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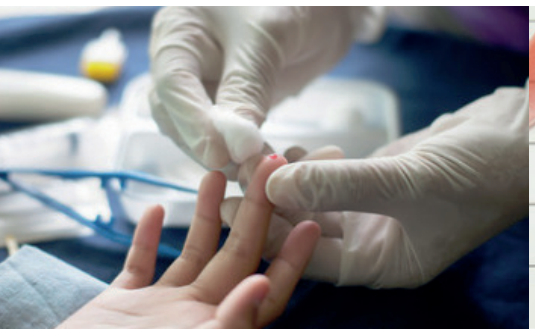

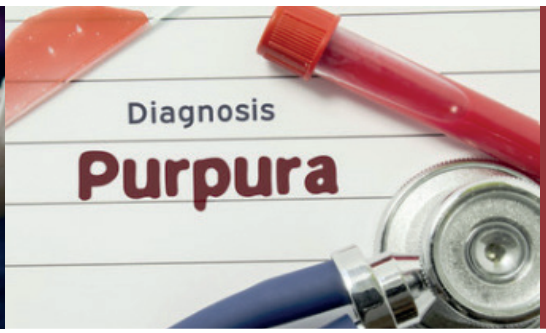

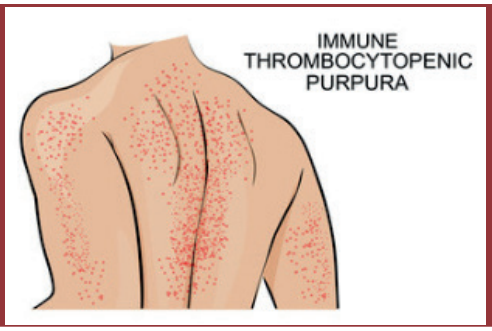

Immune Thrombocytopenia (ITP)

A resource for healthcare professionals

Dear Colleague

We are very pleased to present the second edition of "Immune thrombocytopenia (ITP): A resource for healthcare professionals" by 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 latest information and up-to-date recommendations for addressing both short-term and long-term management of patient and family needs.

The second edition Immune thrombocytopenia (ITP) Learning Program was made possible by a sponsorship from Swedish Orphan Biovitrum AG ("Sobi").

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.

Yours sincerely,

Erik Aerts

President

Haematology Nurses and Healthcare Professionals Group

The Haematology Nurses & Healthcare Professionals Group thanks the following individuals for their review and contributions to this tutorial:

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The ITP Learning Program is also available online at

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Summary Points

- 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: Understanding Immune Thrombocytopenia
    1. History of immune thrombocytopenia
B. Epidemiology
C. Pathophysiology
    1. Normal platelet production
    2. Primary immune thrombocytopenia
    3. Secondary immune thrombocytopenia
D. Terminology and Definitions in ITP

References

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, 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 are 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 1953).

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

The pathophysiology of ITP is complex and is not yet completely understood. The widely accepted cause is the premature destruction of antibody-coated platelets by the spleen, liver, or both through interaction with Fcγ receptors. Other mechanisms of platelet destruction are possible, such as abnormalities in the function of T cells and involvement of CD8 cells (Cooper 2019).

ITP may be a primary condition, or it may be caused by other diseases, medications or infections, for example.

Normal platelet production

Platelets are produced in bone marrow by megakaryocytes, which are highly specialized precursor cells. Platelet production is the final stage of megakaryocyte development. The current understanding of platelet formation describes the process as beginning with the mechanical extension of proplatelet elongations by megakaryocytes into the sinusoidal blood vessels of bone marrow. Released proplatelets continue to mature in the vasculature and ultimately release individual platelets from their tips (Thon 2010) (**Figure 1**).

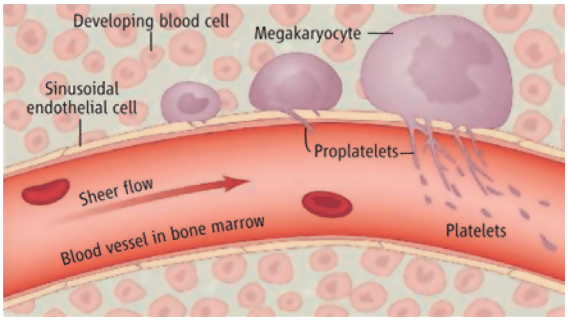

Figure 1: Natural platelet production.

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 physiological processes such as wound healing and inflammatory/immune responses and in pathological developments including atherosclerosis and tumor metastasis (Pluthero 2016).

Under normal conditions, the number of platelets circulating through the body is approximately 140 to 440 x 10^9/L and have a mean life span of 7 to 10 days.

What triggers the immune system to produce autoantibodies directed against platelets, as happens in ITP, 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 relative 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.

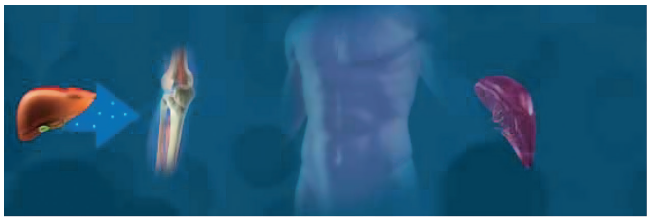

Figure 2a: Normal platelet homeostasis. Thrombopoietin, a hormone produced at a fixed rate in the liver, is the key regulator of platelet production

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

Primary immune thrombocytopenia

80% of the adults with ITP have primary ITP (Lambert 2017). 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 the immune system to platelet antigens and formation of antibodies that target glycoprotein IIa/IIIa on platelets causing their destruction by macrophages or cytotoxic T cells (**Figures 3a and 3b**)
- is caused by underlying immune dysregulation such as decreased regulatory T cell populations, abnormal cytokine profiles and an altered Th1/Th2 balance

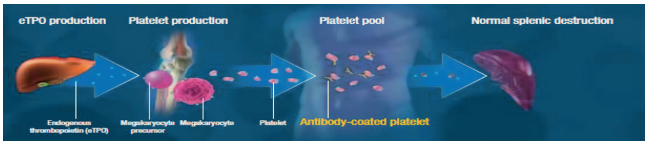

Figure 3a: Increased peripheral destruction of platelets in ITP. In ITP, antibodies bind to glycoproteins on healthy circulating platelets

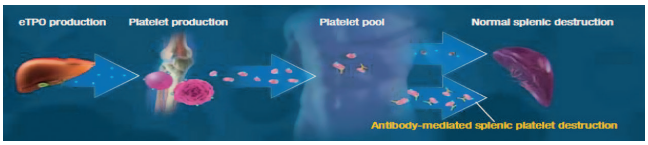

Figure 3b: Increased peripheral destruction of platelets in ITP. Antibody-coated platelets are recognized by macrophages primarily in the spleen leading to their destruction

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

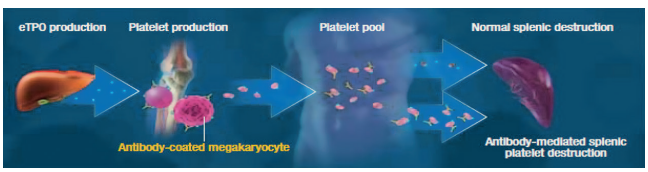

Figure 4a: Insufficient platelet production in ITP. Antibodies bind to and damage megakaryocytes in the bone marrow rendering them immature and less productive

Table 1: Examples of Secondary Causes of Immune Thrombocytopenia	
Autoimmune disorders	Systemic lupus erythematosus, antiphospholipid syndrome, connective tissue disease, immune thyroid disease, inflammatory bowel disease, Evans syndrome, rheumatoid arthritis, transplant-associated ITP
Congenital immune deficiencies	Common variable immune deficiency (CVID), autoimmune lymphoproliferative syndrome (ALPS)
Infection	HIV and AIDS, hepatitis C virus, Helicobacter pylori, CMV, EBV, influenza
Use of certain drugs	Heparin, penicillin, rifampicin, vancomycin, nonsteroidal anti-inflammatory drugs (NSAID), acetaminophen, quinine sulphate, checkpoint inhibitors
Lymphoproliferative disorders	Chronic lymphocytic leukemia, Hodgkin's lymphoma
Vaccinations	Measles, mumps, rubella, varicella, COVID, influenza
AIDS, autoimmune deficiency disease; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HIV, human immune deficiency virus Adapted from: Cooper 2019; Khan 2017	

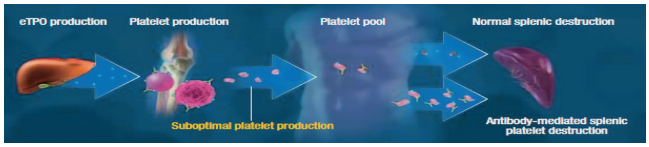

Figure 4b: Insufficient platelet production in ITP. Fewer megakaryocytes and an inappropriately low endogenous thrombopoietin level result in an insufficient production of platelets

Secondary immune thrombocytopenia

Secondary ITP is a heterogeneous group of disorders, where the specific factor causing ITP, such as associated medical conditions or precipitants, can be identified (Abadi 2015). The distinction between primary and secondary ITP is of clinical relevance because of different natural histories and the choice of treatments, including the need to treat the underlying condition in secondary ITP. The known causes of secondary ITP include autoimmune disorders, infections, drugs and vaccinations and malignancies (**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.

