Diagnosis and management of primary immune thrombocytopenia in adults

Immune thrombocytopenia is an autoimmune mediated disease characterized by thrombocytopenia (platelet count <100x10^9/litre) and is seen in response to an unknown immune stimulus. It may occur in isolation, known as primary immune thrombocytopenia, or in association with another disease, secondary immune thrombocytopenia (*Table 1*), which accounts for 20% of cases of immune thrombocytopenia. The prevalence of immune thrombocytopenia in adults is estimated at 5.6–20 per 100 000 population, with prevalence increasing with age (Fogarty, 2009).

The pathophysiology of immune thrombocytopenia is believed to involve an interplay of three factors: autoimmune destruction of platelets mediated by antiplatelet antibodies, impaired production of platelets, and destruction of platelets by T-cells (Lambert and Gernsheimer, 2017).

Immune thrombocytopenia has three stages: newly diagnosed (0–3 months), persistent (3–12 months) and chronic (>12 months).

Table 1. Secondary causes of immune thrombocytopenia and symptoms to ascertain in the history

Cause		Symptoms
Autoimmune diseases	■ Systemic lupus erythematosus ■ Rheumatoid arthritis ■ Antiphospholipid syndrome ■ Evans syndrome	■ Rash or joint pains ■ History of clots or recurrent miscarriages
Lymphoproliferative disorders, e.g. chronic lymphocytic leukaemia		Fever, night sweats, weight loss (B symptoms) Any lymphadenopathy ('lumps and bumps')
Infectious diseases	■ HIV ■ Hepatitis C ■ *Helicobacter pylori* ■ Cytomegalovirus, varicella zoster virus	■ Risk of exposure to blood-borne viruses – sexual history, blood transfusions, use of intravenous drugs ■ Any indigestion symptoms, ethnicity ■ Exposure to ill contacts
Miscellaneous: Quinine, common variable immunodeficiency, vaccination side effect		Recurrent infections especially respiratory tract infections and diarrhoea

Clinical presentation and diagnosis

Many patients with immune thrombocytopenia are asymptomatic on presentation, with the abnormal blood result identified incidentally. Some patients experience bleeding, which can range from mild skin manifestations (*Table 2*) to more serious mucosal bleeding (bleeding from the mouth or nose, into urine or stool, or menorrhagia). Life-threatening bleeding, such as intracranial bleeding, is a rare presentation of immune thrombocytopenia (affecting ~1.4% of adult patients). Serious bleeding is more common with increasing age (Neunert et al, 2011).

Immune thrombocytopenia is a diagnosis of exclusion. A thorough history and examination is essential to exclude other causes of thrombocytopenia (*Table 3*) and to identify potential secondary causes. Current guidelines (British Committee for Standards in Haematology General Haematology Task Force, 2003) recommend a range of tests to assist with the diagnosis (*Table 4*). A full blood count with a blood film is essential to confirm true thrombocytopenia, and assess platelet morphology and the morphology of other cell lineages. In immune thrombocytopenia there are normal red cells and leucocytes with a reduction in platelet numbers and occasional large platelet forms seen (as a result of the bone marrow releasing larger megakaryocyte particles in response to the reduction in platelet number).

Additional tests including a direct antiglobulin test to assess for haemolysis may be informative. If positive with a low haemoglobin, this may indicate a diagnosis of Evans syndrome (autoimmune haemolytic anaemia with thrombocytopenia). Immune thrombocytopenia may be associated with viral illnesses, such as HIV and hepatitis C, and serological markers for these should be tested. There is conflicting evidence regarding the routine testing for *Helicobacter pylori* in all patients with suspected immune thrombocytopenia. *H. pylori*-associated

Table 2. Skin manifestations of immune thrombocytopenia

Skin condition	Manifestation
Petechiae	Small, flat, red lesions seen most often in dependent positions – lower legs or sacrum in recumbent patients
'Dry' purpura	Coalesced petechiae (i.e. large, flat, red-purple lesions), also more common in dependent position. Seen on the skin
'Wet' purpura	As dry purpura in appearance but seen on the mucous membranes – typically identified in the mouth. May indicate a risk of more serious bleeding

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Table 3. Essential points in the history and examination of a patient with suspected immune thrombocytopenia

History taking	Bleeding history – to establish duration of thrombocytopenia and severity
	Presence of B symptoms, i.e. fever, weight loss, night sweats (to identify possible lymphoproliferative disorders or HIV)
	Risk factors for HIV, hepatitis B/C
	Drug history, including over the counter and herbal medicines
	Family history of bleeding or low platelets to identify genetic low platelet syndrome, e.g. MYH9-related thrombocytopenia (also known as May–Hegglin anomaly)
	Alcohol history
	Recent vaccination history
Examination	Areas of bleeding – skin or mucosa, e.g. presence of petechiae or purpura
	Presence of lymphadenopathy or organomegaly (liver or spleen) – if present, suggests a secondary cause for immune thrombocytopenia. Mild splenomegaly may be found in children with immune thrombocytopenia
	Joint swelling or rash suggestive of autoimmune disease, e.g. systemic lupus erythematosus

immune thrombocytopenia is more common in certain geographical areas, e.g. south-east Asia, and so the decision to test for *H. pylori* should be based on patient ethnicity, the presence of symptoms and whether eradication therapy would be undertaken if testing was positive. In some patients there may be a response in platelet counts with *H. pylori* eradication (Neunert et al, 2011).

