Primary immune thrombocytopenia in adults

Guidelines for diagnosis and treatment anno 2013 proposed by the Belgian Hematological Society

A. Janssens, C. Lambert, G. Bries, A. Bosly, D. Selleslag, Y. Beguin

The Belgian Hematological Society (BHS) guideline panel on adult primary immune thrombocytopenia (ITP) reviewed the recent literature on diagnosis and treatment to make recommendations on the best strategies for frontline and subsequent-line treatment. No treatment is necessary for patients with platelet counts higher than 30000/µl in the absence of bleeding symptoms. Patients newly diagnosed or relapsing after a long-term treatment-free period can be managed with corticosteroids with or without intravenous immunoglobulins. A second line therapy is indicated for those patients who are intolerant or unresponsive to or relapse after initial corticosteroid treatment and have a risk of bleeding. The guideline panel recommends splenectomy as it is the treatment with the highest curative potential and an acceptable safety profile. If possible, splenectomy should be delayed to at least twelve months after diagnosis as spontaneous remission can occur in this time period. Thrombopoietin receptor (TPO-R) agonists are recommended for patients who are refractory to or relapse after splenectomy or who have a contra-indication to splenectomy irrespective of the duration of ITP. The guideline panel agrees that rituximab, azathioprine, cyclophosphamide, cyclosporine A, danazol, dapsone, mycophenolate mofetil and vincristine/vinblastine are potential treatment options, especially for patients refractory to TPO-R agonists.

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Introduction with definitions

Immune thrombocytopenia is an acquired autoimmune disease characterised by an isolated low platelet count number (<100,000/µl). The disorder is classified as primary immune thrombocytopenia (ITP) in the absence of any obvious initiating and/or underlying cause, and as secondary ITP in association with autoimmune disorders (systemic lupus erythematosus (SLE), the antiphospholipid syndrome (APS), etc.), some immunodeficiency syndromes (CVID, adult lymphoproliferative syndrome, etc.), lymphoproliferative disorders (chronic lymphocytic

Authors: A. Janssens, MD[1], C. Lambert, MD[2], G. Bries, MD, PhD[3], A. Bosly, MD, PhD[4], D. Selleslag, MD[5], Y. Beguin, MD, PhD[6]. [1]Universitaire Ziekenhuizen Leuven, Department of Hematology, Leuven, Belgium. [2]Cliniques universitaire Saint-Luc, Department of Hematology, Brussels, Belgium. [3]AZ Turnhout, Department of Hematology, Turnhout, Belgium. [4]CHU de Mont-Godinne, Department of Hematology, Godinne, Belgium. [5]AZ Sint-Jan Brugge, Department of Hematology, Brugge, Belgium. [6]CHU Sart-Tilman, Department of Hematology, Liège, Belgium.

Please send all correspondence to: A. Janssens, MD, Universitaire Ziekenhuizen Leuven, Department of Hematology, Herestraat 49, 3000 Leuven, Belgium, tel: +32 16 346880, email: Ann.janssens@uzleuven.be.

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leukemia, Hodgkin's disease, large granular T-lymphocyte proliferation, etc.), persistent infections (human immunodeficiency virus, hepatitis C virus or H pylori) and vaccination.[1,2] No reliable test exist that can be used to establish the diagnosis of ITP.

ITP can be further defined as newly diagnosed (lasting less than three months after diagnosis), persistent (lasting three to twelve months when spontaneous remission is not reached or complete response to therapy is not maintained) and chronic ITP (lasting for more than twelve months).[1]

Incidence

Data on epidemiology are limited. The incidence of newly diagnosed ITP among adults ranges from two to four per 100,000 persons per year.[3] Due to the chronicity of the disease the prevalence goes up to ±2 per 10,000 of the population. However ITP is still a rare disease and answers to the criteria of an orphan disease (prevalence <5/10000).

