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Expert Report on Immune Thrombocytopenia: Current Diagnostics and Treatment – Recommendations from an Expert Group from Austria, Germany, and Switzerland

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1. Introduction

Immune thrombocytopenia (ITP) is a rare and orphan disease. The following recommendations are meant to assist physicians, dentists, and other health-care professionals who do not often see ITP patients. The expert report is an update of the German ITP guidelines from 2018 to 2021 [1, 2]. With few exceptions, only current literature from 2020–2022 was referenced. For older references, please refer to the previous publications.

2. Baseline Information

2.1 Definition of ITP

ITP is an acquired immune disorder. It should only be diagnosed if the platelet count is repeatedly below 100,000/μL. One distinguishes primary from secondary forms of ITP.

The acronym ITP stands for immune thrombocytopenia and has replaced the older term idiopathic thrombocytopenic purpura according to international consensus. Unfortunately, the current ICD-10 version (ICD-10 2019) still uses the term "idiopathic thrombocytopenic purpura" for D69.3.

According to international agreement, ITP should only be diagnosed when the platelet count is repeatedly below 100,000/μL. The reason is that mild thrombocytopenia between 100,000 and 150,000/μL is common and usually does not require therapy. This does not mean that one need not look for the cause of persistent mild thrombocytopenia. It could be the first symptom of another, more serious hematologic disorder or a drug side effect with the potential to worsen in the future [3].

For the classification of thrombocytopenias, see Table 1. Primary ITP, where there is no identifiable triggering cause, is distinguished from secondary forms, in

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Table 1. Classification of thrombocytopenias

Impaired platelet production	Increased platelet consumption
– Damage to the bone marrow (drugs, alcohol, cytostatics, etc.) – Infiltration and displacement of the bone marrow (hematological neoplasms, less commonly solid tumors) – Myelofibrosis – Myelodysplastic syndromes – Bone marrow hypo-/aplasia, paroxysmal nocturnal hemoglobinuria – Wiskott-Aldrich syndrome (has also increased consumption) – Severe vitamin deficiency – Severe iron deficiency – Rare genetic defects: Bernard-Soulier syndrome, et al. **In ITP bone marrow platelet production can also be impaired**	**Primary immune thrombocytopenia** – No underlying cause identifiable **Secondary immune thrombocytopenia** – Drug-induced immune reaction – Autoimmune diseases – Antiphospholipid syndrome – Immunodeficiency syndromes [common variable immunodeficiency syndrome, autoimmune lymphoproliferative syndrome (Canale-Smith syndrome), Wiskott-Aldrich syndrome (also has impaired platelet production) – Evans syndrome (associated with lymphoma, CLL) – Hepatitis, HIV, and other viral infections – Vaccine-related **Other immune thrombocytopenias (not ITP)** – Heparin-induced thrombocytopenia – Vaccine-induced thrombotic thrombocytopenia – Thrombocytopenia after GP IIb/IIIa inhibitor administration – Posttransfusion purpura – Pregnancy-associated thrombocytopenia – Neonatal alloimmune thrombocytopenia – Cyclic thrombocytopenia **Other consumptive thrombocytopenias (non-immunological)** – Microangiopathic hemolytic anemias (TTP, HUS, aHUS) – Consumption coagulopathy – Von Willebrand syndrome type 2B and platelet-type (pseudo) von Willebrand syndrome – Massive pulmonary embolism – Large hemangioendotheliomas (e.g., Kasabach-Merritt syndrome)
Thrombocytopenias in other disorders – Splenomegaly – Liver disease – Massive hemorrhage – Severe infections incl. COVID-19	
Laboratory artefacts – Pseudothrombocytopenia (EDTA-induced thrombocytopenia)	

which immune thrombocytopenia is triggered by autoimmune diseases, lymphomas, drugs, and other disorders. Approximately 80% of ITP cases are primary and 20% are secondary (see also chapter 19.1).

2.2 Function of Platelets beyond Coagulation

Platelets are involved in numerous physiological processes other than clotting:

- inflammation and immune defense,
- cell growth, including tumor cell growth,
- vascular growth and endothelial stabilization,
- neurobiological functions.

The involvement of platelets in immune defense explains why changes in platelet counts are commonly found with viral and bacterial infections. Their neurobiological function could account for neurological symptoms and, especially, fatigue in patients with ITP.

2.3 Epidemiology

The annual incidence rate of ITP is 2–4 new cases per 100,000 adults, satisfying the definition of an orphan disease. The prevalence is 9–26 per 100,000.

In recent years, there seems to be a trend toward a higher age at onset (~60 years). Almost one-third of patients are more than 70 years old [4, 5].

In children and adolescents, the annual incidence rate of ITP is 2–7 new cases per 100,000 and the prevalence 4–5 per 100,000.

