

Recommendation box 1

Recommendations for diagnosis of primary ITP

The diagnosis of ITP is based principally on the exclusion of other causes of isolated thrombocytopenia using patient history, physical examination, blood count and evaluation of the peripheral blood film. If therapy is administered, platelet count should be closely monitored for response as a diagnostic aid.

In children a complete history, physical examination, full blood count and an expert analysis of the peripheral blood smear should be evaluated at initial diagnosis (Grade C recommendation). Based on the evidence currently available, when there is isolated thrombocytopenia and no abnormal features present on physical examination or examination of the blood smear a bone marrow aspiration is not required in children (Grade B recommendation).

Bone marrow examination is appropriate in patients >60 years old (Evidence level IIb, Grade B recommendation), in those relapsing after remission, in patients not responding to first-line therapy options, and where splenectomy is considered (Evidence level III, Grade C recommendation). This examination should ideally include an aspirate, biopsy, flow cytometry and cytogenetics (Evidence level IV, Grade C recommendation).

The detection of *H. pylori* infection, with the urea breath test or the stool antigen test, should be included in the initial work-up of adults in appropriate clinical settings (Evidence level IIa, Grade B recommendation)

The majority of authors routinely tested for HIV and HCV in all adult patients (Evidence level IIb).

Quantitative Ig level testing is indicated to exclude an immune deficiency syndrome (Evidence level IV, Grade C recommendation), or when treatment with intravenous immunoglobulin is considered. In children, Ig level testing may be considered at baseline, and should be measured in those children with persistent or chronic ITP as part of a reassessment evaluation.

Recommendation box 2

Consensus-based recommendation for target platelet counts during surgery in adults:*,^

(Evidence level IV)

Dental prophylaxis (descaling, deep cleaning)	$\geq 20\text{--}30 \times 10^9/\text{L}$
Simple extractions	$\geq 30 \times 10^9/\text{L}$
Complex extractions	$\geq 50 \times 10^9/\text{L}$
Regional dental block	$\geq 30 \times 10^9/\text{L}$
Minor surgery	$\geq 50 \times 10^9/\text{L}$
Major surgery	$\geq 80 \times 10^9/\text{L}$
Major neurosurgery	$\geq 100 \times 10^9/\text{L}$
Splenectomy	see Splenectomy section
Obstetrics	see Thrombocytopenia in pregnancy

***Adult patients considered to be at 'typical' bleeding risk from surgery.²³ Target platelet count depends on the clinical situation and urgency and need for procedure**

^Concomitant use of antifibrinolytics immediately prior to the procedure may be helpful (see Emergency treatment section)

Recommendation box 3

Recommendations for first-line treatment (initial treatment for newly diagnosed patients):

Corticosteroids (prednisone 0.5–2 mg/kg/day) is the standard first-line treatment for adults with ITP who need treatment and do not have a relative contraindication to its use (e.g. diabetes, psychiatric disorders). Prednisone is continued at full dose for 10–28 days then tapered.

Use of IVIg or IV anti-D may be appropriate in patients with bleeding, at high risk of bleeding, or who are unresponsive to prednisone.

Certain patients may have contradictions to high-dose steroid therapy (e.g. insulin-dependent diabetes) and may be managed with only IVIg or IV anti-D as first-line therapy.

Recommendation box 4

Recommendations for emergency treatment (on-demand treatment):

A combination of first-line treatments, including high-dose IV corticosteroids and usually IVIg, should be used initially in emergency situations where there is an urgent need to increase the platelet count within 24 hours (Grade C recommendation). Platelet transfusions may be essential. Additional options may

include IV anti-D, vincristine, anti-fibrinolytics in combination with first-line therapies (Grade C recommendation) and emergency splenectomy.

Recommendation box 5

Recommendations for second-line therapy in adults – medical:

TPO-receptor agonists (romiplostim and eltrombopag) have provided excellent responses in both splenectomized and non-splenectomized patients (Grade A recommendation, Evidence level Ib). Response to TPO-receptor agonists persists for up to 4 years and often allows other ITP therapy to be reduced or discontinued. Cessation of treatment will lead to return of thrombocytopenia in most cases.

Evidence from a systematic review of multiple uncontrolled trials shows a response to rituximab in over half relapsed/refractory patients. Long-term durable responses occur in 15–20% of patients (Grade B recommendation, Evidence level IIa). Hepatitis B status needs to be determined prior to treatment (Grade C recommendation, Evidence level IV).

