Platelets Disorder

Mu’ta University 2024

Classification of platelet disorders

Quantitative disorders

- Abnormal distribution
- Dilution effect
- Decreased production
- Increased destruction

Qualitative disorders

- Inherited disorders (rare)
- Acquired disorders
  - Medications
  - Chronic renal failure
  - Cardiopulmonary bypass

Thrombocytopenia

Thrombocytopenia is defined as a platelet count of <150 × 10^9/L (reference range varies depending on local laboratory standard).

Thrombocytopenia occurs from:

decreased production, increased destruction, or sequestration of platelets

TABLE 20-2 Classification of Thrombocytopenia

Decreased Platelet Production

Marrow failure syndromes
Congenital
Acquired: Aplastic anemia, paroxysmal nocturnal hemoglobinuria
Hematologic malignancies
Marrow infiltration: Cancer, granuloma
Myelofibrosis: Primary or secondary
Nutritional: Vitamin B_{12} and folate deficiencies
Physical damage to the bone marrow: Radiation, alcohol, chemotherapy

Increased Splenic Sequestration

Portal hypertension
Felty syndrome
Lysosomal storage disorders
Infiltrative hematologic malignancies
Extramedullary hematopoiesis

Increased Platelet Clearance

Immune-mediated mechanisms
Immune thrombocytopenic
Thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome
Post-transfusion purpura
Heparin-induced thrombocytopenia
Non–immune-mediated mechanisms
DIC
Local consumption (aortic aneurysm)
Acute hemorrhage

Infections Associated With Thrombocytopenia

HIV, HHV-6, ehrlichiosis, rickettsia, malaria, hepatitis C, CMV, Epstein-Barr, *Helicobacter pylori*, *Escherichia coli* O157

CMV, cytomegalovirus; DIC, disseminated intravascular coagulation; HHV-6, human herpesvirus 6.

Approach to the thrombocytopenic patient

- History
  - Is the patient bleeding?
  - Are there symptoms of a secondary illness? (neoplasm, infection, autoimmune disease)
  - Is there a history of medications, alcohol use, or recent transfusion?
  - Are there risk factors for HIV infection?
  - Is there a family history of thrombocytopenia?
  - Do the sites of bleeding suggest a platelet defect?
- Assess the number and function of platelets
  - CBC with peripheral smear
  - Platelet function study

Physical Examination

Primary hemostasis defects often cause mucosal bleeding and excessive bruising.

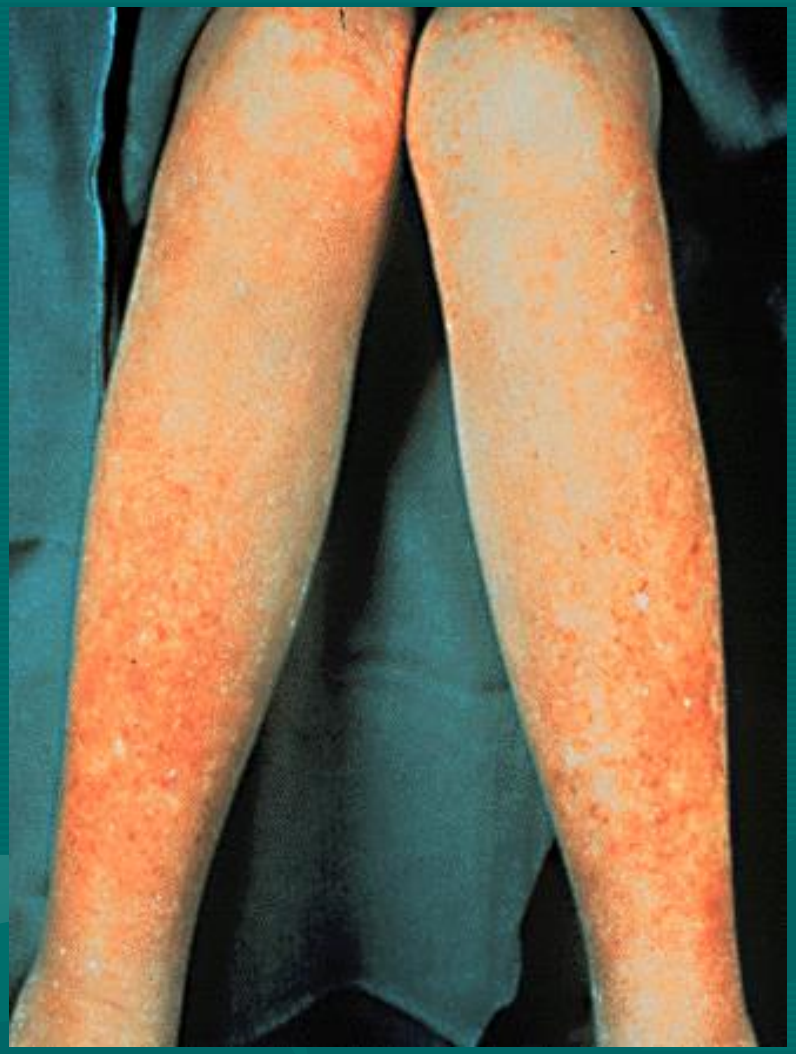
Petechiae: <2 mm subcutaneous bleeding, do not blanch with pressure, typically present in areas subject to increased hydrostatic force (the lower legs and periorbital area)