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 2: Suggested Descriptive Terminology for ITP	
Term	**Description**
Newly diagnosed	< 3 months 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 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
Durable response	Platelet count ≥ 30 x 10^9/L and at least doubling of the baseline count at 6 mo
Early response	Platelet count ≥ 30 x 10^9/L and at least doubling baseline at 1 wk
Initial response	Platelet count ≥ 30 x 10^9/L and at least doubling baseline at 1 mo
Remission	Platelet count > 100 x 10^9/L at 12 mo
Sources: Rodeghiero 2009; Provan 2019	

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Summary Points

- 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 intracranial hemorrhage
- There is no standard diagnostic test for ITP; 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

Module II: Establishing a Diagnosis of Immune Thrombocytopenia

A. Introduction
B. Patient History, 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
    3. Reduced health-related quality of life
G. Future Perspectives

References

Introduction

Primary immune thrombocytopenia (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.

Information collected during a medical history and physical 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 thrombocytopenia or bleeding. [See Resources for a list of drugs and herbal medicines that affect platelet function]. The medical history, physical exam and investigations 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

The diagnosis of ITP can be challenging. A presumptive diagnosis is made when other causes of thrombocytopenia are ruled out: That is, there is no "gold standard" test to reliably establish a diagnosis (Provan 2019). Of interest, the practice of obtaining routine complete blood counts (CBCs) (full blood counts [FBC]) has led to the identification of asymptomatic primary ITP because of a serendipitous finding of a low platelet count.

According to the American Society for Hematology recommendations, the basic evaluation for the diagnosis of ITP in children and adults should include a patient history, family history, physical examination, CBC and reticulocyte count, peripheral blood smear, quantitative Ig level measurement (in children, blood group (Rh), HIV testing (in the appropriate geographic setting), and HBV (Neunert 2019).

Patient History, Presentation and Physical Findings

Taking a clinical history helps to collect accurate data and to guide and direct the next steps in the diagnostic process. Examples of areas to address when assessing the patient's history include

- Any bleeding after surgical or dental procedures?
- Any abnormalities in platelet counts found in previous blood counts?
- Prior exposure to drugs and toxins
- Recent foreign travel and vaccinations
- Recent infections
- Prior transfusions with blood products
- Incidence and degree of bleeding (including characteristics of menstrual bleeding)
- Family history of thrombocytopenia or bleeding disorders (Provan 2019).

Results of a physical examination are generally normal except for bleeding manifestations, which are 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, purpura, ecchymosis (**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

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

	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

N/A, not applicable; PE, physical examination; *Also referred to as bulla, vesicle and/or blister
Adapted from: Page 2007

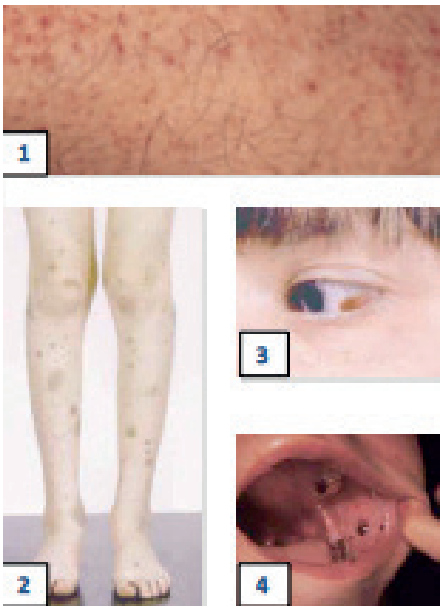

Figure 1: Images of bleeding in patients with ITP. 1. Petechiae; 2. Purpura and hematoma; 3. Conjunctival hemorrhage; 4. Submucosal bleeding. Images 1 and 4 courtesy of Drew Provan; Images 2 and 3 courtesy of Douglas Cines and James Bussel

Diagnostic Procedures

Peripheral blood count and smear

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. 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.

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 should be evaluated by a qualified hematologist or pathologist and is useful to verify the size of platelets and the presence of normal red and white blood cells to exclude a diagnosis of myelodysplastic syndrome or leukemia.

Bone marrow examination.

Bone marrow examination may be informative in patients with systemic symptoms, abnormal signs, or with suspicion of a different diagnosis. Bone marrow examination can be performed during consideration of splenectomy or before starting a new treatment.15-18 If performed, the bone marrow examination should include an aspirate, a biopsy, flow cytometry, and cytogenetic analysis (evidence level IIb-IV) to help to distinguish ITP from lymphoproliferative disorders, myelodysplastic syndrome, or primary bone marrow disorders.19 In elderly patients or those not responding to corticosteroids or IVIg, next-generation sequencing (NGS) panels should be considered to assess for genes associated with clonal malignancy. Approximately one third of ITP patients have increased bone marrow reticulin; however, this is not correlated with disease severity, clinical features, or comorbidities and, thus, should not dispute the diagnosis unless there are significant amounts of type I collagen seen on the trichrome stain (evidence level III).(Updated international consensus report on the investigation and management of primary immune thrombocytopenia. D. Provan et al blood Advances 2019

Diagnostic examinations for adults and children with suspected ITP are described below in terms of their benefit to establish a diagnosis (**Table 2**).

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 time
Quantitative immunoglobulin level measurement	Antinuclear antibodies	Studies of platelet survival
Blood group (Rh)	Viral PCR for parvovirus, EBV and CMV	Serum complement assay
Direct antiglobulin test	Bone marrow aspiration in atypical and refractory disease)	
Testing for H. Pylori, HIV, HCV, hepatitis B antibody status		

CMV, cytomegalovirus; EBV, Epstein Barr virus; H. pylori, Helicobacter pylori; PCR, polymerase chain reaction; Rh, rhesus
Adapted from:
Lambert 2017; Matzdorff 2018; Provan 2019

Prognosis and Survival

The percentage of patients who obtain a cure of ITP (i.e., complete absence of any disease manifestations, normal platelet count) is very low. A majority of patients do obtain a response to treatment and remission of their disease and many are able to discontinue therapy completely. 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 2015).

- 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)
- 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. While there is no known cure for ITP, most patients achieve a hemostatic platelet count with treatment (Kuter 2021). In general, adult ITP patients have a very low rate of spontaneous remission without therapy, which is estimated to be between 0.9% (Pizzuto 1984) and 10.3% (Stasi 1995). Patients who are newly diagnosed and those with persistent disease may have a remission rate with therapy of up to 32% (Newland 2016).

Consequences of Clinical Manifestations of ITP

Bleeding

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). 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).

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 x 10^9/L
- In a study of newly diagnosed ITP patients, platelet counts < 20 x 10^9/L and < 10 x 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)
- Newly diagnosed
- Previous minor bleeding (Neunert 2015; Arnold 2015)

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 2018

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]

Thrombotic events

A diagnosis of ITP places the patient paradoxically 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
- 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)

[See Module 4 for more detailed information on thrombotic events.]

