis C or human immunodeficiency virus (HIV). May be characterized by external and/or internal bleeding, but many patients present as asymptomatic.
- Primarily characterized by reduced platelet counts. No abnormal platelet morphology.
- Classified based on disease duration: acute (< 3 months), persistent (3–12 months), or chronic (> 12 months).
  - Acute: Most common ITP type and more common in children, with males and females affected equally. Majority (80%) of pediatric cases are self-limited and resolve within 1 year and often sooner.
  - Chronic: Mostly affects adults; prevalence in women 2 to 3 times that in men. Proportion of adults with chronic ITP exceeds 50% in most series. Adolescents with ITP have clinical course similar to adults.
- Updated guidelines for management of ITP were published in 2019 by the American Society of Hematology and by an international panel.[3,4]

Onset and Symptoms[1-3]

- Many patients asymptomatic at diagnosis
- Easy or excessive bruising/bleeding
- Rash-like petechiae and/or purpura on skin and mucous membranes (eg, mouth)
- Nosebleeds; bleeding from the gums during dental work; other uncontrolled bleeding, including blood in urine or stool; hematomas; menorrhagia in women
- Rarely, life-threatening intracranial bleeding
- Fatigue and reduced quality of life

Diagnosis[5]

- Diagnosis based on exclusion of other potential causes (eg, primary marrow disorder or drug-induced immune thrombocytopenia caused by antithrombotic agents such as abciximab) and careful clinical evaluation, based on suspicion of ITP; no specific diagnostic test available. A trial of steroids is often diagnostic as no other cause of thrombocytopenia would respond to this.
- Workup: history, physical examination, CBC with differential, peripheral blood smear.
- Antiplatelet antibody testing should *not* be performed; *not* diagnostic and does *not* correlate with outcomes (though antiplatelet antibodies found in 50% patients).
- Clinical history should ascertain: recent infectious symptoms, possible effects of medications, liver disease, and rheumatologic and lymphoproliferative disorders.
- Screen all adults for HIV, hepatitis C.

- Potential additional testing (healthcare provider discretion): other viral serologies, antiphospholipid antibodies, anti–nuclear acid antibodies, thyroid function test, Coombs test, testing for *Helicobacter pylori*, DIC panel, tests for type 2 von Willebrand disease and similar bleeding disorders, and quantitative immunoglobulins.
- Bone marrow biopsies indicated when increased risk of myelodysplastic syndromes (selected patients > 60 years old), or in patient with suspicious peripheral smear or suspected bone marrow failure syndrome.

Treatment and Patient Education[3,5]

- Current ASH guidelines (updated in 2019) recommend corticosteroid treatment for severe thrombocytopenia (platelet count < 30,000 µL) and/or newly diagnosed disease with clinically important bleeding.
- Hospital admission recommended for newly diagnosed adults with minimal/no bleeding and platelet counts < 20,000 µL.
- Close observation recommended for platelet counts 20,000 µL–30,000 µL.
- Regular monitoring and patient counseling for counts 30,000 µL–50,000 µL; educate on signs/symptoms requiring urgent evaluation, including sudden drops in platelet counts.
- *New ASH recommendation*: Corticosteroids (dexamethasone, prednisone) still frontline therapy for newly diagnosed ITP in adults, but not beyond 6 weeks.
  - If fast response needed, add intravenous immunoglobulin (IVIG) to corticosteroids.
  - IVIG and anti-D therapy recommended if corticosteroids contraindicated.
- *New ASH recommendation*: Thrombopoietin receptor agonists (eltrombopag, romiplostim, or avatrombopag) as front-line treatment, due to good response rates seen at 1 month and durable responses.
  - Second-line treatment: rituximab (preferred) and splenectomy.
  - Refractory ITP: Post-splenectomy, consider rituximab, corticosteroids, thrombopoetin receptor agonists.
  - Third-line treatment options: azathioprine (antimetabolite), cyclophosphamide, danazol, fostamatinib (SYK inhibitor), other immunosuppressants.

