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

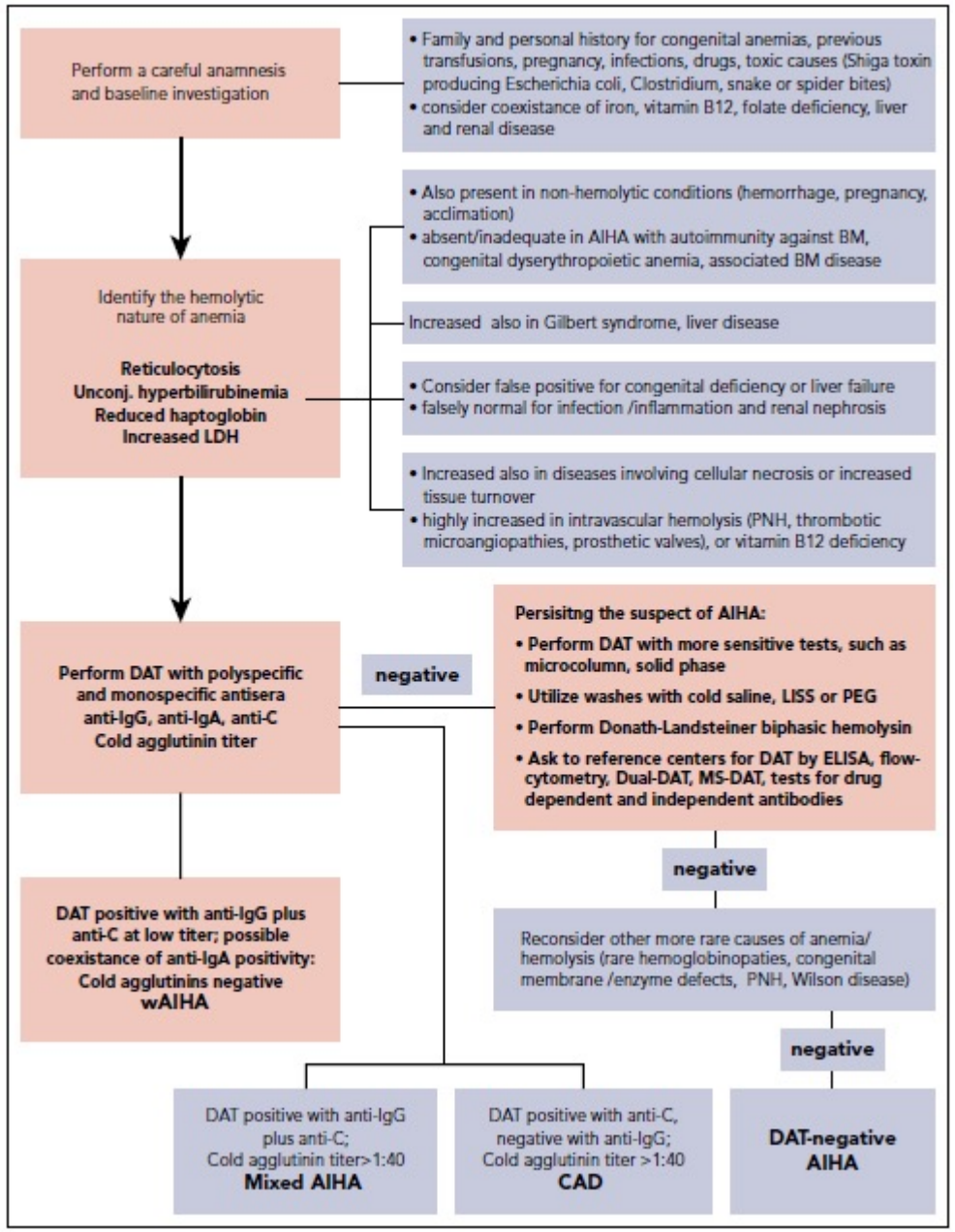
- Physical findings
  - Excessive fatigue, may be abrupt
  - Lightheadedness
  - Dark urine
  - Jaundice
  - Pallor
  - Palpitations
  - Symptoms associated with the underlying illness (may be undiagnosed in some cases)
- Laboratory findings
  - Normocytic anemia with spherocytes found on the peripheral 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