ITP affect all age groups. In children the onset of ITP is typically abrupt and is frequently preceded by a febrile illness. Unlike adults, >70% of children with ITP have a normal platelet count one year after diagnosis.[4]
The incidence of ITP among men and women is generally similar except in middle age where women are more frequently affected.[3]

Pathogenesis

Increased understanding of the pathophysiology underlying ITP has shown that not only accelerated peripheral platelet destruction but also suppression of the production of new platelets can be responsible for the persistence of thrombocytopenia in several patients. Antibody loaded platelets bind to macrophages and dendritic cells and are removed by the reticulo-endothelial system (RES), primarily the spleen. More recently, it has been shown that platelets can also be destroyed by T-cells. Platelet production is frequently reduced because autoantibodies against platelet glycoproteins bind to megakaryocytes, interfere with their maturation and lead to apoptosis. Besides, the level of thrombopoietin (TPO), the primary growth factor for the regulation of platelet production, in ITP is relatively low compared to patients with thrombocytopenia resulting from megakaryocytic hypoplasia. This means that the primary underlying mechanism may vary between patients, explaining why response to treatment also differs.[5]

Clinical presentation

Many patients remain asymptomatic with the diagnosis of ITP made only after a routine blood test. Others may have bleeding symptoms ranging from skin bleeding (petechiae, purpura, bruises [dry purpura]) to mucosal bleeding (gingival bleeding, mouth blisters, epistaxis, blood in stool or urine, heavy menstrual bleeding) or deep bleeding (intracranial, abdominal bleeding, etc. [wet purpura]) appearing spontaneously or after trauma. Bleeding symptoms have mostly been reported in patients with a platelet count of less than 30,000/μl.[5]

Factors influencing the bleeding risk are age, comorbidities, lifestyle, need for invasive procedures, need of treatment with anticoagulant or antiplatelet agents, etc.

Consequences

- Major impact on quality of life: at least as bad as patients with diabetes.[6]
- Effect on daily activities.[5]
- Burden on the healthcare system: higher costs, longer hospital admissions and higher in hospital mortality rate.[5]

Diagnostic work up[2,7-11]

- Personal history (prescription and non-prescription drugs, alcohol abuse, consumption of quinine, recent transfusions,etc.).
- Familial history (excluding inherited thrombocytopenias).
- Physical examination (with attention to node-bearing areas, including sizes of liver and spleen).
- A complete blood count with peripheral blood smear examination (exclude platelet aggregates (pseudothrombocytopenia), platelet aberrations, red and white cell abnormalities).
- Immunoglobulin levels (exclude CVID).
- Direct antiglobulin test with reticulocytes (exclude Evan's syndrome).
- Coagulation tests (exclude DIC, Von Willebrand disease type 2).
- Blood group (for transfusion policy).
- Antinuclear factor, antiphospholipid antibodies,

lupus anticoagulant (exclude APS).
- Thyroid function, antithyroid antibodies (exclude thyroid dysfunction).
- Pregnancy test in women of child bearing potential (exclude gestational thrombocytopenia).
- Virology: Hepatitis C, HIV, HB.
- H pylori (antigen in stool or urea breath test).
- Bone marrow aspirate and biopsy (with immunophenotyping and karyotyping) (in selected patients with abnormal physical examination (lymphadenopathy, organomegaly) or blood count or blood smear abnormalities and in patients >60 years to exclude myelodysplasia or an indolent lymphoma).
- Chest radiograph (exclude chest disease).
- Abdominal ultrasound (exclude abdominal organ disease).

Additional work up before second-line treatment[2,7-11]

- Biological fitness (performance status (PS), and comorbidities (organ function).
- Bone marrow aspirate and biopsy (if not done previously, if no clear response to first-line treatment and before splenectomy).

Indications for initiation of treatment[12]

- Active bleeding OR platelets <10,000/µl
  Treatment is obligatory.
- No or mild bleeding AND platelets 10-30,000/µl
  Treatment is a potential option after evaluation of patient characteristics.
- No bleeding AND platelets >30,000/µl
  No need for treatment unless special circumstances.

