# The General Practice Guide to Autoimmune Diseases

Edited by Y. Shoenfeld and P. L. Meroni

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# Autoimmune thrombocytopenic purpura

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## 1 Introduction

Immune thrombocytopenic purpura (ITP) is a relatively common, immune-mediated disorder affecting approximately 5–10 adults per 100 000 in the western world. It is characterised by isolated thrombocytopenia ($< 100 \times 10^9$/L), and the absence of any obvious initiating and/or underlying cause for the thrombocytopenia [1].

The mechanisms of thrombocytopenia are increased platelet destruction mediated primarily by autoantibodies but also by direct T-cell cytotoxicity against platelets, and decreased platelet production.

The disease can be classified by duration into acute, persistent (3–12 months), and chronic (>1 year), and by patient age (adult or childhood) [2].

*Paediatric ITP* is usually an acute, self-limiting disease preceded by a viral infection or rarely, following immunisation (e.g. MMR). More than 60 % of paediatric patients recover spontaneously within 6 months. In contrast, *adult ITP* exhibits an insidious onset and normally follows a chronic course; spontaneous remissions rarely occur. The median age at diagnosis is 56 years; it is more prevalent in women aged 30–60 years, and equally prevalent in both sexes above the age of 60 [3].

Signs and symptoms vary widely, ranging from asymptomatic or minimal bruising to bleeding episodes including gastrointestinal, skin, mucosal or rarely, intracranial haemorrhage (Fig. 1).

Several factors can contribute to the risk of bleeding and should be evaluated before the appropriate management is determined: the severity of the thrombocytopenia (correlates to some extent with bleeding risk), age, lifestyle factors and uraemia.

Mortality rate is low, ranging from 1–2 %, and can be attributed equally to severe bleeding and infections secondary to immunosuppressive therapy.

The investigation and management of ITP patients vary widely, in part because of the understanding that ITP is a more benign disease than previously thought, and should be treated conservatively, reserving aggressive treatment for patients with severe and symptomatic thrombocytopenia [2].

## 2 Diagnostic criteria

### 2.1 Clinical Criteria

- Mild skin and mucosal purpuric rash/ecchymoses.
- Bleeding tendency (see Table 1).

### 2.2 Laboratory Criteria

- Isolated thrombocytopenia ($< 100 \times 10^3$/ml).

**Table 1.** Signs and symptoms of ITP.

| System | Symptoms |
|---|---|
| | None (asymptomatic) |
| Skin or mucosa | Easy bruising, petechiae, nose bleeds, gum bleeding |
| Genitourinary | Gynaecologic bleeding, haematuria |
| Gastrointestinal | Abdominal pain, upper or lower GI bleeding |
| CNS | Headache, intracranial haemorrhage |
| General | Fatigue, sleep disturbances |

## 3 Diagnostic measurements for experts

ITP is a disease characterised by thrombocytopenia that may accompany a purpurial rash and bleeding tendency. The diagnosis is made when the patient's history, physical examination, laboratory results (including complete blood count) and

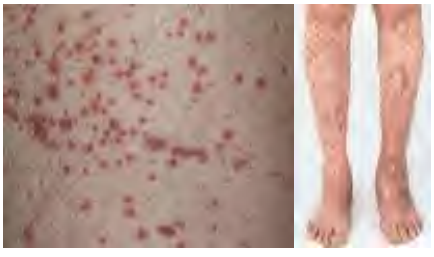

**Figure 1.** Typical purpuric rash of ITP.

peripheral blood smear do not raise another possible aetiology for the thrombocytopenia. Response to ITP-specific therapies could be also supportive of the diagnosis [1].

After ruling out possible alternative causes for thrombocytopenia by a review of the patient's history and physical examination (discussed later), evaluation of peripheral blood smear by haematologist must be made in order to look for blood cell abnormalities not characteristic of ITP (e. g. schistocytes in thrombotic thrombocytopenic purpura).