Immunosuppressive agents, including mycophenolate mofetil, cyclophosphamide and azathioprine may be used in patients failing other therapies. Danazol and dapsone are 'corticosteroid-sparing' agents that may be particularly useful in elderly patients and in those in whom splenectomy is contraindicated (Grade B recommendation, Evidence level IIa/IIb).

Cyclosporin A (2.5–3 mg/kg/day) increases the platelet count as a single agent or in combination with prednisone. In some patients, the side-effect profile restricts its use (Grade B recommendation).

Recommendation box 6

Recommendations for second-line therapy – surgery:

Splenectomy remains the treatment option with by far the highest likelihood of producing cure. In general, it is recommended to wait at least 6 months from diagnosis before performing splenectomy due to the chance of spontaneous remission (Grade C recommendation, Evidence level IV)

When available, indium-labeled autologous platelet scanning may be useful prior to splenectomy to confirm that the spleen is the main site of platelet sequestration (Grade B recommendation, Evidence level III).

Accessory splenic tissue is common and should be sought in those who relapse after an initial durable response to splenectomy (Grade C recommendation).

Appropriate vaccination against *S pneumoniae*, *N meningitidis* and *H influenzae* must be provided; recent treatment with rituximab may impair vaccination efficacy.

Recommendation box 7

Recommendations for patients failing first- and second-line therapies:

TPO-receptor agonists (romiplostim and eltrombopag) have produced excellent response rates in both splenectomized and non-splenectomized patients including those with relapsed/refractory disease unresponsive to numerous other approaches (Grade A recommendation, Evidence level Ib).

Other therapies that have been used as last resorts include combination chemotherapy, campath-1H and HSCT. The side effects of these treatment options may be severe and the data supporting their use are limited (Grade B recommendation; Evidence level IIb).

Recommendation box 8

Recommendations for investigation of suspected ITP in pregnancy:

As in non-pregnant patients, the diagnosis of ITP is one of exclusion using the patient history, physical examination, blood count and blood smear examination (Grade C recommendation). Bone marrow examination is not recommended for the diagnosis of ITP in pregnancy (Grade C recommendation).

Recommended tests specifically for the diagnosis of thrombocytopenia in pregnancy are: coagulation screening (prothrombin time [PT], activated partial thromboplastin time [APTT], fibrinogen), liver function tests including bilirubin, albumin, total protein, transferases, gamma-glutamyl transferase and alkaline phosphatase, APLA including anticardiolipin antibodies and lupus anticoagulant, SLE serology, review of the peripheral blood smear and reticulocyte count.

Anti-platelet antibody testing does not predict neonatal thrombocytopenia unlike with alloimmune thrombocytopenia (Grade C recommendation).

Recommendation box 9

Recommendations for the treatment of maternal ITP:

Counseling for women with ITP wishing to become pregnant is recommended (Evidence level IV, Grade C recommendation)

Oral corticosteroids or IVIg are considered first-line treatment (Grade C recommendation). IV anti-D in Rh(D)-positive non-splenectomized women appears to be well tolerated and effective based on results from a pilot study (Grade B recommendation, Evidence Level IIb). All have a similar response rate to those in adult ITP patients (Evidence level IV)

Combining first-line therapies (prednisone with IVIg or IV anti-D) may elicit a response in patients' refractory to single agents alone (Grade C recommendation; Evidence Level IV). HDMP in combination with IVIg or azathioprine is suggested for patients refractory to oral corticosteroids or IVIg (Grade C recommendation)

Splenectomy is rarely performed in pregnancy, but is best performed in the second trimester if absolutely necessary. (Evidence level III, Grade C recommendation)

Recommendation box 10

Recommendations for management of delivery and newborn infants:

The mode of delivery must be determined by obstetric indications (Grade B recommendation)

Cordocentesis and fetal scalp blood sampling should be avoided in the management of ITP in pregnancy (Grade C recommendation)

Procedures during labor that may be associated with increased hemorrhagic risk to the fetus should be avoided – specifically use of a) fetal scalp electrodes, b) fetal blood sampling, c) ventouse delivery and d) rotational forceps (Grade C recommendation)

Neonatal alloimmune thrombocytopenia should be excluded if the neonate presents with severe thrombocytopenia (Grade C recommendation)

Recommendation box 11

Recommendations for obstetric anesthetics and venous thromboembolism:

The mother with a rapidly falling count should be observed more closely than those with low, but stable levels (Grade C recommendation).

