

Thrombocytopenia and platelet function disorders

What is thrombocytopenia?

Thrombocytopenia means a reduction in the platelet count below the normal lower limit, which is usually defined as $150 \times 10^9/L$.^[1] This can have a variety of causes, including a reduction in platelet production, a reduction in platelet survival, and dilution of platelet numbers resulting from the transfusion of platelet-poor blood.

Correlation between platelet count and the risk of bleeding is uncertain.^[14] The risk of bleeding is not based on the platelet count alone; age, comorbidity, the need for anticoagulation, risk of trauma, and any need for surgery should also be considered when managing people with thrombocytopenia.^[2]

Platelet function abnormalities (thrombocytopathy) include a range of inherited and acquired defects of platelet function. Thrombocytopathy may cause a thrombotic or a bleeding tendency or may be part of a wider disorder such as myelodysplasia.

Causes of thrombocytopenia (aetiology)

A low platelet count may be due to a variety of different causes – eg, the initial manifestation of infections such as HIV and hepatitis C virus or it may reflect the activity of life-threatening disorders such as the thrombotic microangiopathies.^[3]

Disorders affecting platelet production

Congenital

- Megakaryocytic hypoplasia - underdevelopment of megakaryocytes which normally develop in bone marrow and fragment to produce platelets - usually of autoimmune or infectious origin.
- Thrombocytopenia/absent radii (TAR syndrome) - radial aplasia or hypoplasia and thrombocytopenia.
- Bernard-Soulier syndrome (BSS).
- Wiskott-Aldrich syndrome (WAS) - an X-linked recessive disease characterised by thrombocytopenia, lymphopenia and depressed cellular immunity, eczema, malignant lymphoma.
- May-Hegglin anomaly: thrombocytopenia, giant platelets and leukocyte inclusions (Döhle leukocyte inclusions).
- Congenital leukaemia - eg, in association with [Down's syndrome](#).
- [Fanconi's anaemia](#).

Decreased production (disorders of bone marrow)

See also the separate [Bone marrow and bone marrow failure](#) article.

- Viral infections - eg, herpes simplex, cytomegalovirus, varicella-zoster, Epstein-Barr, rubella, enterovirus, mumps, hepatitis, HIV.
- [Aplastic anaemia](#).
- Marrow infiltration by a malignancy - eg, leukaemia, lymphoma, [myeloma](#), [metastatic malignant disease](#).
- Drugs - eg, chemotherapy or valproic acid.^[14]
- Chronic alcohol abuse.^[14]
- [Paroxysmal nocturnal haemoglobinuria](#).
- Megaloblastic anaemia.
- Myelofibrosis.
- Miliary tuberculosis.

Decreased platelet survival

- Immune - immune thrombocytopenia, systemic lupus erythematosus, rheumatoid arthritis, sarcoidosis, antiphospholipid syndrome.
- Post-transfusion thrombocytopenic purpura (PTTP):
 - Antigens on transfused platelets can lead to destruction of not just the transfused platelets but the patient's own platelets too.
 - It starts about 10 days after transfusion but can last several weeks or even several months.
- Neonatal alloimmune thrombocytopenia (NAIT):
 - Occurs when the mother produces antibodies against fetal platelets with paternal antigens.
 - It is the most common cause of severe neonatal thrombocytopenia.
 - It often follows an apparently uneventful pregnancy but the risk of intracranial haemorrhage is high and mortality is high too.
 - Unlike haemolytic disease of the newborn, it commonly occurs in first pregnancies.
- Drug-induced - eg, heparin, carbamazepine, ibuprofen, quinidine, quinine, rifampin, sulfamethoxazole, trimethoprim and vancomycin. [4] [5]
- Thrombotic thrombocytopenic purpura.
- Haemolytic uraemic syndrome.
- Disseminated intravascular coagulation (DIC).
- Pregnancy - mild thrombocytopenia can occur in normal pregnancy^[14]; moderate-severe thrombocytopenia occurs in HELLP syndrome, characterised by:
 - Haemolysis.
 - EL (elevated liver) enzymes.
 - LP (low platelet) count.
- Cardiopulmonary bypass.

- [Splenomegaly and hypersplenism](#), which may be associated with a variety of conditions – eg, cirrhosis, malaria, lymphoma.
- Kasabach–Merritt syndrome (cavernous haemangiomas with severe thrombocytopenia, and features of disseminated intravascular coagulation).

Dilutional thrombocytopenia

This is caused by transfusion of large volumes of blood which may be depleted of functioning platelets, resulting from prolonged storage.