Treatment

Before initiating treatment consideration must be given to:

- Patient related factors such as age, PS, comorbidities, life style (sedentary versus active) and patient wishes.
- Disease related factors such as platelet count and previous major bleeding.
- Additional risk factors for bleeding such as the use of antiplatelet and anticoagulant agents, uremia, poorly controlled hypertension, aneurysm, fever, chronic liver disease, history of peptic ulcer, etc.
- Treatment related factors such as expected response, contraindications to and side-effects from particular treatment modalities.
- The need of medical intervention that may cause bleeding *(Table 1)*.[7]
- Easy access to care facilities.

Table 1. Safe platelet count for medical interventions in patients with platelet production problems[7]

Dentistry	≥ 10 to 20 x 0000/µl
Extractions (simple)	≥ 30 x 0000/µl
Extractions (complex, molar	≥ 50 x 0000/µl
Lumbar puncture	≥ 50 x 0000/µl
GI endoscopy with biopsy	≥ 20 x 0000/µl
Bronchoscopy	≥ 20 x 0000/µl (≥ 50 if also biopsy)
Organ biopsy	≥ 50 x 0000/µl (<for bone marrow biopsy)
Minor surgery	≥ 50 x 0000/µl
Major and neurosurgery	≥ 80 x 0000/µl
Epidural anesthesia	≥ 80 x 0000/µl
(No equivalent data are available for ITP patients, the individual bleeding history must be considered)	

The main treatment goal in all ITP patients must be to maintain a safe platelet count to prevent or stop bleeding and not to normalize the platelet count, to decrease activity restrictions and improve quality of life with a minimum of exposure to potentially toxic therapy.[12]

When is hospitalisation for ITP justified?

The decision to hospitalise a patient with ITP is based primarily on the haemorrhage situation (patients with signs of mucosal or deep bleeding are frequently admitted) and on factors influencing the bleeding risk (age, comorbidities, need for treatment with anticoagulant or antiplatelet agents, etc.).

Treatment of newly diagnosed ITP

Newly diagnosed ITP patients are managed with corticosteroids with or without intravenous immunoglobulins (IVIg) depending on the severity of thrombocytopenia and/or of bleeding signs and symptoms. Although impressive responses are seen using these therapeutic agents, these responses are usually short lived. Thus, in adults, ITP is very frequently characterised by relapses upon tapering or discontinuation of treatment, requiring repeated courses of medical intervention.[2,7-10]

Characteristics of treatment with corticosteroids and IVIg are shown in *Tables 2 and 3*.

Platelet transfusions are only indicated in case of life-threatening bleeding together with the administration of corticosteroids and IVIg.

Table 2. Characteristics of treatment with corticosteroids

•	No preference to choose prednisone, (methyl) prednisolone (dexamethasone is also an option).
•	Starting dose: 0.5 to 2 mg/kg/d predniso(lo)ne or equivalent.
•	Full dose for 7-14 d.
•	Tapering: slow tapering during the following two to three months if responsive, rapid tapering if not responsive.
•	Short term response: 75-80%.
•	Durable response: <30%.
•	Mode of action: impairs antibody formation, antibody binding by platelets and clearance of antibody loaded platelets by RES, increase thrombopoiesis, improves hemostasis, etc.
•	Side effects: changing facial and body features, skin fragility, arterial hypertension, myopathy, diabetes mellitus (DM), psychological problems, osteoporosis, osteonecrosis, cataract, glaucoma, etc.
•	More side effects compared with other therapies leading to dose reduction and treatment discontinuation.
•	Absolute contraindication for steroids: acute viral infection (Herpes Simplex virus, Herpes Zoster virus, etc.), HBsurface Ag positive chronic active hepatitis.
•	Relative contraindication for steroids: peptic ulcera, bacterial infections, tuberculosis, mycoses, parasitosis, uncontrolled hypertension, DM, osteoporosis, psychosis, glaucoma, and recent enteroanastomosis.
•	Cheap.