Reduced health-related quality of life

Both disease- and treatment-related factors can affect health-related quality of life (HRQoL). Most notably, fatigue, which is related to thrombocytopenia, is a primary contributor to a reduced HRQoL. HRQoL may also be affected by psychosocial factors including feelings of social isolation, depression, and the fear of bleeding and disease progression (Kuter 2021). The decline in HRQoL results in impaired physical and mental health, and low levels of emotional well-being (Mannering 2024).

Treatment of ITP improves the patient's HRQoL, including fatigue, with thrombopoietin receptor agonists (TOP-RA) probably having a greater degree of effect (Kuter 2021).

[See Module 4 for more detailed information on fatigue and quality of life.]

Future Perspectives

There is a need for more extensive research to be conducted to identify prognostic biomarkers to better diagnose ITP, forecast how ITP might progress, predict prognosis, and estimate the effectiveness of treatment. Also, larger, controlled clinical studies are needed to help define a possible relationship between platelet function and risk of bleeding.

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 (< 10 cm); bleeding from mucous membranes; epistaxis (< 1 h duration); subconjunctival hemorrhages; vaginal bleeding (< 2 pads/day required)
2 (no transfusion required)	Hematomas, ecchymosis (> 10 cm); epistaxis (> 1 h 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

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Summary Points

- Splenectomy used to be the main treatment for ITP and 2/3 of patients achieve initial remission with the procedure when performed early in the course of disease
- Because of the risks involved with splenectomy (higher risk of thrombosis, and infections), the high risk of ITP relapse a couple of years after surgery, and patient non-acceptance of the procedure, splenectomy is no longer widely used
- There is a discrepancy between the platelet count and the propensity to bleed, so 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 underlining the importance of identifying individualized treatments
- Thrombocytopenia develops in 5% to 10% of women during pregnancy or in the immediate post-partum period, however 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. When to start treatment
    2. Initial treatment of newly diagnosed patients
    3. Subsequent treatment
    4. Treatment of patients failing multiple therapies
    5. Management of acute bleeding
C. ITP in Special Populations
    1. Management in elderly patients
        i. Recommended ITP management
        ii. Management of bleeding
    2. Management in pregnancy
D. Nursing Implications of Agents Commonly used in Managing ITP
E. Future Perspectives

References

Introduction

Goals and aims of treatment

Most adults with immune thrombocytopenia (ITP) tend to have an event-free course, but those with more severe thrombocytopenia usually require treatment (Lo 2014). Treatment options have widened as new molecules receive regulatory approval based on favorable clinical trial results. Splenectomy, which was once the initial treatment for ITP, is now recommended only after failure of medical therapies and is used depending on patient age and comorbidities.

Treatment choices for ITP should be individualized and are affected by patient- and disease-related factors such as:

- Therapy tolerance
- Activity and lifestyle
- Comorbid conditions, especially those predisposing to bleeding
- Patient age
- Patient expectations, level of anxiety
- Extent of bleeding
- Need for upcoming procedures
- Level of fatigue
- Known treatment side effects (Provan 2019; Neunert 2019).

Situational factors affecting treatment choice include:

- Accessibility of care
- Cost of treatment
- Financial resources of the patient
- Financial resources of the publicly funded healthcare system
- National licensing and availability of a treatment
- Country-specific treatment guidelines (Provan 2019).

Table 1: Principles of ITP Treatment

Principle	Practical Considerations
Decide when treatment is needed and when it can safely be withheld	Observation alone is generally 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 may be 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)
Resolve bleeding events/prevent severe bleeding by providing adequate hemostasis	Treatment should maintain a target platelet level > 20-30 x 10^9/L (at least for symptomatic patients)

IVIg, intravenous immunoglobulin; TPO-RA, thrombopoietin receptor agonists
Sources: Provan 2021; Neunert 2019; Arnold 2015

Table 2: Goals of ITP Treatment according to Phase of Disease

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	Maintain safe platelet counts
Unresponsive, severe refractory disease (after splenectomy or after several lines of treatment)	Minimize the risk of bleeding and treatment-related toxicity; an increased platelet count is not the main goal

Adapted from: Rodeghiero 2014

Treatment Strategies

When to treat

The decision to further observe any clinical manifestations of ITP in a patient or administer treatment is highly complex and varies based on comorbidities, medications, and age, all of which affect the risk of bleeding (Kuter 2021). Although bleeding risk is rarely related to a distinct platelet count, bleeding risk tends to increase when platelets are < 20 x 10^9/L. Therefore, according to updated international consensus treatment guidelines, treatment is rarely indicated in patients with platelet counts > 20 x 10^9 /L in the absence of bleeding and treatment should be aimed to attain a minimum platelet count of 20 to 30 x 10^9/L (Provan 2019). Treatment with corticosteroids may be appropriate, however, in those with comorbidities, taking anticoagulant or antiplatelet medication, with upcoming procedures, and for elderly patients (> 60 years).

First-line treatment for newly diagnosed patients

There is emerging data suggesting that first-line therapy may increase response rate and potentially reduce the evolution to chronic-phase ITP (Kuter 2021). Standard first-line treatment for ITP generally includes single or combination treatment with corticosteroids (prednisone, dexamethasone) and/or intravenous immunoglobulin (IVIg) (Neuert 2019; Provan 2019). The American Society of Hematology (ASH) suggests corticosteroids in adults with newly diagnosed ITP and a platelet count of < 30 x 10^9 /L who are asymptomatic or have minor mucocutaneous bleeding (Neunert 2019). Observation is suggested in newly diagnosed patients with a platelet count of ≥ 30 x 10^9 /L who are asymptomatic or have minor mucocutaneous bleeding (Neunert 2019).

Corticosteroids prevent the destruction of platelets by macrophages within the spleen and liver thereby increasing platelet levels.

In newly diagnosed patients who require treatment, predniso(lo)ne is the recommended initial treatment (Provan 2019) (**Table 3**). 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)

If a response to treatment is seen (e.g., platelets > 50 x 10^9/L) the predniso(lo)ne should be tapered, aiming to stop predniso(lo)ne by 6 weeks (maximum 8 weeks), even if the platelet count drops during the taper (Provan 2019). Longer administration of steroids should be avoided. In patients who are unable to take high-dose corticosteroid therapy (i.e., patients who are insulin dependent or those with uncontrolled diabetes, or with psychiatric disorders or active infection), monotherapy with IVIg may be appropriate.

Subsequent treatment

Subsequent, or second-line, treatment is used if a patient fails to respond or maintain an adequate platelet count 6 to 8 weeks after corticosteroids have been tapered (**Figure 1**). The goal of subsequent treatment is to establish a durable platelet response and minimize bleeding events with a safe, tolerable and convenient longer-term treatment (Cuker 2018). Drugs used in subsequent treatment with the most clinical trial and real-world data are rituximab and TPO-RA agonists. However, there are many medical therapy options with few adverse events available as subsequent treatment (Provan 2019). Not all of these treatments are available in all countries and treatment recommendations should be modified based on available agents and patient preference.

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

Agent	Suggested dose and schedule
Predniso(lo)ne	1 mg/kg/day orally (max dose 80 mg) for 2 – 3 weeks, taper dose over 6 – 8 weeks (Provan 2019) or 0.5 to 2.0 mg/kg/day (Neunert 2019)
OR	
Dexamethasone	40 mg orally daily for 4 days, 4–6 cycles every 14–28 days
AND	
Immunoglobulins (IVIg)[1]	1 g/kg/day i.v. for 1 or 2 consecutive days; may be repeated

i.v., intravenous
[1] May be appropriate in patients with bleeding/at high risk for bleeding, requiring surgical procedure, or are unresponsive to predniso(lo)ne
Sources: Provan 2019; Neunert 2019)

