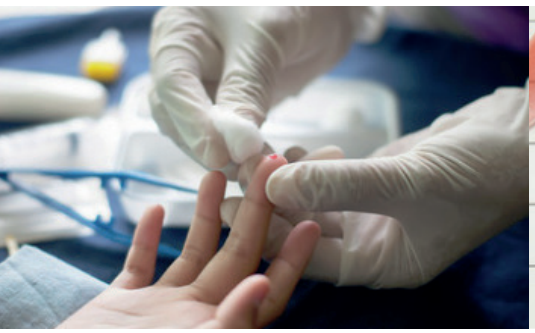
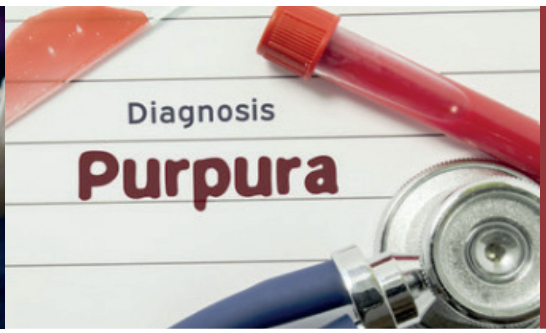
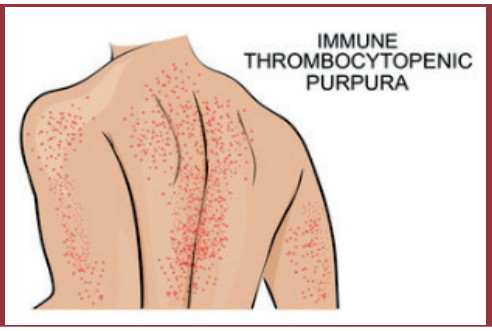
HNHCP
Haematology Nurses & Healthcare Professionals Group







Immune Thrombocytopenia (ITP)

A resource for healthcare professionals

Dear Colleague

It is with great pleasure that we present the learning program:

Immune thrombocytopenia (ITP): A resource for healthcare professionals on behalf of the Haematology Nurses and Healthcare Professionals Group.

A faculty of specialist nurses working in the field of haematology/oncology, haematologists/oncologists, and patient advocates have collaborated to develop this program dedicated to learning about Immune thrombocytopenia (ITP).

This program features topics relevant to the multidisciplinary team approach to caring for patients with ITP and their relatives. Nurses, other allied health care professionals and patient organizations play an important role in this process and the group is excited to share with you the most current information and up-to-date recommendations for addressing both short-term and long-term management of patient and family needs.

The Immune thrombocytopenia (ITP) Learning Program was made possible by grants from Amgen, Octapharma and Novartis Pharma Switzerland AG.

On behalf of the faculty and the Haematology Nurses and Healthcare Professionals Group who developed this resource, we hope that the ITP Learning Program will be of value to you in your care of patients with Immune thrombocytopenia.

Sincerely,

Erik Aerts

President

Haematology Nurses and Healthcare Professionals Group

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The ITP Learning Program is also available online at
www.hemcare.org

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Contents

Quick Facts

- Immune thrombocytopenia (ITP) is an autoimmune disorder characterized by a reduction in circulating blood platelet count
- Two major mechanisms contribute to the development of primary ITP: increased peripheral destruction of platelets (most common) and insufficient production of platelets in the bone marrow
- Destruction occurs when antibody-coated platelets are recognized by macrophages (primarily in the spleen) and destroyed
- Decreased production occurs as a result of two pathologies:
  - antibodies bind to and damage megakaryocytes in the bone marrow rendering them immature and less productive
  - fewer megakaryocytes and a low endogenous thrombopoietin level lead to decreased platelet production
- Secondary ITP, less common than primary ITP, is a heterogeneous group of disorders caused by autoimmune disorders, infections, drugs and vaccinations

Module I: Understanding Immune Thrombocytopenia

A. Introduction to Immune Thrombocytopenia

B. Normal Platelet Production

C. Incidence

D. Pathophysiology

    1. Primary ITP

    2. Secondary ITP

E. Terminology and Definitions in ITP

INTRODUCTION: Understanding Immune Thrombocytopenia

Immune thrombocytopenia (ITP), previously referred to as idiopathic thrombocytopenia purpura, is an autoimmune disorder affecting platelets. The disorder is characterized by a reduction in circulating blood platelet count.

Whereas in healthy adults the normal platelet count ranges from 150-450 x 10^9/L, the platelet count falls to < 100 x 10^9/L in ITP.

In ITP the patient's immune system produces antibodies directed against platelet antigens, resulting in platelet destruction and suppression of platelet production in the bone marrow. Patients with ITP are, therefore, at risk of serious bleeding events; specifically, gastrointestinal hemorrhage and intracranial hemorrhage.

Although greater understanding of ITP has contributed to progress in the diagnosis and treatment of ITP, extensive data from clinical trials is lacking (Abadi 2015).

History of ITP

ITP was originally described in 1735 by a German physician, Paul Gottlieb Werlhof, and was therefore known as Werlhof's disease (Nakhoul 2006). In 1916, Paul Kaznelson reported the first successful treatment for ITP after a patient showed a response to splenectomy (Kaznelson 1916). Splenectomy was then used as the first-line therapy for ITP until 1950. In 1951, William J Harrington and James W Hollingsworth established that ITP was an autoimmune condition (Harrington 1951). They postulated that the destruction of platelets in ITP was caused by a factor circulating in blood. Their experiment included Harrington receiving blood from an ITP patient, which within 3 hours resulted in his platelet count dropping to a seriously low level, causing a seizure. It took 5 days for his platelet count to return to normal levels. Antibodies, usually immunoglobulin G, specific to platelet membrane glycoproteins (GPIIb-IIIa complex is the most common) have since been identified as the circulating blood factor involved in the destruction of platelets in ITP (Tomer 2005; Li 2001; Fujisawa 1992; Shulman 1965) Harrington 1965).

Epidemiology

ITP affects people of both sexes and all ages—there is no typical ITP patient. ITP is estimated to affect approximately 3.3/100,000 adults/year (Lambert 2017) and between 1.9 and 6.4/100,000 children/year (Terrell 2010). While there is a predilection for females in younger adults, in persons > 65 years, the prevalence of ITP in men and women is evenly distributed (Fogarty 2009; Schoonen 2009; Moulis 2014).

While ITP is often self-limited in children [see Module 5], in adults it is more often a chronic disorder (Lambert 2017). The underlying disease process in childhood ITP and adult ITP may be fundamentally different, as evidenced by the rate of chronic ITP in these populations (Schulze 2011). More than 20% of patients with ITP have other immune disorders (e.g. systemic lupus erythematosus, immune thyroid disease) or chronic infections (Liebman 2009; Cines 2009).

Pathophysiology

Platelets are produced in the bone marrow and make up only a very small proportion (<1%) of whole blood and are only about 20% of the diameter of red blood cells. Platelets play a role in physiologic processes such as wound healing and inflammatory/immune responses and in pathological developments including atherosclerosis and tumor metastasis (Pluthero 2016).

What triggers the immune system to produce autoantibodies directed against platelets is currently unknown. The key modulator of platelet production is thrombopoietin (Kaushansky 1998). Endogenous thrombopoietin binds to receptors on megakaryocytes in the bone marrow, stimulating them to produce platelets (Figure 1). Platelets are normally cleared from the circulation through the spleen (Figures 2a, 2b, 2c). The rate of platelet production is inversely related to the endogenous thrombopoietin level, but in ITP there is a functional deficiency in thrombopoietin that contributes to thrombocytopenia (Kuter 2009). Once released into the circulation, platelets have a lifespan of approximately 10 days. Achieving a balance between thrombopoietin production and the number of circulating platelets can be affected by infections and inflammation.

Normal platelet production

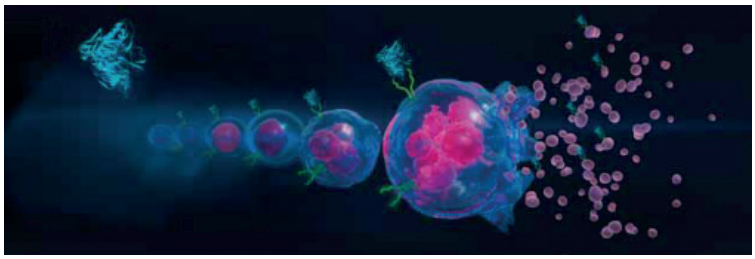

Figure 1: Natural platelet production. eTPO, endogenous thrombopoietin; TPO-R, thrombopoietin receptor. Image courtesy of Amgen

Figure 2a: Normal platelet homeostasis. Thrombopoietin, a hormone produced at a fixed rate in the liver, is the key regulator of platelet production

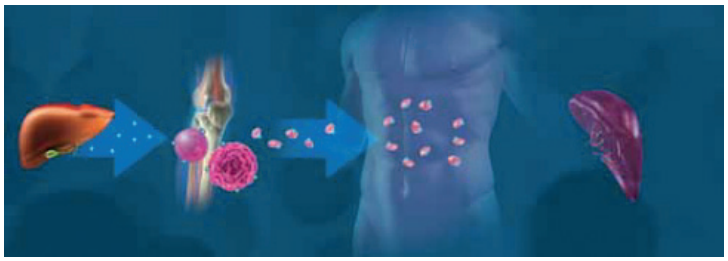

Figure 2b: Normal platelet homeostasis. Endogenous thrombopoietin stimulates bone marrow megakaryocytes via the thrombopoietin receptor to produce platelets, which are released into the circulation and have a lifespan of approximately 10 days

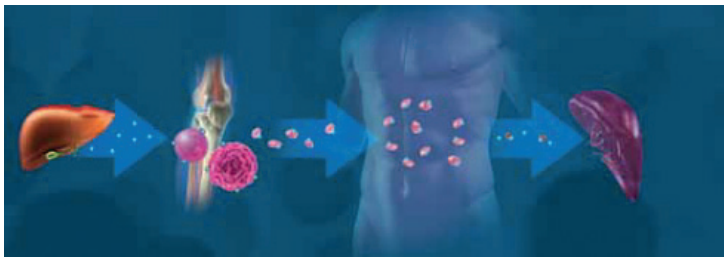

Figure 2c: Normal platelet homeostasis. Ageing platelets are naturally cleared from circulation. They are phagocytosed by macrophages mainly in the spleen, but also in the liver and bone marrow

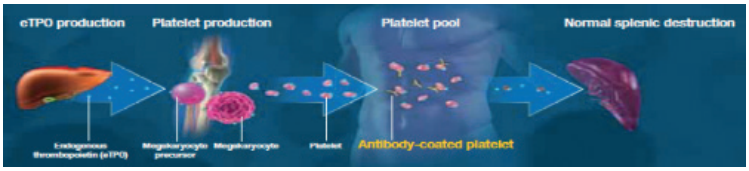

Figure 3a: Increased peripheral destruction of platelets in ITP. In ITP, antibodies bind to glycoproteins on healthy circulating platelets

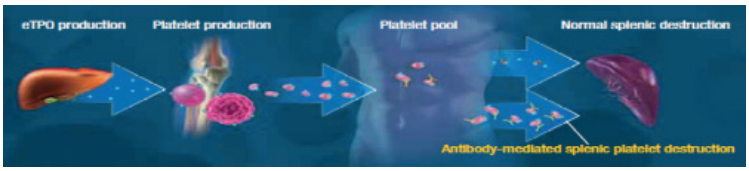

Figure 3b: Increased peripheral destruction of platelets in ITP. Antibody-coated platelets are recognized by macrophages primarily in the spleen leading to their destruction

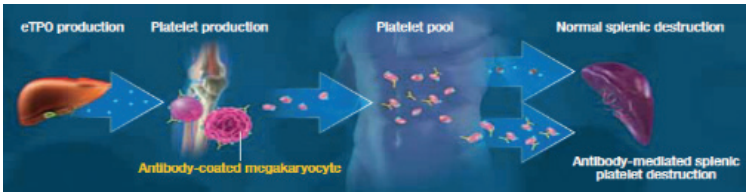

Figure 4a: Insufficient platelet production in ITP. Antibodies bind to and damage megakaryocytes in the bone marrow rendering them immature and less productive

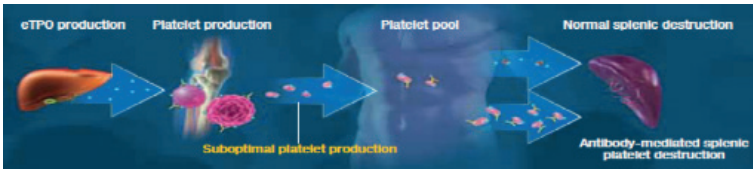

Figure 4b: Insufficient platelet production in ITP. Fewer megakaryocytes and an inappropriately low endogenous thrombopoietin level result in an insufficient production of platelets

Primary immune thrombocytopenia

Two major mechanisms contribute to the development of primary ITP:

- Increased peripheral destruction of platelets (most common cause)
- Insufficient production of platelets in the bone marrow (Khan 2017)

Increased platelet destruction

- involves loss of self-tolerance of platelet antigens and formation of antibodies that target glycoprotein IIa/IIIb, as well as IIb, Ib/X and V on platelets causing their destruction by macrophages or cytotoxic T cells (Figures 3a and 3b)
- is caused by an underlying immune dysregulation such as decreased regulatory T cell populations, abnormal cytokine profiles and an altered Th1/Th2 balance

Decreased platelet production stems from impaired function and growth of megakaryocytes and an insufficient level of thrombopoietin (Figures 4a and 4b).

80% of the adults with ITP have primary ITP (Lambert 2017).

Secondary immune thrombocytopenia

Secondary ITP is a heterogeneous group of disorders, where the specific factor causing ITP is known (Abadi 2015). The known causes of secondary ITP include autoimmune disorders, infections, drugs and vaccinations (Table 1).