Table 3. Characteristics of treatment with immunoglobulins

•	Start dose: 400 mg/kg/d for five days or 1 g/kg/d for one or two days.
•	Short term response: ± 80%, rapid response.
•	Durable response: only in few patients, relapse between 14-28d.
•	Repeated infusions possible.
•	Mode of action: impairs clearance of antibody loaded platelets by macrophages, impairs B cell function, increases T suppressor cells.
•	Side effects: infusion related, headache, aseptic meningitis, renal impairment (only for preparations containing sucrose).
•	Expensive.

Treatment of persistent ITP (lasting 3 to 12 months after diagnosis) and chronic ITP (lasting >12 months after diagnosis)

Indications for the start of treatment in persistent and chronic ITP are identical to those of newly diagnosed ITP.

Relapse after a long treatment free interval can be managed by restarting first line treatment being steroids with or without IVIg.[2,7-10] A long-term steroid treatment must be avoided, although in some patients a long-term treatment with steroids under

Table 4. Second and subsequent treatment options for relapsing and refractory adult ITP

Retreatment options		
Corticosteroids		Prednisone or equivalent: 0,5-2mg/kg/d po Dexamethasone: 40mg/d x 4d q 14-28d, 4-6 courses po
Immunoglobulins		400mg/kg/d x5d or 1g/kg/d x1-2d IV
Second- or further line treatment options		
Splenectomy		
TPO-R agonists		
	Romiplostim	1-10 µg/kg/wk sc
	Eltrombopag	25-75 mg/d po
Rituximab		
375 mg/m²/wk for 4wks or 100 mg/wk for 4wks IV		
Other options (listed alphabetically Table 4 bis)		

Table 4 bis. Other options (listed alphabetically)

	Dose	Toxicities
Azathioprine	1-2 mg/kg/d po	Neutropenia, transaminase elevation, pancreatitie, etc.
Cyclophosphamide	1-2 mg/kg/d po 500-1000 mg 4wks IV	Nausea, vomiting, sterility, secondary acute myeloid leukemia, etc.
Cyclosporine	4-5 mg/kg/d po (through blood levels 100-200 ng/ml)	Renal insufficiency, hypertension, neuropathy, hypertrichosis, tremor, gingival hyperplasia, etc.
Danazol	400-800 mg/d po	Weight gain, hair loss, liver dysfunction, myalgia, amenorrhea, etc.
Dapsone	75-100 mg/d po	Abdominal distension, anorexia, nausea, hemolytic anemia if glucose 6-phosphate dehydrogenase deficiency, etc.
Mycophenolate mofetil	1000 mg bid po	Headache, anorexia, nausea, abdominal distention, etc.
Vincristine	1-2 mg/wk IV max for 6 wks	Neuropathy, constipation, hair loss, etc.
Vinblastine	5-10 mg/wk IV max for 6 wks	Neuropathy, constipation, hair loss, etc.

the Cushing-threshold (<5 mg prednisone/day or equivalent) with close monitoring of adverse events can be considered.[7]

A second line therapy is indicated for those patients unresponsive to, relapsing during or shortly after tapering of steroids *(Table 4)*. Immunoglobulin administration is a valuable treatment option especially if a fast platelet increase is to be achieved. However the chance to achieve a durable response after IVIg is low.[2,7-10]

For decades, splenectomy has been the standard management for ITP patients with persistent low platelets and a high bleeding risk, unresponsive or intolerant to corticosteroids. Two-thirds of patients attain a durable remission. Morbidity and mortality of laparoscopic splenectomy are low in the hands of experienced surgeons. The incidence of overwhelming sepsis is reduced with recommended vaccination protocols and antibiotics initiated at first sign of a systemic febrile illness. However, physicians and patients frequently opt to postpone the removal of this healthy organ.[2,7-10] As spontaneous remission of ITP up to twelve months after diagnosis can occur in adults, an attempt should be made to delay splenectomy until after this point.[13] Characteristics of splenectomy with the relative contraindications for surgery are shown in *Tables 5 and 6*.