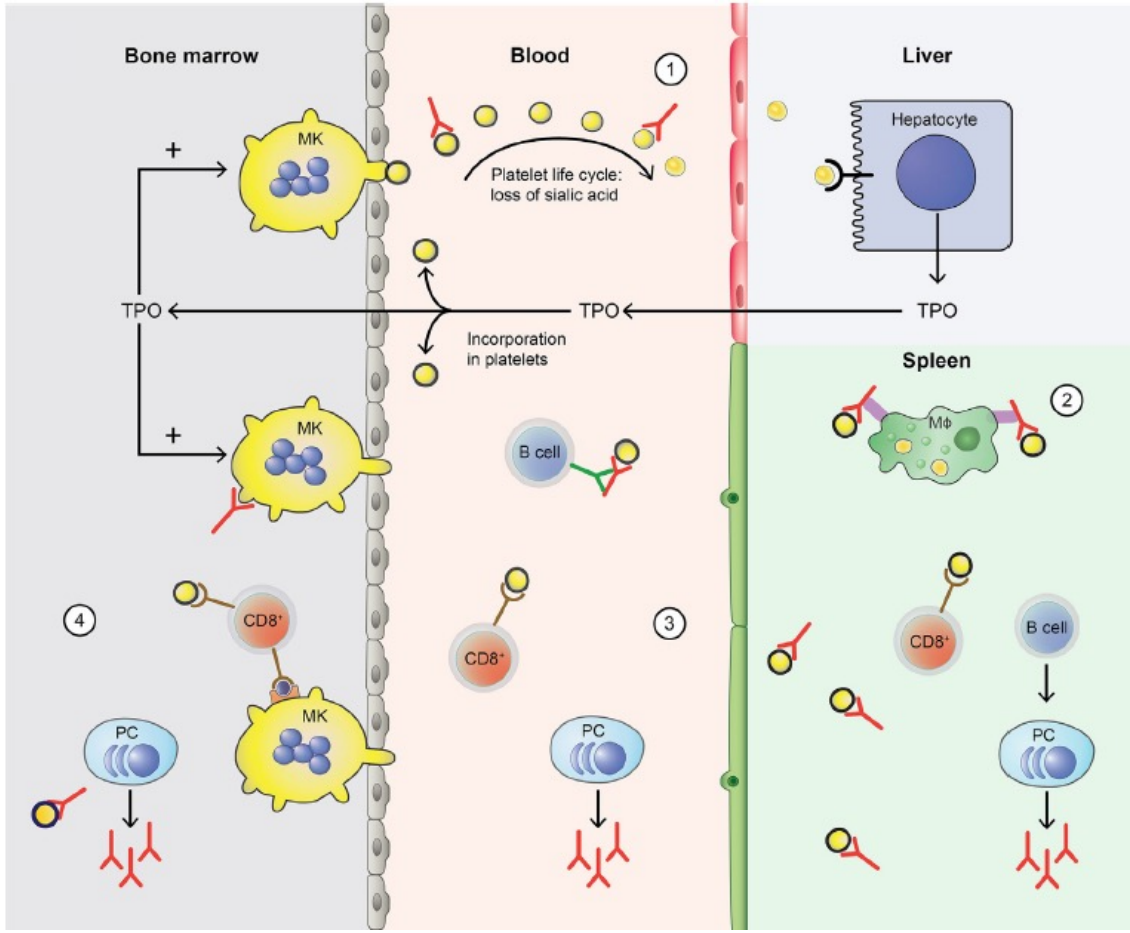
Barcellini W, et al. *Blood*. 2021;137(10):1283-1294.

