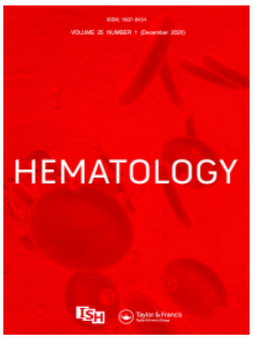

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Iraqi consensus recommendations for the diagnosis and management of immune thrombocytopenia

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Iraqi consensus recommendations for the diagnosis and management of immune thrombocytopenia

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ABSTRACT

Background and Objectives: The management of ITP has evolved with evidence-based international guidelines. However, Iraq's unique challenges, including variations in clinical practice and treatment disparities, necessitate localized guidance to bridge global recommendations and real-world practice. This expert consensus aims to provide a comprehensive and practical framework for diagnosing and managing ITP within the Iraqi healthcare setting.

Methods: A 16-member multidisciplinary ITP specialist panel (Iraq, Norway, UK), including hematologists, laboratory experts, and related specialists, conducted a systematic PubMed / PubMed Central / Embase review (January 2003–December 2024) using key terms 'primary immune thrombocytopenia' and 'idiopathic thrombocytopenic purpura' (English human studies, excluding conference abstracts). Using a modified Delphi method, consensus was reached on 43 ITP diagnosis/treatment/management statements. After a single voting round, the panel refined the recommendations to ensure their applicability to Iraq's healthcare system. Final recommendations were categorized using evidence grading system.

Results: Corticosteroids were the preferred first-line therapy, with intravenous immunoglobulin (IVIG) reserved for urgent platelet elevation. The panel discouraged prolonged corticosteroid use due to adverse effects and defined clear criteria for second-line therapies. Thrombopoietin receptor agonists (TPO-RAs) and rituximab were recommended second-line, while splenectomy was considered a last resort, only after the failure of multiple medical therapies. Special populations received tailored recommendations, including pregnant patients, pediatric cases, and high-thrombosis-risk individuals. Recommendations incorporated quality of life, emphasizing patient-centered care and minimizing unnecessary medication exposure.

Conclusion: This expert consensus provides a structured, evidence-informed approach to ITP diagnosis and management in Iraq, balancing best practices with local healthcare realities.

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Immune thrombocytopenia (ITP); Cconsensus guidelines; ITP diagnosis; ITP management; corticosteroids ; rituximab ; thrombopoietin receptor agonists (TPO-RAs); refractory ITP

Introduction

In recent years, the landscape of immune thrombocytopenia (ITP) management has evolved significantly, driven by advancements in clinical research and therapeutic modalities [1]. In regions like Iraq, where healthcare infrastructure and resources are limited, it is crucial to adapt global guidelines to fit local realities. In 2010, an International Consensus Report (Updated in 2019) on the management and investigation of primary ITP provided a foundational framework for clinical practice [2,3]. While other guidelines, such as those by the American Society of Hematology (ASH), further delineated evidence-based approaches [4].

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However, the applicability of these guidelines to the Iraqi healthcare setting warrants inspection. To address this, a survey study was conducted in 2023 to assess the current landscape of ITP diagnosis and management in Iraq. The findings underscored several key observations: a predominant reliance on conventional diagnostic tests, limited accessibility to specialized investigations, and a notable preference for corticosteroids as first-line therapy, while immunosuppressant drugs are preferred as second- and third-line therapies**.** Furthermore, the survey revealed a disparity between guideline awareness and utilization among hematologists, with only a subset referring to established guidelines, primarily the ASH guideline [5].

The conclusion drawn from this survey study emphasizes the imperative of developing localized guidelines tailored to the Iraqi healthcare context. Such guidelines would not only enhance the standardization of care but also optimize resource allocation and patient outcomes. Moreover, they would facilitate the identification of patients who stand to benefit most from treatment, thereby minimizing unnecessary medication exposure and enhancing individualized care delivery.

In light of these findings, the present consensus report aims to bridge the gap between global recommendations and local realities in Iraq. By synthesizing the latest evidence with insights collected from the survey study, this report seeks to provide a comprehensive and pragmatic framework for the diagnosis and management of ITP in the Iraqi setting. Drawing upon the expertise of local hematologists and considering the unique challenges faced within the Iraqi healthcare system, this consensus report endeavors to empower practitioners with actionable recommendations that prioritize patient-centric care.

Methods

Panel composition

The consensus panel comprised 16 experts in the field of immune thrombocytopenia (ITP). The panelists were chosen for their acknowledged expertise in both clinical practice and research, ensuring representation from a variety of backgrounds and geographic regions. The panel included hematologists from different Iraqi hematology centers, Norway, and the United Kingdom, as well as an Iraqi pediatric hematologist.

Ethical considerations

Since this study involved expert consensus rather than patient data, ethical approval was sought solely for the Delphi process from the Iraqi Society of Hematology (Reference No. 357). All panelists provided written informed consent before participating in voting. No patient-level data was collected, and thus no additional ethical approvals were required.

Literature review

A literature search was conducted using the PubMed, PubMed Central, and Excerpta Medica Database (Embase) electronic databases. Search terms included variations of 'primary immune thrombocytopenia,' 'immune thrombocytopenic purpura,' and 'idiopathic thrombocytopenic purpura,' limited to articles published between January 2003 and December 2024. Filters were applied to include only human studies published in English, comprising clinical trials, observational research, and guidelines. Conference abstracts were excluded from the search. Additionally, a comprehensive approach was taken to ensure a broad evidence base by incorporating meta-analyses and qualitative studies. While our literature review aimed to be comprehensive, it served to inform expert discussion rather than to meet systematic review criteria. The inclusion of diverse study designs allowed for a thorough evaluation of existing literature relevant to ITP diagnosis and management. Collaboration with experts in the field and consultation with patient advocacy groups provided valuable insights and perspectives, enriching the interpretation and application of the findings.

Evidence grading and recommendations development

Selected articles underwent rigorous evaluation for methodological quality and relevance. The evidence grading system used in previous international consensus was applied, categorizing evidence into grades

Table 1. Grading system employed to append recommendations.

Strength of recommendation	
1	Strong
2	Weak
Levels of Evidence	
A	High meta-analysis quality
B	Robust phase 3 studies
C	Phase 2 studies or high-quality case series
D	consensus of an expert panel

A, B, and C based on predefined criteria [6,7]. Recommendations were formulated based on the strength of the evidence, with consensus achieved through discussion and consensus meetings among panel members (Table 1).

Consensus building

Expert opinions on the consensus statements were gathered using a modified Delphi method, a well-established consensus technique frequently used when clinical data is limited. The process involved several structured phases, ensuring a systematic and transparent approach to developing the recommendations [8]. Based on the literature review and expert discussions, 43 consensus statements were developed, covering diagnostic criteria, treatment approaches, management of refractory ITP, special populations (pregnancy and pediatric cases), and considerations for thrombosis risk and treatment tapering. These statements were then distributed to panelists for anonymous voting. Panelists rated their level of agreement on a five-point Likert scale with the following options: 1: strongly agree, 2: agree, 3: neither agree nor disagree, 4: disagree, and 5: strongly disagree. A score of 1 or 2 was determined as 'Agreement'. A predefined threshold of $\geq$70% agreement was required for a statement to be accepted. The majority of statements achieved the required 70% agreement in the first round, eliminating the need for additional Delphi rounds or modifications. However, panel discussions were conducted to refine the recommendations and ensure their applicability within the Iraqi healthcare system. To foster transparency and accountability, detailed documentation of the consensus process, including meeting minutes and voting records, was maintained.

Review and dissemination

The final consensus document underwent thorough review and approval by all panel members before submission. Plans for dissemination included publication in peer-reviewed journals and distribution through professional societies, syndicates, ministries of health, and patient support organizations. To extend the reach of the findings, additional online webinars and educational workshops could be organized to educate healthcare professionals and relevant stakeholders on the implementation of the recommendations. Collaborations with governmental bodies and international health organizations could also be explored to integrate the recommendations into policy frameworks and global health agendas. Moreover, the development of interactive multimedia resources such as videos, infographics, and digital toolkits could enhance accessibility and engagement among diverse audiences, including patients and caregivers. Evaluation metrics may be established to monitor the uptake and impact of the consensus recommendations on clinical practice and patient outcomes, with periodic reviews and updates planned to ensure continued relevance and effectiveness over time.

Diagnostic approach in patients with suspected ITP

Thrombocytopenia is a common hematological condition with a variety of potential causes. Establishing a diagnosis can be challenging, and correctly identifying the underlying cause is crucial for making appropriate management decisions for thrombocytopenic patients [9].

Unfortunately, there is no test available to reliably establish the diagnosis of ITP and the diagnosis remains one of exclusion. Although a positive response to ITP-specific treatments like corticosteroids, IVIG, or anti-D

can aid in confirming the diagnosis, it does not definitively rule out secondary ITP, as several secondary types of ITP also respond to these treatments [3].

When the patient's medical history, physical examination, complete blood count (CBC), and peripheral blood smear evaluation do not reveal any other possible reasons of thrombocytopenia, ITP is presumed to be the provisional diagnosis [3].

The diagnostic threshold is often defined as a platelet count of less than 100×10^9/L. Using a standardized cutoff, instead of relying on local reference ranges or frequency distribution-based thresholds, improves practicality and enables easier cross-study comparisons [10,11].

Basic evaluation

Patient history

Thrombocytopenia can result from various conditions, including systemic diseases, infections, medications, and primary hematologic disorders. When assessing chronic thrombocytopenia or alternative bleeding disorders, it is important to consider history of heavy menstrual bleeding, bleeding following prior surgeries, dental procedures, or trauma to estimate potential duration of thrombocytopenia.

Consideration should be given to inherited thrombocytopenia in patients who have had persistent thrombocytopenia since birth, do not respond to initial treatment, or have a family history of bleeding disorders or thrombocytopenia [2].

Physical examination

Physical examination should involve looking for signs associated with thrombocytopenia including mucocutaneous bleeding, petechiae and ecchymoses. Examining for hepatosplenomegaly, lymphadenopathy and evidence of liver disease can be useful in exclude other conditions mimicking ITP [12].

Ideally, the physical examination should show no abnormalities apart from bleeding symptoms. The presence of moderate to severe splenomegaly may indicate another cause of thrombocytopenia. Additionally, constitutional symptoms like weight loss, fever, splenomegaly, hepatomegaly, or lymphadenopathy should raise suspicion of an underlying condition [3].

The expert panel reached 100% consensus agreement ($n = 16$) on the importance of a thorough patient history and physical examination in the initial workup for the diagnosis of ITP.

Expert consensus statement 1

- Full clinical history regarding:
  - The type & duration of bleeding, as well as family history of bleeding tendency, to exclude inherited platelets disorders (Grade 1D).
  - Medication history, manifestations of other autoimmune diseases or infections (viral and bacterial) (Grade 1D).
- A comprehensive physical examination especially focusing on bleeding manifestations as well as hepatosplenomegaly and lymphadenopathy, is necessary (Grade 1D).
- Complete blood count including platelet count & differential WBC count and blood film examination by expert hematologist is essential (Grade 1D).
- Bone marrow evaluation is generally not recommended for the diagnosis of ITP when thrombocytopenia is the only abnormal finding (Grade 1C).
- Routine tests for HCV and HIV in adult patients are recommended (Grade 1B).
- HBV, ANA, antiphospholipid antibodies and thyroid function can be considered in initial workup (Grade 2D).
- *H. pylori* infection, should be assessed with the urea breath test or stool antigen test in adults with gastrointestinal symptoms but not routinely in children. Eradication therapy is recommended if the infection is present (Grade 1B).

• *Comple blood count (CBC)*

A complete blood count (CBC) should reveal isolated thrombocytopenia without the presence of anemia or leukopenia in differential counts. It can serve as the initial test for diagnosing ITP (Grade 1D) [13].

• *Peripheral blood smear*

Evaluation of the peripheral blood smear should be conducted by a qualified hematologist. The peripheral blood smear typically presents as normal except for the presence of thrombocytopenia, although platelets may be slightly enlarged in certain cases. Red cells and leukocytes morphology remain normal. It is crucial to rule out the presence of schistocytes (red cell fragments) and nucleated red blood cells, as these often indicate a microangiopathic hemolytic anemia associated with conditions like thrombotic thrombocytopenic purpura [14,15]. As well as to exclude morphological abnormalities that raise suspicion of myelodysplastic syndromes (MDS) or immature mononuclear cells. If platelet aggregates are observed, EDTA-dependent platelet agglutination-induced pseudothrombocytopenia should be ruled out by reanalyzing the platelet count using a citrated blood tube (Grade 1D) [3].

The expert panel reached 100% consensus agreement ($n = 16$) on the importance of a complete blood count and a peripheral blood smear assessment by an expert hematologist as part of the initial workup for diagnosing ITP.

• *Bone marrow examination*

Current guidelines indicate that a bone marrow examination is generally not required for most patients with ITP, regardless of age (Grade 1 C) [2–4,10,16]. However, this examination may be indicated in certain situations. These include: (i) abnormal peripheral blood counts or morphology, (ii) systemic symptoms or organomegaly suggestive of alternative diagnoses, (iii) poor or absent response to conventional treatments, (iv) refractory cases where diagnostic uncertainty persists and (v) when splenectomy planned (Grade 2 D) [2–4,15,17,18]. When a bone marrow examination is conducted, it should involve an aspirate & biopsy, cytogenetic tests, and flow cytometry (Grade 2 D). These evaluations assist in differentiating ITP from other disorders, including lymphoproliferative diseases, myelodysplastic syndromes, aplastic anemia, and other primary bone marrow disorders [19].

The expert panel reached an 81.25% consensus agreement ($n = 13$) that a bone marrow examination is not needed for the initial diagnosis of ITP in cases of isolated thrombocytopenia.

Expert consensus statement 2

- Bone marrow examination is not usually needed for diagnosing ITP in cases of isolated thrombocytopenia (Grade 1 C).
- Bone marrow examination should be performed to rule out other conditions.
- Indications of bone marrow examination (Grade 2D).
  - In addition to thrombocytopenia, abnormal laboratory findings, including abnormal peripheral blood cells counts or morphology.
  - Atypical physical examination and history findings (e.g. enlarged lymph nodes, hepatosplenomegaly, B symptoms and weight loss)
  - Poor response to conventional treatments: Failure to achieve response with corticosteroids, IVIG, or anti-D.
  - Refractory ITP
  - Prior to splenectomy, to exclude other diagnostic possibilities
- Bone marrow examination should include an aspirate and biopsy (Grade 2D).

• *HIV, HBV and HCV testing*

In newly diagnosed adult patients, testing for HCV and HIV is recommended (Grade 1B) [3,4,15]. In patients receiving immunosuppressive therapy or rituximab, we also recommend HBV testing due to the endemic nature of hepatitis B in our country, as HBV reactivation may occur spontaneously, during or after the course of treatment (Grade 2D) [20,21].

The expert panel reached a 100% consensus agreement ($n = 16$) on the importance of virology screening as part of the initial workup for diagnosing ITP.

H. Pylori testing

This test should be considered in adults experiencing digestive symptoms, particularly those from areas with a high prevalence of *H. pylori* infection (Grade 1B) [15]. Screening for *H. pylori* typically involves the use of the urea breath test and stool antigen tests, as antibody testing is associated with high rates of both false-

positive and false-negative results and cannot reliably determine whether the infection is active or occurred in the past. The lack of consistent correlation between the duration of ITP and response to *H. pylori* treatment in many studies suggests that screening for *H. pylori* could be conducted at any point in time, not solely at the time of diagnosis [21]. Eradication of *H. pylori* may lead to improved platelet counts in adults with recent-onset ITP or those with milder forms of thrombocytopenia [20,22]. However, it appears to be less effective in patients with chronic severe ITP, especially those with platelet counts persistently below 30×10^9/L and a long duration of the disease [23].

The expert panel reached an 81.25% consensus agreement ($n = 13$) on the importance of *H. pylori* testing as part of the initial workup for diagnosing ITP.

- ***ANA test & ENA profile***

In Iraq, we recommended antinuclear antibody (ANA) test initially to minimize the misdiagnosis rate (Grade 2D). More than 85% of hematologist in Iraq recommend ANA test as initial test for ITP workup [5]. ANA-positive primary ITP may resemble the preclinical stage of connective tissue diseases, especially SLE [24–26]. ITP patients with a positive ANA test are likely to achieve a better response to hydroxychloroquine and rituximab treatment, although their long-term outcome is unfavorable [25,27].

In ANA-positive cases, identifying the specificity of extractable nuclear antigen (ENA) profiles is crucial, as it helps distinguish between different types of autoimmune connective tissue diseases (Grade 2D) [28].

The expert panel reached an 87.5% consensus agreement ($n = 14$) on the importance of the ANA test and ENA profile as part of the initial workup for diagnosing ITP.

- ***Thyroid function screen***

Thyroid disorders can lead to thrombocytopenia through various mechanisms, and autoimmune thyroid disease is frequently found in patients with ITP [29–31]. Mild to moderate thrombocytopenia can be seen with thyrotoxicosis and hypothyroidism; therefore, ITP patients may be further screened with a thyroid-stimulating hormone assay to detect subclinical thyroid disease (Grade 2D) [29–31]. Treating the underlying thyroid disorder may significantly improve platelet count and can either cause remission of disease or improve the response to standard ITP therapy [32].

The expert panel reached a 100% consensus agreement ($n = 16$) on the importance of thyroid function screening as part of the initial workup for diagnosing ITP

Other helpful tests

- ***Direct antiglobulin test (not routinely recommended)***

Direct antiglobulin testing is indicated in patients with concurrent anemia and an elevated reticulocyte count, or in those for whom intravenous anti-D immunoglobulin treatment is being considered [33].

- ***Blood group Rh(D) typing***

Blood group Rh(D) typing is important if anti-D immunoglobulin is being considered [3].

- ***Antiphospholipid antibodies (APLAs)***

Antiphospholipid antibodies (APLAs) including anticardiolipin antibodies, are found in approximately 20–40% of patients with ITP. Despite their prevalence, the presence of APLA does not seem to influence the response to treatment in ITP but may indicate increased risk of thromboembolism [34,35].

- ***Cytogenetic test***

Congenital thrombocytopenia should be suspected in patients with a relevant family history, suggestive clinical symptoms, prior thrombocytopenia, or inadequate response to first-line therapy. Genetic testing is recommended in such cases [15].

Tests not available in Iraq

Access to new high-cost investigation is difficult in developing countries like Iraq. Unfortunately, advance tests for the diagnosis of ITP are not available [5].

- ***Quantitative immunoglobulins level testing***

It can be considered in children with chronic or persistent ITP as part of a re-evaluation process [5]. However, routine testing for immunoglobulins levels is not necessary for all patients [33].

- ***Platelet autoantibody testing***

Testing for platelet autoantibodies is not included in the routine workup for newly diagnosed ITP; however, it should be reserved for patients with persistent or chronic ITP who present with an unusual disease progression [36].

- ***Next-generation sequencing (NGS)***

If the patient reports that thrombocytopenia is present in other family members, the diagnosis of ITP should be reconsidered. In such situations, uncommon familial thrombocytopenias, including Bernard-Soulier syndrome, platelet-type (pseudo) von Willebrand disease, MYH9-related thrombocytopenia, Glanzmann thrombasthenia, and other similar conditions, should be taken into account [37,38].