Commonly used Terms in Immune Thrombocytopenia

The previous use of limited clinical and laboratory parameters to define and classify ITP led to a lack of standardized definitions and terminology in the classification of the disorder. Newly developed standardization of terms allows for better comparison of research study results and the application of guidelines to be used in managing patients with ITP (Table 2).

The previously used term "acute ITP" has now been replaced with "newly diagnosed ITP", which refers to the first 3 months after establishing a diagnosis. Further, agreement has been reached on the use of terms to describe subsequent phases of ITP and treatment response (Table 2).

Table 1: Causes of Secondary Immune Thrombocytopenia

Autoimmune Disorders	Congenital immune deficiencies	Infections	Drugs	Vaccinations
Systemic lupus erythematosus Antiphospholipid syndrome	Common variable immune deficiency Autoimmune lymphoproliferative syndrome	HIV Hepatitis C virus Helicobacter pylori	Heparin Penicillin Nonsteroidal anti-inflammatory drugs (NSAID)	Measles Mumps Rubella Varicella

Adapted from: Khan AM, Mydra H, Nevarez A. Clinical practice updates in the management of immune thrombocytopenia. Pharmacy and Therapeutics 2017;42(12):756-763
Lakshmanan S, Cuker A. Contemporary management of primary immune thrombocytopenia in adults. J Thrombosis and Haemostasis 2012; 10:1988-1998

Table 2: Suggested Descriptive Terminology for ITP

Term	Description
Newly diagnosed	< 3 month duration of ITP
Persistent	3 to 12 month duration of ITP
Chronic	> 12 month duration of ITP
Severe	Clinically relevant bleeding of sufficient magnitude to mandate treatment or requiring additional interventions or increase in drug dose
Refractory	Presence of severe ITP after splenectomy or pharmacologic treatment
Response	Platelet count ≥ 30 x 10^9/L and a greater than twofold increase in platelet count from baseline measured on 2 occasions > 7 days apart
Complete response	Platelet count ≥ 100 x 10^9/L measured on 2 occasions > 7 days apart

Source: Rodeghiero F, Stasi R, Gernsheimer T et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Blood 2009; 113:2386-2393

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Quick Facts

- Immune thrombocytopenia (ITP) is a heterogeneous disease and progression of the disease is impossible to predict
- The clinical presentation of ITP ranges from asymptomatic thrombocytopenia to bruising to life-threatening gastrointestinal and intracranial hemorrhages
- An important step in the diagnostic process is to rule out any other condition or disease that may be causing thrombocytopenia
- Platelet count alone at the time of diagnosis is insufficient in predicting clinical outcome
- Even at similar platelet counts, patients may have bleeding manifestations ranging from none to severe
- Intracranial hemorrhage is a life-threatening consequence of ITP; fortunately, overall risk and incidence are low
- A diagnosis of ITP places the patient at risk for the development of venous and arterial thrombotic events

Module II: Establishing a Diagnosis of Immune Thrombocytopenia

A. Introduction

B. Presentation and Physical Findings

C. Diagnostic Procedures

    1. Bleeding assessment

D. Differential Diagnosis

E. Prognosis and Survival

F. Consequences of Clinical Manifestations of ITP

    1. Bleeding

    2. Thrombotic events

G. Future Perspectives

Introduction

Primary ITP is an autoimmune disorder characterized by a platelet count < 100 x 10^9/L with or without bleeding manifestations, in the absence of other causes or disorders that may be associated with thrombocytopenia.

The diagnosis of primary ITP is based on the exclusion of other etiologies of thrombocytopenia. Patients are typically otherwise healthy but with a lowered platelet count. Patients with thrombocytopenia can be misdiagnosed as having ITP, often leading to an inappropriate use of therapies (Neylon 2003).

A diagnosis of secondary ITP broadly includes all forms of immune-mediated thrombocytopenia due to recognizable underlying disease or to exposure to drugs. It is of clinical importance to make a distinction between primary and secondary forms of ITP: the aim of treatment for secondary ITP is directed toward identifying and eliminating the underlying cause or associated disease causing the thrombocytopenia.

Of interest, the practice of obtaining routine complete blood counts (CBCs) (known as full blood counts [FBC] in some countries) has led to the identification of asymptomatic primary ITP because of a serendipitous finding of a low platelet count.

Presentation and Physical Findings

The signs and symptoms of ITP are highly variable. The clinical presentation can range from asymptomatic thrombocytopenia to nuisance bruising to life-threatening intracranial hemorrhage. Most adults with ITP present with platelet counts of 30 to 50 x 10^9/L; often with an insidious onset of thrombocytopenia with no obvious trigger, which follows a chronic course (Lo 2014). However, platelet count alone at the time of diagnosis is an unreliable predictor of clinical outcome (Neunert 2015) as some patients may have only minor bleeding with a low platelet count. While minor bleeding at the time of diagnosis is of concern, it is generally not associated with significant morbidity.

Table 1: Assessment of Bleeding: the TP Bleeding Scale (site specific)

Parameter of interest	Bleeding Severity Score		
Site	**0**	**1**	**2**
Skin (PE)	None	1 to 5 bruises and/or scattered petechiae	>5 bruises >2 cm and/or diffuse petechiae
Oral (PE)	None	1 blood blister* or >5 petechiae or gum bleeding (gingival bleeding) that clears easily with rinsing	Multiple blood blisters and/or gum bleeding
Skin (history)	None	1to 5 bruises (ecchymosis) and/or scattered petechiae	>5 bruises >2cm and/or diffuse petechiae
Epistaxis	None	Blood when blowing nose and/or epistaxis <5 min (per episode)	Bleeding >5 min (per episode)
Gastrointestinal	None	Occult blood	Gross blood
Urinary	None	Microscopic (per dipstick)	Macroscopic
Gynecological	None (normal period)	Spotting not at time of normal period	Bleeding > spotting not at time of period or very heavy period
Pulmonary	None	N/A	Yes
Intracranial hemorrhage	None	N/A	Yes
Subconjunctival hemorrhage	None	Yes	N/A

PE, physical examination; *Also referred to as bulla, vesicle and/or blister
Adapted from: Page LK, Psaila B, The immune thrombocytopenic purpura (ITP) bleeding score: assessment of bleeding in patients with ITP. Br J Haematology 2007; 138:245-248

Generally, bleeding is more likely to occur when the platelet count is < 20 to 30 x 10^9/L (Table 1). Most commonly, bleeding is mucocutaneous (gums, blood blisters in the mouth) and menorrhagia. Other possible sites of bleeding at diagnosis in symptomatic patients include:

- petechiae or purpura (Figure 1)
- unusual or easy bruising (ecchymosis) (Figure 1)
- frequent/heavy nose bleeds (epistaxis)

Intracranial hemorrhage, a severe bleeding complication, is relatively rare and occurs in approximately 1% to 1.5% of adults (Matzdorff 2018).

Other patient complaints at the time of diagnosis may include:

- complaint of exhaustion and fatigue
- complaint of depressive disorders (Efficace 2016)
- insomnia
- heartburn, loss of appetite
- loss of hair
- anxiety related to bleeding

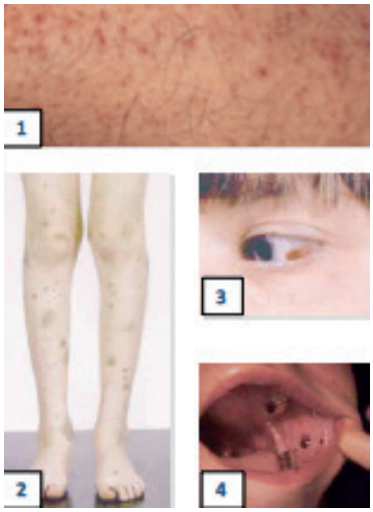

Figure 1: Images of bleeding in patients with ITP. 1. Petechiae; 2. Purpura and hematoma; 3. Conjunctival hemorrhage; 4. Submucosal bleeding. Images 1 and 4 courtesy of Drew Provan; Images 2 and 3 courtesy of Douglas Cines and James Bussel

Diagnostic Procedures

Information collected during a medical history exam could identify previous illnesses or medications that lower platelet count or cause bleeding to establish a diagnosis of secondary ITP as a first step in finding the cause of the thrombocytopenia or bleeding. [See Resources for a list of drugs and herbal medicines that affect platelet function]. The medical history and physical exam serve to:

- establish a diagnosis of ITP
- distinguish between primary and secondary ITP
- determine the appropriate course of treatment
- characterize the type, severity and duration of bleeding

A diagnosis of ITP should only be made if the platelet count is repeatedly < 100 x 10^9/L (Matzdorff 2018). A CBC will often show normal blood counts except for low platelet counts (Table 2). A peripheral blood smear can exclude pseudothrombocytopenia, an in vitro artefact caused by platelets clumping in the test tube that may indicate a falsely low platelet count when using automatic cell counters. A peripheral blood smear can also verify the size of platelets and the presence of normal red and white blood cells to exclude a diagnosis of leukemia or aplastic anemia. Platelet function tests, independent of platelet count, are useful in identifying bleeding severity.

A bone marrow aspiration should be performed if unusual cells are identified in the absence of other plausible causes of thrombocytopenia or in patients older than 60 years without atypical findings.

Understanding bleeding risk and underlying determinants of bleeding is important to recognize patients who may require pharmacologic therapy even if platelet counts are in higher ranges (Lambert 2017).

Prognosis and Survival

Overall, the outcome of ITP is variable, highly individualized and it is extremely difficult to predict the course of the disease (Table 3). Morbidity and mortality in adults is low (Provan 2015b).

- Mortality in adults is approximately 0% to 7% (Matzdorff 2018), representing an improvement likely due to a decrease in the use of corticosteroids and an increase in the use of thrombopoietin receptor agonists (TPO-RAs) (Bussel 2009; Kuter 2008)

Table 2: Recommended Diagnostic Approaches for ITP

Tests of definitive benefit	Tests of potential benefit	Tests of unproven benefit
Patient/family history	Glycoprotein-specific antibody	Thrombopoietin
Physical examination	Antiphospholipid antibodies	Reticulated platelets
CBC and reticulocyte count Coagulation profile	Antithyroid antibodies and thyroid function	Platelet-associated IgG
Peripheral blood smear	Pregnancy test in women of childbearing age	Bleeding
Quantitative immunoglobulin level measurement	Antinuclear antibodies	Studies of platelet survival
Blood group (Rh)	Viral PCR for parvovirus and CMV	Serum complement assay
Direct antiglobulin test	Bone marrow aspiration (may be useful in refractory disease) though no longer recommended in patients with platelet count >60	
Testing for H. Pylori, HIV, HCV, hepatitis B antibody status		

CMV, cytomegalovirus; H. pylori, Helicobacter pylori; PCR, polymerase chain reaction; Rh, rhesus
Adapted from: Provan D, Stasi R, Newland AC, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. Adv Ther 2015a; 32:875–887
Lambert MP, Gernsheimer TB. Clinical updates in adult immune thrombocytopenia. Blood 2017;129(21):2829-2835
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- However, primary chronic ITP has been associated with substantially increased long-term risk of infections, hemorrhagic episodes requiring hospitalization, hematologic malignancies and mortality (Norgaard 2011)

The majority of adults with ITP experience mild and stable disease requiring no treatment. In one prospective study, initial treatment for ITP was required in more than 80% of patients and 37% achieved cure at one year of follow up with no need for disease-modifying treatment (Grimaldi-Bensouda 2016).

Table 3: Prognosis and Risk Indicators

Indicators for self-limited disease course	Indicators for risk of chronic disease course	Indicators for risk of severe hemorrhage
Child, young adult	Adult, especially if > 60 years	Platelet count <20 to 30 x 10^9/L Multiple hematomas
Previous infection	No previous infection or other disorder	Mucosal hemorrhage
Abrupt disease onset	Insidious onset	History of severe bleeding Hematuria
Acute bleeding at presentation	Minor bleeding at presentation or incidental thrombocytopenia without bleeding	No response to steroid treatment Infection, fever Age >60 years

Adapted from: Matzdorff A, Meyter O, Ostermann H et al. Immune thrombocytopenia – current diagnostics and therapy: recommendations of a joint working group of DGHO, ÖGHO, SGH, GPOH, and DGTI. Oncol Res Treat 2018; 41 (suppl 5):1-30

Consequences of Clinical Manifestations of ITP: Bleeding Risk

Platelets are essential for primary hemostasis; bleeding in ITP is most commonly a result of a failure to prevent leakage of blood from small blood vessels. Fortunately, life-threatening or severe bleeding is a rare event affecting approximately 9.6% of adults with newly diagnosed or chronic ITP (Neunert 2015).