At a platelet count of $>70 \times 10^9/L$, regional axial anaesthesia can be considered.

Non-steroidal anti-inflammatory drugs should be avoided for post-partum or post-operative analgesia in women with platelet counts $<80 \times 10^9/L$ because of increased hemorrhagic risk (Evidence level IV, Grade C recommendation).

All women with ITP and at an increased risk for thromboembolism should receive appropriate prophylaxis for VTE (Evidence level IV, Grade C recommendation).

Recommendation box 12

Recommendations for initial investigation of suspected childhood ITP: In children a complete history, physical examination, full blood count and an expert analysis of the peripheral blood smear should be evaluated at initial diagnosis (Grade C recommendation). Based on the evidence currently available, when there is isolated thrombocytopenia and no abnormal features present on physical examination or examination of the blood smear a bone marrow aspiration is not required in children (Grade B recommendation).

Recommendation box 13

Recommendations for clinical classification of ITP:

Clinical classification should be used to define disease severity (Evidence level IIb, Grade B recommendation). Treatment should be considered based on a combination of clinical symptoms, the circulating platelet count and impact of ITP on the patient's quality of life (Evidence level IIb, Grade B recommendation).

Recommendation box 14

Recommendations for watch and wait policy:

Children with acute ITP and mild clinical disease may be managed expectantly with supportive advice and a 24-hour contact point, irrespective of platelet count (Grade B recommendation). Patients should be re-evaluated to ensure that no evidence of evolution to a serious bone marrow disorder or evidence of a secondary form of the disease is present (Evidence Level IV, Grade C recommendation). The frequency of clinical and laboratory monitoring should be based on clinical symptoms and the trend in platelet counts.

Recommendation box 15

Recommendation for children wishing to take part in strenuous activity:

Intermittent platelet-enhancing treatment may be given to cover activities with appropriate discussion of the risks versus the benefits of treatment (including costs and medication-associated adverse events; Grade C recommendation).

Recommendation box 16

Recommendations for first-line management in children:

The majority of children can be managed with watchful waiting as described.

In the presence of serious bleeding, IVIg and anti-D can raise the platelet count rapidly. IVIg is effective when given as a single dose of 0.8–1.0 g/kg (Grade A recommendation, Evidence level Ib). Anti-D immunoglobulin has similar efficacy to IVIg when given as a single dose of 75 µg/kg and is rarely associated with severe hemolysis (Grade A recommendation, Level Ib evidence).

In general, a short course of 1–2 mg/kg/day of prednisone may be given, with treatment titrated against the platelet count and with rapid tapering (Grade A recommendation, Evidence level Ib). Alternatively, a higher dose of corticosteroids 4 mg/kg/day for 4 days may be used (Grade B recommendation, Evidence level III).

Recommendation box 17

Recommendations for emergency treatment in children:

Platelet transfusions in combination with IV steroids, and IVIg or IV anti-D should be given for ICH or other life-threatening or serious bleeding.

Local surgical or neurosurgical control of bleeding should be considered in conjunction with emergency platelet raising therapy (see adult section) (Evidence level IV, Grade C recommendation).

Recommendation box 18

Recommendations for second-line treatment of ITP in children:

Rituximab has been used successfully and may provide an alternative to splenectomy in some children (Grade B recommendation, Evidence level IIa and IIb). However, additional studies are required to evaluate the long-term safety of rituximab in children. TPO-receptor agonists require more studies in the pediatric population before they can be recommended for use (Grade C recommendation, Evidence Level IV)

Therapy with pulsed high-dose steroids or regular IVIg/anti-D may control bleeding while awaiting spontaneous remission or while considering disease-altering treatment.

Combination therapies (see adult section) may provide responses in some children with refractory ITP; however, the possibility of severe toxicity must be considered when administering multiple therapies (Grade C recommendation, Evidence Level IIb, III).

Recommendation box 19

Recommendations for splenectomy in children with chronic ITP:

Splenectomy is rarely indicated in childhood ITP (Grade C recommendation) and should be undertaken in consultation with a hematologist experienced in the management of children with ITP. It may be justified for life-threatening bleeding and for children with chronic unremitting and severe ITP with bleeding symptoms, whose disease has been present for more than 12–24 months and who have a demonstrable impairment of their quality of life (Grade B recommendation, Evidence level IIb).