NOTES
THROMBOCYTOPENIA

GENERALLY, WHAT IS IT?

PATHOLOGY & CAUSES

- Acquired/inherited disorders: impaired platelet function, decreased platelet count, sequelae
- Accelerated destruction/consumption → decreased platelets

SIGNS & SYMPTOMS

- Mucocutaneous bleeding (e.g. epistaxis, gingival bleeding, petechiae, purpura)

DIAGNOSIS

LAB RESULTS

- Complete blood count (CBC)
- Peripheral blood smear analysis
- Platelet function tests

TREATMENT

OTHER INTERVENTIONS

- Mitigate complications of deranged platelet function

HEPARIN-INDUCED THROMBOCYTOPENIA (HIT)

osms.it/heparin-induced-thrombocytopenia

PATHOLOGY & CAUSES

- Acquired platelet disorder
  - Accelerated thrombosis in arteries, veins → consumptive thrombocytopenia.
  - Occurs in individuals exposed to unfractionated heparin/low molecular weight heparin (LMWH)
  - AKA heparin-induced thrombocytopenia thrombosis (HITT)
- Exposure to heparin/LMWH → IgG autoantibodies formed against heparin → platelet factor 4 (PF4) binds to heparin → antibody-heparin-PF4 complex → increased platelet activation → thrombosis formation in arteries, veins
- Increased consumption of platelets for clotting + removal of antibody-heparin-PF4 complexes by macrophages of reticuloendothelial system → thrombocytopenia
  - Thrombocytopenia usually not sufficient to cause significant bleeding
- Classified by severity, timing, degree of drop in platelet count drop, antibody mediation

RISK FACTORS

- 5% individuals exposed to unfractionated/LMWH
  - Unfractionated > LMWH

- Dose
  - Prophylactic dose > therapeutic doses > intermittent heparin flushes
- More common in individuals who are biologically female

HIT TYPES

HIT TYPE 1	HIT TYPE 2
Transient, mild, not clinically significant	Complications can be life-threatening
Onset: 1-4 days after exposure	Onset: 5-10 days after exposure
Not antibody mediated; may be caused by heparin-induced platelet aggregation	Antibody mediated (IgG)
Nadir platelet count: 100,000/microL; usually returns to normal, even with continued heparin administration	Mean nadir platelet count: 60,000/microL

COMPLICATIONS

- Venous thromboembolism (VTE)
- Occlusion of large lower limb arteries by platelet rich "white clots" → limb ischemia, necrosis, gangrene, loss of limbs
- Skin necrosis
- Organ infarction
  - Kidney, myocardial infarction; cerebrovascular insult
- Adrenal hemorrhage
  - Adrenal vein thrombosis
- Heparin-induced anaphylactoid reactions

SIGNS & SYMPTOMS

- Skin necrosis at injection site
- Acute systemic reaction after IV heparin bolus
  - Fever with chills, tachycardia, hypertension, dyspnea
- Limb ischemia, organ infarction

DIAGNOSIS

LAB RESULTS

HIT antibody testing

- HIT immunoassay
  - ELISA for anti-PF4 antibodies
  - PF4 antibodies in individual's serum
  - *Colorimetric change:* optical density (OD), HIT antibody concentration
  - Higher OD = higher antibody titer = HIT
- Functional assay
  - Serotonin release assay (SRA)
  - Serotonin release from platelets, ability of HIT antibodies from individual's serum to activate test platelets
  - Release of serotonin + therapeutic heparin concentration
- Heparin-induced platelet aggregation (HIPA) assay
  - Platelet aggregation with no heparin, low/high heparin concentration
  - Minimal platelet aggregation with no heparin, high heparin concentrations; strong aggregation with low heparin concentrations

OTHER DIAGNOSTICS

- History of exposure to unfractionated heparin
- New venous/arterial thrombosis

MNEMONIC: 4Ts

Diagnosis of Thrombocytopenia

Thrombocytopenia: CBC, fall in platelet count

Timing: fall in platelet count, 5–10 days after heparin initiation

Thrombosis: venous/arterial thrombosis, sequelae

O**T**her: no other explanations

TREATMENT

MEDICATIONS

- Immediate discontinuation of heparin
- Administration of non-heparin anticoagulant (e.g. fondaparinux, argatroban)
  - Transition to warfarin/other outpatient anticoagulant after stabilization