The prevalence is much lower in children than in adults because pediatric ITP less often becomes chronic. Boys are more commonly affected than girls, especially in infancy and early childhood. In middle age, women are more frequently affected than men. After the age of 60, men again predominate. The incidence of ITP in children is up to two times higher in the spring than in the summer, possibly reflecting the higher incidence of viral infections in the spring.

Table 2. Pathomechanisms of ITP (see also Fig. 1)

Antiplatelet autoantibodies
– Antibodies link platelets to Fc receptors of macrophages with subsequent phagocytosis and destruction in spleen and liver
– Degradation of sialic acid residues on platelet surface glycoproteins (desialylation). Desialylated platelets bind to the Ashwell-Morell receptor in the liver and are then degraded
– Induction of complement-mediated platelet damage
– Bind to platelet surface receptors (GP IIb/IIIa, GP Ib/IX, and others) and impair their function
T lymphocytes
– Reduced numbers of regulatory T lymphocytes (T-Regs) lead to immune dysregulation
– Direct damage to platelets and megakaryocytes by autoreactive cytotoxic T lymphocytes
Impairment of thrombopoiesis
– Autoantibodies cause damage to megakaryocytes and reduce thrombopoiesis
– Increased degradation of thrombopoietin
– Inadequate thrombopoietin production (relative thrombopoietin deficiency)

The incidence of ITP is significantly lower in African-Americans than in Europeans Therefore, blacks with thrombocytopenia should be carefully evaluated to confirm ITP and not another type of thrombocytopenia [6]. ITP appears to be as common in the Asia-Pacific region as in Europe.

Incidence and Prevalence Estimates for Germany

When one combines the current population numbers of Germany with the above incidence and prevalence rates, 1,600 to 3,700 new ITP cases annually (children and adults) and 6,800 to 18,700 patients with preexisting ITP can be expected. Of these, about half, i.e., 3,500 to 9,000 patients, might require treatment.

2.4 ITP Is an Orphan Disease

Diseases with a prevalence of less than 5 per 10,000 are referred to as rare or "orphan diseases" in Europe (in the US, <7.5 per 10,000; in Australia, <1 per 10,000). This is more than just an arbitrary discriminator; it has immediate, practical implications. Patients with rare diseases typically are geographically dispersed, and there are only a few experts and centers, which are available to them. It is a challenge both financially and organizationally to enroll adequate numbers of patients for clinical trials, and access to expert treatment and care options is not always apparent to patients. In individual cases, this can lead to considerable delays in diagnosis.

3. Pathophysiology

ITP is not hereditary; it is an acquired form of thrombocytopenia. It is caused by an autoimmune reaction directed against both circulating platelets in the peripheral blood and megakaryocytes in the bone marrow, which leads to both enhanced platelet degradation and decreased production of new platelets.

The immune reaction in ITP is based on different and complementary mechanisms (see Table 2 and Fig. 1; for review, see [7, 8]). This explains the observation that there are patients who respond partially or not at all to one treatment and much better to another; furthermore, the pathophysiologic mechanisms might differ from patient to patient. This ultimately leads to the concept of combination therapy for multiply resistant/relapsed ITP (see chapter 15).

Note: There are isolated reports of familial clustering of ITP cases and a genetic predisposition to develop autoimmune diseases. However, these cases are so rare that they should only be considered if all other forms of hereditary thrombocytopenias have been excluded.

4. Clinic

Typical bleeding signs of ITP are petechiae and mucosal hemorrhages; large hematomas and joint hemorrhages are unusual. In addition, many patients complain of exhaustion, fatigue, and even depressive disorders (see chapter 19.9).

Typical Bleeding Symptoms of ITP:

- petechiae on the legs, less frequently on the trunk and arms (on the arms after tourniquet or blood pressure measurement),
- oral and nasal mucosal hemorrhages,
- urogenital bleeding, heavy menstrual bleeding,
- bleeding and hematomas even with minor trauma,
- rarely, internal organ bleeding, e.g., intracranial hemorrhage (<1–2%) [9],
- the bleeding tendency in ITP patients is not as severe as in patients with a similar degree of thrombocytope-

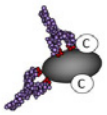
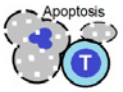
Pathomechanism	Impaired platelet production in bone marrow	Damage to circulating platelets from autoantibodies and complement	Apoptosis of platelets and megakaryocytes by autoreactive T-lymphocytes	Destruction of platelets in the spleen	Destruction of platelets in the liver
					