Azathioprine, cyclophosphamide, cyclosporine A, danazol, dapsone, mycophenolate mofetil and vincristine have been used after treatment failure in both splenectomised and non-splenectomised patients for decades. These treatment options are characterised by variable individual responses after days, weeks to months and significant long-term side effects such as immune suppression (except for danazol and dapsone), which must be considered by patient and physician.[2,7-10] Some characteristics of these agents are shown in *Table 4*.

Rituximab has been used for treating relapsing and refractory ITP patients for almost ten years. Randomised controlled trials are not available to establish optimal dose, schedule and timing of rituximab administration and to confirm efficacy and reveal long-term safety. For these reasons, rituximab has still no license for treating ITP.[14] In systematic reviews however a favourable overall response rate of approximately 60% with a complete response rate of 40% was estimated.[15] Responses seem comparable for splenectomised and non-splenectomised patients. A median duration of response of approximately six and twelve months was observed for partial and complete responders, respectively.[15-16] Twenty-one percent of adult chronic ITP patients maintained a treatment-free response for at least five years after treatment with standard-dose rituximab without major toxicity.[17]

The second-generation thrombopoietic agents (romiplostim and eltrombopag) have confirmed the hypothesis that stimulating platelet production is a valid treatment approach in ITP. TPO-Receptor (R) agonists have been associated with more durable

platelet responses and less treatment failure compared to placebo or standard of care (SOC) in adult chronic (defined in all trials as ITP lasting >6 mo) ITP patients, regardless of splenectomy status.[18-20] Efficacy data seem identical for patients included with acute or persistent ITP.[21] The response rates obtained in the pivotal studies were reproduced in open-label studies even when patients with severe comorbidities and older age were enrolled.[18,19,22] Patients relapsing after or refractory to rituximab seem to be as responsive as cohorts where previous exposure to rituximab was lower.[22] Treatment with TPO-R agonists results in a reduction of bleeding events, in less use of rescue medication or splenectomy and permits the majority of patients receiving concurrent ITP drugs to reduce or discontinue these therapies and avoid further immunosuppression *(Table 7)*.[18,19] An additional role of the TPO-R agonists may be to use the drug intermittently around the time of an anticipated bleeding risk. TPO-R agonists are very well tolerated. However, due to the fact that experience with TPO-R agonists in the clinic does not exceed seven years, a high index of suspicion for possible risks of long-term use of TPO-R agonists is warranted *(Table 8)*. In addition, the cost of treating a patient for several months or even years may be considerable.
In Belgium, the TPO-R agonists, romiplostim and eltrombopag, are reimbursed for the treatment of chronic adult ITP patients (ITP lasting >12 mo) refractory or intolerant to corticosteroids after splenectomy or when surgery is contraindicated.

For adult ITP patients who are intolerant or unresponsive to or relapse after initial corticosteroid treatment and have a risk of bleeding (platelets <30000/μl OR bleeding symptoms), the BHS guideline panel on adult ITP:

1: Recommends
- Splenectomy as it is the only treatment with a curative potential and has an acceptable safety profile. If possible, splenectomy should be delayed to at least twelve months after diagnosis as spontaneous remission can occur in this time period.
- TPO-R agonists for patients who are refractory to or relapse after splenectomy or who have a contra-indication to splenectomy irrespective of the duration of ITP.