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

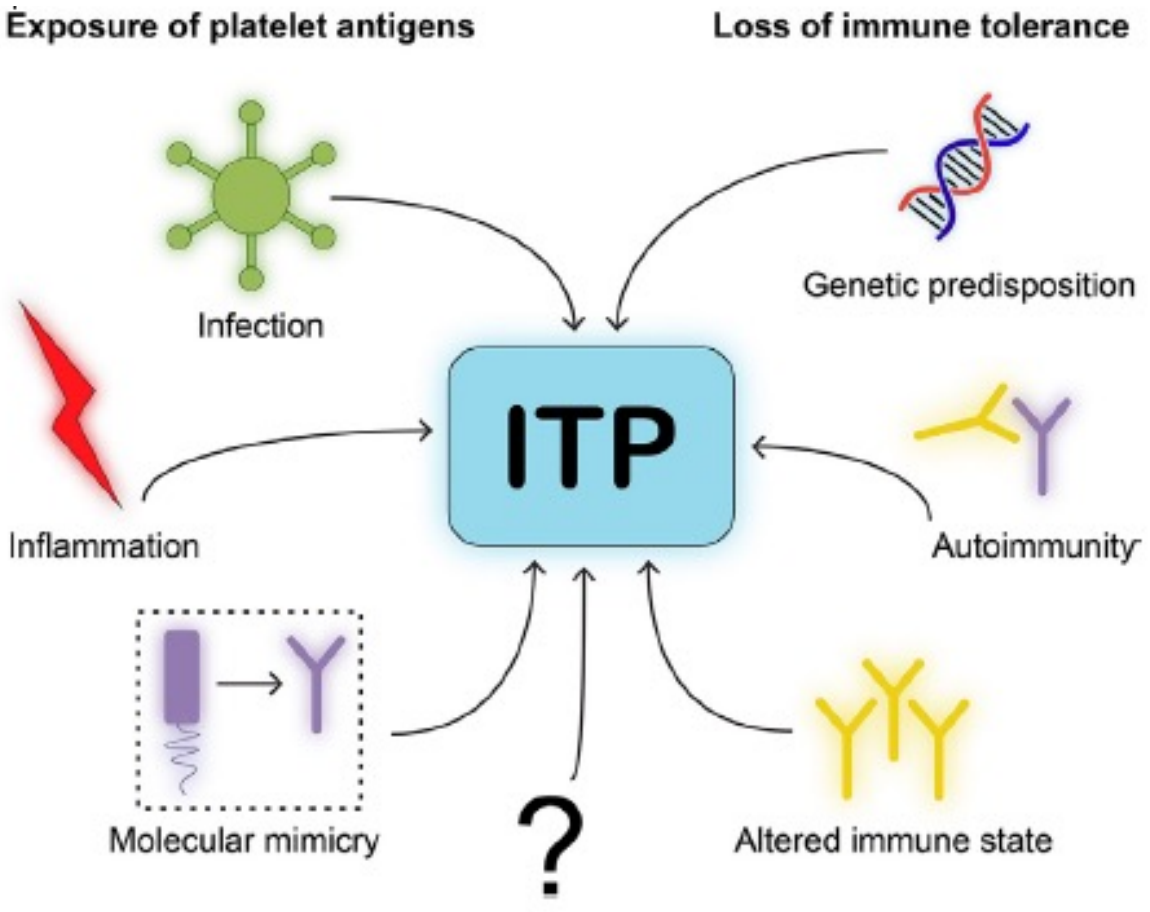
- Definition: unexplained low platelet count of < 100 × 10^9/L (platelet count < 100,000)
  - Previously known as idiopathic thrombocytopenia purpura
- Thrombocytopenia mediated by
  - Autoantibodies and autoreactive CD8+ cytotoxic T cells (Tc)
    - Directly lyse platelets
    - Inhibit megakaryocytes (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