Ecchymoses: >3 mm black-and-blue patches due to rupture of small vessels from trauma

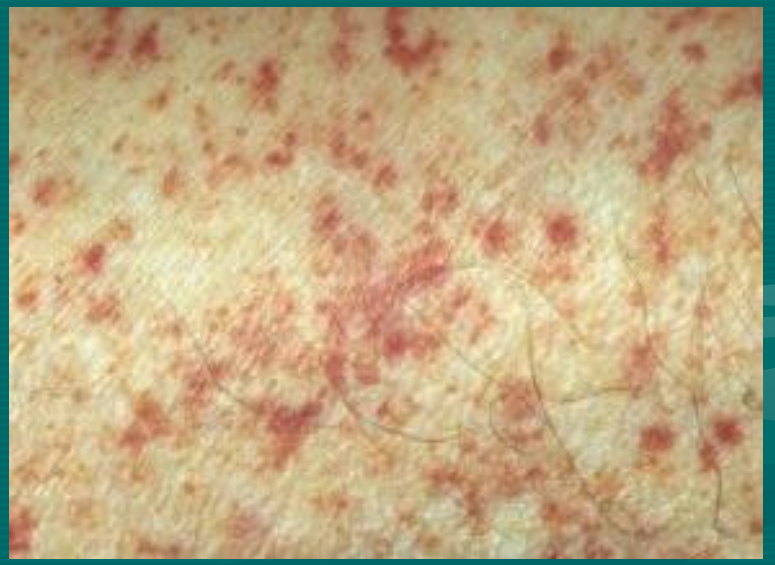
Secondary hemostasis defects can result in hematomas, hemarthroses, or prolonged bleeding after trauma or surgery

Sites of bleeding in thrombocytopenia

- Skin and mucous membranes
  - Petechiae
  - Ecchymosis (unusual)
  - Hemorrhagic vesicles
  - Gingival bleeding and epistaxis
- Menorrhagia
- Gastrointestinal bleeding
- Intracranial bleeding



Petechiae



Do not blanch with pressure
(cf. angiomas)

Not palpable
(cf. vasculitis)

Immune Thrombocytopenia

Immune thrombocytopenia (ITP) is an acquired immune disorder in which antiplatelet antibodies cause shortened platelet survival and suppress megakaryopoiesis leading to thrombocytopenia and increased bleeding risk.

Etiologies of ITP include:

- idiopathic (primary),
- associated with coexisting conditions (secondary),
- drug induced.

In primary ITP, autoantibodies bind to platelet surface antigens and cause premature clearance by the reticuloendothelial system in addition to immune-mediated suppression of platelet production.

Secondary ITP occurs in the setting of systemic lupus erythematosus (SLE), antiphospholipid antibody syndrome (APS), HIV, hepatitis C virus (HCV), Helicobacter pylori, and lymphoproliferative disorders.

Drug-dependent ITP results from drug–platelet interactions prompting antibody binding.

Medications linked to thrombocytopenia include:

Quinidine and quinine; platelet inhibitors abciximab, eptifibatide, tirofiban, and ticlopidine; antibiotics; linezolid, rifampin, sulfonamides, and vancomycin; the anticonvulsants; phenytoin, valproic acid, and carbamazepine; analgesics acetaminophen, naproxen, and diclofenac.

Clinical Presentation

ITP typically presents as mild mucocutaneous bleeding and petechiae or incidental thrombocytopenia.

Occasionally, ITP can present as major bleeding.

Risk of bleeding is highest with platelet counts <30 × 10^9/L.