A bone marrow examination is rarely required in patients, and is only done when there is diagnostic uncertainty (e.g. other blood count parameters are abnormal suggesting a primary marrow disorder) or where patients become refractory to standard treatment and reassessment is required to ensure there are no secondary diagnoses (British Committee for Standards in Haematology General Haematology Task Force, 2003).

Table 4. Laboratory tests in immune thrombocytopenia

Full blood count and blood film
Direct antiglobulin test and blood type
HIV, hepatitis B and hepatitis C testing
Helicobacter pylori (stool antigen) – can be considered
From British Committee for Standards in Haematology General Haematology Task Force (2003)

Management of immune thrombocytopenia in adults

This review covers the management of primary immune thrombocytopenia in adults. In secondary immune thrombocytopenia treatment is aimed at the underlying disease. If the platelet count falls and the patient is symptomatic, this may warrant targeted treatment and is usually treated similarly to primary immune thrombocytopenia.

The goal of immune thrombocytopenia management is to reduce the bleeding risk and maintain the platelet count at a safe level; it is not necessary to normalize the platelet count. Typically treatment for immune thrombocytopenia is initiated at platelet levels <$30x10^9$/litre, although higher platelet counts may warrant treatment if the patient has symptomatic bleeding, e.g. heavy menorrhagia.

First-line treatment

Corticosteroids are used first line for immune thrombocytopenia. A typical course is prednisolone 1 mg/kg/day for 2–4 weeks with steroid tapering. Evidence suggests that a short course of high dose dexamethasone, e.g. 40 mg for 4 days (equivalent prednisolone dose 400 mg/day), may be more effective at increasing the platelet count and inducing remission. Matschke et al (2016) compared repeated courses of pulsed high-dose dexamethasone with 2–4 weeks daily prednisolone in patients with immune thrombocytopenia. All patients responded to treatment but the high-dose dexamethasone group were more likely to have a sustained response with 77% of this group being in remission at 1 year compared with 22% of the prednisolone group (P=0.027). Side effects between both groups were similar.

Patients should be advised of toxicities with steroids including indigestion, insomnia, mood change and, with prolonged or repeated courses, the risk of hyperglycaemia, hypertension and osteoporosis. A proton-pump inhibitor should be given concomitantly. Of note the currently recruiting FLIGHT study (Pell et al, 2018) is comparing the use of steroids alone with steroids plus mycophenolate mofetil in patients newly diagnosed with immune thrombocytopenia in an effort to assess if there is a role for steroid-sparing agents upfront.

Intravenous immunoglobulin, a blood product of pooled plasma rich in antibodies, has similar efficacy to corticosteroids in the first-line management of immune thrombocytopenia, and is used where a rapid increase in platelet count is required, e.g. peri-procedurally or in active bleeding. The initial recommended dose is 1 g/kg (Neunert et al, 2011). Intravenous immunoglobulin and steroids can be used in combination when a rapid response is essential. Intravenous immunoglobulin should be used with caution in patients with impaired renal function because of the risk of precipitating renal failure. Thrombosis is another rare but serious adverse effect.

Anti-D immunoglobulin is as effective as intravenous immunoglobulin in increasing platelet counts. It is immunoglobulin G derived from multiple donors, but has a smaller donor pool than intravenous immunoglobulin so the theoretical risk of infection is lower. It is only appropriate in rhesus D-positive patients who are non-splenectomised and should be avoided in patients with autoimmune haemolytic anaemia as it can cause severe, sometimes fatal, haemolysis (Provan et al, 2010). Patients should have their blood group and a direct antiglobulin test checked before considering anti-D. The licensed dose is 50 µg/kg and some patients may require premedication with paracetamol and/or steroids to reduce the risk of febrile reactions.

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Second-line treatment

A proportion of patients will develop chronic immune thrombocytopenia and require second-line treatment. The aim is to minimize exposure to steroids and blood products while maintaining a safe platelet count. Where patients fail to respond to multiple second-line agents then the diagnosis should be revisited and a secondary cause sought. A bone marrow biopsy may be warranted at this stage.

Immunosuppressive treatment including rituximab

In chronic immune thrombocytopenia an array of immunosuppressive agents can be used second line. The strongest evidence is for rituximab, an anti-CD20 monoclonal antibody. In a systematic review of rituximab in immune thrombocytopenia (Arnold et al, 2007) 62.5% of patients' platelet counts increased to >50 x10^9/litre with a median time to response of 1–2 months. The response lasted for a median 11 months (range 2–48 months). About 20% of patients have a sustained response at 5 years post-treatment (Lambert and Gernsheimer, 2017).