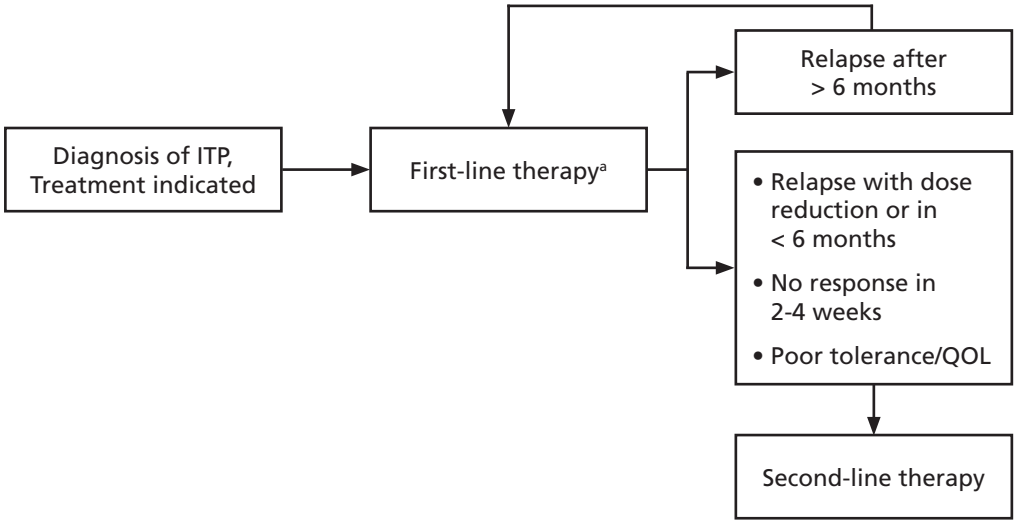

Figure 1: Selection of patients for second-line treatment. QoL, quality of life. [a]Corticosteroids are standard first-line therapy and may be combined with IVIg if a more rapid platelet response is required. IVIg can be used as first-line treatment if corticosteroids are contraindicated. Second-line therapy may be considered if relapse occurs after tapering steroids for 6 to 8 weeks.
Adapted from: Cuker 2018.

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

Thrombopoietin-receptor agonists (TPO-RA)

The TPO-RAs are the most commonly used second-line treatments and have markedly changed the approach to treating ITP. Clinical trials have shown response rates as high as 93%, often starting in 7 to 14 days of treatment, minimal side effects, a sustained length of effect, and improved HRQoL. TPO-RA agents administered at an early stage of disease may induce rapid responses (Newland 2016) and clinical data shows that the TPO-RA agents are as effective in early ITP (< 1 year duration) as they are in chronic ITP (≥ 1 year duration) (Kuter 2021).
TPO-RA agents stimulate megakaryocyte proliferation and platelet production. Three products are available and currently approved: romiplostim, eltrombopag and avatrombopag. Switching 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. In up to a third of patients, the TPO-RA agonist can be discontinued, and patients remain in remission (treatment-free remission) with safe or normal platelet counts off therapy (Mahevas 2016; Newland 2016).

- Romiplostim is given as a weekly subcutaneous injection
- Eltrombopag is taken orally as a tablet but with dietary restriction, whereby milk, bread and other calcium-containing food must be avoided for at least 2 hours before and 4 hours after taking a dose
- Avatrombopag is taken orally as a tablet and has no dietary restrictions

Anti CD20 monoclonal antibody

- Rituximab induces a 40% to 60% complete response rate after a single course and a 55% to 75% overall response rate (Cuker 2015).
- A meta-analysis of 5 trials showed that complete responses were more likely with rituximab than with standard of care and that rituximab can improve platelet count response at 6 months (Chugh 2015).

Immunosuppressive agents

- Mycophenolate mofetil (MMF), an antiproliferative immunosuppressant, has been used in patients failing other therapies.

In the past, splenectomy has been the most commonly used second-line therapy. Current practice guidelines recommend consideration of splenectomy after 12 to 24 months of medical treatment (Provan 2019; Neunert 2019). Complications and high risk of relapse following splenectomy have led to fewer procedures being performed. Splenectomized patients require lifelong management to prevent life-threatening sepsis (e.g., vaccinations and prophylactic antibiotics) and thrombosis as well as surveillance for disease relapse (**Tables 4 and 5**). Splenectomy is now considered as last resort therapy. A platelet sequestration radioisotope scan is recommended to assess the likelihood of response before proceeding to splenectomy.

Table 4: Suggested Doses and Administration Schedules of Agents Recommended as Subsequent Treatment		
Agent	**Dose/Schedule**	**Time to response**
TPO-RA • Eltrombopag • Romiplostim • Avatrombopag	Eltrombopag daily tablets (25–75 mg) Romiplostim 1–10 mcg/kg/The minimum dose necessary to maintain a target platelet count/prevent bleeding should be used Avatrombopag tablets taken weekly or daily, up to 40 mg daily.	1 to 4 weeks
Anti-CD20 Antibody • Rituximab	100 mg to 375 mg/m^2/week over 4 consecutive weekly infusions Efficacy may be affected by age, sex and duration of ITP	Approximately 2 months
Mycophenolate mofetil (MMF)*	500 mg – 1g twice daily	Approx. 4 to 6 weeks
Tyrosine kinase inhibitor • Fostamatinib	100 mg twice daily increasing to 150 mg twice daily after 4 weeks depending on tolerability (should not exceed 300 mg/day)	2 to 8 weeks
*Not widely approved for use in ITP; use and doses based on individual treatment center practices Sources: Cuker 2018; Cooper 2017; Lakshmanan 2012		

Table 5: Advantages and Disadvantages of Second-line Treatment Options		
Treatment	**Advantages**	**Disadvantages**
Splenectomy	Cost-effective; Long-term safety data available No long-term medical ITP treatment needed	Risks of surgery/anesthesia; Difficult to predict response; not curative Increased risk of infection and venous thromboembolism; Requires long-term prophylactic antibiotics and monitoring; Possible increased risk of malignancy. High risk of ITP relapse
Mycophenolate mofetil (MMF)*	Good efficacy; Cost effective but more side effects; 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) Can cause bone marrow dysplasia
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 • Avatrombopag	High response rates; Generally well tolerated; Not immunosuppressive Avatrombopag – oral formulation; no dietary restriction; can be used in liver disease	Need for longer term treatment and monitoring; Risk of bone marrow fibrosis, thrombosis; not to be used in pregnancy 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
Tyrosine kinase inhibitor • Fostamatinib		Side effects include diarrhea and hypertension
SC, subcutaneous; TPO-RA, thrombopoietin receptor agonists Sources: Bradbury 2021; Abdelwahab 2024; Cuker 2015; Cooper 2017		

Treatment of refractory and chronic ITP

Many adult patients relapse after the discontinuation of steroid treatment and other patients fail to achieve a response in platelet count to multiple treatments and are then at risk of bleeding. Chronic ITP generally refers to patients with ITP lasting for more than 12 months (Cooper 2017). There are no current studies that address the correct sequence of subsequent medical therapies for refractory and chronic ITP.

Few factors have been identified as associated with refractoriness to ITP treatments with a strong level of evidence (**Figure 1**). However, it should be noted that 1) ITP is a rare disease, and 2) refractory disease in ITP occurs rarely. This situation poses challenges in that there are a low number of patients available for clinical trials limiting the power of a study to detect a meaningful treatment effect, and small study populations limit the ability to randomize or stratify trials.