Numerous uncommon genetic causes of thrombocytopenia can be identified by using next-generation sequencing (NGS) panels. This raises the question of whether patients with unexplained thrombocytopenia, especially those who show little or no response to standard treatments, should be tested for a genetic cause. Anyhow, genetic testing should only be investigated if it has a clinical application, such as suggesting a new treatment option or necessitating an alteration in the existing treatment. Additionally, these panels should only be used if genetic expertise is available to interpret the results accurately [37,38].

Although the focus of NGS testing is primarily to distinguish inherited thrombocytopenias from primary ITP, the panel noted that Evans syndrome should also be considered in the differential diagnosis when additional cytopenias (autoimmune hemolytic anemia and/or neutropenia) are present. In such cases, clinical and laboratory evaluation, including a direct antiglobulin test, is more informative than NGS, and exclusion of Evans syndrome is recommended before confirming a diagnosis of primary ITP [39,40].

Classification of ITP

ITP may be classified as primary or secondary:

I. Primary ITP

Primary ITP is an autoimmune disorder characterized by isolated thrombocytopenia (platelet count $< 100 \times 10^9$/L) without other identifiable causes of thrombocytopenia or conditions causing immune thrombocytopenia [3,11].

II. Secondary ITP

Secondary ITP includes all forms of immune-mediated thrombocytopenia that are not classified as primary ITP [11]. However, when ITP is a consequence of an underlying condition (such as lymphoproliferative disorder, viral infection e.g. HIV or HCV, or other autoimmune diseases e.g. SLE) this could be the main focus of management rather than the ITP [3]. Secondary causes and differential diagnosis of ITP are summarized in Table 2.

ITP can also be categorized based on the duration of the disease:

1. ***Newly Diagnosed ITP:*** Refers to the initial phase occurring within 3 months from diagnosis.
2. ***Persistent ITP:*** Extends from 3 to 12 months from diagnosis. Includes patients who do not achieve spontaneous remission or fail to maintain a complete response off therapy.
3. ***Chronic ITP:*** It is considered when the duration exceeding 12 months from diagnosis [3,11].

Table 2. Secondary causes and differential diagnosis of ITP [41].

Variable	Laboratory and clinical findings	Additional findings and tests to support diagnosis
ITP differential diagnosis		
Pseudo thrombocytopenia	Phenomena in vitro, without any symptoms.	Platelet aggregation on peripheral blood smear and platelet count in citrated blood should be repeated.
Liver or renal disease	Signs, symptoms, and medical history	Liver and renal function tests as well as abdominal imaging, including spleen and liver.
Myelodysplastic syndrome and acute leukemia	Abnormal peripheral blood smears with further cytopenias	Bone marrow examination using cytogenetic tests and flow cytometry.
Anemia aplastic	Pancytopenia	Bone marrow examination and cytogenetic analysis.
Thrombocytopenia caused by genetic illnesses (e.g. MYH9-related disorders and Bernard-Soulier syndrome)	Family history of thrombocytopenia, young age at the time of presentation, peripheral blood smear reveals abnormal size and morphological characteristics of platelets or abnormalities seen in neutrophils, further clinical disorders such as deafness and renal disease in patients with MYH9-related disease.	Mean platelet volume, peripheral blood smear, and genetic analysis.
Thrombotic thrombocytopenic purpura	Neurological symptoms, fever, abdominal pain.	Schistocytes in peripheral blood smear, low ADAMTS13 & haptoglobin levels, high LDH, and a Coombs negative hemolytic anemia.
Heparin-induced thrombocytopenia	History of heparin exposure and venous thrombosis.	Platelet factor 4-heparin antibody testing and platelet-activation assays.
Secondary causes of ITP		
Drug induced	Abrupt onset with the start of a new drug (e.g. acetaminophen, abciximab, carbamazepine, rifampicin, vancomycin, quinine or quinidine).	If available, tests to identify drug-dependent antibodies.
Lymphoproliferative disease	Night sweats, weight loss, splenomegaly or lymphadenopathy.	Peripheral blood smear, bone marrow examination, flow cytometry, protein electrophoresis, imaging of neck, chest, and abdominal to detect splenomegaly or lymphadenopathy.
Immunodeficiency syndrome (such as common variable immunodeficiency and autoimmune lymphoproliferative disease)	Hypogammaglobulinemia, cytopenias, frequent infections (e.g. sinus or chest infections), lymphadenopathy, colitis, splenomegaly.	Genetic testing, lymphocyte subset count, and immunoglobulin quantification.
Infection (such as *H. pylori*, CMV, EBV, HCV, HBV, HIV, and AIDS).	Further suggestive symptoms and signs; at-risk populations.	*H. pylori* breath or stool antigen tests; PCR and serologic testing for CMV, EBV, HBV, HCV and HIV.
Additional autoimmune diseases (such as antiphospholipid syndrome, rheumatoid arthritis, and SLE).	Hair loss, sun sensitivity, mouth ulcers, rash, bone pain and recurrent thrombosis.	Tests for rheumatoid factor, antinuclear antibodies, antiphospholipid antibodies, and anti-cyclic citrullinated peptide antibodies.
Evans Syndrome	Concomitant hemolytic anemia with a positive Coombs test and thrombocytopenia.	Peripheral-blood smear; Coombs test; measurements of LDH and haptoglobin levels.

Note: ADAMTS13 denotes a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; AIDS acquired immunodeficiency syndrome; CMV cytomegalovirus; EBV Epstein–Barr virus; HBV hepatitis B virus; HCV hepatitis C virus; HIV human immunodeficiency virus; LDH lactate dehydrogenase; MYH9 gene encoding nonmuscle myosin heavy chain 9; PCR polymerase chain reaction; and SLE systemic lupus erythematosus.

Goals of treating ITP

The primary goal of treating ITP is to achieve a safe platelet count, sufficient to prevent major bleeding, rather than normalizing platelet levels (Grade 1 C) [11]. Fatal bleeding incidents are primarily reported in adults ITP patients when platelet counts below $20–30 \times 10^9$/L [11,42,43].

Due to the potential toxicity of available treatments, it is crucial to avoid unnecessary treatment in asymptomatic patients with mild thrombocytopenia [11]. Most guidelines recommend considering treatment when platelet counts fall below $20–30 \times 10^9$/L in adult patients (Grade 2 C) [4,11,44–46].

Treatment options should consider the severity of the condition and the patient's age, as the risk of bleeding and mortality rates generally increase with advancing age [11]. For patients with comorbidities (particularly those on anticoagulant or antiplatelet therapy), planned procedures, or more than minor bleeding, clinical judgment should consider their elevated bleeding risk by maintaining higher platelet counts in these settings [42,43,47].

In general, international guidelines considered a response if there is no sign of bleeding and the platelet count is $\geq 30 \times 10^9$/L (at least twice as high as the baseline). On the other hand, the complete response is considered when the platelet counts of at least 100×10^9/L without any bleeding signs [15].

The expert panel reached an 87.5% consensus agreement ($n = 14$) that the goal of treatment is to achieve a safe platelet count of $20–30 \times 10^9$/L, with treatment consideration only when the platelet count drops below this level.

Expert consensus statement 3

- The main aim of treatment is to achieve a safe platelet count tailored to each patient's individual needs, rather than to normalize platelet levels (Grade 1C).
- In adult patients with newly diagnosed ITP and a platelet count $\geq 30 \times 10^9$ /L without symptoms or minor mucocutaneous bleeding, we recommend observation rather than corticosteroids (Grade 2C).
- Higher platelet thresholds may be desirable in these settings:
  - Patients with serious bleeding
  - Patients who are scheduled for procedures or those with high-risk jobs.
  - Patients who have additional comorbidities (requiring anticoagulant and antiplatelet drugs).

Inpatient versus outpatient treatment

ITP treatment is usually provided as an outpatient care, except in cases of: active and critical bleeding, the need for anticoagulant drugs, the requirement for careful patient observation, or if the patient presents with platelet counts $\leq 10 \times 10^9$/L (Grade 2 D) [4,5,48]. Potential uncertainties about the diagnosis, the necessity to monitor changes in platelet counts, the risk of bleeding complications, and the need to ensure proper administration of treatment may also justify hospitalization [49].

The expert panel reached an 87.5% consensus agreement ($n = 14$) that ITP patients can be treated as outpatients rather than inpatients.

Expert consensus statement 4

ITP patients can be treated as outpatients (Grade 2D), but hospital admission may be beneficial for those with:

- Severe life threating bleeding e.g. organ bleeding that requires rapid elevation of platelets count.
- Hematuria due to thrombocytopenia.
- New diagnosis with platelet count $\leq 10 \times 10^9$.
- Social concerns: Individuals with limited social support, those residing distant from the medical centers, or patients whose follow-up is uncertain.
- Major comorbidities & high risk of bleeding: Using concomitant medications that carry a high risk of hemorrhage.

The severity of bleeding

The management of ITP is generally guided by the severity of bleeding. Several bleeding scores have been developed to assess this severity [3,50,51]; however, despite their frequent use in research, they are often time-consuming and impractical for routine clinical practice [50]. Instead, it is recommended to use the WHO bleeding grades or the National Cancer Institute's Common Terminology Criteria for Adverse Events, as these are well-recognized by healthcare providers from various specialties. For pediatric patients, the updated bleeding scale for pediatric patients is advised (Tables 3 and 4) [50].

Emergency treatment

Patients with internal bleeding, or those requiring emergency surgery, necessitate urgent and aggressive therapy. Hospitalization is essential, accompanied by the implementation of general measures to stop

Table 3. Bleeding grades according to the WHO and the NCI Common Terminology Criteria for Adverse Events (CTCAE v5.0) [50].

WHO bleeding grade	Definition
0	• There are no signs of bleeding.
I (no need for a transfusion)	• Petechiae • Ecchymoses (less than 10 cm) and tiny hematomas. • Mucosal bleeding (nose, mouth). • Epistaxis (less than one hour long; no medical assistance is required). • Subconjunctival bleeding. • Vaginal bleeding (requires no more than two sanitary napkins every day, not influenced by menstruation).
II (no need for a transfusion)	• Ecchymoses (more than10 cm), hematomas • Epistaxis (more than one hour long; medical assistance is required). • Retinal hemorrhage without vision impairment • Vaginal bleeding (requires more than two sanitary napkins every day, not influenced by menstruation). • Hematochezia, hematuria, hemoptysis, hematemesis and melena. • Oozing from the sites of punctures • Joint and muscle bleeding
III (transfusion is needed)	• Epistaxis • Mucosal bleeding (nose, mouth) • Vaginal bleeding • Hematochezia, hematuria, hemoptysis, hematemesis and melena. • Oozing from the sites of punctures • Joint and muscle bleeding.
IV (Critical conditions, life-threating; transfusion is needed)	• Retinal hemorrhage with vision impairment • CNS bleeding • Hemorrhages in other organs with functional impairment (lungs, kidneys, muscles, joints, etc.) • Fatal bleeding (in the NCI CTCAE graded as V)

Table 4. Updated bleeding scale for pediatric patients with ITP [3].

Grade	Bleeding	Management strategy
Grade 1 (minor)	$\leq$ 5 tiny bruises ($\leq$ 3 cm in diameter), a few petechiae ($\leq$100 total), no mucosal bleeding or just mild bleeding.	Follow up
Grade 2 (mild)	> 5 sizable bruises (> 3 cm in diameter), and/or > 100 petechiae, no mucosal bleeding or just mild bleeding.	Follow up
Grade 3 (moderate)	Distressful lifestyle, moderate bleeding, and visible mucosal bleeding.	Start treatment to reach grade 1 or 2
Grade 4 (severe)	Hemoglobin reduction greater than 2 g/dL due to suspected internal hemorrhage, severe bleeding, or mucosal bleeding.	Start treatment

bleeding or minimize bleeding risk. These measures include stopping drugs that inhibit platelet function/anticoagulants, maintaining blood pressure control, and addressing other contributing factors [52].

Immediate treatment is required for patients displaying severe bleeding symptoms, particularly when the platelet count is $\leq 20 \times 10^9$/L. The severity of bleeding is frequently assessed subjectively by the clinician [3]. In Iraq, Grade IV bleeding is categorized as life-threatening based on the WHO and NCI Common Terminology Criteria for Adverse Events (CTCAE v5.0). This classification aligns with the revised bleeding scale for pediatric ITP patients (Table 4) [3,50].

In cases of life-threatening bleeding, a combined treatment is recommended, consisting of intravenous immunoglobulin (IVIG) at a dose of 1–2 g/kg, along with corticosteroids, such as high-dose dexamethasone (40 mg administered intravenously daily for 4 days) or methylprednisolone (up to 1000 mg intravenously per day for 1–5 days) (Grade 1 D) [15].

The expert panel reached a 100% consensus agreement ($n = 16$) on the use of IV corticosteroids and IVIG in emergency situations.

Despite the lack of research on platelet transfusion in ITP, this is reserved for cases experiencing active, life-threatening bleeding who do not respond to other treatments to achieve hemostasis (Table 3).

Concomitant IVIG and platelet transfusions may help to quickly restore sufficient platelet counts and stop bleeding, and can be beneficial before urgent surgical procedures (Grade 1D) [3].

The expert panel reached a 100% consensus agreement ($n = 16$) on platelet transfusion in cases of life-threatening bleeding.

TPO-RAs can be considered in cases of critical bleeding. We recommend starting with the maximum dose, as it is easier to titrate the dose down than to wait for effects and then increase the dose after one or more weeks of treatment. Romiplostim, as a parenteral agent, is more frequently available in inpatient formularies and is more easily titrated than the oral agents eltrombopag and avatrombopag (Grade 2D) [53].

The expert panel reached a 100% consensus agreement ($n = 16$) on the use of romiplostim as an additional option when there is no response to IV corticosteroids and IVIG in cases of life-threatening bleeding.

In rare instances of multiply relapsed or refractory cases, as well as in cases with potentially fatal bleeding, the use of vinca alkaloids may be considered (Grade 2D). Some studies have reported success with vincristine administered at a dose of 1–2 mg intravenously (over 4–6 h) once a week for 2–4 doses, with treatment effects typically observed within 48 h [15].

The expert panel reached an 81.25% consensus agreement ($n = 13$) on the use of vincristine in ITP patients with life-threatening bleeding or those requiring urgent surgical procedures.

Antifibrinolytic treatment with tranexamic acid (up to 1000 mg intravenously three times a day) and supportive blood transfusions can be helpful [4,43]. Local measures such as endoscopic cautery need to be considered in gastrointestinal bleeding and epistaxis (Grade 1D) [15].

The expert panel reached a 100% consensus agreement ($n = 16$) on the use of tranexamic acid and local measures in emergency situations.

Expert consensus statement 5

- Recommendations for life-threatening bleeding:
  - ❖ In emergency situations requiring a rapid increase in platelet count within 24 h, a combination of initial treatments, including IV corticosteroids and IVIG, should be administered (Grade 1D).
  - ❖ Platelet transfusions may be utilized solely in cases of life-threatening bleeding, particularly in the context of intracranial hemorrhage (ICH) or prior to urgent surgical procedures (Grade 1D).
  - ❖ If there is no good response to IVIG, corticosteroids, and platelet transfusion, additional options may be considered (Grade 2D):
    - ➢ TPO-RAs (romiplostim 10 mcg/kg administered subcutaneously weekly).
    - ➢ Vinca alkaloids (vincristine).

First-line treatment

Once the decision to initiate treatment for a patient with ITP has been made, and if the patient's condition is not life-threatening conditions, corticosteroids are typically the first-line therapy [52]. **Corticosteroids** are cost-effective and often result in a rapid increase in platelet counts within 1–2 weeks in approximately 75% of patients. However, long-term remission is observed in only about 25% of patients [42,43,54,55]. While corticosteroids are associated with common and predictable side effects, they remain a cornerstone of ITP management. Various corticosteroids, including prednisone, prednisolone, methylprednisolone, and dexamethasone, are available for treatment. Prednisolone has traditionally been favored as the initial choice, although recent studies suggest that dexamethasone may offer higher response rates and more prolonged remission. Nevertheless, prednisolone continues to be the preferred first-line corticosteroid option (Grade 1 C) [42,43].

The expert panel reached a 100% consensus agreement ($n = 16$) on the use of corticosteroids as the initial therapeutic option for ITP patients with a platelet count $<30 \times 10^9$/L.

The continuation of corticosteroids treatment beyond 6–8 weeks was associated with a significantly high risk of side effects and potential harm [4,42]. Most of clinical practice guidelines recommend limiting

corticosteroids treatment to no more than 6–8 weeks (including tapering) in adults with ITP receiving initial therapy (Grade 1C) [56].

The expert panel reached an 87.5% consensus agreement ($n = 14$) against the prolonged use of corticosteroids for more than 6–8 weeks in initial treatment.

If patients do not respond to the maximum steroids dose after 2 weeks, they are considered to have steroid-resistant ITP. Steroid dependence is characterized by the continuous requirement for steroids (prednisolone > 5 mg/d or equivalent) or frequent need of courses of steroids to maintain a platelet count above 30×10^9/L or to avoid bleeding [54,55].

The expert panel reached an 81.25% consensus agreement ($n = 13$) on the prolonged use of low-dose prednisolone (≤5 mg/day) as maintenance therapy, which should only be continued after discussion with the patient and explanation of the potential side effects of steroids.

Expert consensus statement 6

- The initial therapeutic options for ITP patients with a platelet count $<30 \times 10^9$/L, active bleeding and high risk of bleeding typically include corticosteroids (Grade 1 C).
- In adult patients with newly diagnosed ITP, a short course (6–8 weeks) of prednisolone is recommended over a prolonged course (> 6–8 weeks, including treatment and tapering) (Grade 1 C).
- Corticosteroids can be administered for 2 weeks, followed by dose reduction and discontinuation over the next 6 weeks (Grade 1 C).
- Remission is defined as a platelet count of $\geq 30 \times 10^9$ in the absence of any specific treatment for ITP.
- Steroid-resistant ITP is diagnosed if patients do not respond to maximum steroids dose within 2 weeks.
- Steroid dependence is characterized by the continuous requirement for steroids (prednisolone > 5 mg/d or equivalent) or frequent courses of steroids to maintain a platelet count above 30×10^9/L or to prevent bleeding.
- Low-dose prednisolone (≤ 5 mg/day) should only be maintained after discussing with the patient and explaining the potential side effects of steroids (Grade 2 D).

Which corticosteroids should be used?

There is currently no consensus on whether dexamethasone or prednisolone is preferred. The initial rationale for using dexamethasone (due to its perceived higher cure rate) has not been substantiated, so practitioners tend to choose one based on their own and their patients' preferences [57].

A recent meta-analysis showed that dexamethasone has similar overall response rates to prednisolone [58]. The ASH guidelines express low confidence that high-dose dexamethasone improves remission rates. Additionally, standard prednisolone treatment followed by tapering has been associated with greater platelet stability compared to dexamethasone pulse therapy [4,59].