Table 5. Characteristics of splenectomy in adult ITP

Most effective durable treatment for adults (± 66% long-term normal platelets, ± 14% no response, ± 20% late failures)	
Laparoscopic splenectomy: less postoperative pain, less infectious complications, earlier diet tolerance, shorter hospital stay but more hemorrhagic complications compared to open splenectomy	
No preoperative characteristic can reliably predict success of splenectomy (^{111}In platelet survival: if only splenic sequestration, 90% responders; less response if platelets very low, more than 3 previous treatments, elderly)	
Perioperative complications: (comparable to other minor surgical procedures and general anesthesia)	
Mortality	1% for laparotomy 0.2% for laparoscopy
Morbidity	13% for laparotomy 10% for laparoscopy
Acute venous thromboembolism: low but increased frequency (appropriate thrombosis prophylaxis postoperative especially when risk factors for thrombosis present, acetylsalicylic acid (ASA) if platelets >500,000/μl)	
Acute portal vein thrombosis: can occur in the first three months; range from asymptomatic to fatal; higher after laparoscopy; start diagnostic investigations in patients with cramping abdominal pain, depressed bowel sounds and generalized bowel tenderness	
Long-term effects	
Overwhelming post-splenectomy infection (OPSI) (mostly Streptococcus (S) pneumoniae, Neiseria (N) meningitidis, Haemophilus (H) Influenzae but also E. Coli, Capnocytophagia canimorsus, group B streptococcus, Ehrlichia and plasmodium spp (cavé travellers!)	
Appropriate and timely (2 to 4wks before or otherwise 2wks after splenectomy) immunization against:	
•	S. pneumoniae i.e. Prevenar 13®, 1 injection.
•	N. meningitidis i.e. Meningitec®, Menjugate® or Neisvac-C®, 1 injection.
•	H. Influenzae i.e. ActHib®, 1 injection.
Annual flu vaccine.	
Education of patient regarding risk of overwhelming infection.	
Prompt treatment of infection life-long!	
Cost: in most countries affordable.	

2: Suggests
- Rituximab, azathioprine, cyclophosphamide, cyclosporine A, danazol, dapsone, mycophenolate

Table 6. Relative contraindications for splenectomy

Platelet count	<20,000/µl before surgery (platelets >20,000/µl are ideal to limit the risk of postoperative bleeding, to minimize trauma to upper airway during general anesthesia).
Geriatric patient	
Comorbidities	Uncontrolled diabetes mellitus Heart failure, ischemic heart disease, Arrythmias, valvular disease Uncontrolled arterial hypertension COPD, asthma Renal insufficiency (Cr >2 mg/dl) History of stroke Severe obesity
Low functional capacity	

mofetil and vincristine/vinblastine are potential treatment options, especially for patients refractory to TPO-R agonists.

ITP in pregnancy[25,26]

ITP is an uncommon but important cause of thrombocytopenia in pregnancy. Disorders that can cause thrombocytopenia in non-pregnant women must of course be excluded (drug-, viral-induced thrombocytopenia, ITP secondary to SLE or APS, etc.). Other causes of thrombocytopenia specific for the setting of pregnancy are gestational thrombocytopenia, microangiopathic thrombotic syndromes, preeclampsia, HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome and acute fatty liver of pregnancy. These disorders must be separated from ITP because their successful management differs completely from the management of ITP *(Table 9)*. Pregnant women with ITP require careful monitoring (monthly till week 28, every two weeks till week 36, weekly till delivery). The indications for treatment of the pregnant woman do not differ from those of a non-pregnant person. However, a platelet count of 50,000/µl is recommended for vaginal delivery and caesarean section and a platelet count of 80,000/µl is recommended for epidural anesthesia. If treatment is necessary prednisone 1 mg/kg/d (pre-pregnancy weight) or equivalent can be started and gradually titrated to the lowest effective dose (avoid high doses in first trimester to prevent congenital anomalies and prolonged high doses because of exaggerated toxicity during pregnancy). IVIg are also considered as an appropriate first-line treatment