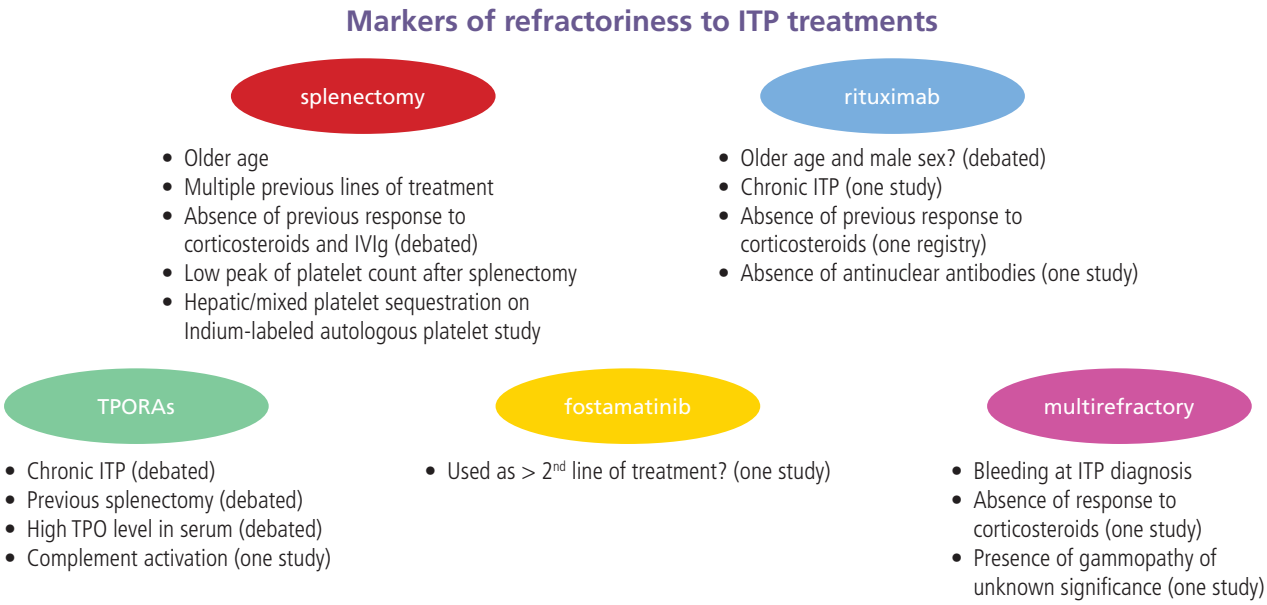

Figure 1. Evidence-based markers of refractoriness to treatments for refractory ITP.
TPO, thrombopoietin, TPO-RA, thrombopoietin receptor agonist.
Source: Moulis 2023

It is important to reassess/reconfirm the diagnosis of ITP and exclude non-autoimmune causes of thrombocytopenia before initiating treatment in patients whose disease has not responded to multiple therapies (Cuker 2016). Observation without treatment in most asymptomatic patients with a platelet count of ≥ 20 to 30 x 10^9/L may be appropriate depending on individual patient circumstances including lifestyle (**Figure 2**).

Treatment for these patients 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 are significant in patients with ITP that is refractory to treatment (Mahevas 2016). Improvement of ITP may occur at any time, but who will improve and when is unpredictable (Provan 2019).

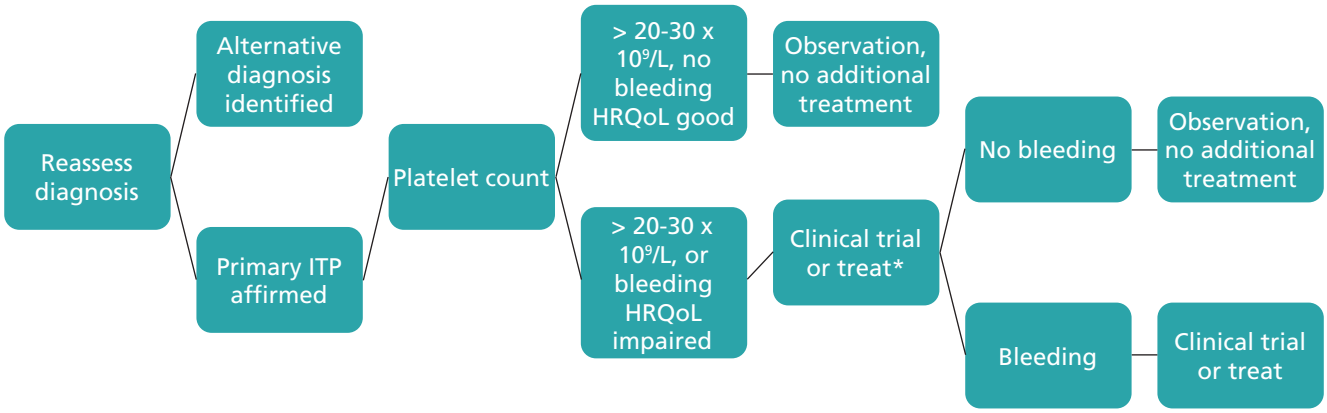

Figure 2: Proposed management of refractory ITP in adults. Adapted from: Cuker 2016

There are several approaches to managing patients with refractory or chronic ITP:

- Administration once (or for only 1 course) intended to induce a long-term response (rituximab, splenectomy)
- Continued or chronic administration of an agent (low-dose corticosteroids, immunosuppressive agents, TPO-RAs)
- Combination treatment such as
  - Immunosuppressive treatment + TPO-RA has shown great promise (Mahevas 2016)
  - Other treatment options include additional immunosuppressive agents such as cyclophosphamide, rapamycin sirolimus, and anti-TNF agents
  - Intermittent use of IVIg and steroids for acute episodes
  - Novel agents such as fostamatinib, BTK inhibitors, FcRn inhibitors, anti-plasma cell inhibitors (Cooper 2017)
  - Older agents (e.g. azathioprine, dapsone) (**Table 6**)

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) or low-grade lymphoproliferative disease

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 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,

Table 6: 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
Avatrombopag	20 mg weekly up to 40 mg daily	1 to 2
MMF	250-100 mg orally daily	4 to 6
Fostamatininb	100 -150 mg twice a day	1 to 6

i.v., intravenously; SC, subcutaneously; [a] Patients already taking intermediate or high doses of prednisone
Source: Cuker 2016

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 and are mainly based on bleeding symptoms and platelet count, although other factors to consider include disease duration, other medications, comorbidities, expected tolerance, accessibility of care, HRQoL, and patient expectations. 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

Second -line or subsequent 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 (deferred for at least 12 months and/or as a last treatment option)
- possibly fostamatinib after accumulation of more clinical data in this population (Crickx 2023)

Real-life data seem to support the use of TPO-RAs in older patients, reporting good efficacy and safety (Palandri 2021). However, in this study there was a considerable risk of thrombosis and authors encourage a careful assessment of risk-benefit balance between thrombotic and bleeding events before initiating TPO-RA therapy.

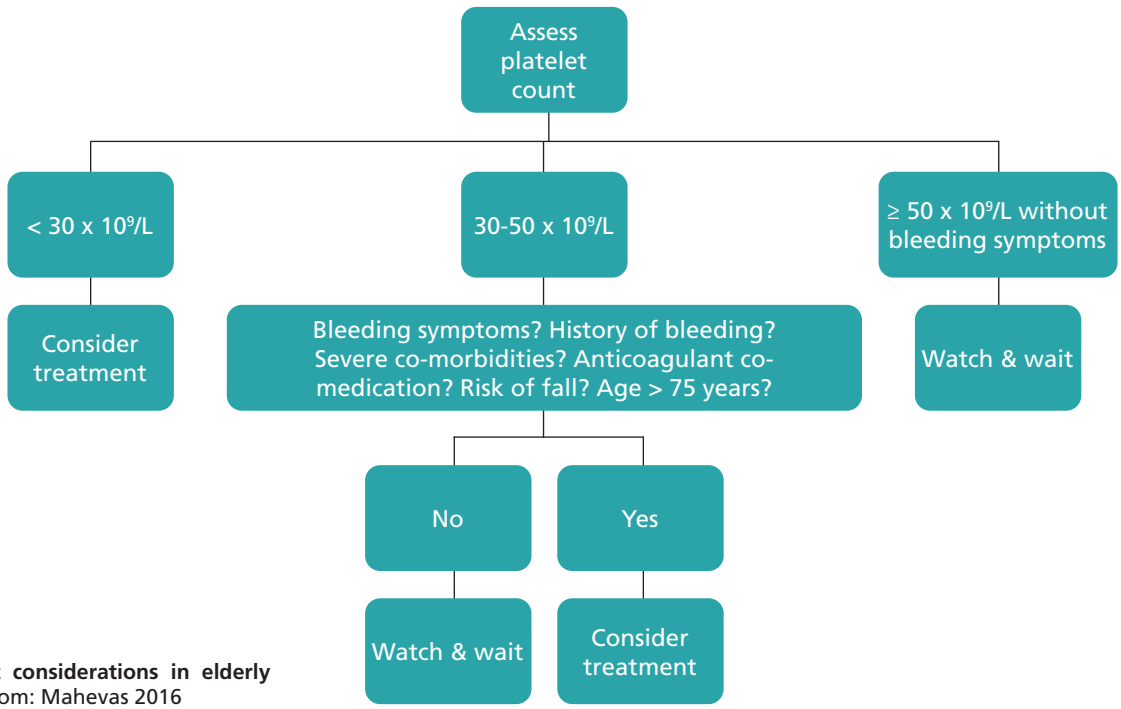

Figure 3: Treatment considerations in elderly patients. Adapted from: Mahevas 2016

Management 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 in older patients (Mahevas 2016). Drugs interfering with hemostasis should be stopped immediately.

