Thrombocytopenia in the Hospitalized Setting

Thrombocytopenia, a common finding in hospitalized patients, can result from a variety of causes ranging from benign to life-threatening. This pamphlet provides students with a detailed guide to evaluate, diagnose, and treat thrombocytopenia in the hospital setting, with case scenarios to apply the knowledge.

Evaluation

- **Definition:** Thrombocytopenia is defined as a platelet count <150,000/μL; severe if <50,000/μL, critical if <20,000/μL (increased bleeding risk).
- History:
  - **Symptoms:** Easy bruising, petechiae, purpura, epistaxis, gingival bleeding, hematuria, melena, or heavy menstrual bleeding.
  - **Risk Factors:** Recent infections (viral, bacterial), medications (e.g., heparin, chemotherapy), alcohol use, liver disease, malignancy, recent transfusions, or surgeries (e.g., cardiopulmonary bypass).
  - **Systemic Symptoms:** Fever (infections, malignancy), weight loss (malignancy), night sweats (lymphoma), or neurologic symptoms (TTP).
- Physical Exam:
  - **Skin:** Petechiae (pinpoint red spots), purpura (larger bruises), ecchymosis.
  - **Mucosal Bleeding:** Epistaxis, gingival bleeding, conjunctival hemorrhage.
  - **Organomegaly:** Splenomegaly (sequestration, cirrhosis), lymphadenopathy (malignancy, infections).
  - **Neurologic:** Altered mental status, focal deficits (TTP, HUS).
- Initial Labs:
  - **CBC:** Platelet count, mean platelet volume (MPV), check for anemia (hemolysis, bleeding) or leukopenia (marrow failure).
  - **Peripheral Smear:** Assess platelet morphology (large platelets = destruction; small = marrow failure), schistocytes (TTP/HUS), blasts (leukemia).
  - **PT/INR, PTT:** Assess for coagulopathy (DIC, liver disease).

Causes

- Decreased Platelet Production:
  - Bone Marrow Suppression:
    - **Chemotherapy:** Cyclophosphamide, cisplatin (direct marrow toxicity), pancytopenia.
    - **Radiation:** Pelvic/spinal radiation → Hypocellular marrow.
    - **Alcohol:** Direct toxicity to megakaryocytes, often with macrocytosis.
  - Infections:
    - **Viral:** HIV (marrow suppression, immune destruction), HCV (cirrhosis, hypersplenism), EBV/CMV (marrow suppression), parvovirus B19 (pure red cell aplasia with thrombocytopenia in sickle cell).
    - **Bacterial:** Sepsis (endotoxin-mediated suppression), TB (marrow infiltration).
  - Marrow Infiltration:
    - **Leukemia:** AML/ALL (blasts replace marrow), pancytopenia, blasts on smear.
    - **Lymphoma:** Bone marrow involvement (e.g., DLBCL, CLL), often with lymphadenopathy.
    - **Metastatic Cancer:** Breast, prostate, lung (marrow fibrosis), teardrop cells on smear.
- Nutritional Deficiencies:
  - **B12/Folate Deficiency:** Megaloblastic anemia, pancytopenia, hypersegmented neutrophils.
- **Aplastic Anemia:** Idiopathic, post-viral (e.g., parvovirus, hepatitis), drugs (chloramphenicol), hypocellular marrow, pancytopenia.
- **Myelodysplastic Syndrome (MDS)**: Dysplastic megakaryocytes, often progresses to AML, pancytopenia.
- Increased Platelet Destruction:
  - Immune-Mediated:
    - **Immune Thrombocytopenia (ITP):** Primary (idiopathic) or secondary (SLE, HIV, HCV), isolated thrombocytopenia, large platelets on smear.
    - **Drug-Induced Immune Thrombocytopenia:** Quinine, vancomycin, sulfonamides → Anti-platelet antibodies, rapid onset (days-weeks).
    - **Heparin-Induced Thrombocytopenia (HIT):** Heparin exposure (5-10 days), 4T score (Thrombocytopenia, Timing, Thrombosis, oTher causes), antibodies to PF4-heparin complex, thrombosis risk.
  - Non-Immune-Mediated:
    - **Thrombotic Thrombocytopenic Purpura (TTP):** ADAMTS13 deficiency → Microthrombi, schistocytes, pentad (thrombocytopenia, MAHA, renal failure, neurologic symptoms, fever).