Platelet function disorders

Inherited platelet function disorders (where the number of platelets may be normal or lower than normal) ^[15]:

- Severe disorders of platelet function: WAS, Glanzmann's thrombasthenia (GT), ^[6] BSS.
- Disorders of receptors and signal transduction: platelet cyclo-oxygenase deficiency, thromboxane synthase deficiency, thromboxane A2 receptor defect, ADP receptor defect.
- Disorders of platelet adhesion: von Willebrand's disease (vWD).
- Disorders of the platelet granules: idiopathic dense-granule disorder (d-storage pool disease), Hermansky–Pudlak syndrome, [Chediak-Higashi syndrome](#), grey platelet syndrome, Paris-Trousseau/Jacobsen's syndrome.
- Idiopathic alpha- and dense-granule storage pool disease.
- Disorders of phospholipid exposure; Scott syndrome.

Acquired platelet function disorders: ^[7]

- Medications and chemicals – eg, aspirin, other non-steroidal anti-inflammatory drugs (NSAIDs), clopidogrel, dipyridamole, beta-lactam antibiotics, dextran, alcohol.
- Some herbal supplements and foods – eg, ginkgo biloba, garlic, bilberry, ginger, ginseng.
- Chronic kidney disease.

- Heart valve disease, cardiopulmonary bypass, extracorporeal membrane oxygenation.
- Acquired vWD may occur in patients with aortic stenosis and has also been described in association with other conditions – eg, Wilms' tumour, hypothyroidism.
- Myeloproliferative disorders – eg, essential thrombocythaemia, polycythaemia vera.
- Myelodysplastic syndromes.
- Paraproteins, especially multiple myeloma and Waldenström's macroglobulinaemia.
- Antibody-induced platelet dysfunction: bleeding in patients with ITP usually occurs at very low platelet counts. Occasionally, patients will have bleeding symptoms with only mild-to-moderate thrombocytopenia.

Pseudothrombocytopenia

- This can occur when platelets undergo a phenomenon called 'clumping'. In this situation, the platelets stick together, causing a false low reading when passed through an auto-analyser.
- The condition is caused by the action of ethylenediaminetetraacetic acid (EDTA) used as an anticoagulant. It occurs in about 0.1% of the population but can also be associated with infections with HIV, rubella, and cytomegalovirus, autoimmune disorders, neoplastic diseases, thrombotic disorders and possibly trauma.
- It is not indicative of a bleeding diathesis or platelet dysfunction. If an abnormally low platelet count is detected in the absence of a suggestive medical history, examination of a peripheral blood smear on a freshly taken specimen should be performed.^[8] More accurate results can then be attained using a different anticoagulant for future FBC tests.^[16]

Symptoms of thrombocytopenia (presentation)

Careful and thorough history and examination, including any features associated with platelet dysfunction and any indication of the underlying cause.^[9]

History

- Epistaxis, particularly if excessive, frequent or prolonged.
- Bleeding gums or bleeding from tooth extractions.
- Haemoptysis, haematemesis, haematuria, haematochezia (passage of bright red blood with bowel movements) and melaena - not usually seen in the initial stages, but a bleeding disorder can exacerbate them if there is any secondary pathology.
- Metromenorrhagia - especially seen in vWD and is often made worse when an NSAID is given to treat dysmenorrhoea.
- Postpartum haemorrhage.
- Excessive bleeding during or after surgery - even minor (congenital bleeding disorder often presents as excessive bleeding after circumcision).
- Bleeding after aspirin.
- Spontaneous bruising.

Examination

This may reveal petechiae (<2 mm), purpura (0.2-1 cm) and ecchymoses on the skin.

Other abnormalities on examination may provide an indication of an underlying cause. It is essential to look for any indication of lymphadenopathy and/or hepatosplenomegaly.

Diagnosing thrombocytopenia (investigations)^[7]

A thorough history and examination are essential, with consideration of any history or indication of a possible underlying cause, and any history of abnormal bleeding.

When a low platelet count is picked up incidentally, the FBC must be repeated and a blood smear performed.^[2]

Initial laboratory test should include FBC with differential and a blood film, prothrombin time, activated partial thromboplastin time (aPTT), renal function and TFTs.

HIV and HCV tests should be carried out as thrombocytopenia may be the only sign of infection for several years.^[17]

Bone marrow examination may be required for patients over 60 years of age, unless **immune thrombocytopenia** can be confidently diagnosed, (mainly to exclude dysplasia) and in those with systemic symptoms or signs suggestive of haematological cancer.^[2]

Specific assays of inherited platelet dysfunction include:^[10]

- Light transmission aggregometry: evaluates the aggregation or clumping of platelets in response to aggregating stimuli.
- Flow cytometry: should be used in the investigation or confirmation of GT, BSS and Scott syndrome, and may also be used to investigate abnormalities in the collagen and thrombin receptors.
- Measurement of total and released nucleotides: provides an important additional diagnostic tool usually in conjunction with aggregometry for determining whether there is any specific deficiency in dense granule numbers or their content (eg, storage pool disease), or specific defect(s) in degranulation (eg, release defects).
- Platelet alpha granule proteins and beta-thromboglobulin can be measured by ELISA, radioimmunoassay or Western blotting and may be helpful for the diagnosis of Quebec platelet disorder.