- Vinblastine (not more than 10 mg) could be added in case of severe bleeding
- Off-label use of high dose TPO-RAs as salvage therapy (Crickx 2023)

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.

- Counseling for women with ITP wishing to become pregnant is recommended
- 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 recommend maintaining a platelet count between 20 and 30 x 10^9/L in a nonbleeding patient is safe for most of the pregnancy (**Table 7**). A platelet count > 50 x 10^9/L late in the third trimester is recommended and a count ≥ 50 x 10^9/L is preferred for delivery (Provan 2019).

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).

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).

Table 7: Recommended Treatments for ITP during Pregnancy

First-line treatment	Second-line treatment	Treatments to avoid
Corticosteroids Low-dose corticosteroids: prednisone 20 mg/day, adjusted to minimum dose necessary; taper after delivery	Combine initial treatments or add agents (i.e., high-dose methylprednisolone(lo)ne + IVIg or azathioprine); Cyclosporin A + azathioprine; Rituximab. Splenectomy in rare cases, performed in second trimester	Immunosuppressive agents such as MMF, vinca alkaloids. TPO-RAs in exceptional circumstances and only in third trimester near delivery
IVIg		
IV anti-D in Rh(D) +, nonsplenectomized women		

Source: Provan 2019

Nursing Implications of Agents Commonly used in Treating ITP

Corticosteroids are known to cause various – sometimes serious – side effects that may limit their use (**Table 8**).

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

Table 8: 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
Source: Faiman 2008

To ensure drug bioavailability, which affects the effectiveness of drug therapy, agents used to manage ITP should be administered in the correct dose, by the prescribed delivery method while paying attention to precautions in terms of possible food and drug interactions. **Table 9** describes precautions to be taken when administering agents commonly used in ITP management; however, drug labelling and consultation with a pharmacist should be considered to ensure safe and effective drug delivery.

Table 9: Nursing Implications in the Administration of ITP Treatments

Drug	Implications
Rituximab (Anti-CD20)	Severe infusion reactions can occur: premedicate patients with an antihistamine and acetaminophen prior to administration; 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
Eltrombopag (oral administration)	Administer on empty stomach, 1 hour before or 2 hours after eating; dairy products may decrease absorption; Reduce dose in Asian populations; potential drug interactions (i.e., cholesterol-lowering statins) Warning: may increase risk of severe hepatotoxicity
Avatrombopag (oral tablet)	Administer with food; potential drug interactions
Romiplostim (sc administration)	Titrate weekly per label

Table 9: Nursing Implications in the Administration of ITP Treatments	
Drug	**Implications**
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-splenectomized; 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
Fostamatinib (oral administration)	May be taken with/without food; concomitant administration with strong CYP 3A4 may increase exposure
sc. subcutaneous Sources: Boral 2016; Catala-Lopez 2015; Khan 2017; Marangon 2017; Matzdorff 2018	

Future Perspectives

Several novel therapies are being studied for the management of ITP including. BTK inhibitors, anti B and combined anti-plasma cell inhibitors.

Anti-D monoclonal antibody (no licence in UK or Europe)

Anti-D has been used as first-line management of ITP. The efficacy is related to an immune-related process to clear anti-D coated erythrocytes, which prevents the reticuloendothelial system from destructing antibody-coated platelets. Rozrolimupab is a recombinant anti-D monoclonal antibody currently being evaluated in clinical trials. Anti-D is not available in all countries.

T-cell targeting therapies

The mechanism of action of anti-CD 154 and anti-CD40 agents is the disruption of activation pathways between T cells and antigen-presenting cells, T helper cells and B cells.

Bruton tyrosine kinase inhibitors (BTK)

BTK mediates the development, proliferation, apoptosis and antibody production of B cells. It also mediates the activation of macrophages and regulates phagocytosis. Rilzabrutinib is an oral, reversible small molecule selective BTK inhibitor exhibiting potential as treatment for ITP. It has shown to be safe and well tolerated in phase 1 trials.

Rilzabrutinib clinical studies are ongoing. Orelabrutinib, a highly selective BTK inhibitor, is being evaluated in trials for refractory ITP.

Bortezomib is a proteasome inhibitor shown in preclinical study to improve thrombocytopenia in ITP. It has also shown effectiveness in treating relapsed ITP (Song 2021)

Given the potential impact of BTK inhibition on autoantibody production and phagocyte-mediated platelet destruction, as well as a convenient oral route of administration, BTK is a potentially promising new target in the treatment of ITP. The main concern regarding use of ibrutinib and other currently approved BTK inhibitors for the treatment of ITP is inhibition of platelet function.

There is clinical research being undertaken to evaluate novel therapies for the medical treatment of refractory ITP. Novel agents being evaluated include:

Plasma cell depletion via targeting CD38

B-cell targeted therapies do not target the non-dividing, long-lived plasma cells in the bone marrow and spleen that chronically produce platelet autoantibodies in ITP. Therefore, agents depleting these cells (i.e., rituximab) are of interest and represent a novel treatment target. Depletion of long-lived platelet autoantibody-producing plasma cells may allow for treatment responses in patients with otherwise refractory ITP (Al-Samkari 2023). Other CD38 targeting agents currently in clinical trials for use in ITP treatment include daratumumab and mezagitamab.

Complement inhibition

Agents that target the complement system to reduce platelet destruction are being evaluated in patients with refractory ITP. These include sutimlimab and iptacopan.

Novel agent to increase thrombopoiesis

New TRO-RA agents are in clinical studies or in the pipeline. Amifostine a thiophosphate prodrug, is being investigated in combination with rituximab as management for refractory ITP.

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Summary Points

- 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 for Patients and Families

D. Providing Support to Patients : Health-related Quality of Life Considerations

References

Comprehensive Management of the patient with ITP

ITP is associated with physical as well as psychosocial stress for those who are affected by the disorder. The impact of ITP, especially fatigue, is substantial, yet often underrecognized. ITP can impair health-related quality of life (HRQoL) across the emotional, functional, reproductive, and health domains, and impacts activities of daily living (Provan 2019).

Two key roles of nurses and other healthcare professionals in regard to managing and supporting 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.

Although it is generally acknowledged that there is no "magic" platelet count that differentiates the risk of bleeding from no risk, patients with a count < 20 x 10^9/L are considered at risk of bleeding. Life-threatening bleeding can occur even if the platelet count is < 30 x 10^9/L in sites such as:

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

There is a lack of clinical evidence on treatments aimed at urgently increasing platelet counts in patients requiring urgent surgery, those at high risk for bleeding, or those with active central nervous system, gastrointestinal, or genitourinary bleeding. (Provan 2019). However, patients presenting with severe bleeding manifestations, particularly if the platelet count is ≤ 20 x 10^9/L require initiation of immediate treatment (**Box 1**).

Box 1. Recommendations for treating and managing life-threatening bleeding:
Combination treatment such as corticosteroids (500 mg to 1 g/day x 3) i.v. + IVIg 1 g/kg on days 1 ± 2 (Arnold 2015)
Platelet transfusions in the presence of life-threatening bleeding, with or without IVIg (Provan 2019; Boral 2016)
Consideration of a TPO-RA if no significant response to IVIg and platelet transfusion in patients currently on corticosteroids (Provan 2019)
Other treatments: anti-D, vincristine or vinblastine, antifibrinolytics in combination with other initial therapies (Provan 2019)
Hormonal therapy in the presence of significant vaginal hemorrhage (Cooper 2017)

Other general measures to treat bleeding include discontinuation of drugs known to reduce platelet function, control of blood pressure, inhibition of menses and efforts to minimize trauma.