        - **Hemolytic Uremic Syndrome (HUS):** Shiga toxin (E. coli O157:H7), atypical HUS (complement dysregulation), MAHA, renal failure.
        - **Disseminated Intravascular Coagulation (DIC):** Sepsis, trauma, malignancy → Consumptive coagulopathy, schistocytes, high D-dimer, low fibrinogen.
- **Mechanical:** Prosthetic valves, ECMO, IABP → Platelet shearing, schistocytes.
- Platelet Sequestration:
    - Splenomegaly/Hypersplenism:
        - **Cirrhosis:** Portal hypertension, hypersplenism, often with thrombocytopenia and leukopenia.
        - **Myelofibrosis:** Splenomegaly, teardrop cells, marrow fibrosis.
        - **Infections:** Malaria, leishmaniasis → Splenic sequestration, parasitemia on smear.
- **Kasabach-Merritt Syndrome:** Hemangioma → Localized DIC, consumptive thrombocytopenia.
- Dilutional:
    - **Massive Transfusion:** >10 units PRBCs in 24h → Dilution of platelets, often with coagulopathy.
    - **Fluid Resuscitation:** Large-volume saline/IV fluids → Dilutional effect.
- Pseudothrombocytopenia:
    - EDTA-Dependent Agglutination: Platelet clumping in vitro (EDTA anticoagulant), normal count on citrate tube.
- **Cold Agglutinins:** Platelet clumping due to cold-reactive antibodies, often with hemolysis.
- Other Causes:
    - Pregnancy-Related:
        - **Gestational Thrombocytopenia:** Mild (platelets 100,000-150,000/µL), benign, resolves postpartum.
        - **Preeclampsia/HELLP:** Hypertension, hemolysis, elevated liver enzymes, low platelets (HELLP), often at term.
- **Antiphospholipid Syndrome (APS):** Lupus anticoagulant, anti-cardiolipin antibodies → Thrombosis, thrombocytopenia.
- **Vitamin C Deficiency:** Scurvy, poor nutrition, bleeding gums, mild thrombocytopenia.Hypothermia: Severe (<32°C) → Impaired megakaryocyte function, often in trauma.

Diagnostic Workup

- Step 1: Assess Severity and Timing:
  - **Platelet Count:** <50,000/µL (bleeding risk); <20,000/µL (spontaneous bleeding).
  - **Acute vs. Chronic:** Acute (e.g., TTP, HIT); chronic (e.g., cirrhosis, ITP).
- Step 2: Peripheral Smear:
  - **Large Platelets:** ITP, drug-induced (increased destruction).
  - **Small Platelets:** Marrow failure (aplastic anemia, MDS).
  - **Schistocytes:** TTP, HUS, DIC (MAHA).
  - **Blasts:** Leukemia.
  - **Clumping:** Pseudothrombocytopenia (repeat CBC with citrate tube).
- Step 3: Additional Labs:
  - Immune-Mediated:
    - **ITP:** Isolated thrombocytopenia, normal smear (except large platelets), anti-platelet antibodies (not routinely needed).
    - **HIT:** 4T score ≥4, PF4-heparin ELISA, serotonin release assay (SRA), thrombosis (e.g., DVT, PE).
  - Microangiopathic:
    - **TTP:** ADAMTS13 activity (<10%), schistocytes, high LDH, renal dysfunction.
    - **HUS:** Shiga toxin PCR (E. coli), renal failure, normal ADAMTS13.
    - **DIC:** High D-dimer, low fibrinogen, prolonged PT/PTT, underlying cause (sepsis, malignancy).
  - Marrow Failure:
    - **Aplastic Anemia:** Pancytopenia, bone marrow biopsy (hypocellular).
    - **Leukemia:** Blasts on smear, bone marrow biopsy (hypercellular, >20% blasts).
  - **B12/Folate:** Low B12/folate, high MMA/homocysteine, hypersegmented neutrophils.
  - Infections:
    - **HIV/HCV:** Viral load, CD4 count, cirrhosis (HCV).
    - **Malaria:** Thick/thin smear, rapid diagnostic test (PfHRP2).
  - **Sepsis:** Blood cultures, lactate, procalcitonin.
  - Other:
    - **Liver Function Tests (LFTs):** Cirrhosis (low albumin, high bilirubin), hypersplenism.
    - **SPEP/UPEP:** Multiple myeloma (monoclonal spike).
    - **Lupus Anticoagulant:** APS (thrombosis, recurrent miscarriage).
- Step 4: Imaging/Tests:
  - **Ultrasound:** Splenomegaly (cirrhosis, myelofibrosis).