- Electron microscopy is very useful for defining ultrastructural abnormalities associated with a variety of platelet defects.
- Molecular genetic diagnosis of heritable platelet disorders may offer valuable confirmation of diagnosis in affected individuals, in family members where phenotypic testing of platelets is impractical and for antenatal diagnosis.
- Bone marrow examination is not usually required except in those with an atypical course, or a large spleen, or if splenectomy is contemplated.
- Testing for drug-dependent platelet antibodies - this is not widely available but may be useful in severe disease where the diagnosis is in doubt. ^[11]

Further investigations and management will depend on the suspected or confirmed underlying cause. See links in the section 'Aetiology', above.

Managing thrombocytopenia ^[2]

- Patients with modest isolated thrombocytopenia (platelet count $100-150 \times 10^9/L$) without atypical features (eg, lymphadenopathy or fever) do not require referral to hospital, especially if the blood counts are stable.
- It is prudent occasionally to recheck the FBC in primary care to ensure that blood counts do not deteriorate or to be aware of any other condition becoming evident.
- If the results of the FBC are unchanged when repeated six weeks later, it is usually safe to extend the follow-up interval to several months.
- Patients must be aware that they should be seen straightaway if new symptoms such as bruising or bleeding occur.
- Indications for urgent referral include severe thrombocytopenia ($< 20 \times 10^9/L$), severe bleeding, and red cell fragments or blasts on the blood film.
- Referral is also warranted if the patient has constitutional symptoms, bruising, minor bleeding, or abnormalities on examination (eg, lymph nodes or splenomegaly) or the blood film (eg, dysplastic changes).

- Referral to or discussion with a haematologist is reasonable if the platelet count is less than $100 \times 10^9/L$ or the patient also has anaemia, neutropenia, or other changes in the blood count - eg, macrocytosis.

Further management depends on the underlying cause.

Management of inherited platelet disorders ^[12] ^[13]

- Platelet transfusions are frequently needed for patients with severe platelet dysfunction but usually unnecessary for mild-to-moderate bleeding. They should be used selectively and sparingly because of the risk of alloimmunisation against HLA antigens and/or platelet glycoproteins. To reduce the risk, HLA-matched single donors of platelets should be used. If such donors are unavailable, leukocyte-depleted blood components should be used.
- Topical measures (compression with gauze soaked with tranexamic acid, fibrin sealants, splints for dental extractions and packing for nosebleeds).
- Antifibrinolytic agents are useful for minor surgery and as adjuncts for other treatment modalities.
- Desmopressin increases plasma levels of vWF and factor VIII giving rise to increased platelet adhesiveness and aggregation associated with shortened bleeding time.
- Stem cell or bone marrow transplantation has been successful for some patients.
- Female hormones: excessive bleeding during menarche in patients with GT or BSS can be controlled by high doses of oestrogen followed by high doses of oral oestrogen-progestogen. Menorrhagia later in life can be managed by continuous oral contraceptives. Depo-medroxyprogesterone acetate administered every three months is an alternative when combined oral contraceptives are contra-indicated.
- Measures to prevent bleeding include vaccination against hepatitis B, avoidance of NSAIDs, good dental hygiene and correction of iron deficiency.

Management of acquired platelet disorders ^[7]

- Treatment of patients with suspected platelet dysfunction is generally specific to the underlying cause but may include desmopressin and platelet transfusion.
- Antifibrinolytic therapy (epsilon aminocaproic acid or tranexamic acid) may be useful, especially for mucosal bleeding, but should not be used in patients with haematuria or DIC.
- rFVIIa has been used to treat bleeding in patients with acquired and inherited platelet disorders, but is associated with an increased risk of thrombosis.

Prognosis

The prognosis is very variable and depends on the underlying condition.

Further reading

- [The ITP Support Association](#)
- [Jinna S, Khandhar PB; Thrombocytopenia.](#)
- [Platelet Function Disorders](#); Cincinnati Children's
- [Yan L, Xu S, Yang X, et al; Decision-Making Error in Platelet Transfusion Caused by EDTA-Dependent Pseudothrombocytopenia: a Case Report and Literature Review. Clin Lab. 2024 Jan 1;70\(1\). doi: 10.7754/Clin.Lab.2023.230703.](#)

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