- Even at similar platelet counts, patients may have bleeding manifestations ranging from none to severe (Piel-Julian 2017)

The severity of bleeding correlates with the severity of thrombocytopenia

- Most instances of life-threatening bleeding occur either spontaneously or following minor trauma when the platelet count is $<10 \times 10^9$/L
- In a study of newly diagnosed ITP patients, platelet counts $<20 \times 10^9$/L and $<10 \times 10^9$/L were thresholds with major increased risk for both any bleeding and mucosal bleeding (Piel-Julian 2017)

Predictors of severe bleeding include:

- Increased patient age
- Presence of severe thrombocytopenia (platelet count < 10 to 20 x 10^9/L) (Neunert 2015)
- Newly diagnosed (Neunert 2015)
- Previous minor bleeding (Neunert 2015; Arnold 2015)

Overall risk of intracranial hemorrhage is reported to be between 1.4% and 1.9% (Piel-Julian 2017) and tends to occur more frequently in patients with chronic ITP (Neunert 2015). Studies suggest that intracranial hemorrhage is more likely to occur in patients who

- Present with more bleeding symptoms, including more hematuria and more internal hemorrhage than other ITP patients
- Have received previous treatment for ITP

[Management of bleeding is presented in Module 4]

Consequences of Clinical Manifestations of ITP: Thrombotic Events

A diagnosis of ITP places the patient at risk for the development of venous and arterial thrombotic events. Possible causes and risk factors for these events include:

- Circulating platelet-leucocyte-monocyte aggregates
- Endothelium-activating antibodies
- A larger proportion of young activated platelets

Table 4: Bleeding Grades according to WHO and NCI common Terminology Criteria for Adverse Events (CTCAE v4.0)

Bleeding grade	Definition
0	No signs of bleeding
1	Petechiae; small hematomas, ecchymosis (<10cm); bleeding from mucous membranes; epistaxis (<1h duration); subconjunctival hemorrhages; vaginal bleeding (<2 pads/day required)
2 (no transfusion required)	Hematomas, ecchymosis (>10cm); epistaxis (>1h duration); retinal bleeding without visual impairment; vaginal bleeding (>2 pads/day required); melena, hematemesis, hemoptysis, hematuria, hematochezia; bleeding from puncture sites; bleeding in muscles and joints
3 (transfusion required)	Epistaxis; bleeding from mucous membranes; vaginal bleeding; melena, hematemesis, hemoptysis, hematuria, hematochezia; bleeding from puncture sites; bleeding in muscles and joints
4 (life threatening, potential permanent functional impairment)	Retinal hemorrhage with visual impairment; central nervous system bleeding; hemorrhages in organs with functional impairment; fatal bleeding

Source: National Cancer Institute: NCI Common Terminology Criteria for Adverse Events CTCAE v4.03: 2010. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm

- Increased platelet micro-particle release
- Co-morbidities
- Therapeutic interventions [antiphospholipid antibodies, splenectomy (Ruggeri 2014), intravenous immunoglobulin [IVIg] (Guo 2018), steroids (Ruggeri 2014)]
- Older age (Ruggeri 2014)
- History of vascular risk factors (Ruggeri 2014)

Future Perspectives

There is a need for basic research to identify markers predictive of which patients would benefit most from a specific therapy. Also, larger, controlled clinical studies are needed to help define a possible relationship between platelet function and risk of bleeding.

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Quick Facts

- Splenectomy is the traditional curative approach to ITP and 2/3 of patients achieve remission for more than 10 years with the procedure
- Because of the risks involved with splenectomy (one of which is a higher risk of thrombosis), the procedure is not widely accepted by patients
- It is generally agreed that platelet count is less important than overall bleeding symptoms when considering the optimal time to initiate treatment
- Corticosteroids, with or without intravenous immunoglobulin (IVIg), are standard first-line treatment for adults; relapse is common after corticosteroids are tapered
- Patients with refractory ITP have a high morbidity and mortality risk
- Elderly patients with ITP tend to have more co-morbidities and a higher overall mortality rate relative to younger patients
- Thrombocytopenia develops in 5%-10% of women during pregnancy or in the immediate post-partum period
- Severe maternal or neonatal bleeding is rare when pregnant women are managed by an experienced, multidisciplinary team

Module III: Treatment of Immune Thrombocytopenia

A. Introduction
    1. Goals and aims of treatment
B. Treatment Strategies
    1. First-line treatment
    2. Second-line treatment
    3. Treatment of patients with chronic ITP
    4. Treatment of patients with refractory ITP
    5. Management of acute bleeding
C. ITP in Special Populations
    1. Management in elderly patients
    2. Management in pregnancy
D. Nursing Implications of Agents Commonly used in Treating ITP
E. Future Perspectives

Introduction: Treatment Strategies

Most adults with ITP tend to have an event-free course, but those with more severe thrombocytopenia usually require treatment (Lo 2014). Treatment choices for ITP are highly individualized and are affected by factors such as:

- Therapy tolerance
- Lifestyle
- Comorbid conditions, especially those predisposing to bleeding
- Patient age
- Bleeding symptoms
- Need for upcoming procedures
- Known treatment side effects (Neunert 2013)

While various treatment options are available for managing ITP, treatment recommendations are primarily based on clinical expertise and observations rather than evidence derived from clinical trials (Rodeghiero 2009).

The two most important considerations to be taken into account when planning treatment are:

- Disease severity
- Risk of bleeding

Treatment should be initiated in patients with a platelet count between 10 to 30 x 10^9/L in the presence of:

- Blood blisters in the mouth
- Organ bleeding
- Hematuria, menorrhagia
- Anemia and microcytosis caused by bleeding
- Adverse impact of ITP on lifestyle (Cooper 2017)

Spontaneous remissions in adults who have never been treated for ITP are uncommon. More frequently, ITP becomes persistent (3-12 months duration) or chronic (>12 months duration) and second-line treatment may be required (Neunert 2011).

Generally, patients with a persistent platelet count > 30 x 10^9/L are not at risk of serious bleeding and can be managed with observation alone (Rodeghiero 2009), although there is a lack of evidence to support this threshold.

Table 1: Principles of ITP Treatment

Principle	Practical Considerations
Decide when treatment is needed and when it can safely be withheld	Observation alone is safe with platelet count >30 x 10^9/L and no bleeding
Use the least toxic treatment at the lowest dose when treating patients with chronic ITP	Avoid long-term treatment with corticosteroids
Combination therapy is required for emergency treatment of ITP	Rapid-acting therapies with short duration of effect (platelet transfusions) should be combined with slower-onset treatments with prolonged effects (IVIg, high-dose corticosteroids, TPO-RA)
A durable platelet count response may be achieved with early aggressive therapy	Rituximab or TPO-RA agents* administered at an early stage of disease may improve long-term outcomes; clinical trials are required to provide evidence of effectiveness

IVIg, intravenous immunoglobulin; TPO-RA, thrombopoietin receptor agonists; *not currently approved in Europe for first-line treatment of ITP
Adapted from: Arnold DM. Bleeding complications in immune thrombocytopenia. Hematology Am Soc Hematol Educ Program. 2015;2015:237-242

Table 2: Principles of ITP Treatment

Phase of Disease	Goal of Treatment
Initial treatment	Obtain a safe platelet count to rapidly reduce bleeding manifestations or bleeding risk until disease remission or durable response are reached; improve quality of life
Persistent disease	Defer/avoid toxic immunosuppression or splenectomy
Chronic disease	Curative aim
Unresponsive, severe refractory disease (after splenectomy or after several lines of treatment)	Minimize the risk of bleeding and treatment-related toxicity; increase platelet count is not the main goal

Adapted from: Rodeghiero F, Ruggeri M. Treatment of immune thrombocytopenia in adults: the role of thrombopoietin-receptor agonists. Semin Hematol 2014; 52:16-24

First-line Treatment for ITP

Standard first-line treatment for ITP generally includes single or combination treatment with corticosteroids (prednisone, dexamethasone) and/or intravenous immunoglobulin (IVIg) (Provan 2015). Corticosteroids prevent the destruction of platelets by macrophages within the spleen and liver thereby increasing platelet levels.

Prednisone 1 to 2 mg/kg/day for 2-4 weeks has been the standard first-line treatment for ITP in newly diagnosed patients. Response to treatment is usually observed within several days to weeks.

- Although most patients respond, relapse is common after corticosteroids are tapered
- 40% to 60% of patients maintain a response at 6 months after initial treatment with standard dose prednis(ol)one (Cuker 2015)
- 20%-30% maintain a response beyond 1 to 2 years (Cuker 2018)

Second-line Treatment for ITP

Second-line treatment is used if a patient fails to respond to first-line treatment or relapses following a treatment response. Second-line therapy should be reserved for patients with persistent, symptomatic disease. The goal of second-line treatment is to establish a durable platelet response and minimize bleeding events with a safe, tolerable and convenient longer-term treatment (Cuker 2018). Controversies exist, however, over the optimal agents to be used in second-line treatment (Lakshmanan 2012).

Before initiating second-line treatment, a re-evaluation of diagnosis should be performed to rule-out potential non-immune causes and secondary causes of ITP.

Splenectomy has been the most commonly used second-line therapy. Despite early response rates of 80%-85% (Cuker 2018; Provan 2015), and 5-year response rates of 60%-70% (Provan 2015), complications following splenectomy have led to fewer procedures being performed. Splenectomized patients require lifelong management to prevent sepsis (e.g., vaccinations and prophylactic antibiotics) as well as surveillance for disease relapse [see Tables 4 and 5].

Combinations of treatment may be beneficial as second-line treatment.

Other treatments used in patients who fail to respond to first-line treatment include:

- Rituximab: an anti-CD20 monoclonal antibody, induces a 40% to 60% complete response rate after a single course; 55% to 75% overall response rate (Cuker 2015). Unfortunately the 5 year follow-up shows response rates of 20%.
- TPO-RAs: stimulate megakaryocyte proliferation and platelet production; switching between two TPO-RAs may be helpful to address poor responses, large fluctuations in platelet responses or problems with route of administration. Re-administration of a TPO-RA may be resumed without loss of efficacy after a TPO-RA is stopped. Although efficacy is high with response

Table 3: Suggested Doses and Administration Schedules of First-line ITP Treatment

Agent	Suggested dose and schedule	Time to response
Dexamethasone	40 mg orally daily for 4 days, 4-6 cycles every 14-28 days	Several days to several weeks
Methylprednisolone	125 mg -1,000 mg i.v. for 1-5 days followed by prednisone 1 mg/kg/day and dose titration	2 to 7 days
Predniso(lo)ne	1-2 mg/kg/day orally or i.v. for 1-2 wks. After response, weekly dose titration in 10 mg steps	Several days to several weeks
Immunoglobulins (IVIg)	0.4-1 g/kg/day i.v. for 1-2 days; observe response, repeat once after day 3 if no response	1 to 4 days
Anti-D immune globulin*	50-75 mcg/kg for 1-3 days	1 to 5 days

i.v., intravenous
*Not widely approved for use in ITP; use and doses based on individual treatment center practices
Adapted from: Cuker A, Prak ET, Cines DB. Can immune thrombocytopenia be cured with medical therapy? Semin Thromb Hemost 2015; 41:395-404; Matzdorff A, Meyter O, Ostermann H et al. Immune thrombocytopenia – current diagnostics and therapy: recommendations of a joint working group of DGHO, ÖGHO, SGH, GPOH, and DGTI. Oncol Res Treat 2018; 41 (suppl 5):1-30; Kahn AM, Mydra H, Nevarez A. Clinical practice updates in the management of immune thrombocytopenia. P&T 2017;42:756-763; Lakshmanan S, Cuker A. Contemporary management of primary immune thrombocytopenia in adults. J Thrombosis and Haemostasis 2012; 10:1988-1998

rates of >80% and side effects are few, only 25% to 30% of patients achieve a sustained remission with safe or normal platelet counts off therapy (Provan 2015).

- Eltrombopag has been shown to significantly improve platelet counts and decrease incidence of bleeding in a meta-analysis. Therefore TPO-RA should be considered a chronic treatment. (Elgebaly 2016)
- Romiplostim has been shown to provide platelet response in both splenectomized and nonsplenectomized patients and to maintain counts within a target range in both populations according to a meta-analysis (Cines 2017)

There is a lack of consensus on whether agents such as rituximab and TPO-RAs should be reserved for patients failing to respond to first-line treatment or with a contraindication to splenectomy (Rodeghiero 2014) .

Mycophenolate mofetil (MMF), an antiproliferative immunosuppressant, has also been used a second-line treatment. 50% response rates have been reported in retrospective studies (Taylor 2015).

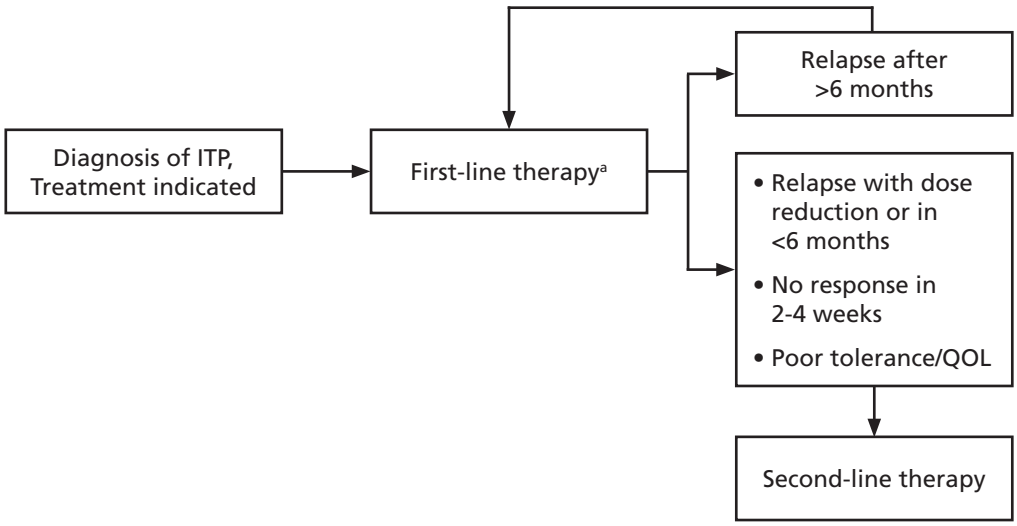

Figure 1: Selection of patients for second-line treatment. QoL, quality of life. [a]Corticosteroids are standard first-line therapy and may be combined with IVIg if a more rapid platelet response is required. IVIg or anti-D can be used as first-line treatment if corticosteroids are contraindicated. Consider anti-D in non-spenectomized, Rh+ patients with negative direct antiglobulin test.