SURGERY

Thromboembolectomy

- If severe limb ischemia, high risk for amputation

IDIOPATHIC THROMBOCYTOPENIC PURPURA (ITP)

osms.it/idiopathic-thrombocytopenic-purpura

PATHOLOGY & CAUSES

- Acquired thrombocytopenia; accelerated immune platelet destruction → bleeding
- AKA, immune thrombocytopenic purpura, autoimmune thrombocytopenic purpura
- B cells produce IgG autoantibodies against platelet glycoproteins (e.g. IIb/IIIa, Ib/IX complexes) → platelets coated with antibodies recognized as "non-self" by splenic macrophages → platelet destruction
  - *Contributing factors:* impaired platelet production, cell-mediated platelet destruction

TYPES

- Classifed by cause, duration, severity

Primary ITP

- Idiopathic

Secondary ITP

- Caused by systemic condition
- Viral infections (most common)
  - HIV, hepatitis C, cytomegalovirus
  - Antibodies against viral antigens cross-react with platelet antigens via molecular mimicry
- Bacterial lipopolysaccharides attach to platelet surfaces → increase phagocytosis of platelets
- Systemic lupus erythematosus, lymphoid malignancy, chronic lymphocytic leukemia
  - Alter immune homeostasis
  - Alterations in T cell-mediated cytotoxicity/suppression of megakaryocyte production, maturation

Drug-induced immune thrombocytopenia (DITP)

- Triggered by drug-dependent platelet antibodies
- Quinidine, phenytoin, valproic acid, rifampin, trimethoprim-sulfamethoxazole, sulfonamides
- Reaction due to drug/metabolites

Severe ITP

- Platelet counts < 10,000–20,000/microL; significant bleeding requires treatment

Refractory ITP

- Severe ITP, fails to respond to/relapses after splenectomy

RISK FACTORS

- Age; genetic/acquired factors

COMPLICATIONS

- Potentially severe hemorrhage (uncommon)
  - Intracranial bleeding, subarachnoid hemorrhage, gastrointestinal (GI) hemorrhage, hematuria, severe menorrhagia

SIGNS & SYMPTOMS

- Bruising easily after minor trauma
- Mucocutaneous bleeding
  - Petechiae, purpura, epistaxis, gingival bleeding

DIAGNOSIS

LAB RESULTS

- CBC
  - Low platelet count
- Peripheral blood smear analysis
  - Scarce platelets
- Flow cytometry-based assays
  - Drug-dependent platelet antibodies

OTHER DIAGNOSTICS

- History of drug implicated in DITP

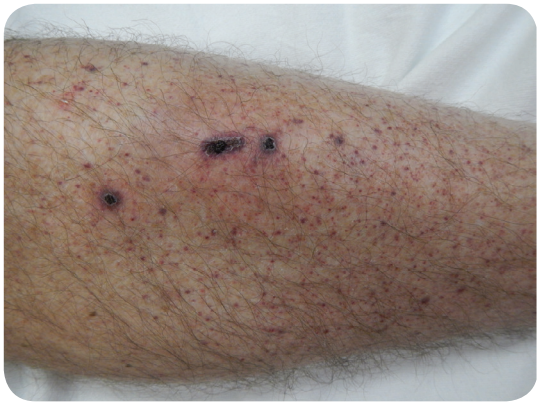

Figure 59.1 Multiple petechiae present in the skin of an individual with ITP. The platelet count was < 5 x 10^9/L.