A bone marrow examination (aspiration and biopsy) may be considered in the following cases: patients over 60, when a splenectomy is considered, and in patients presenting with systemic symptoms not typical of ITP (e. g. fever, weight loss, lymphadenopathy).

Other relevant laboratory tests are anti-phospholipid antibodies which may be present in up to 40 % of ITP patients (recommended in the presence of anti-phospholipid syndrome only), thyroid function tests which include TSH and anti-thyroid antibody owing to the fact that a substantial percentage of ITP patients will develop hypo/hyperthyroidism.

Evaluation of blood group Rh (D) typing and direct anti-globulin test is needed when considering treatment with anti-D immunoglobulin [1].

## 4 Requirements for family practitioners

Many cases of ITP are diagnosed first by the family practitioner incidentally after a routine complete blood cell count. As previously mentioned, patient presentations vary from asymptomatic to history of bleeding episodes, the most serious being intracranial. The patients may consult their general practitioner due to easy bruising, nose and gum bleeding or fatigue. A thorough history and physical examination (should be normal aside from possible purpura; moderate or massive splenomegaly excludes ITP) should be completed, taking into consideration the differential diagnosis of ITP (Table 2). The family doctor should ask about bleeding history (dental procedures, surgeries) to differentiate between the acute and chronic disorders.

The complete blood count should show isolated thrombocytopenia with otherwise normal laboratory results. The practitioner should ask about recent immunisation and transfusions, infectious status (H. pylori, HCV, HIV, CMV and Parvovirus evaluation is recommended), inherited and congenital platelet disorders, exposure to drugs, alcohol and toxins, history of other haematological, autoimmune/immunodeficiency diseases and liver and thyroid disorders [1–2]. In paediatric ITP cases a history of previous infection must be sought.

If the diagnosis of ITP is established, the family practitioner needs to assess relative and absolute contraindications for corticosteroid therapy.

## 5 Follow up

*Clinical observations*

Adult ITP is usually a chronic disease requiring long-term follow-up. Treatment for ITP is considered appropriate only for symptomatic patients and those at risk for bleeding (age > 60 years, platelet count < $20 \times 10^9$/l, history of bleeding episodes, mandated anticoagulant therapy, predisposing profession or lifestyle). As long as the patient is asymptomatic with mild thrombocytopenia (s)he should not be treated, since the main goal of therapy is not to maintain a normal platelet count, but to maintain a safe one [2, 3].

The family practitioner should be aware of any change in platelet count — this requires routine complete blood count monitoring, asking the patient about signs of bleeding, planning of any elective surgery or any other scheduled invasive procedure.

Any change in clinical or laboratory status of the patient requires consultation with a haematologist.

*Expectations*

ITP is a chronic disease with variable prognosis; spontaneous remissions are uncommon. Many patients are asymptomatic or report only minimal bruising, others can experience serious bleeding. The estimated rate of fatal haemorrhage is 0.0162–0.0389 cases per adult patient per year at risk.

Paediatric ITP is usually short-lived with more than 60 % recovering spontaneously within 6 months [1].

**Table 2.** Differential diagnosis of ITP.

| |
|---|
| – Infectious diseases (HIV, HCV, HBV, EBV etc.) |
| – Autoimmune disorders (SLE, Evans syndrome) |
| – Malignancy (e.g. lymphoproliferative disorders) |
| – Liver diseases |
| – Drugs and other toxins |
| – Bone marrow abnormalities (myelofibrosis, aplastic anaemia, myelodysplastic syndrome |
| – Recent immunisation |
| – Inherited thrombocytopenia (e.g. Wiskott-Aldrich syndrome, Bernard-Soulier syndrome etc.) |

*Blood tests*

The main necessary blood test during follow up (in both treated and untreated patients) is CBC — platelet count and haemoglobin should be monitored.

In patients treated with corticosteroids — blood pressure, glucose and potassium values should be monitored and ophthalmologist assessment should be carried out.