Treatment:

Glucocorticoid

IVIG

Biologicals – Rituximab (anti CD20)

Thrombotic thrombocytopenic purpura (TTP)

Its thrombotic microangiopathies (TMAs) caused by platelet–vWF aggregates that resulting in:

Thrombocytopenia, microangiopathic hemolytic anemia (MAHA), and organ ischemia.

Etiology:

Autoantibody-mediated removal of plasma vWF-cleaving protease: A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13), leading to elevated levels of abnormally large vWF multimers, typically causes sporadic TTP. The abnormal vWF multimers spontaneously adhere to platelets and may produce occlusive vWF–platelet aggregates in the microcirculation and subsequent microangiopathy.

Second-hit events may involve endothelial dysfunction or injury.

Clinical Presentation

The complete clinical pentad of TTP, present in <30% of cases, includes

- thrombocytopenia,
- MAHA,
- fever,
- renal dysfunction,
- fluctuating neurologic deficits.

Diagnostic Testing

Thrombotic microangiopathies produce schistocytes (fragmented red cells) and thrombocytopenia on blood smears.

The findings of anemia, elevated reticulocyte count, low or undetectable haptoglobin, and elevated lactate dehydrogenase (LDH) support the presence of hemolysis.

Treatment

The mainstay of therapy for TTP consists of rapid treatment with plasma exchange (PEX) of 1.0–1.5 plasma volumes daily.

PEX is continued for several days after normalization of platelet count and LDH.

Heparin-Induced Thrombocytopenia

(HIT) is an acquired hypercoagulable disorder associated with the use of heparin or heparin-like products and due to autoantibodies targeting the anticoagulant and platelet factor 4 (PF4) complexes.

HIT typically presents with thrombocytopenia or a decrease in platelet count by at least 50% from pre-exposure baseline after exposure to heparin products.

Major complications of HIT consist of arterial and venous thromboembolic events.

Immune-responsive patients produce autoantibodies that bind to PF4/heparin complexes, which can activate platelets, cause thrombocytopenia, and lead to clot formation through increased thrombin generation

Treatment

Eliminate all heparin exposure.

Start warfarin only after the platelet count normalizes to > 150 × 10^9/L, at an initial dose no greater than 5 mg daily

Alternative anticoagulation with a parenteral direct thrombin inhibitor (DTI) (i.e., argatroban or bivalirudin).

Gestational Thrombocytopenia

(platelet counts ≥70 × 10^9/L) is a benign, mild thrombocytopenia associated with pregnancy.

The mechanism of gestational thrombocytopenia remains unknown.

Gestational thrombocytopenia and thrombocytopenia associated with pre-eclampsia and eclampsia usually resolve promptly after delivery.

Thrombocytosis

Thrombocytosis is defined as a platelet count of >450 × 10^9/L by the World Health Organization (WHO).

Thrombocytosis has reactive and clonal etiologies that may coexist.

Reactive thrombocytosis may occur

during recovery from thrombocytopenia; after splenectomy; or in response to iron deficiency, acute infectious or chronic inflammatory states, trauma, and malignancies.

It has low risks of thrombosis or bleeding.

Platelets usually normalize after improvement of the underlying disorder.

If accompanied by thrombotic complications, evaluate for an underlying myeloproliferative disorder.

Essential thrombocytosis (ET) is a chronic myeloproliferative disorder.

Eventual progression to myelofibrosis, acute myeloid leukemia, or myelodysplastic syndrome occurs in a minority of ET patients.

Diagnostic Criteria

In 2016, the WHO revised criteria (requires all four) included:

- Sustained platelet count ≥450 × 10^9/L
- Bone marrow biopsy showing increased mature megakaryocytes and no increase in erythropoiesis or granulopoiesis or reticulin fiber deposition (greater than grade I).
- Exclusion of BCR-ABL1 positive chronic myelogenous leukemia (CML), polycythemia vera, primary myelofibrosis, myelodysplastic syndrome, or other myeloid neoplasm.

Treatment

Treatment typically aims for a platelet count of ≤400 × 10^9/L.

Rx:

Platelet-lowering drugs include hydroxyurea and anagrelide or interferon-α in pregnant patients or females in their childbearing years.