Adapted from: Cuker A. Transitioning patients with immune thrombocytopenia to second-line therapy: challenges and best practices. Am J Hematol 2018; 93:816-823

Table 4: Suggested Doses and Administration Schedules of Second-line Treatment Agents

Agent	Dose/Schedule	Time to response
TPO-RA • Eltrombopag • Romiplostim	Eltrombopag 25-75 mg/day Romiplostim 1 mcg/kg/week The minimum dose necessary to maintain a target platelet count/prevent bleeding should be used	1 to 4 weeks
Anti-CD20 Antibody • Rituximab	100 to 375 mg/m2/week over 4 consecutive weekly infusions Efficacy may be affected by age, sex and duration of ITP	1 to 8 weeks
Mycophenolate mofetil (MMF)*	500 mg twice daily, increasing to 1 g twice daily if tolerated	Approx. 4 to 6 weeks

*Not widely approved for use in ITP; use and doses based on individual treatment center practices
Adapted from: Cuker A. Transitioning patients with immune thrombocytopenia to second-line therapy: challenges and best practices. Am J Hematol 2018; 93:816-823; Cooper N. State of the art – how I manage immune thrombocytopenia. Br J Haematology 2017; 177:39-54; Lakshmanan S, Cuker A. Contemporary management of primary immune thrombocytopenia in adults. J Thrombosis and Haemostasis 2012; 10:1988-1998

Table 5: Advantages and Disadvantages of Second-line Treatment Options		
Treatment	**Advantages**	**Disadvantages**
Splenectomy	Best option for long-term remission Cost-effective; Long-term safety data available	Risks of surgery/anesthesia; Difficult to predict response; Increased risk of infection and venous thromboembolism; Requires long-term monitoring; Possible increased risk of malignancy
Mycophenolate mofetil (MMF)*	Good short term tolerability; Cost effective; Return of immune system function after treatment completion	Unclear long term toxicity; Increased risk of infection; Cannot be used in pregnancy, patients of childbearing age should be counselled about its use; Delayed response rate (4 to 8 weeks)
Anti-CD20 Antibody Rituximab	Treatment time 4 weeks; Generally well tolerated	Limited long-term response; Longer median time to response; Some risk of serious infection; Small risk of infusion reaction
TPO-RA Eltrombopag, Romiplostim	High response rates; Generally well tolerated; Not immunosuppressive	Need for longer term treatment and monitoring; Risk of bone marrow fibrosis, thrombosis; Higher cost; romiplostim requires weekly SC injections; eltrombopag not to be taken with foods containing calcium, interacts with some medications, vitamins or herbs; liver adverse effects
*Not widely approved for use in ITP; use and doses based on individual treatment center practices SC, subcutaneous; TPO-RA, thrombopoietin receptor agonists Adapted from: Cuker A, Prak ET, Cines DB. Can immune thrombocytopenia be cured with medical therapy? Semin Thromb Hemost 2015; 41:395-404; Cooper N. State of the art – how I manage immune thrombocytopenia. Br J Haematology 2017; 177:39-54		

Table 6: Potential Complications of Splenectomy and Related Management	
Risk	**Management**
Risk of infection increases to approximately 5- to 30-fold in the first 90 days post splenectomy with a 1- to 3-fold life-long increase in the risk of invasive bacterial infection and sepsis	Continued use of penicillin prophylaxis; regular vaccination against encapsulated organisms
Risk of thrombosis (>30-fold compared to the general population)	Monitoring for vascular risk factors
Increased risk of cardiovascular disease	Monitor for cardiovascular risk factors; potential for use of statins
Greater risk of pulmonary hypertension and immediate post-operative complications	Close post-operative monitoring
Source: Thai L, Mahevas M, Roudot-Thoraval F et al. Long-term complications after splenectomy in adult chronic immune thrombocytopenia with a minimum follow up of 10 years. First results from a single-center case-control study in 140 patients with primary ITP. Blood 2014; 124:232	

Treatment of Chronic ITP

Chronic ITP refers to patients with ITP lasting for more than 12 months (Cooper 2017). When considering treatment, longer-term toxicities can be an option in patients who do not achieve remission within 12 months of receiving initial treatment (Rodeghiero 2014). Although splenectomy is not widely favored by patients, it is an eventual option if risk of infection is assessed as low.

- Long-term use of eltrombopag was effective and safe in maintaining platelet counts ≥ 50 x 10^9/L in 86% of patients and reducing bleeding in most patients with chronic ITP (Wong 2017)
- Long-term use of romiplostim was an effective and safe means to increase platelet count in 87% of patients with chronic ITP (Bussel 2009).

Treatment options in chronic ITP
On demand therapy is an option for patients at high bleeding risk
Azothioprine
Corticosteroids (using lowest effective dose)
Dapsone, danazole
Hydroxychloroquine
MMF*
Rituximab, repeated doses (with or without steroids)
TPO-RA agent (eltrombopag, romiplostim)
Splenectomy

*Not widely approved for use in ITP; use and doses based on individual treatment center practices
Sources: Cooper N. State of the art – how I manage immune thrombocytopenia. Br J Haematology 2017; 177:39-54; Rodeghiero F, Ruggeri M. ITP and international guidelines: What do we know, what do we need? Le Presse Medicale 2014; 43:e61-e67; Rodeghiero F, Ruggeri M. Treatment of immune thrombocytopenia in adults: the role of thrombopoietin-receptor agonists. Semin Hematol 2014; 52:16-24

Treatment of Refractory ITP

Refractory ITP may occur in patients who have failed to respond to or relapsed on pharmacologic treatment or in those whose disease has relapsed after splenectomy: treatment is aimed at reducing the risk of clinically significant bleeding (Rodeghiero 2014) and improving health-related quality of life (HRQoL) (Cuker 2016). Morbidity and mortality is significant in patients with ITP that is refractory to treatment (Mahevas 2016).

It is important to reassess/reconfirm the diagnosis of ITP, exclude non-autoimmune causes of thrombocytopenia and secondary ITP before initiating treatment in patients with refractory disease (Cuker 2016). Observation without treatment in most asymptomatic patients after splenectomy with a platelet count of ≥20 to 30 x 10^9/L may be appropriate depending on individual patient circumstances including lifestyle.

Combination treatment may be beneficial:

- Immunosuppressive treatment + TPO-RA has shown great promise (Mahevas 2016)
- Other treatment options include additional immunosuppressive agents such as cyclophosphamide, rapamycin and anti-TNF agents
- Intermittent use of IVIg and steroids for acute episodes
- Novel agents (e.g., fostamatinib, toralizumab, ruplizumab, and newer TPO-RAs are in clinical trials (Cooper 2017).

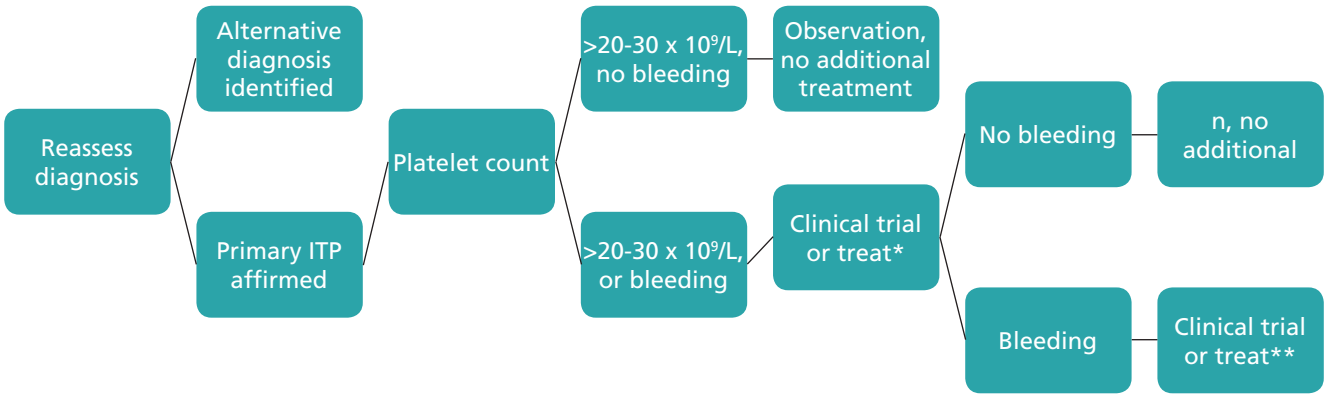

Figure 2: Proposed management of refractory ITP. *Low-dose prednisone, rituximab, romiplostim, eltrombopag; **6-mercaptopurine, azathioprine, cyclosporine A, cyclophosphamide, danazol, dapsone, MMF, vinca alkaloids.

Adapted from: Cuker A, Neunert CE. How I treat refractory immune thrombocytopenia. Blood 2016; 128:1547-1554

Table 7: Options for Initial Treatment for Refractory ITP		
Agent	**Dose**	**Time to response (weeks)**
Low-dose prednisone	≤5 mg orally once per day	N/A[a]
Rituximab	375 mg/m^2 i.v. once per week x 4 (lower dose may be effective)	1 to 8
Romiplostim	1-10 µg/kg SC once per week	1 to 4
Eltrombopag	25-75 mg orally once per day	1 to 2

i.v., intravenously; SC, subcutaneously
aPatients already taking intermediate or high doses of prednisone
Adapted from: Cuker A, Neunert CE. How I treat refractory immune thrombocytopenia. Blood 2016; 128:1547-1554

ITP Management in Special Populations –Considerations in Elderly Patients

Points to consider in elderly patients presenting with thrombocytopenia:

- Drug-induced ITP may be the cause of thrombocytopenia due to poly-medications
- Exclude myelodysplastic syndrome (MDS) as the cause of thrombocytopenia
- Bone marrow examination may be appropriate as a diagnostic test, especially to differentiate between MDS and ITP (Mahevas 2016)

Bleeding manifestations were found to be more frequent and more severe in patients >70 years despite platelet counts comparable to those of younger patients (Provan 2015). This includes intracranial hemorrhage, which is most often seen in older patients who have additional co-morbidities (Provan 2015).

According to one study, older patients (mean age 79 years):

- are more difficult to manage as outpatients
- tend to have longer periods of hospitalization
- have more co-morbidities and a higher overall mortality rate relative to younger controls (mean age, 40 years) (Michel 2011)

Age is a significant risk factor for infection and infection negatively affects 1-year mortality rate in patients >65 years (Hu 2014).

The strategy for treating older patients, especially those >75 years, must take into account:

- the greater risk of bleeding and thrombosis
- the presence of co-morbidities
- possible lower tolerance and higher incidence of more severe adverse events with conventional ITP medications
- possible impaired cognitive function or poor life expectancy
- use of concomitant medications (Mahevas 2016)

In terms of treatment decisions, maintaining a platelet count >30 x 10^9/L in patients older than 60 years with no co-morbidity may be appropriate. By contrast, maintaining a higher platelet count should be considered in the presence of additional risk factors for bleeding such as a previous history of bleeding and presence of certain co-morbidities (severe hypertension, renal insufficiency, severe gastritis or peptic ulcer) (Figure 3) (Mahevas 2016).

- Platelet response rates and number of weeks with a platelet response were slightly higher in patients ≥ 65 years vs patients < 65 treated with romiplostim (Michel 2011)
- In a retrospective study conducted in Korea, there was no difference in the response rate of elderly (≥ 60 years) versus younger (< 60 years) patients following splenectomy; however rates of relapse (45.2% vs 22.6%, respectively) and complications were significantly higher in the elderly patients (Park 2016)

Recommendations for Treatment of Elderly Patients

Treatment decisions should be made in consultation with other healthcare professionals such as cardiologists and geriatricians. Older age places patients at higher risk for infections associated with steroid use and some side effects

of treatments (e.g., MMF) may be more pronounced in older patients (Cooper 2017).

First-line treatment recommendations include:

- A short course (4 weeks) of corticosteroids to limit risks of severe adverse events associated with prolonged corticosteroid treatment (Mahevas 2016; Cooper 2017; Provan 2010)
- Corticosteroids combined with IVIg 0.4-0.5 g/kg body weight for 4-5 days

Second-line treatment options should take patient preferences, co-morbidities, cognitive function, life expectancy, health and medical history, newly diagnosed vs persistent ITP into consideration. Options include:

- rituximab
- TPO-RAs
- dapsone, danazol
- splenectomy (Mahevas 2016)

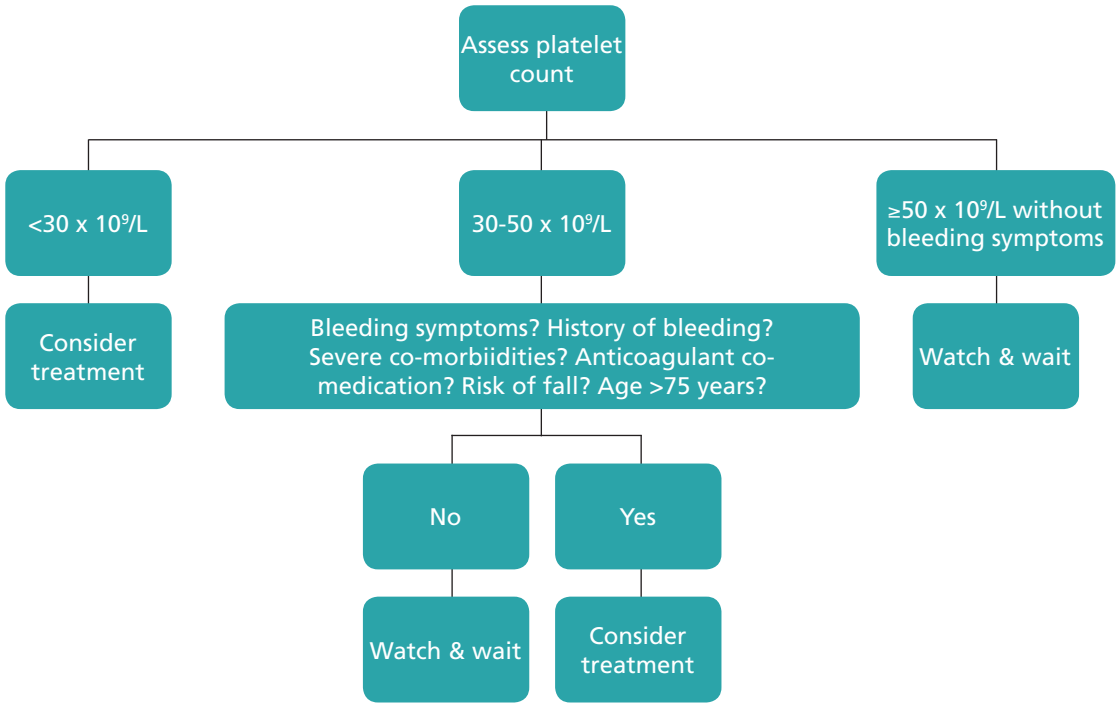

Figure 3: Treatment considerations in elderly patients. Adapted from: Mahevas M, Michel M, Godeau B. How we manage immune thrombocytopenia in the elderly. Br J Haematology 2016; 173:844-856

Treatment of Bleeding in Elderly Patients

Life-threatening bleeding situations (such as visceral or intracranial hemorrhage) should be treated with IVIg and steroids combined with platelet transfusions (Mahevas 2016).