Table 7. Characteristics of treatment with TPO-R agonists

Dosing of TPO-R agonists	
Romiplostim[23]	
•	Start with 1 µg/kg/wk sc.
•	Increase dose by 1 µg/kg/wk if platelet count <50,000/µl till a maximum dose of 10 µg/kg/wk.
•	Maintain dose if platelet count between 50 and 150,000/µl.
•	Reduce dose by 1 µg/kg/wk if platelet count between 150 and 250,000/µl for two weeks.
•	Stop dosing and reassess after 1 week if platelet count >250,000/µl and restart dosing with -1 µg/kg/wk if platelet count <150,000/µl.
•	If platelet count ≥ 50,000/µL for at least four weeks without dose adjustment, assess platelet count once monthly.
•	Consider to administer romiplostim at home (nurse, self-administration).
Eltrombopag[24]	
•	No intake of calcium, iron, magnesium, aluminium rich food 4h before and after ingestion.
•	Start with 50 mg once daily po.
•	If platelet count <50,000/µl after 2 weeks, increase dose to 75 mg once daily.
•	If platelet count between 50 and 150,000/µl, maintain dose.
•	If platelet count between 150 and 250,000/µl, reduce to 25 mg once daily.
•	If platelet count >250,000/µl, stop dosing, monitor platelet count twice weekly and reinitiate at a daily dose reduced by 25 mg if platelet count <100,000/µl.
•	If platelet count ≥50,000/µL for at least 4 weeks without dose adjustment, assess platelet count once monthly.
TPO-R agonists induce durable platelet responses (60% stable responses, 25% variable responses, 15% minor or no response) **and less treatment failures regardless of splenectomy status, response to rituximab and duration of ITP.**	
TPO-R agonists reduce the need of rescue medication (IVIg, splenectomy) **and permit to reduce or discontinue concurrent ITP drugs** (corticosteroids, etc.) **and avoid further immunosuppression.**	
TPO-R agonists reduce bleeding events.	
TPO-R agonists improve health-related quality of life.	
TPO-R agonists are very well tolerated.	
Expensive.	

Table 8. Possible risks of long-term use of TPO-R agonists

Loss of efficacy with prolonged stimulation of megakaryopoiesis.	
Bone marrow fibrosis	
•	Follow up of blood cell count and smear monthly
•	If loss of response, new cytopenia or new morphologic abnormalities, a bone marrow biopsy should be done
Thrombosis	
•	Thrombotic event rate identical with TPO-R agonists, placebo or SOC
•	Thrombosis not correlated with high platelet counts
More severe thrombocytopenia after drug discontinuation (10%)	
Neutralizing antibody formation	
•	A few patients with anti-romiplostim AB but without loss of response;
•	Eltrombopag is not immunogenic
Hepatotoxicity (10% of patients on eltrombopag develop elevated liver enzymes)	
•	Control of liver function before and each 2 weeks during titration and monthly following achievement of a stable dose
Cataract	
•	Recommended to do an ophtalmologic examination before and annually during eltrombopag treatment
Induction of malignancy (not an issue in ITP)	

for ITP during pregnancy. Patients who fail to respond to corticosteroids or IVIg alone may respond to the combination of these agents. Laparoscopic splenectomy can be safely performed in the second trimester with an estimated remission rate of 75%. Splenectomy is not recommended in the first trimester due to the risk of induction of premature labor or in the third trimester due to bad visualisation of the surgical field. Azathioprine and rituximab have been used in pregnant women but immunosuppression can be seen in the neonates. The experience with TPO-R agonists during pregnancy is minimal. This treatment should only be considered if the potential benefit to the mother justifies the potential risk to the fetus. A pregnancy registry has been established to collect information about the effects of TPO-R agonists during pregnancy. There is no correlation between platelet count of the mother and the

Table 9. Thrombocytopenia in pregnancy[25,26]