Prognosis/Outlook[5]

- Treatment not always required; depends on bleeding severity and platelet count.
- Medical or surgical treatment required in selected pediatric cases.
- Acute form typically resolves in weeks or months and platelet count returns to normal within 1 year in 80%.
- Chronic form can last for decades but most patients, even with severe chronic ITP, can stop treatment at some point.
- Recent advances in novel therapies promising for patients with advanced or relapsed/refractory ITP.[6]

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Hemophagocytic Lymphohistiocytosis (FHLH, HLH)

Etiology and Overview[1-4]

- Hystiocytic disorders considered orphan disease; < 200,000 in US.
- Two forms: primary or familial hemophagocytic lymphohistiocytosis (FHLH) and secondary or acquired HLH (no family history).
- In patients with COVID-19, secondary HLH may occur, with cytokine storm responsible for unexplained progressive fever, cytopenia, neurologic and renal impairment, and ARDS (acute respiratory distress syndrome).[5]
- FHLH > autosomal recessive inheritance with 5 subtypes. Genetic cause of type 1 unknown but associated with mutation on chromosome 9; types 2 to 5 caused by mutations in *PRF1*, *UNC13D*, *STX11*, and *STXBP2*, respectively.
- Acquired HLH often diagnosed in older people; causes include infection, immunosuppressive medications, autoimmune diseases, immunodeficiencies, certain cancers or metabolic disorders.
- HLH resulting from immune response to Epstein-Barr or other virus possibly due to X-linked lymphoproliferative disease caused by mutation in *SH2D1A* or *XIAP*.

Onset and Symptoms[1-4]

- Prolonged high fever; irritability and fatigue; liver and spleen dysfunction; cytopenia; enlarged lymph nodes; immunologic dysfunction; skin rash; seizures and coordination problems; eye, facial, and nerve weakness; sudden blindness; and, very rarely, paralysis and coma.

Diagnosis[1-4]

- Identification of mutation in one of the associated genes, 5 or more of the following symptoms: fever; splenomegaly; cytopenia; elevated blood levels of triglycerides or low blood levels of fibrinogen; bone marrow, spleen, or lymph node biopsy reveals hemophagocytosis; suppressed/absent NK cell function; high blood levels of ferritin; elevated blood levels of CD25 (indicating prolonged T-cell activation).

Treatment and Patient Education[1-4]

- Choice of treatment depends on symptom severity, age at onset, underlying cause(s).
- FHLH: Chemoimmunotherapy followed by allogeneic hematopoietic cell transplantation curative, and should be performed as soon as possible after diagnosis.
- Emapalumab approved November 2018 for adult and pediatric (including newborn) patients with primary HLH and refractory, recurrent, or progressive disease or intolerance of conventional HLH therapy.

Prognosis/Outlook[1-4]

- Untreated FHLH: poor prognosis; median survival < 6 months after diagnosis.
- Treated FHLH: poor 5-year survival of 21% to 26%.
- Acquired HLH: higher mortality when associated with tumors (like T-cell lymphoma), lower mortality of 8% to 22% when associated with autoimmune diseases.
- Treatment options improving.

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Castleman's Disease

Etiology and Overview[1]

- Rare, with symptoms similar to those of many other diseases, but all types share specific histologic changes in the lymph nodes, so biopsy is essential to diagnosis.
- Characterized by overproduction of B lymphocytes and other immune cells.
- Some cases linked to human herpesvirus 8 (HHV8). More common in HIV-positive patients.
- Two main subtypes, unicentric and multicentric. Each has different causes, symptoms, and treatments.
  - One unicentric subtype: unicentric Castleman disease (UCD), HHV8-negative associated.
  - Two multicentric subtypes: multicentric Castleman disease (HHV8-positive MCD) and HHV8-negative/idiopathic multicentric Castleman disease (iMCD).
  - Some iMCD patients have specific subform called TAFRO (described below).