- Vinblastine (not more than 8 mg) could be added in case of severe bleeding
- Off-label use of high dose TPO-RAs as salvage therapy (Mahevas 2016)

ITP Management in Special Populations – Considerations in Pregnancy

Thrombocytopenia develops in 5% to 10% of women during pregnancy or in the immediate post-partum period; ITP occurs in 1/1000-10,000 pregnancies or 3% of all cases of thrombocytopenia during pregnancy (Cines 2017a). ITP can occur in the first or early second trimester and is one of the more common causes of thrombocytopenia in early pregnancy. Most women with ITP during pregnancy do not have bleeding symptoms: mild bleeding (easy bruising and purpura) occur in 10%, and moderate bleeding

(epistaxis, bleeding after trauma and mucous membrane bleeding) can occur in 20% (Yan 2016).

Women with symptomatic ITP will need to be closely monitored and treatment will depend on platelet count and risk of maternal hemorrhage.

- 10% of women experience exacerbation of ITP postpartum (Yan 2016).

There is no medical contraindication to women with existing ITP becoming pregnant.

- The risk of severe maternal and neonatal thrombocytopenia during pregnancy in women with ITP is relatively low; however, women who have had a splenectomy should receive special attention and careful monitoring during pregnancy (Loustau 2014)
- Severe maternal or neonatal bleeding is rare when cases are managed by an experienced, multidisciplinary team (Lambert 2017)

A diagnosis of ITP in pregnancy is based on

- Personal history of bleeding or a low platelet count prior to pregnancy
- A family history that excludes hereditary thrombocytopenia
- Exclusion of other disorders
- Retroactive diagnosis using response to ITP therapy

Recommendations for Treatment of ITP in Pregnancy

Current guidelines for treating pregnant women with ITP recommend maintaining a platelet count >20 x 10^9/L during the first two trimesters with a higher level of >50 x 10^9/L near term or if a Caesarean section is required (Lambert 2017).

Platelet counts should be measured starting 3-4 weeks before anticipated delivery or weekly starting at 34 weeks in unstable patients to allow sufficient time for a change in treatment to increase platelet count if required (Cines 2017). Pregnant women with no bleeding and platelet counts >30 x 10^9 generally do not require treatment until delivery is imminent (Gernsheimer 2013).

The risk of a newborn developing ITP are relatively low: 1% to 5% of neonates are born with platelet counts <20 x 10^9/L and up to 5% to 15% require treatment. The risk of intracranial hemorrhage is very low at <1% (Cines 2017a).

Treatment is initiated for bleeding when the platelet count is < 20 to 30 x 10^9/L for a vaginal delivery or < 50 x 10^9/L for a Cesarean section.

- Daily oral prednisone is recommended because it does not cross the placenta in an active form
- Periodic IVIg may be used if corticosteroid treatment fails or its use is limited
- A retrospective study of 235 pregnancies in 195 women found no difference in maternal platelet counts at delivery between corticosteroids and IVIg; treatment response was ~ 40% (Sun 2016)

MMF should be avoided in pregnancy and in women of childbearing age due to its known teratogenicity (Gernsheimer 2013; Cooper 2017).

Other options with potential benefit in treating ITP in pregnancy include:

- E-aminocaproic acid: a safe and effective adjunct before and after delivery in women with severe ITP (Gernsheimer 2013)

Table 8: Recommended Treatments for ITP during Pregnancy

First-line treatment	Second-line treatment	Treatments to avoid
Oral corticosteroids, IVIg	Combination therapy with corticosteroids and IVIg; splenectomy (second trimester); favorable outcomes with anti-RhD immune globulin, cyclosporine and rituximab but these agents cannot be routinely recommended	MMF; azathioprine, cyclosporine A, dapsone; TPO-RA, campath-1H; vinca alkaloids; danazol

Sources: Cines DB, Levine LD. Thrombocytopenia in pregnancy. Blood 2017; DOI 10.1182/blood-2017-05-781971; Cooper N. State of the art – how I manage immune thrombocytopenia. Br J Haematology 2017; 177:39-54; Gernsheimer T, James AH, Stasi R. How I treat thrombocytopenia in pregnancy. Blood 2013; 121:38-47; Lambert MP, Gernsheimer TB. Clinical updates in adult immune thrombocytopenia. Blood 2017; 129:2829-2835

Nursing Implications of Agents Commonly used in Treating ITP

Early recognition of treatment side effects may aide in decreasing their severity. There are a fair number of drugs available to treat ITP with differing mechanisms of action; drug intolerance may necessitate a change in drugs. Titrating and/or adjusting drug doses may also aide in reducing side effects.

[See Module 4 for further details on comprehensive management of patients receiving treatment]

Table 9: Side-effects Associated with Corticosteroid* Administration

Side Effect	Signs and Symptoms
Cardiovascular system	Edema, hypertension, atrial fibrillation
Dermatologic	Acneiform rash; thinning of skin
Endocrine system	Steroid-induced hyperglycemia; adrenal insufficiency; hypogonadism
Gastrointestinal system	Gastric or duodenal ulcer; dyspepsia; flatulence; taste alteration; hiccoughs
Immune system	Leukocytosis; infection
Musculoskeletal system	Proximal muscle weakness/atrophy; osteonecrosis; osteopenia or osteoporosis; muscle cramping
Ophthalmic	Blurred vision; cataracts
Psychiatric	Personality changes, mood alterations; hyperactivity; memory impairment
Changes in overall well-being	Flushing or sweating; insomnia; "let down" effect (fatigue, weakness) after discontinuation
Changes in body image	Weight gain; increased appetite; Cushingoid appearance; hirsutism or alopecia
Adrenal suppression	Weakness, fatigue, malaise; nausea, vomiting, diarrhea, anorexia/weight loss; abdominal pain; headache (usually in the morning); fever; myalgia, arthralgia; psychiatric symptoms
Hyperglycemia, diabetes	Elevated glucose levels, postprandial more so than fasting

*Including dexamethasone, prednisone and prednisolone
Adapted from: Faiman B, Bilotti E, Mangan PA, Rogers K. Steroid-associated side effects in patients with multiple myeloma: Consensus Statement of the IMF Nurse Leadership Board. Clin J Oncol Nursing 2008; 12(3):53-63

Table 10: Nursing Care Implications of Agents Commonly used in Treating ITP

Drug	Implications
Rituximab (Anti-CD20)	Direct correlation between long-term adverse effects and rituximab use alone has not been established; optimal dose for ITP has not been established; because of a risk of viral reactivation, patients should be screened for hepatitis B before administration; attenuates response to vaccines for up to 6 months; Positive response indicators include: female gender, age <40 years, shorter period between diagnosis and rituximab administration
Thrombopoietin Receptor Agonists (TPO-RA)	Doses may be titrated up or down in response to platelet count and patient's general condition; excessive platelet drop after drug discontinuation possible; administration associated with considerable costs; adding a second agent (MMF or steroids) may be beneficial; switching TPO-RA or combining two TPO-RAs may be beneficial; not approved as first-line treatment in Europe
Eltrombopag	Reduce dose in Asians; potential for interaction with cholesterol-lowering statins
Immunoglobulins (IVIg)	May cause allergic reaction, headache, fever, rash; vaccinations may be less effective after IVIg exposure
Azathioprine	Initially often combined with corticosteroids, corticosteroids then tapered
Anti-D* (Rh Immunoglobulin [RhID])	Effective only in Rh-positive patients, with a negative direct antiglobulin test (DAT) and are non-splectomized; not permitted in some European countries
Mycophenolate mofetil (MMF)	Should not be taken by pregnant women or women of childbearing age; should not be taken with some antacids; risk of secondary lymphoma; vaccinations may be less effective

*Not widely approved for use in treating ITP
Sources: Boral LI, Monohan GP, Moirangthem V. Overview of adult immune thrombocytopenia. Pathol Lab Med Open J 2016; 1:21-31; Catala-Lopez F, et al. Risk of thromboembolism with thrombopoietin receptor agonists in adult patients with thrombocytopenia: an updated systematic review and meta-analysis of randomized controlled trials. Medicina Clinica 2015; 145:511-519; Khan AM, Mydra H, Nevarez A. Clinical practice updates in the management of immune thrombocytopenia. P&T 2017;42:756-763; Marangon M, Vianelli N, Palandri F, et al. Rituximab in immune thrombocytopenia: gender, age, and response as predictors of long-term response. Eur J Haematol 2017;98:371–377; Matzdorff A, Meyer O, Ostermann H et al. Immune thrombocytopenia – current diagnostics and therapy: recommendations of a joint working group of DGHO, ÖGHO, SGH, GPOH and DGTI. Oncol Res Treat 2018; 41(suppl 5):1-30; Rodeghiero F, Ruggeri M. Treatment of immune thrombocytopenia in adults: the role of thrombopoietin-receptor agonists. Semin Hematol 2014; 52:16-24

Future Perspectives

Several novel therapies are being studied for the management of ITP including

- Antibodies targeting the CD40-CD154 interaction between B and T cells
- Treatments targeting the Fc receptor and the neonatal Fc receptor
- Treatments targeting downstream signaling after crosslinking of receptors caused by antibody binding (Syk kinase)
- Novel agents to increase platelet production (new TRO-R agents and amifostine)

Clinical studies are needed to identify which patients with more severe thrombocytopenia can be safely managed without pharmacologic treatment (Arnold 2015)

Future trials on the treatment of ITP should possibly focus more on bleeding manifestations and related morbidity than on correcting platelet count: platelet count is a surrogate endpoint with limitations and does not necessarily predict or define clinical outcome (Rodeghiero 2014)

Because of population aging and an increased risk of ITP with increasing age, clinical trials providing evidence for treatment strategies for older patients are needed

Adequate long-term follow-up of patients is necessary to determine whether relapse is truly averted or simply delayed (Neunert 2017)

Tailored therapies need to be developed in the future that can be applied to patients at higher risk of relapse (Neunert 2017)

The efficacy of rituximab seems to be related to antibodies found on platelets; performance of antibody assays prior to treatment may help to individualize treatment by indicating those patients with platelet-bound antibodies and thus a potential for a better response to rituximab (Porcelijn 2017)

There is controversy regarding the optimal second-line treatment in ITP. Future studies are required to compare efficacy, safety, impact on QoL and cost-effectiveness of second-line treatment options (Lakshmanan 2012)

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Quick Facts

- Combination treatment with methylprednisolone and intravenous immunoglobulin (IVIg) can be effective in treating bleeding
- Corticosteroid-associated toxicity appears to be related to both the average dose and cumulative duration of use
- Infusion reactions to rituximab can be minimized with pre-medications
- Patients receiving the thrombopoietin receptor agonist (TPO-RA) eltrombopag should be evaluated for risks associated with changes in liver function and patients receiving eltrombopag or romiplostim should be regularly evaluated for thromboembolic events Minimizing the transient side effects occurring with the administration of IVIg can be achieved by slowing the rate of infusion, particularly during the first two administrations
- To help patients to better cope with a diagnosis of ITP, ascertain the patient's understanding of the disease, dispel any myths and correct any misconceptions, provide support and direct patient to help resources
- Lower platelet counts have been associated with a lower health-related quality of life (HRQoL)

A. Treatment of Acute or Life-threatening Bleeding

B. Management of Treatment Side Effects

- a. Corticosteroids
- b. Rituximab
- c. Thrombopoietin receptor agonists (TPO-RA)
- d. Other agents

C. Providing Education to Patients and Families

D. Recommendations to help Patients live with ITP: Quality of Life Considerations

Introduction: Comprehensive Management of the patient with ITP

ITP is associated with physical as well as psychosocial stress in those affected. Two key roles of nurses and other healthcare professionals in regards to managing patients with ITP involve:

- providing education on ITP, treatment modalities and management of side effects and
- providing support to help both patients and families to cope with the physiological and psychological effects of ITP

Treatment of Acute or Life-threatening Bleeding

It may be advisable to hospitalize patients if they have

1. internal bleeding or profound mucocutaneous bleeding
2. platelet count has fallen below 10 x 10^9/L with a history of significant bleeding or noncompliance
3. platelet count of 10 to 20 x 10^9/L and have been unresponsive to therapy (Cuker 2010)

Treatment of bleeding often depends on the patient's status with greater precautions taken in those who are newly diagnosed: a watch and wait strategy may be taken in those patients who have had ITP for a longer period.

There is some evidence that platelet function in patients who have significant bleeding symptoms may be different than that in patients with similarly low platelet counts but without bleeding (Middelburg 2016).