Management of Treatment Side Effects

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 can lead to significant side effects that may outweigh any benefit, and an absence of evidence of demonstrated increased benefits with longer courses of corticosteroids, ASH favors a short course of corticosteroids (≤ 6 weeks) over longer courses (Neunert 2019) (**Table 1**). The ASH guidelines also recommend routine monitoring for potential corticosteroid side effect regardless of the duration or type of corticosteroid administered. Corticosteroid dose should be tapered rather than discontinued. [See Module 3, Table 8 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, assess impact on mental health on HRQoL; morning vs evening administration of corticosteroids, dose reduction
Osteoporosis, fractures	Bone loss most pronounced in regions such as the lumbar spine, also risk of increased hip fractures	Educate patient on risk of fractures; recommend balanced diet, regular exercise maintenance of weight within recommended range; fall risk assessment in elderly; daily calcium intake 1200-2000 mg + vitamin D supplements 800-1000 IU/day (Laurent 2022)
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, H_2 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, steroids-induced diabetes	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 and wounds with sterile water
Adrenal suppression	Symptoms may be first detected following physiological stress	Be alert to onset of symptoms following illness, surgery or injury or secondary to dose reduction (withdrawal symptoms)
Cardiovascular disease Dyslipidemia	Greater risk with doses ≥ 7.5mg/day	Assess cardiovascular risk factors; regular monitoring of lipid levels

NSAID, non-steroidal anti-inflammatory drugs
Sources: Faiman 2008; Liu 2013; Winkeljohn 2013; Laurent 2022

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 aid in reducing side effects.

Tables 2,3 and 4 provide interventions to manage side effects of agents commonly used to manage ITP.

Table 2: Management of Common Side Effects of Rituximab	
Side Effect	**Management**
Infusion reactions – potentially life-threatening (allergic/anaphylactic reactions; fever, chills, skin rash, urticaria, angioedema, hypotension, ARDS)	Reactions can occur during (especially first infusion) or after administration. Pre-medication with antihistamine and antipyretic 30 minutes prior to administration; adequate hydration; monitor electrolytes and renal function. Inform patient to immediately report any symptoms characteristic of an infusion reaction.
Hypogammaglobinemia	Occurs with multiple courses; Monitor serum immunoglobulin levels before and periodically after rituximab administration
Infection	Patients who are carriers of hepatitis B will need anti-viral therapy and close monitoring; Check hepatitis B and C markers before rituximab including hepatitis B core antibody; suggested vaccination against seasonal flu, Streptococcus pneumoniae, Haemophilus influenzae 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

ARDS, acute respiratory distress syndrome
Source: Cuker 2018; Hanif 2024

Table 3: Management of Common Side Effects of Thrombopoietin Agonists (TPO-RA)	
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
Renal impairment	Monitor renal function; encourage hydration
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
Romiplostim (subcutaneous injection)	risk of thrombotic/thromboembolic complications; Inform patient of headache as common side effect, arthralgias possible
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
Avatrombopag (oral tablet) Fever, fatigue, headache, joint pain, cold symptoms, nausea, swelling in hands & feet	Educate patient/caregiver of possible side effects and discuss self-care measures such as taking acetaminophen, hydration, rest periods; elevate feet/legs, notify HCP is swelling increases or becomes severe or associated with localized pain
Recurrence of thrombocytopenia/ bleeding after treatment completion	Closely monitor for decrease in platelet count, bleeding; discontinue anticoagulants

Table 3: Management of Common Side Effects of Thrombopoietin Agonists (TPO-RA)	
Side Effect	**Management**
All TPO-RAs	
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
	Avoid aspirin/NSAIDS as these can interfere with platelet function

ALT, alanine aminotransferase; HCP, healthcare professional; NSAIDS, non-steroidal anti-inflammatory drugs
Sources: Bussel 2009; Khan 2017; Wong 2017
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
Avatrombopag Summary of Product Characteristics. https://www.ema.europa.eu/en/documents/product-information/doptelet-epar-product-information_en.pdf

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
Fostamatinib	Hypertension; hepatotoxicity; neutropenia	Monitor BP weekly; monitor LFTs; education on risk of diarrhea and self-care measures (dietary changes, hydration, antidiarrheal medications); educate patient on signs/symptoms of infection and preventative measures
Azathioprine	Weakness, sweating, transaminase elevations (generally low/mild incidence); neutropenia, pancreatitis	Monitor for signs/symptoms of infection; instruct patient on measures to prevent and recognize symptoms of infection; monitor neutrophil count; monitor liver enzyme levels
Cyclosporine A	Increase in serum creatinine, hypertension, fatigue, paresthesia, 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 on measures to prevent and recognize symptoms of 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)	Check status of G6PD before starting. Caution in administering to patients from Mediterranean countries (Africans)
Hydroxychloroquine*	Multiple effects on immune system	Monitor for signs/symptoms of infection; instruct patient on measures to prevent and recognize symptoms of infection

Table 4: Management of Common Side Effects of Other Agents used to Treat ITP		
Agent	**Side Effects**	**Management**
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 severe 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 on measures to prevent and recognize symptoms of infection; monitor neutrophil count

*Not widely approved for use in ITP; use and doses based on individual treatment center practices
LFTs, liver function tests
Sources: Boral 2016; Khan 2017; Marangon 2017; Catala-Lopez 2015; Matzdorff 2018

Providing Education for 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 to maintain or improve their HRQoL (**Table 5**).

The list of educational measures to support patients living with ITP is long. Individualized support is best provided when nurses and other healthcare professionals are aware of patient/family expectations, and cultural, social, developmental, and behavioral issues that can affect patients. Collaboration between nursing, medical, and psychosocial healthcare professionals is essential to providing optimal care.

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, walking or another activity the patient enjoys 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

Source: Winkeljohn 2013

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

ITP affects not only the physical state of the patient, but also 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]. Several tools to assess HRQoL are available and include the ITP-PAQ (Kuter 2012), EQ-5D index score (Sanz 2011), and the SF-36 FACIT-Fatigue tool (Khelif 2019).

A healthy lifestyle is important for everyone and being healthy means not only eating healthy foods and being active, but it also means getting enough sleep, managing stress, keeping mind and body fit, and engaging socially. Encourage the patient to assume responsibility for their own health status by taking medications as prescribed, eating a healthy diet, and taking measures to avoid infections and conserve energy for enjoyable activities (**Table 6**).

Table 6: Recommendations to help Patients to Live Better with ITP

Topic	Recommendation
Stress reduction	Work with the patient to identify stress-causing events and actions that may help to reduce stress in their daily life (i.e., physical exercise, engaging in social activities, identifying and pursuing activities that bring them joy, deep breathing relaxation techniques, listening to relaxing audio tapes, talking with a counselor)
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

Source: Winkeljohn 2013; Provan 2019

Impaired HRQoL in patients with ITP is multifactorial and includes, but is not limited to, issues around actual bleeding, fear of bleeding, reduced energy/fatigue, depression, treatment side effects, and the additive influences of underlying or comorbid diseases. As might be expected, HRQoL tends to improve when there is a response to treatment, which is especially true following TPO-RA administration (**Table 7**). (Provan 2019).

Table 7: 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 2018

Table 8: Suggested Platelet Counts for Medical Procedures*	
Procedure	**Platelet Count**
Dental prophylaxis (descaling/ deep cleaning)	> 20 to 30 x 10^9/L
Tooth extraction (simple)	> 30 x 10^9/L
Tooth extraction (complex)	≥ 50 x 10^9/L
Minor surgery	≥ 50 x 10^9/L
Major surgery	≥ 80 x 10^9/L
*Target platelet count depends on the clinical situation and urgency and need for procedure Sources: Boral 2016; Matzdorff 2018; Provan 2019	

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Summary Points

- 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
- The dilemma encountered when treating children is the variation in bleeding tendency among patients despite similarly low platelet counts
- A wait and watch approach is 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

A. Introduction
B. Pathophysiology and Incidence
C. Clinical Presentation
D. Diagnosis
E. Treatment
    1. First-line treatment
    2. Subsequent treatment
    3. Management of bleeding
F. Management of Treatment Side Effects
    1. Management of common side effects of corticosteroids
    2. Management of common side effects of other treatment agents
G. Health-related Quality of Life
H. Future Perspectives

References

Introduction

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.