TREATMENT

MEDICATIONS

Raise platelet count

- High dose glucocorticoids (dexamethasone; prednisone)
- Immune globulin (IVIG)

If no response to above medications

- Rituximab
  - Monoclonal antibody reduces antibody-dependent cytotoxicity, complement-mediated lysis of platelets
- Thrombopoietin (TPO) receptor agonists (e.g. eltrombopag)
  - Increases platelet production by stimulating production of megakaryocytes
- Immunosuppressive agents
  - Danazol, azathioprine, cyclosporine

Medications to avoid

- Antiplatelet agents
  - Aspirin, other nonsteroidal anti-inflammatory drugs (NSAIDs)

SURGERY

- If no response to medication

Splenectomy

- Reduces platelet destruction

OTHER INTERVENTIONS

- Platelet transfusions
  - Clinically significant bleeding

THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP)

osms.it/thrombotic-thrombocytopenic

PATHOLOGY & CAUSES

- Thrombotic microangiopathy (TMA) caused by deficient activity of ADAMTS13 protease
- ADAMTS13 breaks von Willebrand factor (vWF) molecules into smaller multimers, prevents excessive accumulation on endothelial surfaces in microvasculature
- Excessive vWF on endothelial surfaces → increased propensity for platelets to attach, accumulate (esp. in high pressure areas with shearing stress) + endothelial damage → platelet-rich thrombi in microcirculation → tissue ischemia, organ dysfunction, microangiopathic hemolytic anemia (MAHA), thrombocytopenia
- Thrombocytopenia consumptive
  - Increased need for platelets from cyclical clot formation, dissolution
- MAHA
  - Red blood cell (RBC) mechanical fragmentation in microthrombi, damaged vessels → schistocytes
- Organs most affected by TTP in microcirculation
  - Brain, heart, adrenal glands, pancreas, kidneys

CAUSES

- ADAMTS13 deficiency
  - Acquired inhibitory autoantibody (IgG) to ADAMTS13; inherited mutation of *ADAMTS13* gene (minority)

RISK FACTORS

- Increased prevalence in individuals who are biologically female, of African ancestry, diagnosed with systemic lupus erythematosus (SLE)
- Sepsis, liver disease, pancreatitis, cardiac surgery
  - Reduce activity of ADAMTS13
- Pregnancy
  - Decrease in ADAMTS13, increase in vWF, 2nd–3rd trimesters

COMPLICATIONS

- Organ damage
  - Renal insufficiency, focal neurologic/mental status anomalies, arrhythmias

SIGNS & SYMPTOMS

- Classic TTP pentad
  - Thrombocytopenia, MAHA, renal dysfunction, neurologic impairment (e.g. headache, confusion, seizures, coma), fever
- Mucocutaneous bleeding
  - Petechiae, purpura (coalesced petechiae), epistaxis, gingival bleeding
- Intravascular hemolysis → dark urine
- Lightheadedness, abdominal pain, easy bruising, nausea/vomiting

MNEMONIC: RAFT'N

Common signs of Thrombotic thrombocytopenia purpura

Renal problems
Anemia: MAHA associated
Fever
Thrombocytopenia
Neurologic dysfunction

DIAGNOSIS

LAB RESULTS

- CBC
  - Decreased platelet count
  - Increased reticulocyte count
  - Decreased hemoglobin, hematocrit
- Peripheral blood smear analysis
  - Schistocytes, spherocytes
- Hemolysis
  - Elevated lactate dehydrogenase (LDH)
  - Elevated indirect bilirubin
  - Reduced haptoglobin
- Elevated creatinine
  - Renal insufficiency

OTHER DIAGNOSTICS

- ADAMTS13 assay
  - Gel electrophoresis of VWF multimers measures degradation by ADAMTS13
- ADAMTS13 inhibitor assay
  - Autoantibody titer
- Genetic testing
  - *ADAMTS13* gene mutation, if hereditary TTP suspected

TREATMENT

MEDICATIONS

- Glucocorticoids
- Monoclonal antibody

OTHER INTERVENTIONS

- Plasma exchange (PEX)

LAB VALUES IN THROMBOCYTOPENIC DISORDERS

	TTP	ITP	HIT
PLATELETS	↓↓↓	↓↓↓	↓↓
HEMOGLOBIN	↓↓	Normal	Normal
LDH	↑↑↑	Normal	Normal
INDIRECT BILIRUBIN	↑	Normal	Normal
HAPTOGLOBIN	↓	Normal	Normal
RETICULOCYTES	↑	Normal	Normal
SCHISTOCYTES	↑↑↑	Normal	↑