Sites of potentially life-threatening bleeding with a platelet count < 30 x 10^9/L include:

- intracranial
- gastrointestinal
- genitorurinary
- gynecologic
- epistaxis (Boral 2016)

Recommendations for treating and managing bleeding:
Combination treatment such as high dose i.v. methylprednisolone (500 mg to 1 g/day x 3) + IVIg 1 g/kg on days 1 ± 2 (Arnold 2015)
Platelet transfusions in the presence of life threatening bleeding, with or without IVIg (Boral 2016)
Tranexamic acid as adjuvant treatment; useful for oral mucosal hemorrhages, menorrhagia, before dental procedures (Cooper 2017; Matzdorff 2018)
Hormonal therapy in the presence of significant vaginal hemorrhage (Cooper 2017)

Management of Side Effects of Corticosteroids

Corticosteroids, either alone or in combination with intravenous immune globulin (IVIg), are the most commonly used first-line therapy (Lakshmanan 2012). Because longer term use of corticosteroids leads to significant side effects that may outweigh any benefit, these agents are usually prescribed as a short-term treatment (3 to 4 weeks). Toxicities of corticosteroids appear to be related to both the average dose and the cumulative duration of use (Liu 2013). Corticosteroid dose should be tapered rather than discontinued. [See Module 3, Table 9 for details on side effects of corticosteroids]

Table 1: Management of Early & Late Side Effects of Corticosteroids

Side Effect	Notes	Management
Risk of infection	Increased susceptibility to invasive fungal and viral infections	Provide information on signs/symptoms of infection, who to contact should infection occur
Flushing/sweating		Use of cold cloths/ice packs, layer clothing, maintain hydration
Fatigue		Advise patient to adjust activities accordingly to deal with fatigue
Changes in personality Mood swings Sleep disturbances	Early onset	Provide patient/family with counseling and education regarding potential for mood changes that may be severe; morning vs evening administration of corticosteroids, dose reduction
Osteoporosis, fractures		Baseline bone scan if at risk or if longer term (>6 months) treatment prescribed; calcium supplements; physical exercise, daily exposure to sunshine (increase vitamin D absorption)
Weight gain		Evaluation of dietary intake; encourage physical activity
Myopathy	More common at doses ≥10 mg/day	Drug discontinuation/reduction
Edema		Mild: Restriction of salt intake, elevate limbs, elastic compression stockings, increase physical activity Moderate/Severe: Diuretics
Thinning hair, alopecia; hirsutism		Provide information on possible changes in hair changes, avoidance of excessive hair treatments and styling
Gastric ulcers, dyspepsia	Risk increases with concomitant use of NSAIDS	Advise patient to take steroid with food in the morning, avoid greasy, fried, highly acidic foods; elevate head of bed if dyspepsia occurs at night; prophylaxis with antacids, H2 receptor inhibitors, proton pump inhibitors
Acneiform rashes		Mild: Wash face twice daily with an exfoliate, keep affected areas clean Moderate/Severe (cystic or infected papules): Pharmacologic topical treatment
Cataracts, glaucoma	Cataracts are a late complication; nerve damage due to increased intraocular pressure often permanent	Screen for patients at risk (personal/family history of glaucoma, diabetes, myopia, connective tissue disease)
Elevated blood sugar		Advise patient to undergo regular monitoring of blood sugar; provide information on symptoms of hyperglycemia
Hyperglycemia	Occurs within hours of drug exposure; generally improves with dose reductions and reverses with drug discontinuation	Mild: Nutrition counseling to avoid simple carbohydrates/sugars; weight loss; increase physical exercise Moderate: Close monitoring of glucose, start oral hypoglycemic agents if necessary Severe: Evaluate corticosteroid use, start insulin if necessary
Thinning of skin Impairment of wound healing		Protect skin from bruising/injury by wearing long sleeves, caution with activities; cleansing of skin tears with sterile water
Adrenal suppression	Symptoms may be first detected following physiological stress	Be alert to onset of symptoms following illness, surgery or injury
Cardiovascular disease Dyslipidemia	Greater risk with doses ≥7.5mg/day	Assess for cardiovascular risk factors; regular monitoring of lipid levels

NSAID, non-steroidal anti-inflammatory drugs

Adapted from:

Faiman B, Bilotti E, Mangan PA, Rogers K. Steroid-associated side effects in patients with multiple myeloma: Consensus Statement of the IMF Nurse Leadership Board. Clin J Oncol Nursing 2008; 12(3):53-63

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Table 2: Management of Common Side Effects of Rituximab	
Side Effect	**Management**
Hypogammaglobinemia	Occurs with multiple courses; Monitor serum immunoglobulin levels before and periodically after rituximab administration
Infusion reactions (rash, urticarial, fever, myalgia, headache, vomiting, transient hypertension)	Pre-medication with antihistamine and antipyretic 30 minutes prior to administration; adequate hydration; monitor electrolytes and renal function
Infection	Contraindicated in patients with known Hepatitis B; suggested vaccination against seasonal flu, Streptococcus pneumoniae, Haemophilus influenza before starting treatment
Secondary malignancies	Provide education on possible occurrence of secondary malignancies; encourage regular follow-up assessments
Pulmonary embolism	Alert patient to signs & symptoms (unexplained shortness of breath, difficulty breathing, chest pain, coughing, coughing up blood); provide emergency contact information
Pneumonitis	Alert patient to signs & symptoms (shortness of breath, cough)
Central nervous system hemorrhage	Symptoms will vary according to location and amount of bleeding; can include headache, weakness, confusion; alert patient to report any symptoms

Adapted from: Cuker A. Transitioning patients with immune thrombocytopenia to second-line therapy: challenges and best practices. Am J Hematol 2018; 93:816-823

Table 3: Management of Common Side Effects of Thrombopoietin Agonists	
Side Effect	**Management**
Eltrombopag (oral administration)	
Increases in ALT	Baseline liver enzyme test, monitor throughout treatment, closer monitoring in patients with known risk factors; ocular examination with regular follow-up; regularly assess and review dose and administration
Headache, nasopharyngitis, upper respiratory infection	Assess and manage symptoms on an individual basis; provide education to alert patient to possible symptoms and provide individualized management strategies
Cataract formation (potential)	Advise patient to regularly undertake eye exam
Both agents	
Bone marrow reticulin formation, risk of bone marrow fibrosis	Monitor CBC with differential; periodic blood smears; Discontinue treatment if severe changes in cell morphology evident or if platelet levels become exceedingly increased
Increased risk of thromboembolism	Evaluate patient for risks associated with thromboembolic events; advise on risks and symptoms of embolism and to immediately seek medical attention if symptoms occur; caution when administering to patients with cardiac history/cardiac stents, closer monitoring in patients with ≥1 risk factor
Romiplostim (subcutaneous injection)	
Headache, fatigue, epistaxis, arthralgia, dizziness	Administer paracetamol as needed, avoid aspirin/NSAIDS as these can interfere with platelet function
Hypersensitivity reactions	Alert patient to the possibility of occurrence; administer pre-medications if necessary
Upper respiratory tract infections	Alert patient to possibility of this side effect; advise to avoid persons with known infection, take care not to spread infection to others

ALT, alanine aminotransferase; NSAIDS, non-steroidal anti-inflammatory drugs

Sources:

Bussel JB, Kuter DJ, Pullarkat V et al. Safety and efficacy of long-term treatment with romiplostim in thrombocytopenic patients with chronic ITP. Blood 2009; 113:2161-217

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Khan AM, Mydra H, Nevarez A. Clinical practice updates in the management of immune thrombocytopenia. P&T 2017; 42:756-763

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Eltrombopag Summary of Product Characteristics. https://www.medicines.org.uk/emc/product/508/smpc

Romiplostim Summary of Product Characteristics. https://www.medicines.org.uk/emc/product/9325/smpc

Table 4: Management of Common Side Effects of Other Agents used to Treat ITP

Agent	Side Effects	Management
Anti-D (Rh Immunoglobulin [RHIg])*	Headache, fever, chills, nausea, vomiting; disseminated intravascular coagulation (rare); intravascular hemolysis (rare); renal failure (rare)	Administer paracetamol as needed
Azathioprine	Weakness, sweating, transaminase elevations (generally low/mild incidence); neutropenia, pancreatitis	Monitor for signs/symptoms of infection; instruct patient to be alert to preventing and recognizing infection; monitor leukocyte count; monitor liver enzyme levels
Cyclosporine A	Increase in serum creatinine, hypertension, fatigue, paraesthesias, gingival hyperplasia, myalgia, dyspepsia, hypertrichosis, tremor (moderate but transient); kidney failure; hypertension	Should not be administered to patients with known renal insufficiency, caution in administering to elderly patients
Cyclophosphamide*	Bone marrow suppression; bladder cancer and secondary leukemia (rare)	Monitor for signs/symptoms of infection; instruct patient to be alert to preventing and recognizing infection; monitor blood counts
Danazol*	Liver function abnormalities; weight gain, myalgia, hair loss; acne; elevated cholesterol; transaminitis	Monitor liver function with long-term administration
Dapsone	Abdominal distension, anorexia, nausea, methaemoglobinuria, hemolytic anemia in glucose-6-phosphate-dehydrogenase-deficient patients (rare and treatable/reversible); skin rash (severe)	Caution in administering to patients from Mediterranean countries (Africans)
Hydroxychloroquine*	Multiple effects on immune system	Monitor for signs/symptoms of infection; instruct patient to be alert to preventing and recognizing infection
Immunoglobulins (IVIg)	Headaches (mild); flushing, fever, chills, fatigue, nausea, diarrhea, blood pressure changes, tachycardia (all transient) neutropenia; renal insufficiency; aseptic meningitis; thrombosis; anaphylactic reactions in patients with IgA deficiency (rare)	Transient side effects: slow rate of infusion, particularly first two administrations of IVIg; advise patient of possible anaphylactic reactions and to alert healthcare personnel should they occur
Mycophenolate mofetil* (MMF)	Gastrointestinal (nausea, loss of appetite, diarrhea, vomiting); risk of infection (bacterial, fungal, protozoal and new or reactivated viral infections, including opportunistic infections); headache (may be dose-limiting); secondary malignancies	Monitor for signs/symptoms of infection; instruct patient to be alert to preventing and recognizing infection

*Not widely approved for use in ITP; use and doses based on individual treatment center practices

Sources: Boral LI, Monohan GP, Moirangthem V. Overview of adult immune thrombocytopenia. Pathol Lab Med Open J 2016; 1:21-31; Khan AM, Mydra H, Nevarez A. Clinical practice updates in the management of immune thrombocytopenia. P&T 2017; 42:756-763; Marangon M, Vianelli N, Palandri F, et al. Rituximab in immune thrombocytopenia: gender, age, and response as predictors of long-term response. Eur J Haematol 2017;98:371–377; Catala-Lopez F, et al. Risk of thromboembolism with thrombopoietin receptor agonists in adult patients with thrombocytopenia: an updated systematic review and meta-analysis of randomized controlled trials. Medicina Clinica 2015; 145:511-519; Matzdorff A, Meyer O, Ostermann H et al. Immune thrombocytopenia – current diagnostics and therapy: recommendations of a joint working group of DGHO, ÖGHO, SGH, GPOH and DGTI. Oncol Res Treat 2018; 41(suppl 5):1-30

Providing Education to Patients and Families

Nurses and other healthcare professionals provide a key role in educating patients and their families about ITP, how it can affect lifestyle and relationships, treatment options including benefits, side effects, dosing, routes of administration and duration, and how patients might manage treatment and disease side effects.

Table 5: Educational Measures to help Patients to Live Better with ITP

Topic	Key Education Points
Diagnosis	Provide general overview of ITP (pathophysiology, disease course) Ascertain patient's understanding of ITP, dispel myths/correct misconceptions Provide information on rationale and interpretation of diagnostic tests Discuss possible changes in lifestyle, need to provide safe environment, conduct activities in a safe manner to avoid/prevent injury Present and discuss resources available to assist patients/families with psychosocial support and coping mechanisms [see Resources]
Treatment	Discuss medications: dose, schedule, mechanism of action, side effects, precautions, drug interactions Ascertain patient/caregiver understanding of provided information on medications Provide information on who to contact should patient experience an adverse event
Fatigue	Explain possible causes such as corticosteroid administration Encourage regular physical activity such as yoga Advise patient to plan and prioritize daily activities Advise patient to get sufficient sleep and rest Possible referral to physical therapy
Bleeding	Reduce risk of bleeding when conducting activities [see Table 6] Demonstrate ways to apply pressure to bleeding sites or slow/stop bleeding by applying ice to the area of bleeding Advise patient to carry aminocaproic acid or tranexamic acid to help prevent and reduce bleeding Keep over-the-counter nosebleed treatments on hand Make patient aware of the necessity of frequent blood draws and laboratory testing to monitor platelet count Provide information on assistive devices to minimize trauma and the risk of bruising if the patients is at risk for falling

Adapted from: Winkeljohn D. Diagnosis, treatment and management of immune thrombocytopenia. Clin J Onc Nrsg 2013; 17: 654-666

Recommendations to help Patients Live Better with ITP: Quality of Life Considerations

ITP has an affect not only on the physical state of the patient, but also on her or his overall well-being. In addition to the clinical manifestations of bleeding, some patients experience disabling fatigue, fear of bleeding, a restriction in their activities of daily living, withdrawal from professional and recreational activities and a lowered QoL (McMillan 2008). In fact, QoL in patients with ITP is worse than in the general population and may, for some, be worse than reported QoL in patients with chronic diseases such as hypertension, arthritis or certain cancers (McMillan 2008).

Lower platelet counts have been associated with a lower health-related quality of life (HRQoL) (Mathias 2007). One of the newer treatments for ITP, romiplostim, was associated with improved QoL compared with standard treatment (Kuter 2010).

Nurses and other healthcare professionals can help patients and their families to cope with the physiological and psychological effects of ITP by providing support in terms of active listening and asking questions, by providing information and by referral to appropriate resources [see Resources section].

