# Thrombocytopenia

Nichola Cooper

Deepti Radia

## Abstract

Thrombocytopenia (low platelet count) is caused by a number of different factors that either reduce the production of platelets or increase the destruction of platelets. Broadly speaking, these can be divided into immune and non-immune causes. Non-immune causes include inherited causes of abnormalities of megakaryocyte development, infiltration of the bone marrow, liver disease, infection-related and drug-induced. Immune thrombocytopenia (ITP) is caused by antibody- or cell-mediated destruction and can be primary (where a cause is not identified) or secondary to infections, autoimmunity or lymphoproliferative disorders. This article discusses the causes of thrombocytopenia with a focus on ITP.

**Keywords** Eltrombopag; rituximab; romiplostim; thrombocytopenia; thrombopoietin

## Key points

- Platelets are produced in the bone marrow from megakaryocytes
- Thrombopoietin is a principal regulator of platelet production
- Thrombocytopenia can be caused by many things including bone marrow diseases resulting in reduced platelet production, and increased destruction of platelets, as in immune thrombocytopenia
- Antibodies and cytotoxic T cells cause autoimmune destruction of platelets in immune thrombocytopenia
- Treatment of immune thrombocytopenia includes immunosuppression with corticosteroids, mycophenolate mofetil and rituximab, and stimulation of production of platelets with romiplostim and eltrombopag

## Introduction

Platelets (thrombocytes) are circulating non-nucleated cells produced from megakaryocytes and have a lifespan of 7–10 days. Thrombopoietin, produced mainly in the liver, is the principal regulator of platelet production. It is not yet clear what regulates thrombopoietin release and therefore platelet production, although response to infection may play a role, and recognition of old platelets by the Ashwell–Morell receptor in the liver is likely to be important. Normal platelet counts range between $150 \times 10^9$/litre and $400 \times 10^9$/litre. Thrombocytopenia (low platelet count) can arise as a result of multiple different conditions (Table 1). These can be divided into four mechanism-related categories:

- a reduction in platelet production (i.e. marrow failure)
- increased platelet consumption/destruction (reduced platelet lifespan)
- abnormal platelet distribution (e.g. splenomegaly)
- dilutional loss.

Identification of the underlying cause is important in deciding the appropriate treatment.

***Nichola Cooper*** *MA MB BS MD FRCP FRCPath is Consultant Haematologist/Honorary Senior Lecturer at the Hammersmith Hospital, London, UK. She runs a clinical and laboratory research group at the Hammersmith Hospital in immune haematology. Competing interests: Nichola Cooper has given talks at educational meetings sponsored by Novartis and Amgen and has worked as a consultant for Novartis, GSK and Amgen.*

***Deepti Radia*** *MSc MRCPI FRCPath MSc Med Ed is Consultant Haematologist at Guy's and St Thomas' Hospitals NHS Foundation Trust, London, UK. Competing interests: none declared.*

## Immune thrombocytopenia (ITP)

Primary ITP is an acquired immune disorder defined as an isolated thrombocytopenia (all other blood parameters normal) with a platelet count under $100 \times 10^9$/litre. The incidence is approximately 1 in 10,000 population, and it occurs almost equally in men and women apart from the third and fourth decade of life, when there is a slightly higher incidence in women. ITP can happen in any age group, but has a different prognosis in children and adults.

ITP is classified into three stages: newly diagnosed (0–3 months) persistent (3–12 months) and chronic (>12 months).[1] Approximately 30% of adults and 80% of children go into remission within the first year of diagnosis, with a much smaller proportion remitting much later after diagnosis.[1] The cause of ITP is not known, although it can be proceeded by either infection or vaccination.

The pathology of ITP (Figure 1) is complex and involves both antibody and T-cell-mediated disease. Antiplatelet antibodies are directed against both platelets and megakaryocytes. Antibody-coated platelets are targeted for destruction, either by macrophages in the spleen and sometimes the liver, or by direct platelet lysis. Antibodies also target the megakaryocytes and can reduce platelet production.

Regulatory T cells are reduced in patients with ITP, and there is skewing towards a T helper 1 and 17 autoimmune phenotypes. Cytotoxic T cells also directly lyse platelets, and possibly megakaryocytes, although their role in the bone marrow is not clear.[2]

## Symptoms and signs

Most patients with thrombocytopenia are asymptomatic, and a low platelet count is often an incidental finding. Only a proportion of patients present with bleeding symptoms. These range from petechiae (small pinprick red dots) on the skin, increased bruises and, more seriously, mucosal bleeding in the mouth,





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## Causes of thrombocytopenia

**Reduced platelet production**

*Abnormal megakaryocyte development*

- Congenital mutation of c-MPL thrombopoietin receptor
- May–Hegglin syndrome
- Wiskott–Aldrich syndrome
- Drugs, chemicals and viral infections