- **Bone Marrow Biopsy:** Leukemia, lymphoma, aplastic anemia, MDS.
- **CT/PET:** Malignancy (lymphoma, metastatic cancer).

Diagnosis

- Decreased Production:
  - **Aplastic Anemia:** Pancytopenia, hypocellular marrow, no splenomegaly.
  - **Leukemia:** Blasts on smear, bone marrow biopsy (AML: >20% blasts).
  - **B12/Folate Deficiency:** Pancytopenia, hypersegmented neutrophils, low B12/folate.
- Increased Destruction:
  - **ITP:** Isolated thrombocytopenia, large platelets, no systemic symptoms.
  - **HIT:** 4T score ≥4, positive PF4-heparin ELISA, thrombosis, recent heparin exposure.
  - **TTP:** Schistocytes, ADAMTS13 <10%, pentad (MAHA, thrombocytopenia, renal failure, neurologic symptoms, fever).
  - **HUS:** Schistocytes, renal failure, Shiga toxin (typical HUS), normal ADAMTS13.
  - **DIC:** Schistocytes, high D-dimer, low fibrinogen, underlying cause (sepsis, malignancy).
- Sequestration:
  - **Cirrhosis:** Splenomegaly, low platelets/leukocytes, LFT abnormalities.
  - **Myelofibrosis:** Teardrop cells, splenomegaly, bone marrow fibrosis.
- Pseudothrombocytopenia: Platelet clumping on smear, normal count with citrate tube.

Diagnostic Approach Table

Category	Key Labs	Diagnosis	Notes
Decreased Production	Bone marrow biopsy, B12/folate	Aplastic anemia: Hypocellular marrow Leukemia: Blasts >20%	Check for HIV/HCV; blasts require urgent consult.
Increased Destruction	Coombs, ADAMTS13, PF4-heparin ELISA	ITP: Isolated thrombocytopenia HIT: 4T score ≥4, thrombosis	Schistocytes in TTP/HUS; avoid heparin in HIT.
Sequestration	LFTs, ultrasound (spleen)	Cirrhosis: Splenomegaly, low albumin	Check for malaria in sequestration.