Table 6: Recommendations to help Patients to Live Better with ITP	
Topic	**Recommendation**
Taking non-ITP medications	Avoid medicines that can potentially affect platelet count (blood-thinning agents, anti-inflammatory agents, platelet aggregation inhibitors); closely monitor patients who do require anticoagulants for managing other medical conditions Use acetaminophen-containing medications for pain and fever
Sexual relations	Not restricted, care should be exercised if platelet count is low and/or patient has active bleeding
Physical activities	Avoid any activity with high risk of injury (combat and contact sports); wear gloves when working with knives or other tools and for gardening; wear protective clothing (helmets, knee, elbow or wrist pads)
Personal hygiene	Use soft toothbrush; avoid dental flossing with oral bleeding; maintain regular dental health assessments; use an electric shaver; avoid constipation, do not use suppositories or enemas
Travel	Air travel: undertake recommended in-flight exercises to prevent deep vein thrombosis, wear support stockings, avoid alcohol and drink plenty of water
Other	Wear a medical alert/identification bracelet; carry an identification/health care with information on ITP
Adapted from: Winkeljohn D. Diagnosis, treatment and management of immune thrombocytopenia. Clin J Onc Nrsg 2013; 17: 654-666	

Table 7: Suggested Platelet Counts for Medical Procedures*	
Procedure	**Platelet Count**
Minimally invasive procedures*	Generally, platelet count is not a good predictor of bleeding; prophylactic platelet transfusion not recommended with platelet count >30 x 10^9/L
Dental cleaning	>20-30 x 10^9/L
Tooth extraction (simple)	>30 x 10^9/L
Minor surgery	>50 x 10^9/L
Major surgery	>80 x 10^9/L
*Includes: liver and kidney biopsies, lumbar puncture, central line placement, bronchoscopy, GI endoscopies, thoracentesis and paracentesis Sources: Boral LI, Monohan GP, Moirangthem V. Overview of adult immune thrombocytopenia. Pathol Lab Med Open J 2016; 1:21-31; Matzdorff A, Meyer O, Ostermann H et al. Immune thrombocytopenia – current diagnostics and therapy: recommendations of a joint working group of DGHO, ÖGHO, SGH, GPOH and DGTI. Oncol Res Treat 2018; 41(suppl 5):1-30	

Table 8: Disease-related Factors with Possible Effect on Quality of Life
ITP-associated non-bleeding symptoms: cognitive impairment, fatigue, weakness, depression
Increased risk of infection
Long, chronic nature of treatment
Side effects of treatment, especially those related to corticosteroids
Social stigmatization from visible hematomas
Increased risks when treating co-morbidities (i.e., increased risk of bleeding from anticoagulation therapy)
Time required for physicians' visits, therapy, hospitalizations
Possible reduction in productivity
Costs of therapy
Disease-related changes/limitations in lifestyle, leisure activities, travel
Source: Matzdorff A, Meyer O, Ostermann H et al. Immune thrombocytopenia – current diagnostics and therapy: recommendations of a joint working group of DGHO, ÖGHO, SGH, GPOH and DGTI. Oncol Res Treat 2018; 41(suppl 5):1-30

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Quick Facts

- Generally, children do not require treatment for immune thrombocytopenia (ITP) unless they have active bleeding; in the majority of cases ITP resolves spontaneously
- The incidence of ITP in children is low with a low risk of intracranial bleeding and an approximate 20% risk of severe bleeding
- Several professional care guidelines recommend pharmacologic treatment based on bleeding and observation (without administration of drugs) in newly diagnosed children without severe bleeding
- The dilemma encountered when treating children is the variation in bleeding tendency among patients despite similarly low platelet counts
- Corticosteroids are often recommended as first-line treatment in children
- Prolonged treatment with corticosteroids may have longer term side effects such as suppression of growth and osteoporosis
- IVIg is frequently used to manage bleeding in children
- The diagnosis of ITP may have a significant impact on health-related quality of life (HRQoL) in children and their families

Module V: Immune Thrombocytopenia in Children

A. Introduction: ITP in Children

B. Pathophysiology and Incidence

C. Clinical Presentation

D. Diagnosis and Differential Diagnosis

E. Consequences of Clinical Manifestations of ITP—Bleeding Risk

F. Treatment

1. First-line treatment
2. Second-line treatment
3. Treatment of chronic disease
4. Treatment of bleeding

G. Management of Treatment Side Effects

1. Management of Common Side Effects of Corticosteroids
2. Management of Common Side Effects of Thrombopoietin Receptor Agonists

H. Predictors of Disease Remission

I. Health-related Quality of Life

J. Future Perspectives

Introduction: Immune thrombocytopenia in Children

Immune thrombocytopenia (ITP) is usually an acute, self-resolving illness in children and only 20% to 25% of children will develop chronic disease (a platelet count <100 x 10^9/L lasting for more than 12 months) (Rodeghiero 2009). Despite the rather mild and transient nature of ITP in most children, the diagnosis, significant bruising (ecchymosis), bleeding and restriction in school and sport activities can have a significant impact on health-related quality of life (HRQoL) for patient and family (Cooper, 2017; Yacobovich 2013).

Pathophysiology and Incidence

ITP in children is typically preceded by a febrile illness and is presumed to be triggered by an acute viral infection or after immunization. The incidence of ITP in children and adolescents is 0.2-0.7 new cases per 10,000 per year (Provan 2015).

- Studies from Germany, UK and Scandinavia estimate the incidence of ITP in children to be between 2.2 and 5.3 per 10,000 in those countries (Mathias 2016)
- Approximately 5000 new cases of pediatric ITP are diagnosed each year in the US (Segal 2006)

Whereby ITP is often a chronic disorder in adults, 70% to 80% of pediatric cases resolve spontaneously within 6 months

- ITP persists in a chronic form in the remaining approximately 20%, which is defined as a platelet count <100,000 x 10^9/L lasting for more than 12 months (Rodeghiero 2009)

[See Module 1 for further details on the pathophysiology of ITP]

Clinical Presentation

ITP in young children usually presents with acute bleeding symptoms, often occurring after an infection (Matzdorff 2018)

- Epistaxis is the most common presenting symptom followed by cutaneous and minor mucosal bleeding
- The incidence of intracranial bleeding in children is very low at < 1% (Cooper 2017)

[See Module 2 for further details on Clinical Presentation]

Diagnosis and Differential Diagnosis

Other forms of thrombocytopenia could mimic ITP and secondary ITP, particularly when platelet reduction is the only laboratory finding. It is important to rule out acute lymphocytic leukemia and primary bone marrow failure as a cause of bleeding, bruising and purpura.

Physical examination of the patient includes assessment for potential sites of bleeding (cutaneous and mucosal) and identification of signs suggestive of secondary ITP or other pathologies.

Laboratory studies include:

- complete blood count (CBC) (known as full blood count [FBC] in some countries), mean platelet volume, peripheral blood smear, reticulated platelet count (determines cause of ITP as either bone marrow suppression or platelet destruction)

[See Module 2 for further details on Diagnosis and Diagnostic Procedures]

Consequences of Clinical Manifestations of ITP: Bleeding Risk

The risk of intracranial bleeding or hemorrhage in children with newly diagnosed or chronic ITP as reported in a systematic review was 0.4% and the risk of severe bleeding was 20% (Neunert 2015).

Predictors of severe bleeding include:

- Severe thrombocytopenia (platelet count < 10 to 20 x 10^9/L)
- Newly-diagnosed ITP
- Previous minor bleeding (Neunert 2015)

Treatment of ITP in Children: Overview

There is great disparity regarding when to treat ITP in children and which agents should be used. However, in light of the rarity of severe bleeding, the absence of evidence that treatment prevents severe bleeding and the known costs and toxicities of treatment, observation alone is often recommended in asymptomatic or minimally symptomatic children with newly diagnosed ITP, irrespective of platelet count (Cuker 2016).

Individual situations, such as age, susceptibility to injury, parental anxiety, proximity to the medical center or psychosocial condition should be taken into consideration

when making decisions about when to initiate treatment.

The aim of treatment, when required, is to rapidly increase the platelet count while minimizing the potential for adverse events.

UK guidelines (Granger 2012), the American Society of Hematology (ASH) (Neunert 2011) and an International Working Group (Rodeghiero 2013) recommend pharmacologic treatment based on bleeding and observation without drug therapy in newly diagnosed patients without severe bleeding.

- Despite these recommendations, many centers routinely treat children when platelet counts fall below < 20 x10^9/L
- By contrast, in one study, the use of observation alone was used in 71% of newly diagnosed pediatric cases of ITP; the presence of thrombocytopenia and bruising was the primary reason to initiate treatment (Schultz 2014)
- In that study, observation alone did not lead to an increase in later treatment or an increase in delayed bleeding symptoms (Schultz 2014)

The dilemma encountered when treating children is the great variation in bleeding tendency among patients despite similarly low platelet counts (2015)

[See Module 3 for detailed information on types of treatment and Module 4 for detailed information on the management of patients with ITP]

First-line Treatment

Recommendations for first line treatment in pediatric patients include:

- Corticosteroids, intravenous immunoglobulin (IVIg) or anti-D, immunosuppressive agents (rituximab) or thrombopoietin receptor agonists (TPO-RAs)
- MMF at low doses may be beneficial (Cooper 2017)
- Ritixumab may benefit children not responsive to steroids or those requiring high doses of steroids (Grace 2018)

Second-line Treatment

The indications, timing and choice of second-line treatment, when needed, are complex and highly variable (Neunert 2008)

Factors identified by physicians as important when selecting second-line treatment are:

- Patient/parental preference age
- Treatment-related side effects
- Long-term toxicity
- Ease of administration
- Possibility of remission
- Perceived efficacy (Grace 2018)

Options for second-line treatment in children include:

- Rituximab
- Oral immunosuppressive agents
- Thrombopoietin receptor agonists (TPO-RAs)
- Immunomodulatory agents
- Intermittent first-line treatments (e.g., IVIg or corticosteroids)
- Splenectomy (Grace 2018; Kim 2017)

However, there is an absence of clinical trial data to support the selection of "best" second-line treatment in pediatric patients with ITP.

A prospective, observational, longitudinal cohort study of treating physicians identified their preferences for individual second-line treatments, and their reasons for preferring these treatments.

Treatment	Reason preferred*
Rituximab	Possibility of long-term remission; patient/parental preference; physician comfort; minimal long-term toxicity; side effect profile
Oral immunosuppression	Ease of administration; minimal long-term toxicity; physician comfort; side effect profile; expected compliance; patient/parental preference
Romiplostim	Side effect profile; perceived efficacy; patient/parental preference; physician comfort; minimal long-term toxicity; expected compliance
Eltrombopag	Ease of administration; side effect profile, minimal long-term toxicity; patient/parental preference; expected compliance

*Preferences with > 40% response
Grace RF, Despotovic JM, Bennett CM et al. Physician decision making in selection of second-line treatments in immune thrombocytopenia in children. Am J Hematology 2018; 93:882-888

Treatment of Chronic Disease

Chronic ITP has been defined as disease persisting longer than 12 months from diagnosis (Rodeghiero 2009). Because of the low bleeding risk in children, even in the setting of severe persistent or chronic thrombocytopenia, observation rather than treatment may be appropriate in asymptomatic or minimally symptomatic cases (Cuker 2016).

A percentage of the children who develop chronic ITP will, however, have significant bleeding symptoms or bleeding risk that requires continuing therapy

There is no consensus on the treatment of chronic ITP in children. Therapeutic options include:

- rituximab, oral immunosuppressive agents, thrombopoietin receptor agonists (TPO-RAs) and splenectomy

In a clinical study, eltrombopag improved platelet counts (≥50 x 10^9/L), reduced bleeding severity and reduced or allowed discontinuation of concomitant treatments for ITP (Kim 2017)

Suggested starting dose of eltrombopag:

- 25 mg/day in children age 1 to < 6 years
- 50 mg/day in children age > 6 years
- 50% decrease in starting dose for patients of East Asian ancestry (Kim 2017)

In a phase 3 double-blind study, romiplostim induced a high rate of platelet response with no new safety signals in children with chronic ITP (Tarantino 2016)

- In this study, the weekly dose of romiplostim was adjusted from 1 µg/kg to 10 µg/kg to target platelet counts of 50 to 200 × 10^9/L (Tarantino 2016)
- Over 6 years, > 90% of children in the study achieved a platelet response, most responding ≥ 75% of the time while receiving an average weekly dose of 4.8 µg/kg (Tarantino 2016)

Treatment of Bleeding

Most children experience only mild bleeding in the form of bruising and petechiae; the risk of severe hemorrhage is related to duration of marked thrombocytopenia and is highly variable (Neunert 2015).

A descriptive, somewhat older study of bleeding events in children showed that platelet transfusions were relatively uncommon. Management of bleeding most commonly involved steroid and IVIG administration (Neunert 2013). Platelet concentrates may be transfused for very heavy bleeding (Matzdorff 2018).

Eltrombopag can be used to treat severe refractory bleeding at the time of presentation (Kim 2017).

Management of Treatment Side Effects

Table 1: Management of Common Side Effects of Corticosteroids

Side effects	Notes	Management
Growth suppression	Dexamethasone and betamethasone associated with a delay in growth and puberty, prednisolone has lower risk	Monitor growth every 6 months and plot on growth curve
Adrenal suppression	Most common cause of adrenal insufficiency in children; symptoms non-specific, exposure to physiological stress may result in adrenal crisis	Symptoms of adrenal crisis include hypotension, shock, decreased consciousness, lethargy, unexplained hypoglycemia, seizures, death; discontinue corticosteroids
Hyperglycemia, diabetes		Closely monitor fasting plasma glucose; educate patient/parents about signs & symptoms of hyperglycemia
Cushing's syndrome	Hallmark features include growth failure or deceleration associated with weight gain, facial plethora, increased fine downy facial hair, round face, diabetes	Gradual reduction in corticosteroid dose
Osteoporosis	May lead to increased risk of bone fractures	Perform serial bone mineral density tests to assess risk; evaluate calcium and vitamin D intake, back pain, physical activity with long term use; encourage proper nutrition, maintenance of healthy weight, regular physical activity

Sources: Liu D, Ahmet A, Ward L et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. Allergy, Asthma & Clin Immunol 2013; 9:30