Qualitative Platelet Disorders

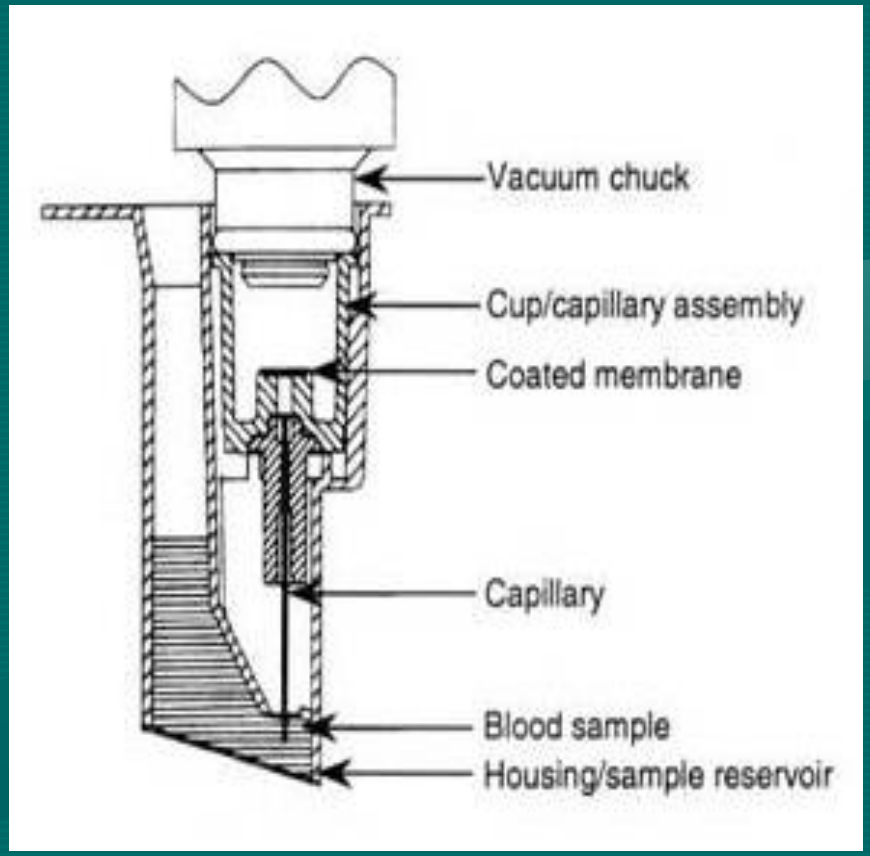
Platelet count, PT, and aPTT and screening tests for vWD are all normal

Present with mucocutaneous bleeding and excessive bruising

Most potent platelet defects produce prolonged PFA-100 closure times. However, a normal PFA-100 does not exclude qualitative platelet disorders.

Platelet function screen

- Replaces the *bleeding time* as a test of platelet function
- PFA-100; ordered as "platelet function screen"
- Blue top tube
- Measures the time it takes for blood to block membrane coated with either collagen/epinephrine or collagen/ADP



Platelet function screen Results

Epi	ADP	Interpretation
Normal	Normal	Normal platelet function
Abnormal	Normal	“Aspirin effect”
Abnormal	Abnormal	Abnormal platelet function
		Valvular heart disease
		Renal failure
		Von Willebrand disease

Classification

Inherited disorders of platelet function include receptor, signal transduction, cyclooxygenase (COX), secretory (e.g., storage pool disease), adhesion, or aggregation defects.

Acquired platelet defects are more common than hereditary platelet qualitative disorders.

Conditions associated with acquired qualitative defects include

Metabolic disorders (uremia, liver failure), myeloproliferative diseases, myelodysplasia, acute leukemia, monoclonal gammopathy, and cardiopulmonary bypass platelet trauma.

Drug-induced platelet dysfunction is a side effect of many drugs, including high-dose penicillin, aspirin (ASA) and other NSAIDs, and ethanol.

Other drug classes, such as β-lactam antibiotics, β-blockers, calcium channel blockers, nitrates, antihistamines, psychotropic drugs, tricyclic antidepressants, and selective serotonin reuptake inhibitors, cause platelet dysfunction in vitro, but they rarely cause bleeding.

Certain foods and herbal products may affect platelet function including

Omega-3 fatty acids, garlic and onion extracts, ginger, gingko, ginseng, and black tree fungus.

Patients should stop using herbal medications and dietary supplements ≥1 week before major surgery.

Platelet transfusions

- Source
  - Platelet concentrate (Random donor)

    Each donor unit should increase platelet count ~10,000 /μl
  - Pheresis platelets (Single donor) = 4-6 units of RDP
- Storage
  - Up to 5 days at room temperature
- "Platelet trigger"
  - Bone marrow suppressed patient (>10-20,000/μl)
  - Bleeding/surgical patient (>50,000/μl)
  - Neurosurgery patient (>100,000)

Thank you