Treatment with methylprednisolone has demonstrated response rates of up to 80%; even though, oral corticosteroids maintenance treatment may be needed due to the short-term response (Grade 2 D). Since 2010, no new data have emerged to recommend methylprednisolone over dexamethasone or prednisolone [3]. In Iraq, oral prednisolone or high-dose dexamethasone remain the preferred options for initial management, with methylprednisolone being the third choice [5].

The expert panel reached an 81.25% consensus agreement ($n = 13$) on the use of dexamethasone for individuals seeking a faster response with shorter exposure to corticosteroids, while prednisolone remains the preferred first choice (100% consensus agreement, $n = 16$).

Expert consensus statement 7

- There is clinical equivalence between prednisolone and dexamethasone as frontline treatments.
- No significant difference has been observed in maintaining response between the two.
- Prednisolone may be preferred for older patients who are less able to withstand the neuropsychiatric adverse effects of dexamethasone (Grade 2 D).
- Dexamethasone is preferred for individuals wishing for a faster response with a shorter exposure time to corticosteroids (Grade 2 D).

Intravenous immunoglobulins (IVIG) are generally recommended for patients with critical bleeding and those with severe thrombocytopenia (platelet count $<10 \times 10^9$) who are at high risk of bleeding. Approximately 80% of ITP patients respond to IVIG, with a response time of 1–2 days. However, most responses are transient and rarely last beyond 3–4 weeks. Common toxicities associated with IVIG include headache, renal impairment, and thrombosis [43,52].

In Iraq, due to the shortage of IVIG, its use is limited to cases where a rapid increase in platelet count is urgently needed [5]. IVIG is typically recommended in: massive hemorrhage, inadequate response to other treatments (corticosteroids in newly diagnosed patient or pre-splenectomy in chronic ITP), and special clinical circumstances (such as pregnancy or periprocedural situations) (Grade 2 D) [15].

The expert panel reached an 87.5% consensus agreement ($n = 14$) on the use of IVIG in ITP patients who require an immediate increase in platelet count.

Expert consensus statement 8

- Using IVIG is restricted to cases where an immediate increase in platelet count is required:
  - Before urgent surgery
  - When high-dose corticosteroids must be avoided or when corticosteroids are contraindicated.
  - Patients with severe, life-threatening bleeding that is unresponsive to other treatment measures.
  - Severe thrombocytopenia (platelet count <10) in the presence of high risk of bleeding (e.g. patient on anticoagulant).

Anti-D immunoglobulin may also be used to maintain platelet counts, particularly in patients scheduled for splenectomy [52]. It is effective in 80% of patients with primary ITP. Compared to IVIG, anti-D immunoglobulin offers a shorter infusion time and is derived from a much smaller donor pool. Anti-D immunoglobulin induces a longer response time than IVIG & it is used in patients who are Rh+ [43]. In fact, this drug is not popular in Iraq as it not preferred as initial treatment [5].

Combination treatment frontline: time to change?

Corticosteroids remain the standard of care, but high failure and relapse rates, along with significant adverse effects from long-term use, continue to drive the search for better treatments [60]. Combining different therapeutic drugs may lead to higher efficacy rates in frontline treatment but the evidence for combination therapy in ITP remains limited [61].

Several prospective trials and retrospective series have evaluated combinations such as corticosteroids with rituximab, TPO-RAs, mycophenolate mofetil (MMF), or all-trans retinoic acid (ATRA) [62].

These studies suggest higher short-term response rates compared with monotherapy; for example, corticosteroids plus rituximab achieved 58–76% sustained responses at 6 months compared with ~36% for corticosteroids alone [61,62]. However, the long-term effects of rituximab and its cost need to be carefully considered [63].

Similarly, dexamethasone combined with eltrombopag showed improved complete response rates in selected cohorts. However, these studies were generally single-center, involved small patient numbers, and had limited follow-up. Toxicities and costs were also greater in the combination arms [60,62].

The combination of ATRA with dexamethasone achieved a CR rate of 68% at 6 months, compared to 41% with dexamethasone alone, without significant adverse effects [61]. While, adding MMF to dexamethasone yielded CR rates of 78% versus 56% with dexamethasone monotherapy after 2 years [61]. However, patients in the MMF group reported worse quality-of-life outcomes, particularly in terms of physical function and fatigue, compared to those treated with glucocorticoids alone [64].

Given these limitations, current evidence does not support combination therapy use as standard first-line treatment. The expert panel reached an 87.5% consensus agreement ($n = 14$) against the use of combination treatment as a frontline approach in newly diagnosed ITP patients.

Table 5 summarizes the different first-line therapies, the time needed to obtain the initial and peak responses, and any potential effects.

Table 5. The various agents for the first-line treatment, along with the time required to achieve the initial & peak responses and possible toxicities [10,11].

Agent/treatment	Reported dose range	Response rate	Time to response	Toxicities
Prednisolone [4,42,65–67]	• 1 mg/kg po daily x 1–4 weeks • Capped dose to 80 mg once daily for patients weighting > 80 kg.	70–80%	3–4 days	• Mood changes • Hypertension • Hyperglycemia • Gastritis • Weight gain • Sleep disturbances
Dexamethasone [4,42,43,52,68,69]	• 40 mg po or iv daily for 4 days, can be repeated after 14–28 days. Maximum 3 courses. • Lower dose (20 m/day, 4 days) can be used in elderly patients.	85%	3–7days	• Hyperglycemia • Hypertension • Gastrointestinal distress. • Weight gain • Insomnia/fatigue • Psychological symptoms like delirium especially affecting the elderly.
IVIG [43,67,70]	• 0.4 mg/kg daily for 5 days • 1 g/kg/day for 2 days	80%	24–48 h	• Infusion reaction • Headache • Aseptic meningitis • Thrombosis
Anti-D [43,67,71]	• 75 ug/kg per dose iv	65%	24–48 h	• Hemolysis

Expert consensus statement 9

- The use of combination therapy as a first-line treatment increases costs and requires more healthcare resources.
- Toxicity was more common in the combination therapy group compared to corticosteroids monotherapy.
- The debate on this approach continues, but no consensus has been reached yet.

Second-line treatment

If first-line treatment with corticosteroids does not result in a response within 2 weeks, second-line therapy should be considered. This approach is also advisable when the first-line treatment is not well-tolerated or provides only a short-term benefit [43,50]. In cases where a positive response is initially achieved but a recurrence happens after more than six months, repeating the first-line treatment may be an appropriate course of action depending on the tolerability of the initial treatment and patient's preference [50].

In fact, no agreement has been reached on the optimal ITP treatment in the second-line. The choice of second-line therapy should take into account factors like the patient's preferences, age, lifestyle, existing medical conditions, and the availability of medications. Similar to first-line treatment, the goal of second-line therapy is often to achieve a platelet count $\geq$20–30 $\times 10^9$/L and to prevent severe bleeding [5,15,56]. In Iraq, rituximab and thrombopoietin receptor agonists (TPO-RAs) are the most popular two options as a second-line [5].

The expert panel reached 87.5% consensus agreement ($n = 14$) regarding corticosteroids rechallenge if recurrence occurs after 6 months. On the other hand, 100% consensus agreement ($n = 16$) was reached for rituximab and TPO-RAs as second-line treatments.

Expert consensus statement 10

Recommendations for second-line treatment:

- In case of thrombocytopenia recurrence after more than 6 months, corticosteroids can be repeated again if initially well tolerated without relevant side effects.
- Second-line treatment can be started in cases of:
  - No response to corticosteroids after 2 weeks
  - Poor tolerance or severe side effects
  - Steroid dependent: Temporary response, but platelets decrease again during tapering
  - Platelets increase and corticosteroids can be discontinued, but then thrombocytopenia recurs within 6 months.
- Drug availability, comorbidities, age, lifestyle, and patient preferences are crucial factors to consider when deciding to initiate second-line treatment and which treatment modality to choose (Grade 1 D).
- In Iraq, rituximab and TPO-RAs are acceptable second-line treatment (Grade 1 C).

Rituximab

It is a chimeric anti-CD20 monoclonal antibody, has demonstrated significant efficacy in treating immune disorders associated with autoantibodies, including ITP. While conventional dosing for rituximab, typically based on doses used in B cell non-Hodgkin's lymphoma treatment (375 mg/m^2 weekly for 4 consecutive weeks), is effective, it may not be optimized for conditions like ITP where B cell mass is presumed to be normal. To address this, a smaller dosage of 100 mg weekly for 4 consecutive weeks (total dose per patient 400 mg, irrespective of body surface area) has been proposed as a potentially effective alternative for autoimmune cytopenia. Rituximab therapy candidates must be free of active bacterial or viral infections, with confirmed negative hepatitis B and hepatitis C testing. Notably, the reduced dosage regimen offers considerable cost savings compared to standard dosing, making it an affordable option even for resource-limited healthcare settings [72]. However, it is anticipated that rituximab usage may decrease with the wider availability of newer TPO-RAs [43].

Thrombopoietin-receptor agonists (TPO-RAs)

Thrombopoietin (TPO) serves as the primary regulator of platelet production. In recent years, several thrombopoietin receptor agonists (TRAs) have been developed to activate the TPO receptor and enhance platelet production. These agonists stimulate megakaryopoiesis, leading to the proliferation and differentiation of megakaryocytes and subsequently increasing platelet counts [42,43,73,74].

In Iraq, only romiplostim has been approved for the treatment of ITP, while eltrombopag and avatrombopag have not yet received approval [5]. Although TPO-RAs have similar mechanisms of action, they may vary in terms of administration requirements and binding sites on TPO receptors. However, direct clinical comparisons between different TPO-RAs have not been conducted [74,75].

Romiplostim

Romiplostim stimulates megakaryopoiesis by activation of the TPO receptor via subcutaneous injection. The increase in platelet count is dose-dependent, with patients typically starting treatment at 1 µg/kg weekly and increasing by 1 µg/kg weekly until the desired platelet count is achieved [43,73]. Romiplostim is the only parenteral TPO-RAs that may be appropriate for patients with gastrointestinal impairments such as diarrhea, vomiting, or a history of GI surgery [75]. Fluctuations in platelet counts can occur in patients receiving romiplostim, and poor platelet responses could be enhanced by adding prednisolone in small dosages (2.5–5 mg) to the treatment regimen [3].

Adverse effects may include headache, fatigue, contusion, upper respiratory tract infection, diarrhea, epistaxis, nasopharyngitis, thromboembolic events (both arterial and venous) and myelofibrosis [43,73].

Eltrombopag

It is an oral small-molecule, has demonstrated efficacy as a short-term treatment for chronic ITP with an initial daily dose of 50 mg, which can be escalated to 75 mg if needed [43,76,77].

It is important to take eltrombopag at least 2 h before or 4 h after consuming products such as antacids, dairy products, or mineral supplements containing polyvalent cations to prevent a significant decrease in eltrombopag absorption [75]. Concomitant administration of eltrombopag with high-calcium food or an antacid containing aluminum and magnesium was associated with significantly reduced systemic exposure [78].

The most common side effects were headache, weakness, hepatotoxicity (transaminitis), thrombosis (venous and arterial) and myelofibrosis [43,76,77,79,80]. During treatment with Eltrombopag, regular monitoring of CBCs and liver function tests should be performed [3].

Avatrombopag

It is an orally administered second-generation TPO-RAs that mimics the natural compound (thrombopoietin) responsible for stimulating the production of platelets associated with durable improvements in platelet count in patients with ITP. The recommended starting dose of avatrombopag is 20 mg once daily then titrated to achieve a stable platelet count between 50 and 150×10^9/L, with platelet levels assessed at least once weekly. Adverse reactions occurring with a frequency of $\geq$ 10% included

Table 6. Comparison of the commercially-available TPO-RAs [74,85].

	Eltrombopag	Romiplostim	Avatrombopag
Administration route	Oral	Subcutaneous	Oral
Dosage frequency	Once daily	Once weekly	Once daily
Dietary restrictions	Yes	N/A	No
Current indications	ITP (children and adults) Thrombocytopenia related to hepatitis C Sever aplastic anemia	ITP (children and adults)	ITP (adults) Periprocedural thrombocytopenia in people with chronic liver disease

Note: N/A: not applicable.

headache, fatigue, contusion, epistaxis, upper respiratory tract infection, arthralgia, gingival bleeding, petechiae and nasopharyngitis [81–83]. Previous studies have noted that platelet counts may increase excessively with avatrombopag overdose, which can lead to thromboembolic complications. These thrombotic events, including portal vein thrombosis, renal vein thrombosis, deep vein thrombosis, cerebral venous sinus thrombosis, and pulmonary embolism, can result in serious consequences. Close monitoring of platelet counts is essential to intervene promptly and treat thromboembolic events in a timely manner [84].

Comparison of the commercially-available TPO-RAs in Iraq are summarized in Table 6.

The goals of treatment with TPO-RAs

The target platelet count range is 50–100 $\times 10^9$/L, and it is not intended for the platelet count to normalize [50]. The aim of treatment is to prevent bleeding with safe platelets levels ($\geq$50 x10^9/L) with minimal toxicity [74,86]. A response is typically seen within 1–2 weeks; however, TPO-RAs should be discontinued if no response is observed 2–4 weeks after reaching the highest dose (Grade 2D) [87].

The expert panel reached 87.5% consensus agreement ($n = 14$) that normalizing the platelet count is not intended goal, and the lowest effective dose of TPO-RAs, sufficient to maintain a platelet count $\geq 50 \times 10^9$/L should be use. The expert panel reached 100% consensus agreement ($n = 16$) that for a response to TPO-RAs, a waiting period of 2–4 weeks after administering the maximum dose is recommended.

Expert consensus statement 11

- Normalization of platelet count is not intended (Grade 1 C).
- The lowest dose of TPO-RAs, sufficient to maintain a platelet count $\geq$50 x10^9/L must be use.
- For a response to TPO-RAs, a waiting period of 2–4 weeks after administering the maximum dose is recommended (Grade 2D).

Timing of TPO-RAs

While there is convincing consensus on the use of TPO-RAs as second-line therapy, the optimal timing for their administration has not been universally established [86]. Most international guidelines recommend TPO-RAs as the preferred second-line treatment for ITP patients who do not respond to previous therapies like corticosteroids or immunoglobulins (Grade 1 A) [75]. An early switch from corticosteroids to a TPO-RA has the dual advantage of sparing patients from corticosteroids overuse and improve long-term clinical outcomes [86].

In Iraq, due to the shortage of TPO-RAs, they can be used in patients with corticosteroid-dependent or refractory ITP after rituximab treatment (Grade 2 D) [5].

The expert panel reached 100% consensus agreement ($n = 16$) on the use of TPO-RAs as second-line treatment for ITP patients. Furthermore, the expert panel reached 100% consensus agreement ($n = 16$) on the use of TPO-RAs after rituximab in situations where there is a shortage of TPO-RAs.

Expert consensus statement 12

- If available TPO-RAs (eltrombopag, romiplostim or avatrombopag) are the preferred second-line treatment for ITP patients who are unresponsive or dependent on previous treatment (e.g. corticosteroids or immunoglobulins) (Grade 1 A).
- In situations where the use of TPO-RAs is limited, they can be considered following rituximab treatment (Grade 2 D).

Discontinuation of TPO-RAs

An overall response is observed in more than 90% of cases on TPO-RAs, whereas durable responses during therapy range from 30% to 60% [4,50].

TPO-RAs dose should be adjusted to maintain a platelet count of $50–100 \times 10^9$/L. In about one-third of patients, the platelet count will remain above 50×10^9/L after the discontinuation of TPO-RAs eliminating the need for further treatment (Grade 2 D) [50,86]. Abruptly discontinuing TPO-RAs may lead to a rapid and deep decrease in platelet count. Therefore, platelet counts should be monitored at least four weeks following the cessation of the medication [50].

There is limited clinical guidance in the literature regarding the tapering or discontinuation of TPO-RAs. Experts recommended that we can started TPO-RAs tapering, with the possibility of discontinuation for individual ITP patients who achieve sustained platelet counts above $50–100 \times 10^9$/L for more than 6 months (Grade 2D). The TPO-RAs dose should be tapered gradually and discontinued with 6–8 week. Tapering should be stopped and dose increased if the platelet count deceases to $< 30–50 \times 10^9$/ L during the tapering process. The suggested protocol for tapering and discontinuing eltrombopag and romiplostim is shown in Figure 1 [50,75,86,87].

The expert panel reached 87.5% consensus agreement ($n = 14$) for dose tapering of TPO-RAs with possible discontinuation for ITP patients achieving sustained platelet counts above 50×10^9/L. Additionally, the expert panel reached 100% consensus agreement ($n = 16$) for early tapering and discontinuation of TPO-RAs if platelets count consistently remain $\geq 200 \times 10^9$/L.

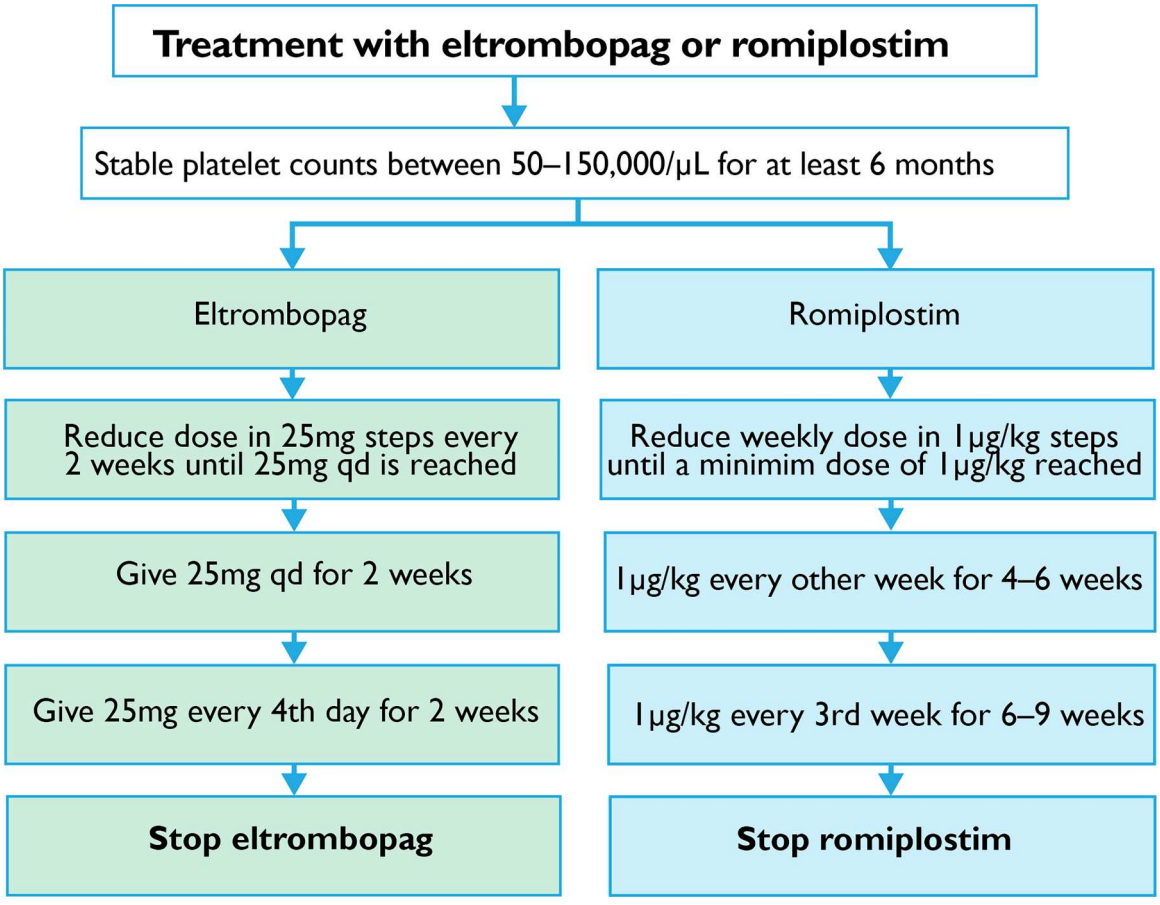


Figure 1. The suggested protocol for tapering and discontinuing eltrombopag and romiplostim.