Other immunosuppressive agents which can be used are azathioprine, mycophenolate mofetil, dapsone, danazol, cyclophosphamide, ciclosporin and vincristine. All these agents can produce a response in platelet count days to weeks after administration. However, there is considerable variability in response rates between patients and insufficient evidence to recommend one agent over another (Neunert et al, 2011).

Thrombopoietin receptor agonists

The thrombopoietin receptor agonists include eltrombopag and romiplostim. These agents stimulate platelet production in the bone marrow by binding to the thrombopoietin receptor and stimulating production of megakaryocytes. Eltrombopag is given as a once-daily tablet while romiplostim is a weekly subcutaneous injection. There is usually a significant increase in platelet number within 1–2 weeks of using these agents but they rarely stimulate remission and maintenance therapy is often needed.

These agents are usually used in patients who have not responded to splenectomy and rituximab, or in patients in whom splenectomy and rituximab are not appropriate, e.g. as a result of frailty or high risk of infection. There are no studies directly comparing romiplostim and eltrombopag and it is assumed that they have equal efficacy. Eltrombopag cannot be taken 4 hours either side of ingestion of dairy products or antacid because of its poor absorption, while romiplostim requires the patient or a carer to administer an injection (Taylor et al, 2017).

Both agents are possibly associated with an increased risk of thrombosis, although a meta-analysis (Catalá-López et al, 2015) suggested that this may not be the case when they are used in patients with immune thrombocytopenia. Eltrombopag can cause liver enzyme derangement and so should be used cautiously in patients with baseline liver dysfunction; a lower starting dose can be used (i.e. 25 mg *vs* 50 mg). Both agents increase bone marrow reticulin content, raising concerns regarding development of bone marrow fibrosis. The significance of this is unclear.

Splenectomy

Splenectomy is an effective second-line treatment for immune thrombocytopenia – 50–60% of patients show sustained platelet count responses at 5 years post-removal (Lambert and Gernsheimer, 2017). It is usually deferred until at least 6 months post-diagnosis because of the long-term risks associated with splenectomy and the chance of spontaneous remission before this time.

Patients with splenectomy are at higher risk of infection (particularly from encapsulated organisms such as Streptococcus), with the risk highest within 3 months postoperatively. A pre- and postoperative vaccination schedule should be followed. Post-splenectomy there is an increased risk of thrombosis and a small long-term increased risk of pulmonary hypertension (British Committee for Standards in Haematology General Haematology Task Force, 2003). The 30-day mortality risk associated with splenectomy is lower when done laparoscopically (0.2%) compared with an open procedure (1%) (Ghanima et al, 2012).

Emergency management of immune thrombocytopenia

Occasions may arise where an urgent increase in platelets is needed, either to facilitate emergency surgery, or in cases of severe bleeding (see platelet target thresholds in *Table 6*). Agents that can be used to rapidly increase the platelet count (within 24 hours) include platelet transfusions, intravenous immunoglobulin and steroids (usually intravenous methylprednisolone) (Provan et al, 2010).

Platelets may be given concurrently with intravenous immunoglobulin and methylprednisolone to increase their lifespan. Tranexamic acid should also be considered (oral or intravenous).

Other options include intravenous anti-D (in Rh+ non-splenectomised patients), single agent vincristine and emergency splenectomy. These are rarely used in clinical practice.

Conclusions

Immune thrombocytopenia is an immune-mediated condition characterized by increased peripheral destruction of platelets with reduced bone marrow platelet production. The majority of patients are diagnosed incidentally or with very mild bleeding on presentation. There have been advances in the treatment strategies for immune thrombocytopenia with the emergence of rituximab and the thrombopoietin receptor analogues. There is reasonable randomized controlled trial evidence for the first-line management of immune thrombocytopenia with steroids

Table 6. Safe platelet count thresholds for common procedures or surgeries

Type of procedure	Platelet count threshold
Insertion of central line	≥20x10^9/litre
Lumbar puncture	≥40x10^9/litre
Major surgery including vaginal delivery (no epidural)	≥50x10^9/litre
Insertion or removal of epidural catheter	≥80x10^9/litre
Neurosurgery or posterior eye surgery	≥100x10^9/litre

Adapted from Estcourt et al (2017)

and intravenous immunoglobulin, but a paucity of evidence exists for second-line immunosuppressive treatment. While national and international guidelines exist for the management of immune thrombocytopenia, choice of second-line treatment is largely based on clinician and patient preference. Further work is required to establish the appropriate timing and order of second-line agents in immune thrombocytopenia. **BJHM**

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KEY POINTS

- Immune thrombocytopenia is a haematological disorder characterized by immune-mediated destruction of platelets and is a diagnosis of exclusion.
- It is important to exclude a secondary cause of immune thrombocytopenia as management in these cases is aimed at controlling the underlying disease.
- The decision to treat in immune thrombocytopenia is based on the platelet count (usually <30x10^9/litre prompting initiation of therapy) and bleeding symptoms. The aim of treatment is to reduce the risk of bleeding, not to normalize the platelet count.
- First-line treatment of immune thrombocytopenia includes steroids and intravenous immunoglobulin. Second-line strategies are more diverse and include immunosuppression, thrombopoietin receptor analogues and splenectomy.

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