## 6 Management

Treatment decision-making should be shared between the clinicians (family doctor and haematologist) and the patient, and should be individualised according to the severity of the disease, patient's age, co-morbidities and presence or absence of current bleeding.

In the uncommon cases of life-threatening haemorrhage or before surgical procedures, immediate therapy must be started. This includes prednisone and IVIG (intra venous immunoglobulins). Other rapid treatment options are high-dose methylprednisolone, platelet transfusion, anti-fibrinolytics and emergency splenectomy [1].

Surprisingly, only a limited number of randomised controlled trials (RCT) using traditional therapies to guide treatment management decisions are known in the literature, in contrast to the new ITP treatments (including thrombopoietic growth factors) for which some evidence-based RCT data already exists.

Nevertheless, once a decision to start therapy has been made, *corticosteroids* are the initial standard of care. Prednisone, prednisolone, methylprednisolone or high-dose dexamethasones (HDD) are commonly used. Approximately two-thirds of patients will respond (partially or completely) during the first week, but only 10–15 % will enjoy a lasting remission [3]. There is some evidence suggesting HDD has an advantage in achieving a sustained response.

If glucocorticosteroids treatment fails, other treatment options (also classified as first-line treatment) includes *IVIG* and *anti-D* in RhD-positive non-splenectomized patients. The beneficial effect of both these treatments is transient (mostly 2–4 weeks), but anti-D can be infused in a shorter time compared to IVIG, may reduce the need for splenectomy and has a potentially longer positive response [1–3].

*Second-line therapy*

Traditionally, *splenectomy* (open or laparoscopic) is considered to be the second-line treatment after first-line therapy has failed. Nevertheless, because spontaneous remissions or improvement may occur 6–12 months after the diagnosis, splenectomy is usually postponed for at least 6 months [1].

Approximately 25 % of patients will relapse after splenectomy and will be defined as having chronic refractory ITP. In these patients the development of accessory spleens should be ruled out [2]. Patients are usually given vaccination against encapsulated bacteria one month before or two weeks after the surgery.

A variety of second-line medical treatment alternatives are available today, both prior to or after splenectomy (with no preference for particular therapy). These therapies include:

1. anti-CD20 monoclonal antibody **Rituximab** — 60 % of patients respond, 40 % have a complete response, [4];
2. **Danazol**, an attenuated androgen response rate > 60 % for > 2 months;
3. **Dapsone**. a corticosteroid-sparing agent — may delay a splenectomy for up to 32 months [1];
4. **Azathioprine** — 45–55 % response rate;
5. **Cyclophosphamide** — 25–85 % response rate with mild–moderate toxicity;
6. **Cyclosporine-A** — clinical improvement in more than 80 % of patients resistant to first-line therapy, 42 % achieved complete remission [1];
7. **Mycophenolate mofetil** (immunosuppressant) and Vinca alkaloids — approximately a 40–50 % response rate, but not a sustained one;
8. **Thrombopoietin receptor agonists**, a novel therapeutic approach intended to stimulate platelet production rather than modulating the immune system — two agents, **Eltrombopag** (non-peptide TPO mimetic, given orally once daily) and **Romiplostim** (peptide TPO mimetic, given subcutaneously once weekly) are FDA-approved for the treatment of ITP: 80–89 % response rate lasting between 1.5 years (Eltrombopag) to 4 years (Romiplostim) with continual administration [5].

*Third-line therapy (for adult failing first-and second-line therapies)*

Approximately 30 % of patients will not achieve satisfactory improvement or will relapse after a splenectomy or after first- and second-line therapies. For this group of patients there are only limited medical options. These need to be discussed with the patient who should be made aware of their toxic side effects: combination chemotherapy (cyclophosphamide, prednisone and vincristine plus azathioprine etoposide); Campath-1H and haematopoietic stem cell transplantation — reserved only for patients with severe chronic refractory ITP with bleeding complications unresponsive to other treatment modalities [1].

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