Expert consensus statement 13

- A dose-reduction or tapering regimen with the potential for discontinuation of TPO-RAs should be considered for individual ITP patients who achieve sustained platelet counts above 50–100 $\times 10^9$/L and have no bleeding for at least 6 months while on TPO-RAs, in the absence of other concomitant treatments (Grade 2 D).
- If platelet counts continuously remain $\geq 200 \times 10^9$/L, tapering to discontinuation can begin earlier (Grade 2 D).

Switching between TPO-RAs

In patients who are refractory or resistant to their first TPO-RAs treatment (showing no improvement in platelet counts after 2–4 weeks of maximum dose administration), switching to an alternate TPO-RAs may be a more suitable option than prescribing third-line therapies. On the other hand, switching may be due to adverse events (AEs), patient preference, and platelet count fluctuations. The outcomes of switching were similar regardless of the direction of the switch (i.e. eltrombopag to romiplostim or romiplostim to eltrombopag) (Grade 1 C) [75,87–89]. There is no cross-resistance among avatrombopag, eltrombopag, and romiplostim; therefore, a decrease in the effectiveness of one treatment does not hinder the efficacy of another [50].

The expert panel reached 100% consensus agreement ($n = 16$) for switching to an alternative TPO-RAs in ITP patients who do not achieve an adequate response or develop unacceptable side effects.

Expert consensus statement 14

- Switching to the alternative TPO-RAs can be an appropriate treatment strategy in patients with ITP, if they do not achieve sustained or adequate response with the first TPO-RAs (Grade 1 C).
- Switching may be due to adverse events (AEs), patient preference, and platelet count fluctuations (Grade 1 C).

Selection of TPO-RAs

Although each of these agents demonstrates comparable initial overall response rates, several considerations impact agent selection [74]. Cost and drug availability are important consideration when deciding to use TPO-RAs treatment, as these agents remain expensive [5,74].

A patient's insurance coverage may determine which treatment is available. In Iraq, romiplostim is provided free of charge to patients in the governmental sector, while eltrombopag is available only in the private sector. Unfortunately, avatrombopag is not available in the country [5].

Eltrombopag and avatrombopag offer the convenience of oral administration, compared with romiplostim which usually requires weekly clinic visits for subcutaneous administration [74]. On the other hand, in contrast to eltrombopag, dietary restrictions are not required with romiplostim and avatrombopag [74]. In chronic ITP with concurrent liver dysfunction, avatrombopag has a low risk of liver-related side effects and is considered preferable for patients with chronic ITP and liver disease (Grade 1 D) [75].

The expert panel reached 93.75% consensus agreement ($n = 15$) for the use of romiplostim and avatrombopag in patients with specific dietary requirements. Additionally, the expert panel reached 100% consensus agreement ($n = 16$) for the use of avatrombopag in ITP patients with concomitant liver dysfunction.

Expert consensus statement 15

- The selection of TPO-RAs depends on:
  - The availability of drugs
  - Individual patient preference: The usage of a weekly subcutaneous injection or a daily oral drug.
- Romiplostim or avatrombopag may be more suitable than eltrombopag for certain ITP patients with specific dietary requirements (Grade 1 D).
- TPO-RAs with a very low risk of hepatic side effects such as avatrombopag, may be preferable for patients with chronic ITP who have concomitant liver dysfunction (Grade 1 D).

Table 7. Second-line agents in ITP patients.

Agent/treatment	Ranges of reported doses	Response rate	Time to response	Toxicities
Rituximab [15,72]	• 375 mg/m^2 4 doses weekly. 100 mg can be used regardless of the body's surface area.	50–70%	• Early response (1–2 weeks) • Late response (8–12) weeks	• Infusion reaction • Increased infection risk as a result of B-cell depletion. • Hepatitis B carrier status should be determined before beginning treatment due to the potential for reactivation. • For as long as six months, rituximab can prevent vaccination responses.
Mycophenolate Mofetil [15,43,90,91]	• 250 mg twice a day. • The dosage can be escalated to 500 mg twice a day after a week. • Dosage of 1 g twice daily can be reached after three weeks.	50–60%	Half of patients respond by 4 weeks.	• Diarrhea • Neutropenia, anemia and risk of viral infections. Prolonged use may lead to progressive multifocal leukoencephalopathy and a slight increase in the risk of cancer.
Azathioprine [15,43,92]	• 50–200 mg per day (1–3 mg/kg)	40–60%	3–4 months	• Leucopenia • Anemia • Hepatotoxicity
Hydroxychloroquine [15,89,93]	• 200 mg twice daily for ANA-positive patients	60%	2–3 months	• Gastrointestinal symptoms and skin rashes. • Rare but dangerous adverse effects include arrhythmias, cardiomyopathy, and retinopathy. For long-term users, yearly assessments by ophthalmologists are advised.
Dapsone [15,43]	• 100 mg/day	50%	3 weeks	• G6PD test before treatment. • Assessment of hemolysis markers such hemoglobin, reticulocyte count, and LDH. • Anorexia, abdominal distension, and methemoglobi-nemia, which causes cyanosis and dyspnea.
Ciclosporin [15,43]	• 3–5 mg/kg daily in two separate dosages (75–300 mg twice daily).	40–60%	1–3 months	• Infections, headache, hypertension, and renal impairment. • To reduce toxicity, trough levels need to be monitored.
Vincristine [94,95]	• 2 mg/dose IV (4–6 weekly doses).	41–86%	7 days	• Neuropathy • Constipation
Vinblastine [96]	• 0.1 mg/kg/week IV for 6 doses.	67–76%	10 days	• Neuropathy • Neutropenia • Rash
Danazol [15,43]	• 400–800 mg po daily	40–50%	3–6 months	• Possibility for liver injury and thrombosis • Androgenic side effects • Before beginning treatment, male's PSA levels need to be assessed.
Eltrombopag [15,76,77,97]	• 50–75 mg po daily	60–90%	2–3 weeks	• The most common adverse effect was anemia. • Hepatobiliary laboratory dysfunction as shown by elevated bilirubin or abnormal aspartate aminotransferase (AST)/alanine aminotransfera-se (ALT).
Romiplostim [15,43,98,99]	• 1 µg/kg/week, the dose can be escalated to 10 µg/kg/week until the optimal response is obtained.	75–85%	1–3 weeks	• Headache, fatigue, epistaxis, arthralgia, headache, sleeplessness, myalgia, and abdominal discomfort.
Avatrombopag [81,85,100]	• 20 mg po daily	84–93%	8–28 days	• Arthralgia, headache, fatigue, epistaxis, confusion, and diarrhea.

Other medical treatments

If rituximab and TPO-RAs are unavailable or ineffective, alternative choices should be considered. Immunosuppressive drugs like azathioprine, cyclosporine and mycophenolate mofetil (MMF) could be utilized for cases who do not respond to corticosteroids. Additionally, dapsone and danazol are viewed as

'corticosteroid-sparing' drugs and can be advantageous for certain cases, such as those for whom splenectomy is not recommended or when alternative treatments are not available (Grade 1 C). Vinca alkaloids are not appropriate for long term treatment due to their potential to cause neurological toxicity (Table 7) [3].

Therapy of refractory ITP

Defining refractory as 'no response to treatment' is subjective, in this consensus 'refractory ITP' was defined as failure to respond to ≥2 distinct lines of therapy. A 'line of therapy' refers to a complete course of a treatment strategy rather than the concurrent use of two drugs. For example, corticosteroids followed by a TPO-RAs would be considered two lines, whereas corticosteroids plus IVIG given together as initial treatment would constitute one line. Lines of therapy may include both emergent measures (such as corticosteroids, IVIG, or anti-D) and disease-modifying agents (such as rituximab, TPO-RAs, or immunosuppressants). This definition is consistent with international consensus reports and ensures clarity when classifying refractory disease [2,4,101,102].

The previous definition of refractory ITP, which considers patients who have failed splenectomy, is certainly outdated, as many patients may never consider splenectomy as a treatment option [103,104]. Approximately 15% of ITP patients do not achieve a durable response after three lines of therapy. ITP is classified as serious when patients experience recurrent, clinically severe bleeding that is unresponsive to several treatment modalities, resulting in high morbidity and mortality [50,87,103].

Most non-responsive patients require a bone marrow examination and should be reassessed to determine the cause of the thrombocytopenia [104]. In refractory patients, it is essential to continually reassess the necessity for therapy. Many patients can lead a relatively normal life with platelet counts below 20×10^9/L, needing only occasional corticosteroids or antifibrinolytic agents [104].

In refractory ITP, the treatment options are as follows:

- **Switching to other TPO-RAs**: Transitioning from one TPO-RAs to another, in addition to employing consecutive treatment, can improve response rates and tolerability, making it a viable option [3,50,87].
- **Combination therapy** (Grade 2 D):
  - TPO-RAs combined with mycophenolate mofetil [3,50,87]
  - TPO-RAs combined with corticosteroids [3,50,87]
  - TPO-RAs combined with cyclosporine, cyclophosphamide, everolimus, or azathioprine [3,50,87].
  - All-trans retinoic acid (ATRA) plus danazol [105].
- **Rituximab**: If has not been used previously, it is highly recommended [104].
- **Splenectomy**: Clinically stable patients should be assessed for splenectomy [3,104].

The expert panel reached 100% consensus agreement ($n = 16$) for the use of combination treatment in refractory ITP patients. Additionally, 100% consensus agreement ($n = 16$) was reached for the use of rituximab in refractory cases if it has not been previously used. Meanwhile, 93.75% consensus agreement ($n = 15$) was reached for splenectomy in refractory patients.

Figure 2 summarize treatment algorithm of ITP patients.

Expert consensus statement 16

- Refractory ITP is defined as a condition in which a patient has not responded to two or more medical therapies following treatment with corticosteroids or IVIG, regardless of whether they have undergone splenectomy.
- For cases who have not responded to multiple treatment lines should:
  - ➢ Reevaluate the diagnosis (e.g. inherited disease must be excluded)
  - ➢ If not already done, perform bone marrow examination.
  - ➢ Reevaluate whether treatment is necessary, taking bleeding risk and platelet level into account.
- Treatment options include:
  - ➢ Switching to other TPO-RAs
  - ➢ Combination therapy
  - ➢ Rituximab if not previously used.
  - ➢ Other monotherapies e.g. mycophenolate mofetil, azathioprine and cyclophosphamide can be used.
  - ➢ Splenectomy

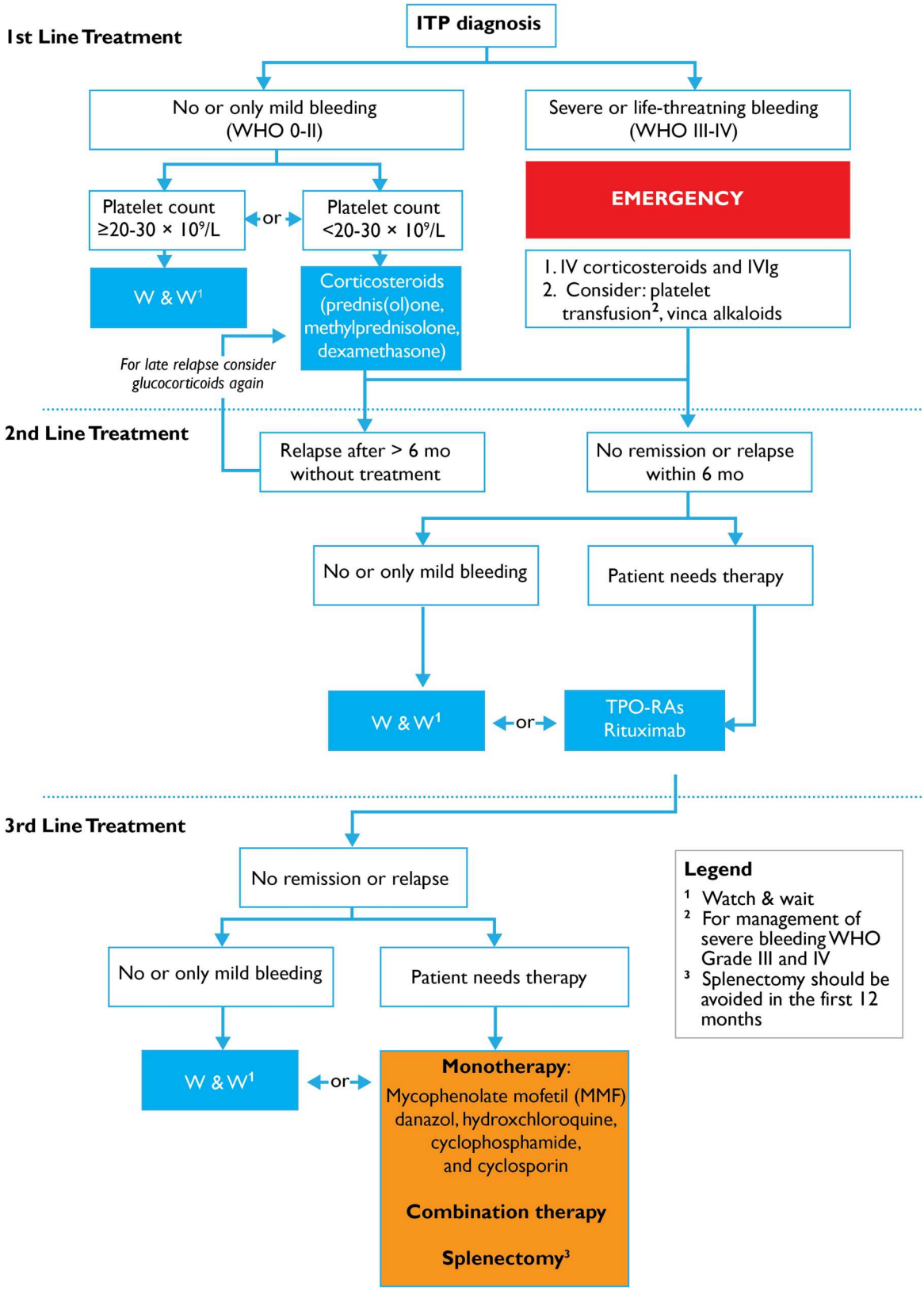


Figure 2. Treatment algorithm of ITP patients.

Splenectomy

Spleen is the primary organ responsible for the destruction of antibody-sensitized platelets, and splenectomy is traditionally considered as the second-line treatment in adults with ITP who do not achieve a safe platelet count with initial therapy [52]. The development of novel treatments, such as anti-CD20 antibodies and TPO-RAs, has increased uncertainty regarding the timing of splenectomy as the standard next step in ITP management [106,107].

Splenectomy remains the treatment option with the highest cure rate for ITP, with reported rates of 60–70% at five years. However, it is important to acknowledge that splenectomy is an invasive and irreversible procedure associated with postoperative complications. Furthermore, its outcome can be unpredictable, leading some physicians and patients to consider alternative approaches [52,106,107].

If feasible, splenectomy is deferred for one year following the diagnosis of ITP because remission may occur spontaneously or as a result of treatment and is usually kept for cases who have not responded to multiple treatment lines (Grade 2 D) [2,108,109].

The expert panel reached 100% consensus agreement ($n = 16$) that splenectomy should not be considered unless TPO-RAs and rituximab have been tried. While, the expert panel reached 87.5% consensus agreement ($n = 14$) on deferring splenectomy until 12–24 months from diagnosis.

Splenectomy should be strongly considered for patients lacking medical alternatives, showing inadequate/transient response to IVIG and corticosteroids, or demonstrating poor response to TPO-RAs [108–111].

Splenectomy may be chosen by young patients who had active lifestyles, such as those who engaged in high-risk activities or contact sports. These individuals often want to stay away from regular checkups and platelet count checks, in addition to the burden of chronic medical treatments (Grade 2 D) [108,111].

The expert panel reached 75% consensus agreement ($n = 12$) on considering splenectomy based on patients' preferences, such as for young patients engaged in high-risk activities or contact sports, noncompliant patients with medications, or those without access to alternative medical care.

Patients should be informed about the risks associated with splenectomy, immunized, and given prophylactic antibiotics [73]. On the other hand, surgical risks are more in elderly patients particularly those with multiple comorbidities that worsen surgical outcomes [109].

Post-splenectomy complications include the risk of severe systemic infection due to the removal of splenic macrophages responsible for filtering and phagocytosing bacteria and other bloodborne pathogens. Although uncommon, overwhelming post-splenectomy infection (OPSI) has a high mortality rate [73,107]. OPSI is typically caused by encapsulated bacteria such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis,* with a case fatality rate exceeding 50%. Additionally, other pathogens implicated in OPSI include *Escherichia coli*, *Pseudomonas aeruginosa*, *Capnocytophaga canimorsus*, group B streptococci, *Enterococcus* spp., *Ehrlichia* spp., and protozoa such as *Plasmodium* spp., leading to malaria [73,107].

Before surgery, patients should receive vaccinations for pneumococcus, *Haemophilus influenzae* type B, and meningococcus. Following splenectomy, annual influenza vaccination is recommended (Grade 1 C) [50].

The expert panel reached 100% consensus agreement ($n = 16$) on administering vaccines at least two weeks prior to surgery and maintaining vaccination according to national guidelines.

It is advisable to maintain a platelet count of $\geq 50 \times 10^9$/L when performing splenectomy. Methods to systematically increase the platelet count, such as high-dose IVIG and platelet transfusion, should be implemented, taking the surgery date into consideration (Grade 2 D) [3]. Recently, a report highlighted a splenectomy performed with the platelet count maintained using TPO-RAs, demonstrating the efficacy of this approach. However, caution is necessary due to the increased risk of postoperative thrombosis [112].

It is essential to note that imaging may be necessary for patients who initially responded well to splenectomy but later experienced a relapse, to exclude the possibility of an accessory spleen developing (Grade 1 D) [15].

The expert panel reached 93.75% consensus agreement ($n = 15$) on maintaining a platelet count of $\geq 50 \times 10^9$/L when performing splenectomy. While the expert panel reached 100% consensus agreement ($n = 16$) on the preference for laparoscopic splenectomy over open splenectomy. At the same time, the expert

panel reached 100% consensus agreement ($n = 16$) on the necessity of recognizing and removing accessory spleens.