Treatment

- General Principles:
  - Treat underlying cause (e.g., stop offending drug, treat infection).
  - Transfuse platelets only if <10,000/μL (prophylactic), <20,000/μL with fever/infection, or <50,000/μL with active bleeding/surgery.
  - Specific Treatments:
    - ITP:
      - **First-Line:** Prednisone 1 mg/kg/day (taper after 4-6 weeks); IVIG 1 g/kg IV x 1-2 days (if bleeding).
      - **Second-Line:** Rituximab 375 mg/m² IV weekly x 4; splenectomy (if refractory).
    - HIT:
      - Stop heparin/LMWH; start non-heparin anticoagulant (argatroban 2 mcg/kg/min IV, titrate to aPTT 1.5-3x baseline).
      - Avoid platelet transfusion (increases thrombosis risk).
    - TTP:
      - **Plasma exchange (PLEX):** Daily until platelets >150,000/μL; steroids (prednisone 1 mg/kg/day).
      - Caplacizumab (anti-vWF) 10 mg IV/SC daily (if ADAMTS13 <10%).
    - HUS:
      - **Supportive:** Dialysis (if AKI), fluids; avoid antibiotics in typical HUS (increases toxin release).
      - **Atypical HUS:** Eculizumab 900 mg IV weekly x 4, then 1200 mg IV q2 weeks.
    - DIC:
      - Treat underlying cause (e.g., antibiotics for sepsis: piperacillin-tazobactam 4.5 g IV q6h).
      - **Supportive:** FFP (if bleeding, 15 mL/kg IV), cryoprecipitate (if fibrinogen <100 mg/dL).
    - Aplastic Anemia:
      - **Immunosuppression:** ATG (40 mg/kg/day IV x 4 days) + cyclosporine (5 mg/kg/day PO).
      - Bone marrow transplant (if <40 years, HLA-matched donor).
    - Leukemia (AML):
      - **Induction chemotherapy:** Cytarabine 100 mg/m² IV daily x 7 days + daunorubicin 60 mg/m² IV x 3 days.
      - **Supportive:** Platelet transfusions (keep >10,000/μL), antibiotics (febrile neutropenia).

- Cirrhosis/Hypersplenism:
  - **Treat portal hypertension:** Propranolol 20 mg PO BID (titrate to HR 55-60 bpm).
  - Splenectomy (if severe, refractory).
- Infections:
  - **HIV:** Antiretroviral therapy (e.g., tenofovir + emtricitabine + dolutegravir).
  - **Malaria:** Artemisinin-based combination therapy (artemether-lumefantrine 20/120 mg, 4 tabs PO BID x 3 days).
- Drug-Induced:
  - Stop offending drug (e.g., quinine, vancomycin); IVIG 1 g/kg IV x 1-2 days (if severe bleeding).
- B12/Folate Deficiency:
  - Cyanocobalamin 1000 mcg IM daily x 7 days, then weekly x 4 weeks, then monthly.
  - Folic acid 1-5 mg PO daily.
- Pregnancy-Related:
  - **Gestational:** Observation (resolves postpartum).
  - **HELLP:** Delivery (if >34 weeks), magnesium sulfate 4 g IV bolus (seizure prophylaxis).

- Platelet Transfusion:
  - 1 unit IV over 30-60 min (increases platelets by 30,000-50,000/μL); use single-donor platelets if refractory.
  - Avoid in TTP/HIT unless life-threatening bleeding (increases thrombosis risk).
- Key Tips:
- **Monitor for bleeding:** Daily CBC, clinical assessment (petechiae, mucosal bleeding).
- Avoid IM injections, NSAIDs, or anticoagulation in severe thrombocytopenia (<50,000/μL).

Treatment Guidelines Table

Cause	Treatment Agent/Dose	Notes
ITP	Steroids, IVIG -Prednisone 1 mg/kg/day -IVIG 1 g/kg IV x 1-2 days	Rituximab or splenectomy if refractory.
HIT	Stop heparin, non-heparin anticoagulant Argatroban 2 mcg/kg/min IV	Avoid platelet transfusion; monitor for thrombosis.
TTP	Plasma exchange, steroids -Daily PLEX -Prednisone 1 mg/kg/day	Continue PLEX until platelets >150,000/μL.

Cause	Treatment Agent/Dose	Notes
Aplastic Anemia	Immunosuppression, Bone marrow transplant ATG 40 mg/kg/day IV x 4 days	Bone marrow transplant if <40 years.

Complications

- Acute:
  - **Bleeding:** Intracranial hemorrhage (ICH, <20,000/μL), GI bleeding, hematuria.
  - **Thrombosis:** HIT (DVT, PE), TTP (microthrombi), PNH (hepatic vein thrombosis).
- Chronic:
  - **Infection:** Post-splenectomy (ITP, cirrhosis) → Risk of encapsulated organisms (S. pneumoniae).
  - **Progression:** MDS → AML (10-30% risk), leukemia-related infections.
- Underlying Disease:
  - **Sepsis:** Multi-organ failure, mortality (DIC).
  - **Cirrhosis:** Variceal bleeding, hepatic encephalopathy.