Table 2: Management of Common Side Effects of Thrombopoietin Agonists		
Side effects	**Notes**	**Management**
Eltrombopag (oral administration)		
Headache, upper respiratory tract infection, nasopharyngitis, diarrhea, transaminitis	Very common	Assess and manage symptoms on an individual basis; provide education to alert parents/patient to possible symptoms and provide individualized management strategies
Risk of severe and potentially life-threatening hepatic toxicity	Mild hepatic toxicity reported in pediatric trials; correction after drug cessation Black box warning for risk of severe/life-threatening hepatic toxicity	Completion of liver function and bilirubin level tests prior to initiating treatment, repeat tests monthly
Cataract formation (potential)	Inconclusive clinical data to support an increased risk of cataract development /progression in children	Screening and follow-up eye examinations in children with significant exposure to corticosteroids
Thrombosis (potential)	Adolescents with other risk factors may have higher risk	Assess risk for developing thrombosis prior to drug initiation
Iron deficiency (potential)		Administer iron supplementation if iron deficiency develops and no other cause is identifiable, space dosing of two drugs
Romiplostim (subcutaneous injection)		
Headache, fatigue, epistaxis, arthralgia, dizziness		Administer paracetamol as needed, avoid aspirin/NSAIDS as these can interfere with platelet function
Hypersensitivity reaction (rash, urticarial, angioedema)		Provide caregivers with information regarding signs and symptoms; provide pre-medications
Upper respiratory tract infection, rhinitis	Very common More common in children	Avoid persons with known infection; symptom management; prevent spread of infection
Upper abdominal pain, oropharyngeal pain	More common in children	Provide caregivers with information regarding signs and symptoms and advice on measures to alleviate pain
Sources: Cooper N. State of the art – how I manage immune thrombocytopenia. Br J Haematology 2017; 177:39-54; Khan AM, Mydra H, Nevarez A. Clinical practice updates in the management of immune thrombocytopenia. P&T 2017; 42:756-763; Kim TO, Despotovic J, Lambert MP. Eltrombopag for use in children with immune thrombocytopenia. Blood Advances 2017; 2:454-461; https://www.medicines.org.uk/emc/product/508/smpc; https://www.medicines.org.uk/emc/product/9325/smpc		

[See Module 3 for more information on treatments and treatment side effects]

Predictors of Disease Remission

Analysis of registry data from the Intercontinental Cooperative ITP Study Group identified the following factors as predictive of disease resolution at 12 and 24 months in children with ITP (Bennett 2016):

- Gender and platelet count at diagnosis were not significantly correlated with remission
- Significant association between remission at 12 months and younger age, higher bleeding grade at diagnosis and treatment with a combination of IVIg and corticosteroids at diagnosis
- Remission at 24 months was associated with younger age and treatment with IVIg and corticosteroids at diagnosis
- Patients <1 year of age had the highest odds of achieving remission at both 12 and 24 months

A nationwide prospective cohort study in France also identified younger age, lower platelet count and, to a lesser extent, male gender as predicting more favorable outcomes (Grimaldi-Bensouda 2017).

Health-related Quality of Life in Children with ITP

Newly diagnosed ITP may have a significant impact on HRQoL in children and their families

- Children may feel restricted in their activities
- Close observation, activity restriction and the onset of severe bleeding may contribute to parental anxiety and a subsequent decrease in HRQoL in the child
- Large skin bleeds may cause embarrassment (Heitink-Polle 2014)

HRQoL in children seems to be related to clinical course of ITP (recovery within 3 to 6 months vs a chronic course) rather than to bleeding severity or treatment modality (Heitink-Polle 2014)

- No differences in HRQoL were found between children receiving IVIg treatment and those treated with observation alone (Heitink-Polle 2014)

Results of an exploratory study suggest an improvement in HRQoL in children and reduced burden to their parents following treatment with romiplostim (Mathias 2016)

[See Module 4 for detailed information on management of the patient with ITP]

Future Perspectives

As physicians often rely on personal preferences and individual therapy characteristics, there is a need to provide evidence-based options for treating early disease through the conduct of randomized clinical trials.

Clinical trials are also needed to identify pediatric populations who will best benefit from TPO-RA use, novel dosing strategies of these agents and comparative trials of patient-related outcomes with these versus other therapeutic options.

TPO-RAs have potential disease modifying effects and may prove beneficial as a first-line treatment; clinical trials are required to provide evidence for this assumption.

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Glossary of Terms*

Term	Definition
Acneiform rash	Dermatoses that resemble acne vulgaris; lesions may be papulopustula, nordular or cystic; develop as a result of infections, hormonal or metabolic abnormalities, genetic disorders and drug reactions
Adrenal suppression	A decline in function of the adrenal glands, leading to decreased levels of adrenal hormones like aldosterone and cortisol in the body. Deficiencies in these hormones can cause a variety of symptoms and can be a medical emergency if levels drop suddenly
Alopecia	Loss of hair especially of the scalp or face
Antibodies	Proteins produced by the immune system that attack foreign antigens (e.g., bacteria, viruses)
Anti-CD20 antibody	A monoclonal antibody against the protein CD20, which is primarily found on the surface of immune system B cells. Rituximab is an anti-CD20 antibody drug
Anti D (Rh immunoglobulin) (RhID)	An anti-D immunoglobulin is an antibody to a common human antigen present on red blood cells; only some people have this antigen, known as D-antigen or Rhesus antigen
Anti-TNF agents	Antibodies that block an inflammatory hormone called tumor necrosis factor (TNF). TNF is produced by white blood cells and causes inflammation
Antigens	Any substance capable of inducing a specific immune response and reacting with the products of that response; that is, with specific antibody or specifically sensitized T lymphocytes or both. Antigens may be soluble substances, such as toxins and foreign proteins, or particulates, such as bacteria and tissue cells
Aplastic anemia	Deficiency of all types of blood cells caused by failure of bone marrow development
Autoimmune (disorder)	The body's immune system reacts against its own tissue to produce antibodies that attack itself
Bone marrow	A soft fatty substance in the cavities of bones, in which blood cells are produced
Bulla, vesicle and blister	Visible raised, thin-walled, circumscribed lesion containing blood. Each bulla (>5mm) is larger than a vesicle.
Complete blood count (CBC)	A measure of the number of blood cells (red and white blood cells, platelets) in the serum
Corticosteroids	Steroid hormones that are either produced by the body or are man-made
Cushing's syndrome	A metabolic disorder caused by overproduction of corticosteroid hormones by the adrenal cortex and often involving obesity, high blood pressure and bone loss
Cytokine	Powerful chemical substances secreted by cells enabling cell-to-cell communication. Cytokines include lymphokines produced by lymphocytes and monokines produced by monocytes and macrophages
Direct antiglobulin test	Used to detect antibodies attached to red blood cells; used to help diagnose the cause of hemolytic anemia. Also called Coombs test
Ecchymosis (purpuric macule, bruises or contusions)	Flat, rounded, or irregular red, blue, purplish, or yellowish green patch, larger than a petechiae. Elevation indicates spreading of an underlying hematoma into the superficial layers of the skin
Epistaxis	Bleeding from the nose; may be anterior or posterior and unilateral or bilateral
Gingival bleeding	Any bleeding from the gums
Health-related quality of life (HRQoL)	A multi-dimensional concept that includes domains related to physical, mental, emotional and social functioning
Hematochezia	The passage of blood in the feces
Hematoma	Skin: Bulging localized accumulation of blood, often with discoloration of overlying skin. Soft tissue and muscles: Localized collection of blood that is visible, palpable or revealed by imaging, may dissect through fascial planes
Hematuria	Blood in the urine; gross hematuria means the blood can be seen with the naked eye

Term	Definition
Hirsutism	Abnormal growth of hair on a person's face and body, especially on a woman
Hypogammaglobinemia	An abnormally low concentration of gamma globulin in the blood and increased risk of infection immunodeficiency - immunological disorder in which some part of the body's immune system is inadequate and resistance to infectious diseases is reduced
Idiopathic	A disease of unknown cause
Immunoglobulin	One of a family of large protein molecules, or antibodies, produced by mature B cells (plasma cells)
Immunomodulatory agents	A chemical agent (such as methotrexate or azathioprine) that modifies the immune response or the functioning of the immune system (as by the stimulation of antibody formation or the inhibition of white blood cell activity)
Immunosuppressive agents	A class of drugs that suppress, or reduce, the strength of the body's immune system
Intracerebral/intracranial hemorrhage	Bleeding that occurs in the brain as a result of either a ruptured or leaking blood vessel
Intravenous immunoglobulin (IVIGg)	A sterile solution of concentrated antibodies extracted from healthy people that is administered directly into a vein
Leukocytosis	An increase in the number of white cells in the blood, especially during an infection
Lymphocytic leukemia	Leukemia marked by an abnormal increase in the number of lymphocytes, which accumulate especially in bone marrow, lymphoid tissue and circulating blood
Megakaryopoiesis	The production of megakaryocytes
Megakaryocyte	A cell in the bone marrow that produces platelets
Menorrhagia	Menstrual periods with abnormally heavy or prolonged bleeding
Microcytosis	A blood disorder characterized by the presence of microcytes (abnormally small red blood cells) in the blood; often associated with anemia
Monoclonal antibodies	A type of protein made in the laboratory that can bind to substances in the body, including cancer cells
Mucocutaneous	Pertaining to or affecting the mucous membrane and skin
Myalgia	Pain in a muscle or group of muscles
Myelodysplastic syndromes (MDS)	Conditions that can occur when the blood-forming cells in the bone marrow become abnormal leading to low numbers of one or more types of blood cells; considered a type of cancer
Myopathy	A disease of muscle tissue
Osteonecrosis	The death of bone tissue
Osteopenia	Reduced bone mass of lesser severity than osteoporosis
Osteoporosis	A condition in which bones become brittle and fragile from loss of tissue, typically as a result of hormonal changes, or deficiency of calcium or vitamin D
Peripheral blood smear	A blood drop on a glass slide used to examine blood cells under the microscope
Petechiae	Red (recent) or purplish (a few days old) discoloration in the skin with a diameter of 0.5—3 mm that does not blanche with pressure and is not palpable
Phagocytosis	The ingestion of bacteria or other material by phagocytes and amoeboid protozoans
Purpura	A type of hematoma. Purple bruises about 1 cm in diameter that are generally round in shape and caused by bleeding under the skin

Term	Definition
Refractory	When a disease or condition does not respond to treatment
Relapse	Return of a disease or signs and symptoms of a disease after a period of improvement
Remission	Period of time when symptoms improve or subside; can be temporary or permanent
Reticulated platelet	An incompletely developed platelet found in the peripheral blood that contains strands of mRNA or rRNA. Small numbers of circulating reticulated platelets, typically <5%, are found in blood as a result of normal maturation from megakaryocytes in the bone marrow
Reticulin fibrosis	A condition in which some of the immature red cells do not mature appropriately
Reticulocyte count	Measures the number of new red/immature blood cells
Subconjunctival hemorrhage	Bright red discoloration underneath the conjunctiva; may assume the appearance of an ecchymosis over time
T cells	Cytotoxic: a T lymphocyte that kills cancer cells, cells that are infected or cells that are damaged Regulatory: (known as suppressor T cells) a sub-population of T cells which modulate the immune system, maintain tolerance to self-antigens and abrogate autoimmune disease
Teratogen	An agent or factor which causes malformation of an embryo
Thrombocytopenia	Low platelet count (<100 x 10^9/L)
Thrombopoiesis	The process of thrombocyte generation
Thrombopoietin	A protein produced at a fixed rate in the liver that is the key regulator of platelet production
Thrombopoietin receptor agonists (TPO-RA)	Medicines that mimic the action of endogenous thrombopoietin to stimulate the production of platelets

*The terms listed in this glossary are not necessarily specific to immune thrombocytopenia. Some terms refer to general concepts in the diagnosis, treatment and management of cancers and other diseases or conditions.

Resources

Professional Societies	
American Society of Hematology (ASH)	www.hematology.org/
European Hematology Association (EHA)	www.ehaweb.org
European Society for Immunodeficiencies (ESID)	www.esid.org
Haematology Nurses & Healthcare Professionals (HNHCP)	http://www.hemcare.org/home.html (e-learning programs available at this site)
Patient Organizations/Sources of Information	
International Patient Organization for Primary Immunodeficiencies (IPOPI)	www.ipopi.org
ITP Support Association	www.itpsupport.org.uk [UK charity supporting those affected by ITP]
ITP Foundation	www.itpfoundation.org [Resource for parents of children with ITP]
Platelet Disorder Support Association	www.pdsa.org [Educational, advocacy, support resource for patients, caregivers, healthcare professionals]
ITPANDME.COM	www.itpandme.com [For patients and families with ITP]
Foundation for Women and Girls with Blood Disorders	http://www.fwgbd.org/ [Raise awareness and provide education on blood disorders in females]
ITP International Alliance	http://www.globalitp.org/ [Intercontinental partnership of ITP patient support organizations committed to education, awareness and establishing a global voice for ITP]
Platelets on the Web	www.ouhsc.edu/platelets [Provides current information on platelet disorders]
ITP-Selbsthilfegruppe Giessen	www.itp-information.de [Website in German]
ITP Patiëntenvereniging Nederland	www.itp-pv.nl [Website in Dutch]

Drugs and Herbal Medicines with the Potential to Affect Platelet Function

Drugs	
Non-steroidal anti-inflammatory	Aspirin, Ibuprofen, Mefanamic acid, Cox-2 inhibitors
Antimicrobial	Penicillins, Cephalosporins, Nitrofurantoin, Hydroxychloroquine,
Anticoagulants	Heparin, Coumarin, Lepirudin, Argatroban, Bivalirudin
Cardiovascular	Beta-adrenergic blockers (e.g., propranolol), Vasodilators (e.g., furosemide), Calcium channel blockers
Thrombolytic agents	Streptokinase, Urokinase, Tissue plasminogen activator
Psychotropic and anesthetic agents	Tricyclic antidepressants (e.g., imipramine), Phenothiazines (e.g., chlorpromazine), Local and general anesthetics (e.g., halothane)
Chemotherapy	Mithramycin, Daunorubicin, Carmustine
Antiplatelet drugs	Phosphodiesterase inhibitors, Dipyridamole, Cilostaqzole
Adenosine diphosphate receptor antagonists	Ticlopidine, Clopidogrel
Glycoprotein IIb/IIIa antagonists	Abcixamab, Eptifibatide, Tirofiban
Miscellaneous agents	Dextrans, Radiographic contrast, Quinidine, Ethanol
Herbal medicines	Ginko, Ginger, Dong quai, Ginseng, Meadosweet, Chamomile, Horse chestnut, Red clover, Garlic, Bilberry, Feverfew, Turmeric, Willow, Motherworth, Fenugreek, Tamarind
Foods	Caffeine, Garlic, Cumin, Turmeric

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