Expert consensus statement 17

- Recommendations for splenectomy:
  - Defer splenectomy until 12–24 months from diagnosis (Grade 2 D)
  - Do not consider splenectomy unless TPO-RAs and rituximab have been tried
  - Platelets count should be kept $\geq 50 \times 10^9$/L pre-splenectomy
  - Increase age associated with lower response rate to splenectomy
  - The long-term hazards of splenectomy should be explained to patients, including the risk of infection and thrombosis. They should also be educated on strategies to mitigate these complications.
- Splenectomy may be a choice in (Grade 2 D):
  - Patients whose are refractory to multiple lines of treatment
  - Patient preference e.g. young patients who engaged in high-risk activities or contact sports
  - Noncompliant patients with medications or for whom access to alternative medical care is unavailable.
- Vaccination against *Haemophilus influenzae*, *Neisseria meningitidis*, and *Streptococcus pneumoniae* must be administered at least two weeks prior to surgery and maintained according to national guidelines. It is important to note that recent treatment with rituximab (within the last 6 months) may reduce the efficacy of these vaccinations (Grade 1 C).
- In terms of effectiveness, laparoscopic splenectomy is comparable to open splenectomy with less complications (Grade 1 C).
- The surgeon should be able to recognize accessory splenic tissue, which is frequently present and must be removed (Grade 1 D).
- Postoperative thromboprophylaxis should be considered in patients undergoing splenectomy as long as the platelet count is >30–50 x10^9/L (Grade 1 D).
- According to national guidelines, prophylactic antibiotics should be administered (Grade 1 D).

Supportive treatment

Platelets transfusion

Platelet transfusions can be administered to hospitalized ITP patients with life-threatening bleeding (intracranial/gastrointestinal/genitourinary) or those requiring invasive surgical procedures (grade 2 D). Platelets act immediately; however, due to their rapid destruction, there is often little increase in the CBC platelet count [15,113,114].

The expert panel reached 93.75% consensus agreement ($n = 15$) on the use of platelet transfusion in life-threatening bleeding complications.

Expert consensus statement 18

- Platelet concentrates can be utilized for critical bleeding to achieve a temporary increase in platelet counts and to help control the bleeding such as cases who have life-threatening bleeding complications (intracranial/gastrointestinal/genitourinary) or urgent invasive surgical procedures (Grade 2 D).

Antifibrinolytics

In patients with severe thrombocytopenia, antifibrinolytic medications (such as oral or intravenous tranexamic acid and e-aminocaproic acid) could be effective in preventing repeated bleeding [15,115]. Tranexamic acid can be administered at a dose of 15–20 mg/kg orally every 8 h, while e-aminocaproic acid can be given at a dose of 1–5 g every 4–6 h (with a maximum dose of 24 g/day). These agents could be beneficial in specific surgical or dental operations or when there is a significant risk of massive hemorrhage. However, their use raises the risk of thrombosis [3,115]. Future studies are needed to optimize the dosing and administration routes (intravenous or oral) [115].

Bone protective therapy

Patients who have been on corticosteroids for a long time and are susceptible to osteopenia, such as post-menopausal women, should have their bone mineral density evaluated. These patients should be treated with vitamin D and calcium supplements. It is recommended that adults should maintain an adequate daily intake of vitamin D (800 IU) and calcium (700–1200 mg) [15,49,116].

Patients at high risk of fracture should be considered for oral alendronate, if contraindicated or poorly tolerated, zoledronic acid is appropriate alternative [116].

Proton pump inhibitors

Routine prophylaxis with proton pump inhibitors for short-term systemic corticosteroids use is not proved [117]. However, adjunctive therapies with proton pump inhibitors in patients with major gastrointestinal bleeding may be helpful [15].

Anti-thrombotic drugs in ITP patients

Patients with primary ITP are at increased risk for venous thromboembolic events compared to patients without this condition [49,118].

One possible explanation for this heightened risk is that the pathophysiology of ITP promotes a prothrombotic state, although the evidence supporting this is currently unclear and weak. Additionally, long-term effect of corticosteroids uses or splenectomy on the risk of thromboembolic events in ITP have not been fully described or explained. The mechanism behind the increased risk of thromboembolic events is likely multifactorial, with various hypotheses proposed. These include elevated levels of microparticles in a thrombocytopenic state, increased levels of antiphospholipid antibodies, and heightened autoantibody-induced injury to the endothelium in severe cases of ITP, all potentially contributing to thrombus formation [119].

Anticoagulation presents a clinical challenge in ITP patients, as it is typically contraindicated when platelet counts are below $50–75 \times 10^9$/L. Patients with ITP who require anticoagulation have been excluded from pivotal studies on newer therapeutic agents, resulting in limited clinical data [120].

Prophylactic anti-coagulants in ITP patients

Prophylactic anticoagulation is usually offered to immobilized medical patients or to postoperative surgical patients. These patients may have a high risk of thromboembolism (e.g. total hip or knee replacement, etc.). This risk has to be weighed against the risk of bleeding in thrombocytopenia [120].

Most guidelines suggest administering thromboprophylaxis if the platelet count remains above 50×10^9/L (Grade 1 D). With lower counts, mechanical prophylaxis (compression stockings, pneumatic devices) should be considered (Grade 2 D) [15,120].

The expert panel reached 75% consensus agreement ($n = 12$) on the administration of prophylactic anticoagulation if the platelet count is $\geq 50 \times 10^9$/L. The expert panel also reached 93.75% consensus agreement ($n = 15$) on the use of compression stockings and pneumatic devices as alternatives if the platelet count remains unsafe.

Expert consensus statement 19

- The risk of thrombosis, either venous or arterial, is increased in patients with primary ITP compared to general population.
- Prophylaxis anti-coagulant can be safely administered if platelets count $\geq 50 \times 10^9$ (Grade 1 D).
- If platelets count fails to raise (compression stockings, pneumatic devices) can be used as alternative (Grade 2 D).

Therapeutic anti-coagulants in ITP patients

For therapeutic dose anticoagulation in ITP patients with severe thrombocytopenia, the following recommendations are made:

- Administer corticosteroids and IVIG to rapidly raise platelet counts to a safe level (i.e. $\geq 50 \times 10^9$).
- Initiate TPO-RAs to maintain platelet counts within a safe range as corticosteroids are tapered and the effects of IVIG begin to diminish.
- Do not provide anticoagulation, regardless of the platelet count, in patients experiencing life-threatening bleeding or bleeding that requires transfusion (World Health Organization [WHO] grade III/IV). In cases of deep vein thrombosis (DVT), consider using a vena cava filter.
- For all other ITP patients (without bleeding, petechiae, or hematomas, and with stable hemoglobin = WHO grade 0/I/II), and platelets count $\geq 50 \times 10^9$consider anticoagulation (Grade 1 D).
- In patients with platelet counts $\geq 50 \times 10^9$, initiate standard-dose therapeutic anticoagulation (Grade 1 D).
- For patients with platelet counts $<50 \times 10^9$, administer half-standard doses and increase to full doses once platelet counts rise to $\geq$50 x10^9 (Grade 1 D) [120,121].

Antiplatelet drugs

- It is typically regarded as safe to provide antiplatelet drugs when platelet counts are $\geq 30 \times 10^9$/L, and dual antiplatelet therapy when platelet counts are $\geq 50 \times 10^9$/L (Grade 1 D) [15].

The expert panel reached 93.75% consensus agreement ($n = 15$) on the administration of therapeutic anticoagulation if the platelet count is $\geq 50 \times 10^9$/L, with dose reduction by half if the platelet count falls below 50×10^9/L. The expert panel also reached 87.5% consensus agreement ($n = 14$) on the administration of antiplatelet drugs if the platelet count is $\geq 30 \times 10^9$/L, while a platelet count of $\geq 50 \times 10^9$/L is considered safe for dual antiplatelet therapy.

Expert consensus statement 20

- Full-dose anticoagulation is considered acceptable in patients with a platelet count of $\geq 50 \times 10^9$/L (Grade 1 D).
- In patients with a platelet count of $< 50 \times 10^9$/L, reduced-dose anticoagulation to the half (Grade 1 D).
- Antiplatelet drugs are usually safe to administer if platelet level is $\geq 30 \times 10^9$/L, while dual antiplatelet drugs are safe if platelet level is $\geq 50 \times 10^9$/L (Grade 1 D).

Other treatments

Prophylaxis with trimethoprim-sulfamethoxazole at a dosage of 80 mg/400 mg twice a day, two to three times a week, should be administered to patients receiving a prolonged course of corticosteroids for more than 4 weeks to prevent infection by Pneumocystis jirovecii [49].

Prophylaxis against herpes virus with acyclovir at a dose of 400 mg per day is advisable for patients over 60 years old, those on prednisolone at daily doses greater than 7.5 mg, or patients with a history of infection with this virus. Additionally, prophylaxis with entecavir at a dose of 0.5 mg per day is recommended for patients with antibodies against HBVc and a positive hepatitis B virus (HBV) antigen test who are undergoing prolonged treatment with prednisolone or receiving immunosuppressants [49].

Preparing for surgery

The optimal platelet target for different surgical procedures remains uncertain, with platelet counts $\geq 50 \times 10^9$/L considered appropriate for lower-risk bleeding procedures, while counts $\geq 80–100 \times 10^9$/L are often targeted for higher-risk surgeries [122]. The minimum platelet count threshold required before invasive procedures is shown in Table 8.

The time available to prepare for interventions plays a crucial role in selecting treatment agents, as their onset of action varies. IVIG typically takes approximately 24–48 h to elicit a response, while corticosteroids

Table 8. Key considerations for surgical procedures in patients with primary ITP [3,15,49,50,112].

Surgery	Target platelet count
Low risk surgical procedure with less chance of bleeding.	$\geq 50 \times 10^9$/L
Low risk surgical procedure at a site that can be compressed.	$\geq 30 \times 10^9$/L
Major surgical procedure, including non-compressible site and thoracic or abdominal surgeries.	$\geq 80 \times 10^9$/L
Brain surgeries	$\geq 100 \times 10^9$/L
Operations on the eye's posterior segment	$\geq 100 \times 10^9$/L
Dental	
Dental cleaning	$\geq 20 \times 10^9$/L
Tooth extraction (simple)	$\geq 30 \times 10^9$/L
Tooth extraction (complex, surgical, molar)	$\geq 50 \times 10^9$/L
Regional anesthetic nerve block for tooth extraction	$\geq 30 \times 10^9$/L
Procedures	
Lumbar puncture (elective)	$\geq 50 \times 10^9$/L
Lumbar puncture (emergency)	$\geq 20 \times 10^9$/L
Spinal/epidural anesthesia	$\geq 70 \times 10^9$/L
Central line placement	$\geq 20 \times 10^9$/L
Gastroscopy combined with a biopsy	$\geq 50 \times 10^9$/L
Bronchoscopy and lavage	$\geq 30 \times 10^9$/L
Bronchoscopy combined with biopsy.	$\geq 50 \times 10^9$/L
Joint aspiration	$\geq 30 \times 10^9$/L
Liver biopsy, transcutaneous	$\geq 50 \times 10^9$/L
Bone marrow biopsy	Thrombocytopenia is not a contraindication.
Other organ punctures and biopsies	$\geq 50 \times 10^9$/L
• Grade 2D	
• There is no risk of bleeding during cataract surgery with laser technology.	

may require three to four days in responsive individuals. However, the accessibility of agents such as IVIG in resource-constrained environments can be challenging [5,122].

For urgent surgical operations, intravenous corticosteroids, IVIG (1 g/kg/day for 2 days) can be administered (Grade 1 B). Platelet transfusion (at induction of anesthesia, and subsequently intra- and/or postoperatively depending on bleeding) must be administered as close as feasible to the procedure's scheduled time or when anesthesia is induced, with expected platelet survival of 1–4 h (Grade 1 C). Procedures should not be postponed to verify an increase in platelet count (Grade 1 D) [15].

Regarding elective surgical interventions (less than 1 week), options consist of IVIG or intravenous corticosteroids (Grade 1 B) [15,52]. Conversely, if there is more time available (more than one week) before elective surgery, oral corticosteroids and TPO-RAs (romiplostim 3 µg/kg subcutaneous weekly) can be considered also (Grade 1 D) [52]. The management of urgent and planned surgical procedures in ITP patients is shown in Table 9.

Table 9. Emergency surgery management [49,50].

Time to surgery	Options for treatment (one or more)
<12–24 h	• Dexamethasone, 40 mg/day × 4 days • IVIG, 1 g/kg/day × 2 days. If needed, another dose is allowed within 1 week of achieving the target platelet count. • Platelet transfusion during or after surgery
1–7 days	• Dexamethasone, 40 mg/day × 4 days • IVIG, 1 g/kg/day × 2 days • Platelet transfusion remains as an option when other therapies have failed.
Management of elective operations	
Time to surgery	**Options for treatment**
<2 weeks	• Dexamethasone, 40 mg/day × 4 days • IVIG, 1 g/kg/day × 2 days • TPO-RAs: ➢ Eltrombopag, 50 mg/day ➢ Avatrombopag, 20 mg/day ➢ Romiplostim, 3 µg/kg/week
4 weeks	• Dexamethasone, 40 mg/day x 4 days • Prednisolone, 0.5–1 mg/kg/day • TPO-RAs: ➢ Eltrombopag, 50 mg/day ➢ Avatrombopag, 20 mg/day ➢ Romiplostim, 3 µg/kg/week

The expert panel reached 100% consensus agreement ($n = 16$) on the use of intravenous corticosteroids and IVIG before urgent surgical procedures, while 93.75% consensus agreement ($n = 15$) was reached for platelet transfusion before or during the procedure. The expert panel also reached 100% consensus agreement ($n = 16$) on the use of corticosteroids, IVIG, and TPO-RAs before elective procedures.

ITP during pregnancy

Thrombocytopenia is a common occurrence in pregnancy, affecting approximately 8–10% of pregnancies. This condition is typically secondary to physiological changes during gestation, including an increase in blood volume, platelet activation, increased platelet clearance, and platelet sequestration in the placenta [123].

ITP manifests in approximately 1 in 1000–10,000 pregnancies. Although ITP accounts for only around 3% of all cases of thrombocytopenia during pregnancy, it remains the most frequent cause of a platelet count below 50×10^9/L detected in the first and second trimesters [124].

In contrast to many autoimmune disorders, ITP frequently exacerbates during pregnancy, and its management is more limited because of the risk of fetal toxicity [15].

Approach to diagnosis

The diagnosis of ITP in pregnant patients follows the same approach as in non-pregnant individuals, but the differential diagnosis should also consider pregnancy-specific conditions like gestational thrombocytopenia and hypertensive disorders related to pregnancy. It is important to note that these conditions usually arise in the later stages of pregnancy, whereas ITP is more likely to be the primary cause of thrombocytopenia in early pregnancy [10,125].

In pregnancy further attention to assessment of blood pressure, urine proteins, hemostatic status and antiphospholipid & antinuclear antibodies (ANAs) (Grade 2 D) [49]. The trimester during which thrombocytopenia develops can provide valuable insights into its etiology. A gradual decline in platelet count occurring in the middle of the second trimester typically indicates gestational thrombocytopenia, while a decline before the second trimester suggests an etiology other than gestational thrombocytopenia [126]. We consider a platelet count $< 80 \times 10^9$/L as a trigger to conduct further investigations for an alternative etiology than gestational thrombocytopenia (Grade 2 D). We consider a diagnosis of gestational thrombocytopenia unlikely if the platelet count is $< 50 \times 10^9$/L [46,125].

The expert panel reached 100% consensus agreement ($n = 16$) that ITP during pregnancy needs exclusion of other pregnancy-specific conditions like gestational thrombocytopenia. However, bone marrow examination is not routinely recommended unless atypical features are present.

Expert consensus statement 21

- The diagnosis of ITP during pregnancy necessitates the exclusion of other causes of thrombocytopenia, particularly gestational thrombocytopenia (Grade 2 D).
- Platelet count $< 80 \times 10^9$/L is a trigger to conduct further investigations for an alternative etiology rather than gestational thrombocytopenia (Grade 2 D).
- We consider a diagnosis of gestational thrombocytopenia unlikely if the platelet count is $< 50 \times 10^9$/L (Grade 2 D).
- Other conditions that should be considered and excluded include HELLP syndrome, pre-eclampsia, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, and specific infectious conditions presenting with distinct clinical features (Grade 2 D).
- Bone marrow examination is generally not advised except if atypical features are present (Grade 2 D).

Prenatal risks and management

ITP often deteriorates during pregnancy, with most women who have pre-existing ITP experiencing a decline in platelet count, and nearly half (49%) requiring treatment. The decision to start therapy usually depends on the severity of thrombocytopenia, the presence of bleeding symptoms, and the stage of the pregnancy [3,127].

Throughout the first and second trimesters, platelet counts may be safely maintained at 20–30 $\times 10^9$/L (Grade 2 D). Higher platelet count targets could be considered in cases where there are signs of bleeding or when a procedure is required [3,15,127].

In the third trimester, platelet levels should be carefully monitored. For both vaginal and caesarean deliveries, a platelet count of $\geq 50 \times 10^9$/L is typically sufficient, while a target of $\geq 75 \times 10^9$/L is recommended for neuraxial anesthesia (Grade 2 D) [3,15,127].

The expert panel reached 75% consensus agreement ($n = 12$) that a platelet count of $\geq$ 20–30 $\times 10^9$/L is safe during pregnancy, 93.75% consensus agreement ($n = 15$) that a platelet count of $\geq 50 \times 10^9$/L is safe for normal vaginal delivery, 87.5% consensus agreement ($n = 14$) that a platelet count of $\geq 50 \times 10^9$/L is safe for cesarean section, 93.75% consensus agreement ($n = 15$) that a platelet count of $\geq 75 \times 10^9$/L is safe for regional axial anesthesia, and 100% consensus agreement ($n = 16$) that prophylactic anticoagulation can safely be administered when needed if the platelet count is $\geq 50 \times 10^9$/L.

Expert consensus statement 22

- Platelets count $\geq$20–30 $\times 10^9$/L is safe through pregnancy (unless there are signs of bleeding or a procedure is required) (Grade 2 D).
- Platelets count $\geq 50 \times 10^9$/L is safe for normal vaginal delivery (Grade 2 D).
- Platelets count $\geq 50 \times 10^9$/L is safe for caesarian section (Grade 2 D).
- The platelets count $\geq 75 \times 10^9$/L is safe for regional axial anesthesia (Grade 2 D).
- The recommended platelet count for pregnant ITP patients require anticoagulation is $\geq 50 \times 10^9$/L (Grade 2 D).

First-line treatment of ITP during pregnancy

It is recommended to use low-dose corticosteroids as initial treatment (Grade 1 D). Prednisolone at a dose of 20 mg/day is advised with subsequent adjustments made to the minimum effective dose, as corticosteroids carry the risk of inducing weight gain, osteoporosis, hypertension, emotional changes, and hyperglycemia. Postpartum, close monitoring of platelet counts is essential, and corticosteroid tapering should be gradual to prevent abrupt decline in platelet level and to safeguard the mother's mental well-being [3,15,128]

IVIG at a dosage of 1–2 g/kg as a single or divided dose is deemed safe during pregnancy (Grade 1 D). IVIG may be required occasionally to sustain adequate platelet levels during pregnancy, particularly in anticipation of labor when a swift increase in platelet count may be necessary [15,128,129].