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

Clinical Presentation

ITP in young children usually presents with acute bleeding symptoms (Matzdorff 2018). Less commonly, bruising and purpura develop slowly over weeks or months, suggesting a chronic evolution. It is important to exclude other common disorders that may resemble ITP.

- 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).

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).

Older children and those with slowly developing ITP may be more likely to develop chronic disease (Provan 2019). For children diagnosed with ITP who show no improvement in platelet count after 3 to 6 months and still require treatment, subsequent evaluation may be necessary.

Recommendations for the clinical classification of ITP in children:

- Clinical classification should be based on disease severity, including degree of bleeding, platelet count, comorbidities and their treatment, and impact of ITP or its therapies on the patient's and family's HRQoL.
- Management should be considered based on clinical classification (Provan 2019).

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 and are considered more important in the treatment decision-making process than just platelet count.

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

Bleeding scores for pediatric patients should be used to assess the severity of ITP; scores often indicate that children do not have serious bleeding problems, despite low platelet counts (**Table 1**).

Table 1. Bleeding Scale for Pediatric Patients with ITP		
Grade	**Bleeding**	**Management approach**
Grade 1 (minor)	Minor bleeding, few petechiae ≤ 100 total) and/or ≤ 5 small bruises (≤ 3 cm in diameter), no mucosal bleeding	Consent for observation
Grade 2 (mild)	Mild bleeding, many petechiae (> 100 total) and/or > 5 large bruises (> 3 cm in diameter), no mucosal bleeding	Consent for observation
Grade 3 (moderate)	Moderate bleeding, overt mucosal bleeding, troublesome lifestyle	Intervention to reach grade 1 or 2
Grade 4 (severe)	Severe bleeding, mucosal bleeding leading to decrease in Hb > 2 g/dL or suspected internal hemorrhage	Intervention
Hb, hemoglobin Source: Provan 2019		

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

First-line Treatment

Most children with newly diagnosed ITP do not have significant bleeding symptoms or other risk factors and may be managed according to the attending hematologist and the family's preferences; most likely, the platelet count will often reach safe levels within a few days. Most often, the child is observed rather than given active treatment of any type, including corticosteroids. A large number of children can be managed without ITP therapy and without experiencing increased rates of severe bleeding. Increased bleeding severity and several other risk factors may become reasons to initiate therapy.

When to initiate treatment in newly diagnosed children:

- Most children can be managed with watchful waiting
- Any severe (grade 4) bleeding requires immediate hospital adminssion and treatment to increase platelet levels until bleeding has decreased
- Moderate (grade 3) bleeding requires hospital review and consideration for admission and therapy

Treatment and hospitalization are recommended when:

- Bleeding worsens or with significant comorbidities
- Risk of intracranial hemorrhage
- Change in behavior or mood consistent with significant depression or irritability
- Parents are anxious about bleeding and do not believe they can control/restrict the child's activities
- Parents are not reliable to bring the child for medical attention
- Child requires anticoagulant or antiplatelet treatment
- There is a greater risk of bleeding due to another medical or psychological issue

Newly diagnosed children and adolescents with moderate (grade 3) bleeding are at higher risk for subsequent grade 4 bleeding and should be considered for early intervention until bleeding has decreased. Children with grade 4 bleeding should be hospitalized and treated immediately (Provan 2019).

The ASH treatment recommendations for children do recommend a short course of corticosteroids (< 7 days) for newly diagnosed children who have non-life-threatening bleeding but are experiencing a diminished HRQoL (Neunert 2019).

Recommendations for initial treatment if required:

IVIg (single dose of 0.8 to 1.0 g/kg), anti-D (single dose 75 µg/g). A second dose of IVIg or anti-D may be given if initial response is suboptimal

Predniso(lo)ne at 4 mg/kg/day in 3 or 4 divided doses for 4 days with no taper, maximum daily dose of 200 mg. Taper predniso(lo)ne if there is an increase in platelets.

If no response within 2 weeks, taper predniso(lo)ne rapidly over 1 week and discontinue (Provan 2019).

Subsequent Treatment

Most children can be managed with watchful waiting. Factors identified by physicians as important when subsequent 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)

Options for subsequent treatment in children include:

- Rescue therapy with corticosteroids, IVIg, and/or anti-D can be used in children being observed to treat acute bleeding episodes if/when they occur
- Children with frequent or severe bleeding episodes or impaired HRQoL should be referred to a pediatric hematologist
- Thrombopoietin receptor agonists (TPO-RAs)[1]; if there is no response to 1 TPO-RA or there is a response that is lost, switch to an alternative TPO-RA[1] and/or consider combining with MMF or another immunosuppressant
- In patients who fail TPO-RAs, especially adolescent females, rituximab[1] and dexamethasone should be considered ([1]Neunert 2019; Provan 2019)

Management 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).

The goal of treatment for emergency bleeding is to increase the platelet count as immediately as possible to minimize or eliminate severe bleeding and continue with platelet count maintenance until bleeding has stopped (**Box 1**).

Box 1. Recommendations for emergency treatment in children at any stage of ITP
Combination therapy, including platelet transfusion, corticosteroids i.v., and IVIg, with or without anti-D (if available). Administer platelet transfusions as a bolus, followed by continuous infusion in combination with high dose i.v. steroids
IVIg, steroids, anti-D can be used to ensure the fastest and most reliable platelet increase
In the presence of intracranial hemorrhage, emergency splenectomy and/or neurosurgical control of bleeding should be considered in conjunction with emergency platelet-increasing therapy
TPO-RAs should be considered; may help acute response in patients and prevent a decrease in platelet count if initial response to emergency intervention is lost
Source: Provan 2019

Management of Treatment Side Effects

Table 2: 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

The nursing management of common side effects of TPO-RAs is presented in Table 3 of Module 4, and the management of other agents used to treat ITP in Table 4 of Module 4.
Sources: Liu 2013

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).

Recommendations for assessment and management of HRQoL outcomes in children with ITP:

- HRQoL should be reported using the Kid's ITP Tool (KIT; or another validated HRQoL scale) before and after treatment, to assess the effect of treatment beyond the platelet count
- HRQoL of children with newly diagnosed ITP improves on disease resolution
- Corticosteroids may worsen HRQoL in children
- TPO-RAs may improve HRQoL, and romiplostim especially appears to improve parental burden (Provan 2019).

Recommendations for school and participation in sporting activities:

- Children and adolescents 5 to 18 years old should engage in ≥ 60 minutes of physical activity per day, ≥ 3 times per week. Activities that promote strong muscles and bones are advised.
- Normal attendance at kindergarten, school or college is highly recommended. School authorities should be provided with information on the risk of bleeding and information about ITP.
- Active participation in low-risk activities should be maintained, irrespective of platelet count.
- Participation in higher risk activities should be discussed with physician/hematologist.
- Choice of treatment and target platelet count must be carefully evaluated based on consultation with family and consideration of the specific activity desired and bleeding tendency of the child (Provan 2019).

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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Notes

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 function
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 in 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 drug (such as methotrexate or azathioprine) that modifies (enhances or suppresses) the immune response.
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)	concentrated antibodies extracted from healthy blood donors 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 increase in the number of abnormal lymphocytes, which accumulate 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 iron deficiency 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 blood cancer and/or pre-leukemia
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 to 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	Seen in the bone marrow when it develops scarring (fibrosis)
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 by megakaryocytes in the bone marrow

*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, VANCOMYCIN, TEICOPLANIN
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
Checkpoint inhibitors	
Antiplatelet drugs	Phosphodiesterase inhibitors, Dipyridamole, Cilostazole
Adenosine diphosphate receptor antagonists	Ticlopidine, Clopidogrel
Glycoprotein IIb/IIIa antagonists	Abciximab, Eptifibatide, Tirofiban
Miscellaneous agents	Dextrans, Radiographic contrast (iodinated contrast media eg.. Gadolinium, Quinidine, Ethanol
Herbal medicines	Ginkgo, Ginger, Dong quai, Ginseng, Meadowsweet, Chamomile, Horse chestnut, Red clover, Garlic, Bilberry, Feverfew, Turmeric, Willow, Motherwort, Fenugreek, Tamarind
Foods	Caffeine, Garlic, Cumin, Turmeric, cranberry juice

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