ITP	
•	diagnosis of exclusion (exclude secondary ITP especially SLE and APS)
•	more likely if history of thrombocytopenia before pregnancy
•	may present at any time during pregnancy
•	serial platelet counts should be obtained in the newborns at birth and in the first week postpartum
Gestational thrombocytopenia	
•	platelets mostly >70000/µl
•	develops in the late second and third trimester
•	not associated with an increase in maternal or fetal complications, newborn not at risk for developing thrombocytopenia
Preeclampsia	
•	arterial hypertension (systolic >140 and/or diastolic blood pressure >90mm Hg), proteinuria (>300 mg/24h) and thrombocytopenia in 50% of patients
•	thrombocytopenia may precede other signs
•	develops after twenty weeks of gestation
•	delivery of the fetus after stabilization of the mother
•	platelet transfusions in the setting of severe thrombocytopenia and bleeding
HELLP syndrome	
•	nausea, malaise, upper right quadrant pain or epigastric pain, microangiopathic hemolytic anemia, abnormal liver function (OT >70U/L) and thrombocytopenia
•	most frequent in third trimester
•	delivery of the fetus after stabilization of the mother
•	platelet transfusions in the setting of severe thrombocytopenia and bleeding
Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS)	
•	microangiopathic hemolytic anemia, thrombocytopenia, neurologic abnormalities, fever and renal dysfuction (neurological changes more pronounced in TTP and renal changes in HUS)
•	TTP most frequent in the second trimester
•	90% of HUS appears in the postpartum period
•	plasma exchange
Acute fatty liver of pregnancy	
•	malaise, anorexia, nausea, vomiting, epigastric or right upper quadrant pain, mental status changes and cholestatic liver abnormalities with DIC
•	typically in primipara in the third trimester
•	delivery of the fetus after stabilisation of the mother

newborn. The most reliable predictor of neonatal thrombocytopenia is a history of low platelet count at delivery in a prior sibling. Platelet counts <20,000 and <50,000/μl were seen in respectively 4 and 10% of neonates. Neonatal intracranial hemorrhage was seen in <1% and was not associated with the mode of delivery. Therefore, the mode of delivery in pregnant ITP patients should be solely dictated by maternal factors. There is no place for fetal scalp vein sampling or percutaneous umbilical blood sampling to predict the platelet count of the newborn. After delivery serial platelet counts should be obtained in the newborns at birth and in the first week postpartum as the onset of thrombocytopenia due to maternal antiplatelet antibodies may be delayed.

Supportive treatment

- Antifibrinolytic agents
- Oral iron supplements if iron deficient.
- Local application of adrenalin soaked nose pads.
- Nasal cautery.
- Hormone preparations to prevent menorrhagia.
- Control of blood pressure.
- Stop ASA, antiplatelet agents, anticoagulation if appropriate: except in case of recent stent, ischemic heart disease, severe peripheral arterial occlusive disease.
- Avoid nonsteroidal anti-inflammatory drugs or ASA.

Conclusion

The main treatment goal in all ITP patients must be to achieve a safe platelet count to prevent or stop bleeding and to decrease activity restrictions and improve quality of life with a minimum of exposure to potentially toxic therapy. The BHS guideline panel on adult ITP reviewed the recent literature on diagnosis and treatment and has made recommendations on the best strategies for frontline and subsequent-line treatment. However, the pros and cons of each treatment option must be discussed in a personalised way with each patient. Psychosocial and medical factors as patient's goals, fears, family support, proximity to medical care, comorbidities, compliance, tolerance of each approach have to be considered in addition to outcomes.

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Key messages:

1. **ITP patients with platelet counts higher than 30000/μl and absence of bleeding signs do not need treatment.**
2. **Corticosteroids with or without intravenous IVIg are the preferred treatment options for patients with ITP newly diagnosed or relapsing after a long-term treatment-free period.**
3. **Splenectomy is recommended as second-line treatment as it is the treatment with the highest curative potential and an acceptable safety profile. If possible, splenectomy should be delayed to at least twelve months after diagnosis as spontaneous remission can occur.**
4. **TPO-R agonists are recommended for patients who are refractory to or relapse after splenectomy or who are unfit for splenectomy, irrespective of the duration of ITP.**
5. **Rituximab, azathioprine, cyclophosphamide, cyclosporine A, danazol, dapsone, mycophenolate mofetil and vincristine/vinblastine are potential treatment options, especially for patients refractory to TPO-R agonists.**

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