The expert panel reached 81.25% consensus agreement ($n = 13$) on the use of low-dose corticosteroids (20 mg) as a first-line treatment during pregnancy, while 100% consensus agreement ($n = 16$) was reached for the use of IVIG in life-threatening hemorrhage.

Expert consensus statement 23

- Discontinue any medication contraindicated in pregnancy e.g. mycophenolate mofetil.
- The first-line of treatment is low-dose corticosteroids. First, 20 mg/d of prednisolone is advised then adjusted to keep lowest effective dose (Grade 1 D).
- IVIG (1–2 g/kg) is considered safe in pregnancy and can be used before delivery or for life-threatening hemorrhage (Grade 1 D).

Second-line treatment of ITP during pregnancy

For patients who do not respond to the first-line treatment or whose platelet levels continue to decline even with ongoing treatment, combination of the first-line drugs or adding new ones may be beneficial. For patients who do not respond to oral corticosteroids alone, the recommended approach is to combine high-dose methylprednisolone with either azathioprine or IVIG (Grade 1 D) [3].

Azathioprine and cyclosporine A have been safely administered to pregnant patients (Grade 1 D). These agents may prove to be effective for individuals with ITP who are unresponsive to other treatments, although it may take several weeks to observe an increase in platelet count [3,126,127].

Rituximab may be considered as a treatment option; however, it carries the risk of neonatal lymphopenia, impaired response to vaccinations, and subsequent infections (Grade 2 D) [3,126,127]. Further immunosuppressive drugs, such as mycophenolate mofetil (MMF) and vinca alkaloids, should be avoided since they have been linked to teratogenicity (Grade 1 D) [3,124,126,127].

Under certain situations, TPO-RAs might be taken into consideration, preferably in the third trimester near labor [3,124,127]. However, due to limited safety data in pregnancy, routine use of these agents is not advised. If TPO-RAs are utilized, romiplostim might be the better option due to its less adverse effects, such as lack of liver toxicity (Grade 2 D) [3,75,126].

Splenectomy is rarely indicated. If necessary, it is advisable to perform the procedure during the second trimester, preferably via laparoscopy and following vaccination according to national guidelines [3,124,126,127].

Platelet transfusions are not routinely recommended, except in cases of significant uncontrolled bleeding or when the platelet count is $<50 \times 109$/L near delivery (Grade 2 D). Aminocaproic acid is a safe, effective adjunct therapy for women with severe ITP or other thrombocytopenic disorders at high bleeding risk, both pre- and post-delivery [124,126].

Regarding second-line treatment during pregnancy, the expert panel reached 100% consensus agreement ($n = 16$) for combination treatment (e.g. corticosteroids and IVIG), TPO-RAs (romiplostim), azathioprine and cyclosporin A. Additionally, 75% consensus agreement ($n = 12$) was reached for the use of rituximab.

Expert consensus statement 24

- Second-line treatment options in pregnancy are:
  - Combination therapy: Corticosteroids + IVIG (Grade 1 D).
  - TPO-RAs (romiplostim) might be considered during late pregnancy if no response or contraindicated to corticosteroids and IVIG (Grade 2 D).
  - Rituximab is potentially a safe treatment option with good maternal and neonatal outcome (Grade 2 D).
  - Pregnant patients can safely use azathioprine and cyclosporine A (Grade 1 D).

Management of delivery

The mode of delivery should be guided by obstetrical indications rather than ITP (Grade 1 C). It is important to avoid procedures that could cause bleeding during labor, particularly rotational forceps, ventouse delivery, fetal scalp electrodes, and fetal blood sampling. Thromboprophylaxis can be considered if the platelet count is $>50 \times 10^9$ /Land the mother is less mobile postpartum. (Grade 1 D) [3,52].

Regarding the management of delivery, the expert panel reached 100% consensus agreement ($n = 16$) that the mode of delivery should be determined by obstetric indications, 100% consensus agreement ($n = 16$) to avoid procedures that increase the risk of bleeding during delivery, and 93.75% consensus agreement ($n = 15$) to avoid the use of NSAIDs for postpartum pain if the platelet count is below 70×10^9/L.

Expert consensus statement 25

- Delivery should be supervised by a skilled and well-trained obstetrician.
- The method of delivery is determined by obstetric indications (Grade 1 C).
- For postoperative or postpartum pain management, women with platelet levels less than 70×10^9 /Lshould not use NSAIDs due to an elevated risk of hemorrhage (Grade 2 D).
- All women who are at a higher risk of thromboembolism, even those with ITP, should get the proper venous thromboembolism prophylaxis. For such cases on anticoagulation, a platelet level $\geq 50 \times 10^9$/L is usually advised. (Grade 1 D).
- Avoid rotational forceps, ventouse delivery, fetal scalp electrodes, and fetal blood sampling (Grade 1 D).

Neonatal risks and management strategies

Post-delivery, it is crucial to closely monitor the neonate, as 21% to 28% may develop thrombocytopenia, likely due to the passive transfer of maternal autoantibodies targeting platelet antigens. Most cases involve mild thrombocytopenia without serious bleeding complications. Fortunately, the incidence of intracranial hemorrhage in neonates is less than 1% [127]. Additionally, a history of splenectomy in the mother has been linked to a worsening of ITP during pregnancy. A mother who has previously had a newborn, whether thrombocytopenic or not, is at an increased likelihood of having another infant with a same platelet level and a risk of neonatal thrombocytopenia [3].

The platelet count from the umbilical cord should be measured either at delivery or as soon as feasible afterward (Grade 1 D). If the cord platelet count is $< 100 \times 10^9$/L, it is recommended to repeat the platelet count daily until it stabilizes (Grade 1 D). There is a high incidence of pseudothrombocytopenia in neonates due to challenges in obtaining unclotted blood during blood draws (Grade 1 D) [3].

When platelet values are $< 50 \times 10^9$/L, a cranial ultrasound should be conducted. If hemorrhage is detected, treatment with IVIG and methylprednisolone should be administered at the lowest effective doses for a short duration, aiming for a platelet count above 100×10^9/L for one week and above 50×10^9/L for an additional week (Grade 2 D). In cases of symptomatic bleeding or if the platelet count falls below 30×10^9/L, platelet transfusion can be administered alongside IVIG (Grade 2 D) [3,49].

The expert panel reached 93.75% consensus agreement ($n = 15$) on the need for cord platelet count evaluation at delivery and 100% consensus agreement ($n = 16$) on the need for daily monitoring of neonatal platelet count if it is abnormal. Additionally, the expert panel reached 100% consensus agreement ($n = 16$) on the administration of corticosteroids, IVIG, and platelet transfusion for neonatal intracranial hemorrhage.

Expert consensus statement 26

- At delivery, a cord platelet count should be evaluated (Grade 1 D)
- Sever thrombocytopenia and major bleeding are uncommon
- Daily monitoring is needed if subnormal platelets count at birth (Grade 1 D)
- There is no correlation between neonatal platelets level and severity of maternal ITP
- In case of neonatal intracranial hemorrhage, the treatment options are:
  - IVIG ± corticosteroids (Grade 2 D)
  - Platelets transfusion (Grade 2 D)

Breastfeeding

Most women with ITP can breastfeed if they choose. However, it is important to recognize that breastfeeding may occasionally lead to persistent neonatal thrombocytopenia, which usually resolves once breastfeeding is stopped. In cases where this occurs, discontinuing breastfeeding is recommended (Grade 2 D). If the mother wishes to resume breastfeeding after the infant's platelet count recovers, she should be encouraged to express breast milk to maintain lactation. Breastfeeding can be restarted once the baby's platelet count improves and remains stable following reintroduction. When providing breastfeeding counseling, the impact of the mother's ITP treatment should be considered, as some medications, such as glucocorticoids and TPO-RAs, can be excreted in breast milk [127]. Data on the safety of TPO-RAs during lactation are limited. Animal studies with eltrombopag indicate that it can cross into breast milk, but its safety for the infant remains unknown. Romiplostim may be a safer option, as its large molecular size likely limits its transfer into breast milk. No data are available on avatrombopag [130].

The expert panel reached 87.5% consensus agreement ($n = 14$) that breastfeeding is not contraindicated for women with ITP. Additionally, the panel reached 93.75% consensus agreement ($n = 15$) that breastfeeding should be temporarily paused if neonatal thrombocytopenia develops and resumed once the platelet count improves.

Expert consensus statement 27

- Breastfeeding should not be discouraged for women with ITP, due to the lack of a clear correlation between breastfeeding and newborn thrombocytopenia (Grade 2 D).
- If severe thrombocytopenia occurs in a breastfed infant, it is advisable to temporarily pause breastfeeding for a few days to observe if there is an improvement in the platelet count (Grade 2 D).
- Breastfeeding can be resumed as soon as the baby's platelet count stabilizes and improves (Grade 2 D).
- There is no universal consensus on the use of TPO-RAs during breastfeeding.

Counseling for women who have ITP or who develop it during pregnancy

Childbearing-age women diagnosed with ITP should realize that pregnancy is not contraindicated. The management of ITP in women who wish to conceive should involve a collaborative approach between a hematologist skilled in ITP management and an obstetrician expert in high-risk pregnancies [3,106,124]. Maternal ITP is a risk factor for preterm birth, and women with chronic ITP tend to experience more adverse outcomes than those with pregnancy-related ITP. However, when managed by an expert team, severe maternal or neonatal bleeding is rare [131].

The expert panel reached 93.75% consensus agreement ($n = 15$) that ITP is not a contraindication for pregnancy. Additionally, the expert panel reached 100% consensus agreement ($n = 16$) that ITP during pregnancy should be managed by a multidisciplinary team (MDT) comprising a hematologist, obstetrician, pediatrician, and neonatologist to minimize potential complications.

Expert consensus statement 28

- Women with ITP generally have favorable pregnancy outcomes, and ITP is not an absolute contraindication to pregnancy.
- Pregnant women with ITP should be managed by a multidisciplinary team (MDT) comprising a hematologist, obstetrician, pediatrician, and neonatologist to minimize potential complications.

Secondary ITP

Secondary ITP accounts for 9–20% of adult ITP cases, with prevalence rising progressively with age [49]. When ITP is associated with another underlying condition, it is classified as secondary ITP. This form is relatively common and often shows a poor response to first-line corticosteroids therapy [50]. In such cases, management of the underlying disease is essential [49].

Common triggers of secondary ITP are:

- Medications
- Infections (e.g. HIV, hepatitis C, *H. pylori*, COVID-19)
- Systemic autoimmune diseases (SLE and antiphospholipid syndrome)
- Primary and secondary immunodeficiency syndromes (e.g. common variable immunodeficiency).
- Hematologic neoplasms such as myelodysplastic syndromes and lymphoproliferative disease (1–2% of all lymphoma and 2–5% of CLL patients develop secondary ITP) [49,50].

In comparison to primary ITP, secondary ITP is less common in children and adolescents, with its incidence increasing as individuals age [50].

Treatment

Secondary ITP may exhibit a poor response to first-line corticosteroids therapy, and there are no specific treatment guidelines since management is determined by the underlying disease and the severity of thrombocytopenia [49,50].

If thrombocytopenia is the main clinical concern, the usual approach for primary ITP should be followed. Initial treatment typically involves corticosteroids and IVIG, while in second-line treatment, rituximab may be a suitable choice, as it carries a lower risk of thrombosis compared to TPO-RAs. There is substantial evidence indicating that TPO-RAs should not be used in SLE or antiphospholipid syndrome, due to the risk of thrombosis [4,49,50].

Splenectomy tends to have lower long-term remission rates in secondary ITP than in primary ITP and can further suppress the immune system, increasing the risk of infections. Consequently, splenectomy should generally be avoided in cases of secondary ITP [49,50].

For patients with secondary ITP resulting from hepatitis C virus infection, antiviral therapy should be considered when there are no contraindications. However, platelet counts must be monitored closely due to the potential for worsened thrombocytopenia associated with interferon treatment. In such cases, IVIG may be an acceptable initial treatment option [4].

For cases with HIV-related ITP, it is advisable to prioritize HIV treatment with antiviral medications before exploring alternative forms of treatment, except if the patient experiences serious hemorrhage [4].

ITP and COVID-19

SARS-CoV-2, similar to other viral agents, can trigger ITP. However, significant thrombocytopenia is rare in patients with COVID-19, and conditions such as heparin-induced thrombocytopenia (HIT), microangiopathic hemolytic anemia (MAHA), and drug-related causes should be evaluated prior to diagnosing ITP [49,132].

Treatment of COVID-19 positive new/relapse ITP patients

The treatment for cases with positive COVID-19 test is further complicated because of both bleeding and thrombotic risks seen in those patients. The treatment options as follow:

Corticosteroids could be the preferred treatment for patients with new or relapsed ITP who are COVID-19 positive. Although, it is essential to limit both the dosage and duration of the therapy. For non-bleeding patients, 20 mg per day as the initial dosage (regardless of body weight) may be appropriate, with adjustments made 3–5 days later if there is no improvement. Prolonged corticosteroids use must be discouraged, and it is advisable to follow the standard practice of tapering the dose after two weeks [49,50,132].

Intravenous immunoglobulin (IVIG) may be required when a rapid increase in platelet level is needed to manage massive hemorrhage. It can also be considered as a second-line treatment if there is no response to corticosteroids. However, IVIG administration requires hospital visits, and its availability may be limited. While complications associated with IVIG are uncommon, they can still be significant [5,49,50,132].

TPO-RAs may be considered as initial therapy in COVID-19 patients with ITP, though caution is advised due to their potential thrombotic risk, which could compound the elevated thromboembolic risk associated with COVID-19. Furthermore, 15% of cases using eltrombopag have been reported to experience hepatobiliary complications, and this medication includes a black box warning for liver injury [49,50,132].

Tranexamic acid works by inhibiting fibrinolysis. It is contraindicated in cases of overt disseminated intravascular coagulation (DIC). When managing bleeding in a patient with COVID-19, the balance of risks associated with bleeding and thrombosis must be carefully assessed. If tranexamic acid is deemed appropriate, treatment duration should be minimized. For oral bleeding, tranexamic acid mouthwashes can be administered for rinsing and expectoration [132].

Immunosuppressant drugs there is concern that COVID-19 positive ITP patients on immunosuppressant drugs may experiencing more severe disease. Rituximab, known for inducing prolonged B cells depletion and serious infections, poses uncertainties regarding its impact on COVID-19 infection risk. It might be advisable to avoid rituximab and immunosuppressant drugs in new or relapsed patients infected with COVID-19 [132].

Platelet transfusions are generally not needed or beneficial and should not be routinely administered to thrombocytopenic COVID-19 patients who are not bleeding. In COVID-19 patients with coagulopathy, platelet transfusions may worsen a prothrombotic state, and in those with ITP, the transfused platelets are likely to be rapidly destroyed, rendering the treatment ineffective. Platelet transfusions should be reserved for cases where bleeding is serious or involves a critical site, like the eyes [50,132].

The expert panel reached 87.5% consensus agreement ($n = 14$) on using minimum-dose corticosteroids as first-line treatment in ITP patients with COVID-19.

The expert panel also reached 87.5% consensus agreement ($n = 14$) on using IVIG as second-line treatment if corticosteroids fail or when a rapid platelet increase is needed.

Regarding TPO-RAs, the expert panel reached 87.5% consensus agreement ($n = 14$) on their use as second-line treatment.

The expert panel also reached 87.5% consensus agreement ($n = 14$) on avoiding rituximab as a second-line treatment.

Finally, the expert panel reached 100% consensus agreement ($n = 16$) regarding limitation of the platelet transfusion to life-threatening conditions only.

Expert consensus statement 29

- **Corticosteroids** are the first-line treatment, with the dosage and duration kept to the minimum necessary (Grade 2 D).
  - For cases who are not bleeding, a starting dose of 20 mg per day may be tried; if no improvement is seen after 3–5 days, the dose may be increased to 1 mg/kg.
  - After two weeks, corticosteroid dosages should be decreased; if there is a favorable response, taper slowly; if not, taper quickly.
- **IVIG** (1 g/kg/day) may be needed to quickly raise the platelet level to control hemorrhage and can also serve as a second-line treatment if corticosteroids fail (Grade 2 D).
- **TPO-RAs** can be used cautiously as it may raise the risk of thrombotic complications, and recognizing eltrombopag-related liver toxicity can be challenging (Grade 2 D).
- **Rituximab** should be avoided because it compromises the patient's ability to produce antibodies. Other immunosuppressants should also be avoided whenever possible for the same reason (Grade 2 D).
- **Platelet transfusions** should only be administered if hemorrhage is considered serious or occurs at a critical site (Grade 2 D).
- **Tranexamic acid** should be used to manage hemorrhage in ITP cases but should be avoided in those with disseminated intravascular coagulation (DIC).

Treatment of COVID-19 positive chronic ITP patients

The management of patients with chronic stable ITP should not change due to the COVID-19 infection; patients should continue their current medications, even if these include corticosteroids and immunosuppressants. However, strict adherence to isolation procedures is essential [132].

Patients with splenectomy are probably not at increased risk of COVID-19 infection but are susceptible to bacterial infections and must be vigilant with their prophylactic antibiotics during this time, as well as up to date with their *Haemophilus influenzae*, *Neisseria meningitidis*, and *Streptococcus pneumoniae* vaccinations [132]. ITP patients not requiring treatment in the last 12 months or on non-immunosuppressive agents such as TPO-RAs are not considered to be at increased risk of COVID-19 infection [132].

The expert panel reached 100% consensus agreement ($n = 16$) that chronic ITP patients infected with COVID-19 should continue their standard treatment with appropriate isolation precautions. The panel also reached 87.5% consensus agreement ($n = 14$) that rituximab and immunosuppressants should be avoided in chronic ITP patients with COVID-19.

Expert consensus statement 30

- Recommendations for COVID-19 positive chronic ITP patients:
  - Chronic ITP patients should continue their standard medications.
  - They should practice shielding measures and self-isolation as necessary.
  - Rituximab and other immunosuppressants should be avoided, as these medications impair antibody production.
  - Splenectomized patients should strictly adhere to antibiotic prophylaxis and ensure their vaccinations are current.

Anticoagulant & thrombotic risks in ITP patients with COVID-19

ITP is associated with a mild elevation in thrombotic risk both arterial and venous. Treatment-related factors such as splenectomy and TPO-RAs may slightly heighten this risk, particularly in the presence of associated antiphospholipid antibodies [132].

Low molecular weight heparin (LMWH) may provide benefits for these patients, but its use and dosage need to be carefully weighed against the bleeding risk, which can be significant in some severe COVID-19 cases, even without thrombocytopenia. If platelet counts drop below 30×10^9/L, it may be necessary to discontinue LMWH and use intermittent pneumatic compression as an alternative (Grade 2 D). LMWH should be reintroduced when the platelet level rises to $\geq 30 \times 10^9$/L. Continuous evaluation of both bleeding and thrombotic risks is crucial during the hospital stay and after discharge [49,132].

The expert panel reached 75% consensus agreement ($n = 12$) on the use of LMWH as prophylaxis if the platelet level is $\geq 30 \times 10^9$/L in hospitalized COVID-19 patients with ITP.

The expert panel reached 87.5% consensus agreement ($n = 14$) for the use of intermittent pneumatic compression instead of LMWH if the platelet count is below 30×10^9/L.