Key Pearls

- **Classify thrombocytopenia by mechanism:** Decreased production (marrow failure), increased destruction (ITP, TTP), sequestration (cirrhosis).
- **Peripheral Smear:** Schistocytes (TTP/HUS), blasts (leukemia), large platelets (ITP)—urgent findings require hematology consult.
- **HIT:** Suspect if platelets drop >50% within 5-10 days of heparin; start argatroban, avoid warfarin initially.
- **TTP:** Pentad (MAHA, thrombocytopenia, renal failure, neurologic symptoms, fever); urgent PLEX.
- **Platelet Transfusion:** Avoid in TTP/HIT unless life-threatening bleeding; use in aplastic anemia, leukemia.
- **Monitor for bleeding:** Daily CBC, clinical assessment; transfuse if <10,000/μL or bleeding.

References

- UpToDate: “Approach to Thrombocytopenia in Adults” (2025).
- AAFP: “Evaluation and Management of Thrombocytopenia” (2024).
- NEJM: “Thrombotic Thrombocytopenic Purpura: Diagnosis and Treatment” (2023).

- Blood: “Heparin-Induced Thrombocytopenia: Pathophysiology and Management” (2024).

Case Scenarios

Case 1: A 45-Year-Old Female with Bruising

- **Presentation:** A 45-year-old female presents with a 2-week history of easy bruising and petechiae on her legs. She denies fever, weight loss, or recent infections. No medications or alcohol use. Physical exam shows petechiae, no splenomegaly or lymphadenopathy.
- **Labs:** Platelet count 15,000/µL, Hgb 12 g/dL, WBC 7,000/µL. Peripheral smear: Large platelets, no schistocytes or blasts. PT/INR, PTT normal.
- **Diagnosis:** Immune Thrombocytopenia (ITP) → Isolated thrombocytopenia, large platelets, no systemic symptoms.
- **Management:** Start prednisone 1 mg/kg/day PO; consider IVIG 1 g/kg IV if bleeding. Monitor platelet count daily. If no response, plan for rituximab or splenectomy. Avoid NSAIDs, IM injections.

Case 2: A 60-Year-Old Male with Confusion and Fever

- **Presentation:** A 60-year-old male with a history of hypertension presents with confusion, fever, and dark urine for 3 days. Exam shows T 38.5°C, confusion, petechiae, and jaundice. No splenomegaly.
- **Labs:** Platelet count 30,000/µL, Hgb 9 g/dL, Cr 2.5 mg/dL, LDH 800 U/L. Peripheral smear: Schistocytes. ADAMTS13 activity <5%. High D-dimer, normal fibrinogen.
- **Diagnosis:** Thrombotic Thrombocytopenic Purpura (TTP) → Pentad (MAHA, thrombocytopenia, renal failure, neurologic symptoms, fever), ADAMTS13 <10%.
- **Management:** Urgent hematology consult. Start plasma exchange (PLEX) daily; prednisone 1 mg/kg/day PO. Avoid platelet transfusion unless life-threatening bleeding. Monitor platelets, renal function, and mental status daily.

Case 3: A 55-Year-Old Male Post-Cardiac Surgery

- **Presentation:** A 55-year-old male, 7 days post-CABG, develops swelling in his left leg. He received heparin during surgery. Exam shows left leg edema, no petechiae. No fever or bleeding.
- **Labs:** Platelet count 80,000/µL (baseline 200,000/µL), 4T score 6 (high probability). PF4-heparin ELISA positive. Doppler: Left leg DVT.
- **Diagnosis:** Heparin-Induced Thrombocytopenia (HIT) → Platelet drop >50% within 5-10 days of heparin, positive PF4-heparin ELISA, thrombosis.

- **Management:** Stop heparin immediately. Start argatroban 2 mcg/kg/min IV (titrate to aPTT 1.5-3x baseline). Avoid warfarin until platelets >150,000/μL. Monitor for additional thrombosis (CT chest if PE suspected).