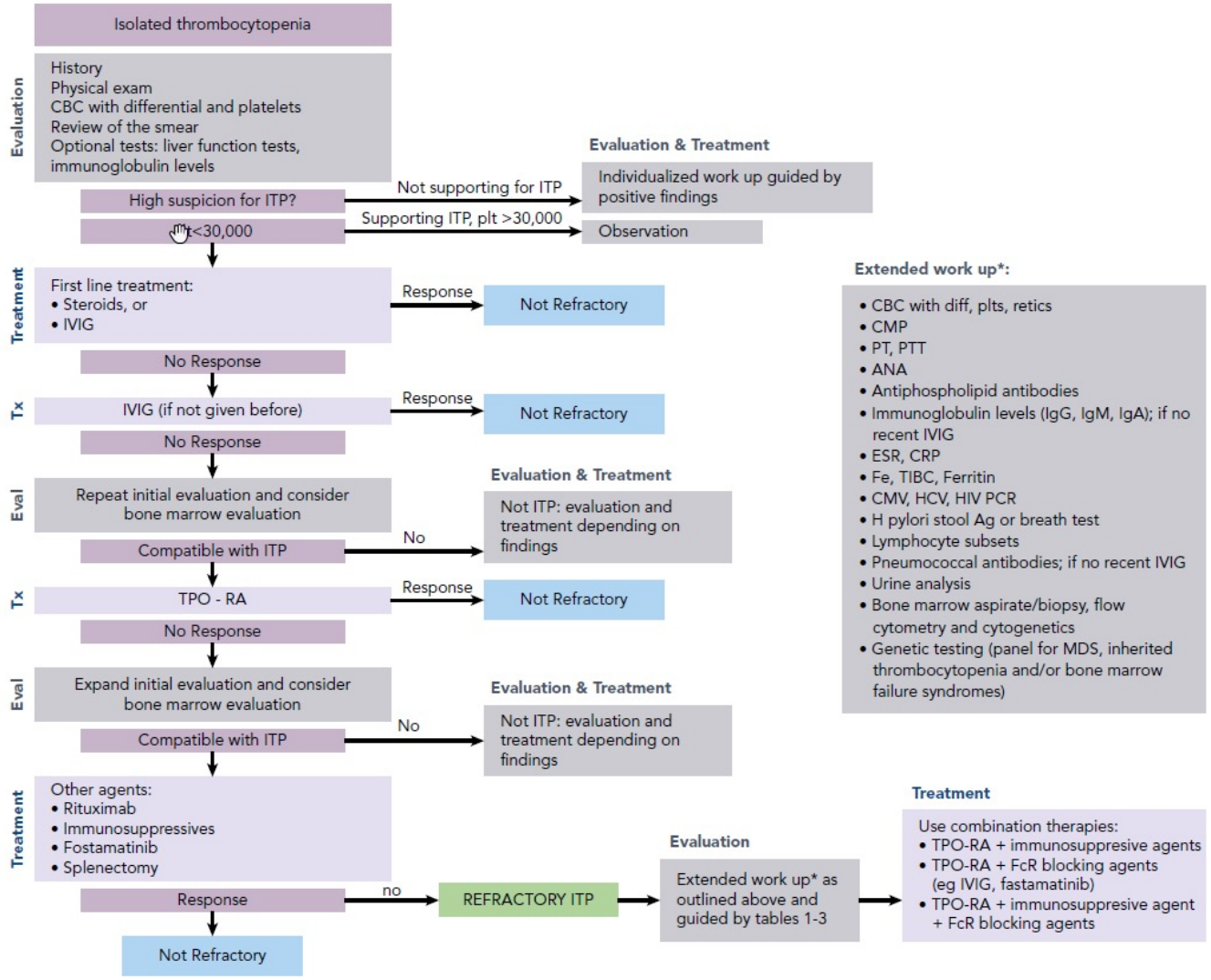
IVIG = intravenous immunoglobulin

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

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/