Expert consensus statement 31

- It is important to recognize that ITP or its treatment may further elevate the thrombotic risk in COVID-19 patients.
- Hospitalized COVID-19 patients with ITP require LMWH thromboprophylaxis based on weight if their platelet level is $\geq 30 \times 10^9$/L and there are no signs of bleeding (Grade 2D).
- For patients with a platelet count below 30×10^9/L, where LMWH is deemed unsafe, intermittent pneumatic compression should be used until it is safe to restart LMWH (Grade 2D).
- Both hemorrhage and thrombotic risks must be regularly assessed during the hospital admission and upon discharge.

ITP and COVID-19 vaccination

COVID-19 vaccination is considered safe for ITP patients with close monitoring of platelet counts. Exacerbations of ITP post vaccination can be developed in response to immunological stimuli. Even when exacerbations are experienced by ITP patients, therapy generally yields a good response. The decrease in platelet count after SARS-CoV-2 vaccination is observed to be similar in both patients with ITP and healthy controls. Risk factors for the exacerbation of ITP following SARS-CoV-2 vaccination include a low platelet count, younger age, current therapy, and prior splenectomy [66,133].

When evaluating the risks associated with vaccination, it is important to consider that COVID-19 infection in unvaccinated ITP patients may lead to further reductions in platelet counts and an increased likelihood of bleeding. Consequently, all ITP patients should be vaccinated against COVID-19. The specific choice of vaccine does not seem to be a significant factor (Grade 2 D) [49,50,134].

The expert panel reached 87.5% consensus agreement ($n = 14$) that COVID-19 vaccination is safe in patients with ITP, with close follow-up through CBC monitoring.

Expert consensus statement 32

- COVID-19 vaccination is safe in patients with ITP with close monitoring of platelet counts (Grade 2 D).
- CBC should be checked 5 days after vaccination (Grade 2 D).

ITP in children

ITP is the most prevalent cause of acquired thrombocytopenia in children, affecting about 2–5 per 100,000 children. Unlike adults, more than 80% of children will experience a transient period of thrombocytopenia that typically resolves spontaneously within 12 months [135,136].

Like in adults, ITP in children is diagnosed through exclusion and is characterized by isolated thrombocytopenia (platelet count $<100 \times 10^9$/L) without any evidence of other underlying condition that could lead to immune thrombocytopenia (secondary ITP) [65].

Primary assessment

History and examination

ITP in children typically affects a previously healthy child, in about two thirds of patients, the disease onset is preceded by an infection in the previous few days to several weeks. The infection is most often an upper respiratory tract viral infection and the interval between the infection and the ITP onset is in the range of two weeks [137]. The disease onset is abrupt with manifestations of the thrombocytopenia such as petechiae, excessive bruising, epistaxis and bleeding [138].

Moreover, in pediatric patients with thrombocytopenia, it is important to consider their vaccination history, particularly regarding the measles, mumps, and rubella (MMR) vaccine. ITP caused by the MMR vaccine typically develops 2–6 weeks after vaccination but is usually self-limiting, presenting with mild to moderate thrombocytopenia [139].

Clinical examination reveals a healthy child who only has bruises and petechiae as manifestation of the low platelet count. There should be no organomegaly and no lymphadenopathy [61].

Children with inherited thrombocytopenia are frequently misdiagnosed with ITP. Inherited diseases need to be considered if thrombocytopenia has been evident following birth, there is evidence of a comparable condition running in the family, presence of characteristic features, or if there is a lack of response to first-line treatment [3,140]. Mean platelet volume can help distinguish ITP from inherited thrombocytopenia; an elevated mean platelet volume may be expected on a smear if numerous large platelets are observed [3,141].

Children's unique diagnostic needs

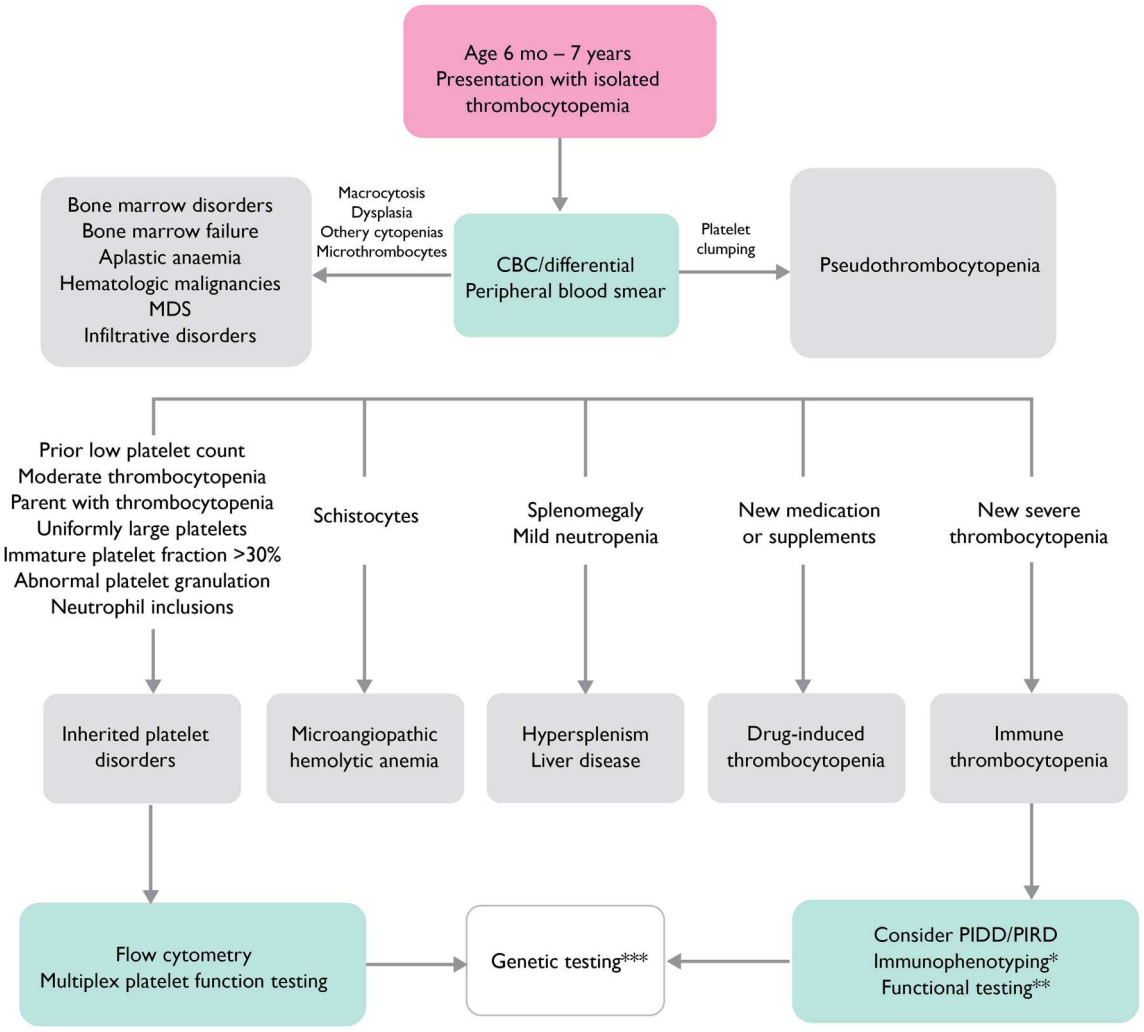
Adolescents and children with a gradual onset of the disease may have a higher likelihood of developing chronic ITP. In challenging, chronic and persistent cases, as well as in patients with multiple autoimmune cytopenias (such as Evans syndrome), it is important to consider further conditions associated with thrombocytopenia, like SLE, chronic viral infections, and autoimmune lymphoproliferative disorder (Figure 3) [3].

Keeping in mind, in pediatric patients routine screening with ANA and thyroid function test is not recommended unless there is signs and symptoms [4].

The expert panel reached 100% consensus agreement ($n = 16$) about the initial assessment of pediatric ITP patients, including a complete history, physical examination, peripheral blood smear, and direct antiglobulin test (DAT) if anti-D therapy is being considered.

Bone marrow examination

Evaluation of the bone marrow in children who recently diagnosed with ITP is only suggested if there are additional abnormalities beyond isolated thrombocytopenia, when there are systemic symptoms (such as bone pain), or if the patient exhibits splenomegaly not attributable to hepatic disease. Bone marrow examination may be also advised in patients where there is minimal or no response to first-line therapies to rule out bone marrow failure; a high mean cell volume, even in the absence of anemia, may suggest marrow failure. In fact, congenital marrow failure or inherited



* Immunglobulin (IgG, IgA, IgM, IgE) levels, T/8/NK subsets including double negative T cells (CD3+CD4–CD8–)
** Polysaccharide vaccine titres, cytokines, and soluble markers (e.g. sCD163 (marker of macrophage activation), sCD25 (elevated in CTLA-4 and LRBA deficiencies))
*** Genetic testing: targeted, exome sequencing, genome sequencing
PID: primary immune deficiency disorders, PRID: primary immune regulatory disorders

Figure 3. Algorithm for the diagnostic evaluation of thrombocytopenia in children.

thrombocytopenia genetic panels need to be taken into account during the bone marrow evaluation. (Grade 2 D) [3,4].

The expert panel reached 93.75% consensus agreement ($n = 15$) that bone marrow examination is not necessary as part of the initial workup in children with ITP. Moreover, the expert panel reached 100% consensus agreement ($n = 16$) that bone marrow examination must be performed if there are atypical findings in the peripheral blood smear, atypical symptoms, or poor response to treatment.

Expert consensus statement 33

- Recommendations for the diagnosis of ITP in children:
  - Complete history, physical examination, complete blood count (CBC), and reticulocyte count are important (Grade 1 D).
  - The peripheral blood smear should typically appear normal, showing variable platelet sizes, which may include large platelets and occasional giant platelets (Grade 1 D).
  - A direct antiglobulin test (DAT) is essential to check for the presence of autoantibodies against erythrocytes. This test is particularly important if anti-D therapy is being considered, as active hemolysis contraindicates the use of anti-D (Grade 1 D).
  - A bone marrow examination is not necessary in children before initiating corticosteroids if the complete blood count (CBC) indicates isolated thrombocytopenia and the blood smear shows no abnormalities beyond thrombocytopenia (Grade 1 C).
  - It is necessary to perform bone marrow examination with cytogenetics assessment if the following criteria are met (Grade 2 D):
    - Abnormal or potentially malignant cells are observed on the blood smear.
    - There are other abnormalities in hemoglobin and/or white blood cells counts, excluding microcytic anemia.
    - The patient presents with hepatosplenomegaly and/or lymphadenopathy.
    - There is a lack of acute response to ITP treatment, which warrants a bone marrow evaluation.

Observation versus management

Initial management

Most children newly diagnosed with ITP are either asymptomatic or exhibit only mild bleeding symptoms. Significant bleeding that necessitates treatment is uncommon, occurring in only 4% of pediatric patients, while intracranial hemorrhage (ICH) reported in less than 1% of cases. Children with ITP have a higher likelihood of spontaneous disease remission compared to adults, with up to 70% of pediatric patients achieving resolution within six months, compared to only 10% of adults [65,104].

Due to the lower risk of severe bleeding regardless of platelet count, the potential for spontaneous remission, and the significant side effects associated with ITP treatments, the initial management for pediatric ITP typically focuses on careful observation [4,42,65]. This approach contrasts with adult ITP patients, who are often treated right away when the platelet count drops below 30×10^9/L, even if they are asymptomatic or only exhibit minor mucocutaneous bleeding [65].

Bleeding scores are useful tools for evaluating the severity of ITP and should be routinely implemented in clinical practice (Tables 3 and 4). These scores reveal that the majority of children that have ITP don't experience massive bleeding, even when platelet counts are low. Regular use of these scores helps clinicians to monitor patients more effectively and make informed decisions about treatment strategies [3].

The expert panel reached 100% consensus agreement ($n = 16$) that children with ITP who have mild bleeding (Grade 1& 2), regardless of platelet count, require only close follow-up and monitoring without treatment.

Expert consensus statement 34

Watch-and-wait policy recommendations according to clinical classification

- Using a pediatric bleeding evaluation score, children and adolescents with ITP who had mild bleeding (grade 1 & 2), regardless of platelet count, can be managed with supportive treatment and close follow up (Grade 2 C).
- Grade 3 bleeding are more likely to require therapy due to higher rates of serious bleeding that necessitate hospital admission and emergency treatment (Grade 2 D).
- All patients require ongoing evaluation to monitor for any worsening of their condition, including assessment of HRQoL and potential evolution into a serious bone marrow disorder or secondary form of ITP (Grade 1 D).
- The frequency of clinical and laboratory assessments should be tailored to HRQoL, the severity of bleeding, platelet counts trends, and the reliability of the patients' relatives (Grade 1 D).

Inpatients versus outpatients

For children already diagnosed with ITP, hospitalization should be limited to those experiencing grade 3 or 4 bleeding. It is important to consider the psychosocial challenges faced by the children and their families, such as a history of noncompliance, behavioral problems, or living far from a healthcare facility, as well as how ITP impacts the child's and relatives' HRQoL. Parents must be instructed to monitor for additional

bleeding signs and provided with a physician's contact information for any necessary support. Outpatient management is recommended for children with ITP who have no bleeding or only mild symptoms, regardless of their platelet counts [4].

The expert panel reached 100% consensus agreement ($n = 16$) that newly diagnosed children with ITP who have mild bleeding can be treated as outpatients. Admission is indicated in cases of active life-threatening bleeding, uncertainty about the diagnosis, children with significant comorbidities, and concerns about social or mental issues.

Expert consensus statement 35

- In children with newly diagnosed ITP who have no or mild bleeding (skin manifestations) only can be treated as outpatients (Grade 1 D).
- Consulting a hematologist again after 24–72 h following the diagnosis are recommended (Grade 1 D).
- The admission may be preferable in (Grade 2 D):

- Grade 4 bleeding
- For cases whose diagnosis is unclear
- Patients with limited social support
- Patients whose follow-up is uncertain or those residing distant from the medical centers
- Significant comorbidities
- Significant risk of bleeding as a result of mental health disorder
- The child on an antiplatelets or anticoagulants.

Management of newly diagnosed ITP in children

The majority of children who are recently diagnosed with ITP typically do not need treatment, as 70% of patients had spontaneous remission within 6 months and 86% of these patients fully recover within 1 year of diagnosis [142]. However, those experiencing moderate (grade 3) bleeding are at an increased risk of progressing to grade 4 bleeding and may require early intervention until their bleeding subsides. Immediate hospitalization and treatment are necessary for children with grade 4 bleeding (Table 4) [3]. Additionally, treatment should be initiated for cases of trauma or scheduled surgical procedures [135].

Emergency treatment in children

In situations where there is organ- or life-threatening bleeding, a combination therapy involving high-dose corticosteroids and IVIG is recommended to achieve the quickest and most significant increase in platelet counts (Grade 1 D). In cases of intracranial hemorrhage (ICH), platelets must be administered alongside medical treatment (Grade 2 D) [3,13,143]. The primary objective is to elevate the platelet count as rapidly as possible to stop or prevent massive hemorrhage, followed by maintaining the platelet count to decrease the possibility of bleeding again [143,144].

The expert panel reached 100% consensus agreement ($n = 16$) about the use of IV corticosteroids and IVIG in life-threatening bleeding. The panel also reached 100% consensus agreement ($n = 16$) for platelet transfusion in severe active bleeding.

Expert consensus statement 36

Urgent treatment of ITP in children with life-threatening bleeding:

- It is advised to use combination therapy, which includes IV corticosteroids & IVIG (Grade 1 D).
- Platelets may be transfused in cases of severe active bleeding, such as intracranial bleeding (Grade 2 D).

First-line treatment

A short course of corticosteroids is appropriate to treat children with ITP initially, it is usually associated with mild side effects in most pediatric patients [4]. Corticosteroids should be limited to maintaining hemostatic platelet counts and used for the shortest duration possible [3].

Table 10. First-line therapies for pediatric ITP [4,42,65,145].

Medication	Dose	Duration	Time to response	Response rate	Common side effects
Prednisolone	0.5–4 mg/kg/day	5–7 days, no taper	2–7 days	50–77%	Weight gain, mood swings, hypertension, hyperglycemia, and gastritis.
Dexamethasone	28 mg/m^2	3 courses every 14–28 days	3–7 days	85%	Weight gain, gastrointestinal irritation, hypertension, hyperglycemia, lethargy and sleep disorders.
IVIG	1 g/kg x 1; if necessary, a second dosage may be administered.	Single dose	24–48 h	More than 80%	Aseptic meningitis, nausea, and headache
Anti-D	50–70 ug/kg x 1	Single dose	24–48 h	75%	Hemolysis, fever, chills, and headache.

In children with newly diagnosed ITP who have non–life-threatening bleeding and/or diminished HRQoL, courses of corticosteroids longer than 7 days are not recommended [4].

For the initial treatment of children with ITP, suitable corticosteroids options include high-dose dexamethasone (28 mg/m^2), and prednisolone administered at different dosages (0.5–4 mg/kg per day). The tapering schedules for these corticosteroids may vary, including possibilities for abrupt discontinuation [3,4].

IVIG is typically administered at a single dose of 0.8–1 g/kg for newly diagnosed patients. This treatment is usually administered with corticosteroids, paracetamol and antihistamines to minimize adverse effects, particularly headaches. IVIG is generally stopped after the platelet count reaches a safe level, at the same time it may be repeated if necessary. Further dose of IVIG can be administered in cases of massive hemorrhage and there is lack of response to the first dose [3].

IV Anti-D can be administered as a short infusion to Rh(D) positive children, and it is typically effective in providing a temporary increase in platelet counts [3,13].

The expert panel reached 100% consensus agreement ($n = 16$) for short course corticosteroids (7 days) rather than a prolonged course in pediatric patients with ITP. Additionally, the panel reached 100% consensus agreement ($n = 16$) that corticosteroids are recommended as first-line treatment rather than anti-D and IVIG.

First-line treatment options for pediatric ITP are listed in Table 10.

Expert consensus statement 37

- In pediatric patients with newly diagnosed ITP who are either asymptomatic or have only minor bleeding, a strategy of observation is preferred over active treatment (Grade 1 D).
- Management should be tailored according to the clinical classification of the disease.
- The clinical classification should take into account the severity of the disease, including platelet counts, the extent of bleeding, any comorbidities & their treatments (particularly anticoagulant), and the effects of ITP or its treatments on the relatives' and patients' (HRQoL) (Grade 1 C).
- The primary goal of treatment should be managing clinically significant hemorrhages rather than focusing solely on increasing platelet counts (Grade 1 C).
- For pediatric patients recently diagnosed with ITP who have non-life-threatening mucosal hemorrhage and reduced HRQoL, a corticosteroid course of 7 days or less is advised over a longer treatment duration (Grade 1 D).
- In pediatric patients with newly diagnosed ITP with non-life-threatening bleeding and diminished HRQoL, corticosteroids are recommended rather than anti-D or IVIG.