*Generalized bone marrow failure*

- Haematological malignancy – leukaemia, aplastic anaemia, myeloma, myelodysplasia, myelofibrosis
- Secondary to cytotoxic drugs and radiotherapy
- Infections – HIV, cytomegalovirus, hepatitis B and C
- Alcohol excess
- Megaloblastic anaemia

**Increased platelet consumption**

*Immune*

- Idiopathic/primary autoimmune (immune thrombocytopenia)
- Secondary – systemic lupus erythematosus, chronic lymphocytic leukaemia, lymphoma
- Infections: HIV, hepatitis B and C, malaria
- Drug-induced, e.g. rifampicin, penicillins, sulphonamides, heparin, quinine
- Post-transfusion purpura
- Thrombotic thrombocytopenic purpura
- Disseminated intravascular haemolysis

**Abnormal distribution of platelets**

- Splenomegaly (up to one-third of the marrow production of platelets can be trapped in the normal spleen at any given time, increasing with massive splenomegaly)

**Dilutional**

- Massive blood transfusion

**Table 1**

from the nose or in the urine or stools. Very rarely, patients develop intracranial haemorrhage, which is fatal in 25% of cases. Bleeding risks increase with age. The platelet count at presentation has some relation to severity of disease.[1]

Taking a full history and examination is very important in ITP to rule out other causes of thrombocytopenia and to assess the extent of bleeding and risks.

## Investigations

ITP is a diagnosis of exclusion of other causes of thrombocytopenia. The full blood count (FBC) usually demonstrates an isolated thrombocytopenia. In cases of significant bleeding associated with ITP, haemoglobin concentration can be low and red cell size abnormal, with microcytosis (if chronic) or macrocytosis (if acute). A blood film is a vital investigation and in ITP shows a reduction in platelet number as well as occasional large platelets.

The size of platelets is also important in the diagnosis. The presence of uniformly very large platelets can be due to inherited causes, such as Bernard–Soulier syndrome. Very small platelets in male infants (especially associated with eczema) can indicate Wiskott–Aldrich syndrome or X-lined thrombocytopenia (see *Inherited bleeding disorders* on pages xxx of this issue). In contrast, patients with ITP have both large and small platelets. Additional abnormalities in the morphology of red cells (the presence of red cell fragments) may suggest an alternative diagnosis, such as thrombotic thrombocytopenic purpura (TTP) (see *Acquired disorders of coagulation* on pages xxx of this issue) or disseminated intravascular haemolysis (DIC). Another cause of an isolated thrombocytopenia is pseudo-thrombocytopenia, an ethylenediaminetetraacetic acid (EDTA) artefact that can be excluded by checking for platelet clumping on the blood film.

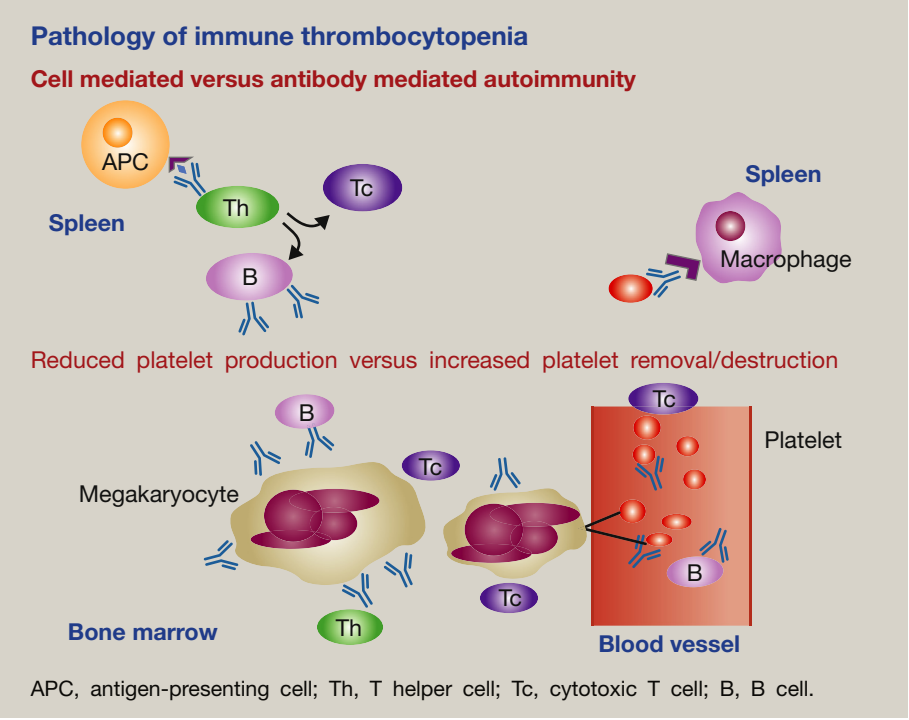


**Figure 1**




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