Onset and Symptoms[1]

- Symptoms often similar to those of common illnesses, certain cancers and autoimmune diseases. Can range from mild symptoms with gradual lymph node enlargement to severe symptoms with sudden onset and life-threatening organ dysfunction.
  - UCD: Milder symptoms; lymph node enlargement in only one region of body, organs rarely affected; no known cases of UCD transformation to MCD.
  - MCD: Symptoms more severe than UCD, lymph node enlargement in multiple areas of body.
- Common symptoms may include: flulike symptoms (fever, loss of appetite, night sweats, nausea/vomiting), weakness/fatigue, unintended weight loss, hepatomegaly/splenomegaly, peripheral neuropathy, cherry hemangioma skin rash, edema, ascites, renal and hepatic dysfunction.

  Common laboratory findings: Platelet count very high or very low, elevated C-reactive protein levels, hypergammaglobulinemia.
- TAFRO symptoms: **t**hrombocytopenia, **a**nasarca, **f**ever (or elevated c-reactive protein), **r**eticulin fibrosis, **o**rganomegaly (splenomegaly, hepatomegaly).

Diagnosis

- Lymph node biopsy and histologic evaluation for specific Castleman's disease features essential.[1,2]
- International Consensus Guidelines for diagnosis and management of UCD (published December 2020), from Castleman Disease Collaborative Network.[3]

Treatment and Patient Education[1]

- UCD: Surgery to completely remove affected large lymph node(s) considered curative if previous clinical and laboratory values return to normal.
- Unresectable UCD with persistent symptoms: Consider radiotherapy, possible use of treatment(s) for iMCD if affected lymph node(s) cannot be entirely removed; medical team should discuss options with patient based on location of enlarged nodes.
- HHV8-positive MCD: Rituximab (anti-CD20 antigen) very effective via B-cell depletion, with less immunosuppression than chemotherapy.
- HHV-negative MCD/iMCD: Siltuximab and tocilizumab (both target IL6) considered first-line therapy; unknown why rituximab does not work as well but rituximab or chemotherapy used when no response to anti-IL6 treatments.

- International Consensus Guidelines for treatment of iMCD, from Castleman Disease Collaborative Network, published in November 2018.[4]
- Castleman Disease Collaborative Network recommends following for UCD after lymph node excision: Annual CT (discontinued after 5 years if patient remains disease-free) and specific tests (CBC, LDH, chemistries with liver and renal function and electrolytes, albumin, CRP, quantitative immunoglobulins).[3]

Prognosis/Outlook[1,3,4]

- UCD: Average survival time after diagnosis 10 years; no impact on normal life expectancy.
- MCD: 5-year OS 65% in 2012 literature review. Castleman Disease Collaborative Network leading global study to update data. Emerging IL6 treatments may improve prognosis.

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Mastocytosis

Etiology and Overview[1-4]

- Occurs at all ages. US prevalence about 1 in 1,000. Slight male predominance in childhood, slight female predominance in adulthood.
- Two forms: skin and systemic
  - Skin mastocytosis more common in children, with about 80% of pediatric cases appearing before age 1 year.
  - Systemic mastocytosis (with pathologic accumulation of mast cells in nonskin tissue, typically bone marrow) more common in adults.
- Some genetic associations; caused by mutations resulting in mast cell clones that overproduce and spontaneously release histamine and other inflammatory mediators in multiple organs, including bone marrow. *KIT* mutation fairly common.

Onset and Symptoms[2]