Expert consensus statement 38

Recommendations for further evaluation in chronic or persistent ITP in children:

- To reassess the diagnosis, a thorough history, physical examination and specialist evaluation of the peripheral blood smear (Grade 1 D).
- If there is no spontaneous increase in platelet counts and no response to treatment, bone marrow aspiration, biopsy, and cytogenetic analysis should be conducted within 3–6 months (Grade 2 D).
- A bone marrow evaluation isn't required before initiating new treatment (e.g. TPO-RAs), except if the diagnosis remains uncertain (Grade 2 D).
- In cases of persistent or chronic ITP that are increasingly challenging to manage, a bone marrow evaluation must be part of the diagnostic reevaluation (Grade 2 D).
- Further assessment may involve testing for the following (Grade 2 D):
  - ❖ Autoimmune diseases, such as lupus, which may necessitate specific treatments (e.g. check for lupus anticoagulant, anti-cardiolipin antibody, APLAs, and ANAs).
  - ❖ Chronic infections like cytomegalovirus, hepatitis, HIV, and/or *H. pylori* in at-risk groups or in cases without alternative explanations.
  - ❖ Combined immunodeficiency diseases
  - ❖ Genetic evaluation for bone marrow failure syndrome and inherited thrombocytopenia
- These investigations must be carried out sooner if there is no expected response to treatment after the anticipated period (Grade 2 D).

Table 11. Second-line therapies for pediatric ITP.

Medication	Dose	Response rate	Time to response	Common side effects
Romiplostim [15,43,98,99,145]	Subcutaneous injection once a week (dose ranges: 1–10 µg/kg), median initial dose in clinical practice: 3–5 µg/kg.	52%	1–3 weeks	Thrombocytosis, thrombosis, marrow fibrosis, and headache.
Eltrombopag [15,43,98,99,145]	Oral prescription 12.5–75 mg daily; if taken with foods or supplements that contain polyvalent cations (like calcium), the medication's effectiveness is reduced.	52%	2–3 weeks	Thrombocytosis, thrombosis, marrow fibrosis, and headache.
Rituximab [15,72,145]	375 mg/m^2 IV every week for four weeks.	40–60%	Early (1–2 weeks) Late response (8–12 weeks)	Hypogammaglobulinemia, neutropenia, and a decreased immune response.
Mycophenolate mofetil [15,43,90,91,145]	Oral drug, 400 mg/m^2 twice a day, up to 1 g twice a day.	52–69%	4 weeks	Headache, anemia, neutropenia, and gastrointestinal side effects.
Splenectomy [145,146]	Open or laparoscopic splenectomy	Durable response: 60–70%.	24–48 h	Risks of post-operative thrombosis, and chronic infections (such as encapsulated organism sepsis).

Chronic / persistent ITP treatment

For children with ITP who show no increase in platelet counts after three to six months and continue to need treatment, various investigations are advised [13]. In such cases, it is crucial to reassess the ITP diagnosis and explore the potential for secondary ITP [135].

The expert panel reached 100% consensus agreement ($n = 16$) that in cases of chronic or persistent ITP in children, the patient must be reevaluated through history, physical examination, and further investigations to exclude other possibilities such as infection, autoimmune diseases, or inherited conditions. The panel also reached 100% consensus agreement ($n = 16$) that bone marrow examination is not needed unless there is doubt about the diagnosis.

While the treatment considerations for newly diagnosed ITP and chronic or persistent ITP share similarities, they may be affected by the increased likelihood of early remission in the initial stages of the disease. In certain cases, especially with newly diagnosed ITP, a strategy of observation combined with short-acting therapies may be the most effective approach [135].

However, for patients with chronic / persistent disease or those experiencing significant bleeding symptoms, longer-acting treatments such as anti-CD20 antibody therapy, TPO-RAs, oral immunosuppressants, or splenectomy may be the preferred option [144]. Compared with rituximab and splenectomy, TPO-RAs provide a stable long-term platelet response and reduce bleeding events [45].

In fact, there is concern about the development of persistent hypogammaglobulinemia after rituximab treatment in the pediatric population. On the other hand, operative complications associated with splenectomy were identified in 5.9% of children while thrombosis was not observed in any of the children [4,45]. ASH guidelines suggested to avoid early splenectomy in the pediatric patients, considering that spontaneous remission is expected to occur in many children [4]. Second-line therapies for pediatric patients are summarized in Table 11.

The expert panel reached 93.75% consensus agreement ($n = 15$) that watchful waiting policy remains a valid option for refractory asymptomatic patients. On the other hand, the panel reached 100% consensus agreement ($n = 16$) that IV corticosteroids & IVIG remain the preferred option in cases of life-threatening bleeding. The expert panel also reached 93.75% consensus agreement ($n = 15$) that rituximab and TPO-RAs are acceptable options for symptomatic refractory pediatric patients with ITP, while splenectomy is rarely indicated in pediatric cases.

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Recommendations for management of pediatric patients with ITP who are unresponsive to first-line treatment:

- A watchful waiting policy remains a valid option (Grade 1 D).
- Rescue therapy with corticosteroids or IVIG can be used in children suffering from severe bleeding episodes (Grade 1 D).
- In pediatric ITP patients with non-life-threatening mucosal bleeding and impaired HRQoL who do not respond to first-line treatment, the suggested options are (Grade 1 D):
  - Rituximab
  - TPO-RAs
  - Rituximab and TPO-RAs are suggested rather than splenectomy.
  - If the response is poor to TPO-RAs or if the initial response diminishes, it may be beneficial to switch to a different TPO-RAs and/or it might be useful to combine it with another immunosuppressant, such as mycophenolate mofetil (MMF).
  - Splenectomy is very rarely indicated in childhood ITP. It must be only considered in children who have not responded to all available medical treatments (Grade 2 D).
- Prior to splenectomy, reevaluate the ITP diagnosis by ruling out other possible causes.

Safety of immunization for children with ITP

Although rare, vaccination is recognized as a potential cause of ITP. Vaccine-associated thrombocytopenia necessitates individualized risk-benefit assessment of vaccination based on clinical context [147].

The frequency of autoimmune reactions associated with vaccines is significantly lower than that associated with naturally occurring infections. Given the cost-effectiveness of vaccines and the fact that their benefits outweigh the risks of inducing autoimmunity, it is important to encourage vaccination [147].

Consequently, post-vaccine ITP should not hinder the vaccination of children. Administering vaccines to children with a prior history of ITP, regardless of whether it was vaccine-associated or not, has been found to be safe and well-tolerated, and vaccination can be resumed after remission [148].

The expert panel reached 93.75% consensus agreement ($n = 15$) that child with ITP should receive vaccination according to schedule. On the other hand, the expert panel reached 81.25% consensus agreement ($n = 13$) about the safety of revaccination after resolution of thrombocytopenia in vaccine induce ITP.

Expert consensus statement 40

- The majority of patients with either a history of ITP or active ITP should receive vaccinations according to schedule (Grade 1 D).
- An exception should be made for patients receiving medications that may weaken the immune system.
- ITP that occurs following vaccination is a treatable condition with a low risk of complications.
- The incidence of ITP following vaccination is significantly lower than the incidence of ITP resulting from the infections that these vaccines prevent.
- It is safe to revaccinate a child who has had vaccine-induced ITP after remission.

Quality of life in ITP patients

ITP exerts a significant and multifaceted impact on patients' health-related quality of life (HRQoL) (Figure 4) [10]. The life quality is poor during the initial phase of the ITP, characterized by frequent bleeding attacks, as both the patients and their relatives are adapting to managing the condition. However, this quality of life tends to improve over time as they gain experience. When assessing treatment effectiveness, it is essential to consider not just platelet counts and bleeding tendencies, but also the overall HRQoL [50]. Patients have expressed concerns not only about bleeding but also regarding lifestyle restrictions, fear of splenectomy, and the side effects of treatments [149]. There is often a discrepancy in treatment goals between patients and physicians. While physicians frequently prioritize 'prevention of bleeding' as the primary therapeutic goal, patients typically consider the restoration of their blood values to 'normal' as the most important goal, alongside a cure. Symptoms such as bleeding (petechiae, hematomas, menorrhagia) and fatigue are central to the patients' focus [50].

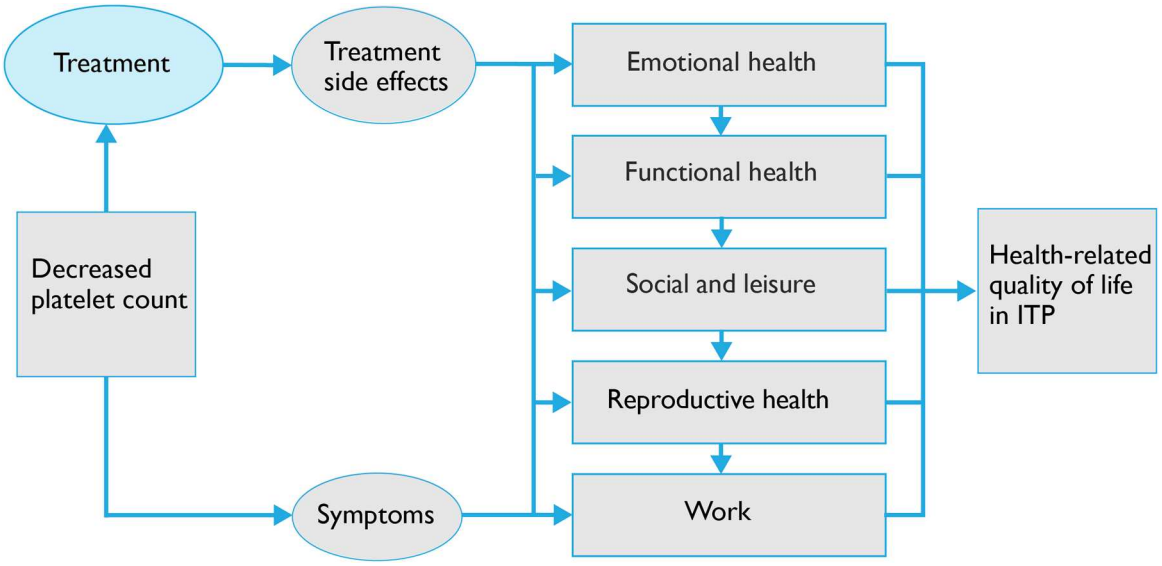

Figure 4. Health-related quality of life in ITP patients.

Factors affecting HRQoL in ITP patients are:

Drugs impact

The challenges associated with treatment, such as frequent hospital visits and adverse effects, can adversely impact the HRQoL for patients with ITP. Ideally, effective treatments should enhance HRQoL; however, studies have shown that ITP patients undergoing active treatment often report poorer HRQoL than anticipated [150].

The most frequently reported adverse effects of ITP treatment were linked to corticosteroid use. Patients with ITP indicated experiencing several side effects from corticosteroids treatment, including anger, insomnia, mood swings, and weight gain. As previously noted, corticosteroids use should be limited to the short term, and repeated courses are not recommended [3,4,58].

Physicians were more worried about severe bleeding than patients were. Many patients reported feeling as though their physicians did not pay appropriate attention to corticosteroids side effects. Awareness of the different opinions about corticosteroids side-effects and risk for bleeding between ITP patients and hematologists may improve management decisions [151]. Other treatment options for managing chronic ITP include immunosuppressants and/or splenectomy, both of which are associated with significant side effects [149].

Previous studies demonstrate that early TPO-RAs prescription improves patients' (HRQoL) while avoiding unacceptable side effects. TPO-RAs medications had a positive impact on patient platelet count and resulted in a reduced need for emergency treatment with minimal noted side effects. The majority of patients and/or families reported a positive impact of TPO-RAs on their HRQoL [152].

The expert panel reached 100% consensus agreement ($n = 16$) that early tapering and discontinuation of treatment will improve HRQoL. Meanwhile, 81.25% consensus agreement ($n = 13$) was reached regarding the early prescription of TPO-RAs and the avoidance of immunosuppressants to support HRQoL.

Expert consensus statement 41

- Maintaining HRQoL is a crucial consideration in the management of patients with ITP and should be thoughtfully evaluated when making treatment decisions.
- Optimization of tapering and discontinuation of ITP therapy in selected patients can improve the quality of life (Grade 1 C).
- Early prescription of TPO-RAs, avoidance of immunosuppressants medications for ITP patients had a positive impact on patients reported HRQoL (Grade 1 C).

- ***Symptoms***

HRQoL is significantly impacted by the fear of experiencing a bleeding episode due to low platelet counts [64]. Petechiae and bruising of unknown origin were among the most frequent patient-reported signs & symptoms. In the same time, anxiety around maintaining stable platelets count was frequently reported in ITP patients [153].

- ***Impact on emotional health***

Unfortunately, over 70% of ITP patients experience anxiety, stress, depression, sleep disturbances and fear concerning their symptoms and fluctuating platelet counts. Nearly half of these patients report that their personal relationships have been impacted, alongside issues related to mental health and self-consciousness [149,153]. Caregivers of children with ITP also encounter difficulties, as they share a significant fear of bleeding, even though they do not experience the disease or its treatment side effects directly [150].

- ***Impact on functional health (energy, fatigue, pain and sleep)***

A strong relationship was evident between ITP symptoms and functional health limitations, particularly highlighting how fatigue impairs daily activities [149]. Fatigue emerges as one of the frequent symptoms experienced by ITP patients. ITP-related fatigue has an unclear etiology, but it is most likely multifactorial [50,150,153]. Although there may be a direct relationship between fatigue and platelet count, a large number of patients still report persistent fatigue even after their thrombocytopenia has improved [50,150].

The expert panel reached 100% consensus agreement ($n = 16$) on the need for early recognition of depression and close monitoring of mental health in ITP patients. Additionally, 100% consensus agreement ($n = 16$) was reached that improving platelet count and reducing the risk of bleeding will enhance HRQoL.

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- Treating physicians should be more vigilant about recognizing symptoms of fatigue and depression to facilitate early detection.
- Elevating platelet counts and reducing the risk of bleeding can enhance the quality of life for numerous patients.

- **Impact on work Absences *(changes in attitudes, career advancement, productivity)***

In a survey, 87% of ITP patients indicated that the condition had affected their ability to work. More than two-thirds reported missing work due to symptoms or treatment related to ITP, while one-third believed their career advancement was hindered by the disease [149].

- ***Social impact***

Adult patients with ITP often face adverse effects on their roles and social lives. Limitations in physical activity caused by thrombocytopenia, decreased social interactions, stigmatization related to mood changes, bleeding, and sleep disorders can all contribute to these social challenges [120,150]. Many patients report feelings of social embarrassment due to visible bruising and a reduced ability to participate in social and recreational activities, including sports, exercise, gardening, and travel [149].

While most ITP patients can engage in sports, it is essential for individuals to discuss their bleeding risk and the type of sport with their physician. Contact sports, such as football, must be discouraged when platelet counts are below 50×10^9/L. Activities like cycling, swimming, and workout sessions are generally considered safe and manageable. However, it is important to note that no sport can be deemed entirely safe or unsafe [120].

- ***Impact on reproductive health***

Participants in the focus groups, both male and female, reported a decline in libido attributed to ITP symptoms and treatment side effects [58]. Female patients expressed concerns about potential infertility and increased menstrual bleeding [149]. Furthermore, ITP can significantly impact sexual activity, leading to

reduced libido in both genders and instances of bruising and bleeding during intercourse, especially among women [150].

Improving the standard of care in children

The concerns of children with ITP differ from those of their parents and adults with the condition, necessitating supportive interventions that are age-appropriate in focus and delivery style. For children, this may involve efforts to minimize hospital visits and blood tests whenever possible [150].

Moreover, it is essential to prevent excessive caution regarding activity restrictions. This can be achieved through clinical networks that connect children with ITP to experienced clinicians, combined with adherence to expert consensus guidelines on best practices [150].

Studies investigating HRQoL in pediatric ITP have shown a significant disease burden on children and their caregivers, mainly due to anxiety regarding bleeding risks and the negative effects on daily activities.

Fatigue is a prevalent symptom in both children and adults with ITP. The underlying causes are likely multifactorial, including immune activation, proinflammatory states, treatment toxicity, activity limitations, and comorbid conditions. Although fatigue often correlates with the severity of thrombocytopenia, it does not consistently improve with ITP-directed therapies [135].

According to the recommendations of the updated international consensus report (2019), it is important to maintain healthy physical activity in children and encouraging maintaining a safe participation in different activities [3].

The expert panel reached 100% consensus agreement ($n = 16$) that ITP patients should maintain regular physical activity and consistent attendance in kindergartens, schools, and universities. Additionally, 100% consensus agreement ($n = 16$) was reached that ITP patients can engage in low-risk activities, while high-risk activities should be avoided unless platelet counts are close to normal, and the risks must be discussed with the patient or family.

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Recommendations for children with ITP regarding school and athletic involvement:

- Children and teenagers between the ages of 5 and 18 should participate in at least 60 min of physical activity daily, at least three days a week, incorporating exercises or sports that enhance muscle and bone strength (Grade 2 D).
- Regular attendance and participation in kindergarten, school and university, according to age, are important. Schools should be provided with information about ITP and its associated risks in a manner that fosters inclusion rather than isolation (Grade 2 D).
- Regardless of platelet counts and continued medication, patient should continue to actively involve in low-risk activities (Grade 2 D).
- Engaging in high-risk activities must be thoroughly discussed with the trainer, school, and family. Prior to engagement, factors such the child's age, bleeding history, platelet count, and the physical demands of the activity should be assessed. (Grade 2 D).
- Engagement in high-risk activities (such as football) should be avoided except if the patient continuously maintains a platelet count close to normal. Otherwise, to guarantee a safe platelet count during the activity, therapy should be given. (Grade 2 D).
- Treatment can be given either continuously or intermittently to cover activities, with careful consideration of the risks versus benefits of both the treatment and the activity. The possibility of injury and psychological health, should be emphasized (Grade 2 D).
- The target platelet count and selection of medications should be thoroughly assessed through comprehensive discussions with the family, considering the child's specific activity goals and bleeding tendencies (Grade 2 D).
- Corticosteroids may negatively impact HRQoL in children, whereas TPO-RAs have the potential to enhance HRQoL in pediatric ITP patients, with romiplostim in particular showing promise in alleviating parental burden (Grade 1 C).

Conclusion

The management of ITP is still a challenge. It is diagnosed by exclusion and necessitates the participation of experienced clinicians. The purpose of these consensus statements is to increase awareness, provide guidance, and support the choices made by healthcare professionals in the real-world management. It is important to manage patients with ITP individually, taking into consideration factors such as age, patient preferences, comorbidities, lifestyle and the availability of drugs.

Many recommendations are based on low levels of evidence. The lack of solid evidence for fundamental clinical problems in ITP highlights the need for revised recommendations that are appropriate for the local treatment setting, and continued cooperative clinical and scientific studies in ITP. There are still information

gaps despite the large number of publications on ITP diagnosis and management, thus current expert opinion and expertise are crucial. These guidelines will be updated as significant therapeutic advances become available in the Iraqi healthcare market in the coming years.

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Ethics approval and consent to participate

This consensus study did not involve human patient data collection. Ethical approval for the expert panel process was obtained from the Iraqi Society of Hematology (Reference No. 357). All participating experts provided written informed consent prior to engagement in the Delphi voting process.

Data availability statement

Data sharing is not applicable to this consensus statement as no datasets were generated or analyzed during the current study.

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