- Urticaria pigmentosa (freckle-like spots), most apparent on skin areas more prone to rubbing, pressure (eg, inner thighs, stomach); blistering seen exclusively in children under 4 years of age.
  - Can transform to hives if skin is scratched or exposed to sudden changes (eg, hot shower); known as Darier's sign and due to mast cell degranulation (release of histamine, other mediators).
- Mast cells sometimes collect in skin to form a single lump/lesion rather than rash.
- Rarely, idiopathic mast cell activation syndrome: encompasses symptoms of anaphylaxis (hives/ swelling, hypotension, shortness of breath, and itching, nausea/vomiting, diarrhea, fainting, headache, uterine cramps/bleeding, flushing, musculoskeletal pain)
- Indolent systemic mastocytosis (ISM): Most common systemic form of mastocytosis. Low mast cell burden (< 5% mast cells in aspirate smears) but no evidence of tissue dysfunction or overt hematologic disorder, with symptoms related to level of mast cell mediators. Macropapular skin lesions in majority of patients. Some patients may present with hepatomegaly, splenomegaly, GI symptoms such as stomach pain, diarrhea (rare; due to accumulation of mast cells in stomach/intestine).
- Systemic smoldering mastocytosis (SSM): high mast cell burden but no evidence of tissue dysfunction or overt hematologic disorder. World Health Organization (WHO) diagnostic criteria comprise two of three "B" findings: > 30% bone marrow infiltration with mast cells or tryptase levels > 200 ng/mL); splenomegaly or hepatomegaly with no hypersplenism or liver dysfunction; hypercellular marrow or presence of mild dysplastic changes but no criteria for diagnosis of another hematologic disorder (eg, myelodysplastic syndromes, myelodysplastic neoplasms).[5]
- Aggressive systemic mastocytosis (ASM): high levels of mast cell infiltrates cause impaired organ function/ organ shutdown (usually liver, gut, bone/bone marrow). High mast cell burden in tissues and signs of tissue dysfunction called "C-findings." One of following C-findings must be present: high-grade marrow infiltration with cytopenias (ANC < 1,000/mL, Hgb < 10 g/dL, platelets < 100,000/ mL); hepatomegaly with liver dysfunction (eg, portal hypertension with ascites); splenomegaly with hypersplenism; malabsorption with hypoalbuminemia, weight loss; osteolytic lesions > 2 cm, with pathologic bone fractures.

Diagnosis of Systemic Mastocytosis[2,6]

- Skin examination for lesions characteristic of mastocytosis (small, brownish, flat or elevated spots sometimes surrounded by reddened skin); lesions urticate (Darier's sign) when stroked several times with tongue depressor.
- Careful palpation of liver, spleen, lymph nodes
- Biopsies of skin and iliac crest bone marrow; aspirated marrow used to test for mutation of mast cell growth receptor *KIT* (*KIT* D816V) and abnormal mast cell CD25 expression.

- Evaluation for presence of mast cell mediators in blood (eg, increased serum levels of tryptase) and urine (increase in 24-hour period of n-methyl histamine, prostaglandin-D_2 and/or its metabolite 11 beta-prostaglandin F2 alpha)
- CBC with differential; LFTs; serum albumin, LDH, alkaline phosphatase

Treatment of Systemic Mastocytosis and Patient Education[1,2,4,5]

- Avoid dietary and environmental triggers of increased release of mast cell mediators.[7]
- Once- or twice-daily dosing of H1 and H2 antihistamines, cromolyn sodium (for GI symptoms), ketotifen, leukotriene-modifying agents, epinephrine (to manage hypotension episodes/anaphylactic shock); possibly, for aggressive mastocytosis: immune modulators, chemotherapy for mast cell cytoreduction (with cladribine, an antimetabolite) as well as interferon-alfa (which is not preferred treatment, due to poor tolerability/flulike side effects)
- Midostaurin (KIT kinase inhibitor) for aggressive form (ASM)
- Epinephrine injectors, with patients instructed on their use in management of anaphylactic reactions
- Bone health monitoring (DEXA scan) for osteoporosis management
- Possible role for stem cell transplant in patients with advanced disease

Prognosis of Systemic Mastocytosis/Outlook[2]

- ISM: life expectancy comparable to general population, with < 5% risk of progression to advanced form of mastocytosis. SSM: higher risk of progression to advanced variant of mastocytosis. ASM: shorter life expectancy, patients more likely to require mast cell cytoreductive therapies.
- NDA submitted December 2020 for avapritinib, a highly selective, potent oral inhibitor of *KIT* D816V, in advanced SM.[8]

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