Corticosteroid		Platelet autoantibodies ↓	Reduced activity of autoreactive T-Lymphocytes ↓	Phagocytosis ↓	Phagocytosis ↓
i.v. Immunglobulins		Platelet autoantibodies ↓ Complement activation ↓	Reduced activity of autoreactive T-Lymphocytes ↓	Phagocytosis ↓	Phagocytosis ↓
TPO-Receptor Agonists	↑ Platelet production				
Fostamatinib		Platelet autoantibodies ↓	Reduced activity of autoreactive T-Lymphocytes ↓	Phagocytosis ↓	Phagocytosis ↓
Rituximab*		Platelet autoantibodies ↓			
Splenectomy		Removes site of antibody producing cells, platelet autoantibodies ↓	Removes site where autoreactive T-lymphocytes are active ↓	Removes site of phagocytosis ↓	
FcRn-Inhibitors*		Platelet autoantibodies ↓			
BTK-Inhibitors*		Platelet autoantibodies ↓	Reduced activity of autoreactive T-lymphocytes ↓	Phagocytosis ↓	Phagocytosis ↓
BAFF-Inhibitors*		Platelet autoantibodies ↓			
Neuraminidase- Inhibitors*					Reduced desialylation and phagocytosis ↓
Daratumumab*		Platelet autoantibodies ↓			
Bortezomib*		Platelet autoantibodies ↓			
Complement-Inhibitors*		Complement activity ↓	Daratumumab*		
All-Trans-Retinoic Acid*		Immune dysregulation ↓ T-Regs**-↑		Immune dysregulation ↓ T-Regs** ↑	
Decitabine*		Immune dysregulation ↓, autoreactive T-lymphocytes ↓, T-Regs** ↑			

Fig. 1. Pathomechanisms of ITP and corresponding treatments (*off-label, see also chapter 18). **T-Reg, regulatory T lymphocytes.

Table 3. Basic diagnostic program at initial presentation when the diagnosis ITP is suspected but not yet certain

Diagnostic test	Remarks
Medical history	Current and previous bleeding, previous diseases, especially infections (COVID-19), medications (anticoagulants!), vaccinations, alcohol, pregnancy, previous thromboses, family history, occupational history
Physical exam	Signs of bleeding, especially in mucous membranes; enlarged lymph nodes; enlarged liver or spleen (an enlarged spleen does not exclude ITP, but would be atypical and should direct suspicion to another disease); exanthem (petechiae should not be palpable, a palpable purpura is not typical for ITP); signs of thrombosis (consider antiphospholipid syndrome)
Complete blood count	Exclude pseudothrombocytopenia by performing platelet counts in EDTA and citrate; if aggregates are also in citrate, use special tubes (S-Monovette® ThromboExact™) Older blood counts are also very helpful to determine if thrombocytopenia was previously present and for how long
Blood smear (always!)	Evaluation by a physician experienced in the diagnosis of hematological diseases
Coagulation parameters	Activated partial thromboplastin time, prothrombin time and international normalized ratio, fibrinogen
Bone marrow	A bone marrow examination is considered if there are atypicial findings in the history or on physicial exam, see also chapter 5.2 and Table 6
Other	In patients with anemia, consider blood loss (perform iron studies) and Evans syndrome (evaluate for hemolysis) To exclude subclinial diabetes, obtain a blood glucose/urine glucose when treatment with corticosteroids is planned Urinalysis for red cells, stool test for occult blood

nia from other causes, e.g., after chemotherapy, in myelodysplastic syndromes, or with leukemia.

- the risk of symptomatic CNS bleeding seems to be particularly high in newly diagnosed ITP, in patients with <30,000 platelets/μL, and after head trauma. In patients with low platelet counts and headache, a head CT should be ordered [10]. **Note:** in patients with thrombocytopenia or severe bleeding at other sites, special MRI techniques often show asymptomatic (!) CNS microbleeds [11].

Large hematomas and joint hemorrhages are not typical for ITP; they are more commonly found in coagulation factor disorders, e.g., hemophilia. In newly diagnosed ITP, 10% of pediatric patients and 20–30% of adult patients have no bleeding symptoms. In chronic ITP, the proportion of patients without bleeding symptoms is 30–40%.

Other symptoms:

- ITP patients are at an increased risk of infection due to immunosuppressive therapies or splenectomy.
- Chronic loss of blood might give rise to iron deficiency and microcytic anemia. Also, it has been reported that eltrombopag, an iron chelator, can lead to iron deficiency in pediatric ITP patients [12] (see also chapter 13.1).
- Many ITP patients complain of exhaustion, fatigue, and even depressive disorders in addition to bleeding. A connection between ITP and cognitive dysfunction has been described (see chapter 19.9).

5. Diagnosis

ITP is a diagnosis of exclusion. There are no physical findings or laboratory tests that can prove ITP.

Some 10 years ago, the American Society of Hematology and the International Working Group proposed criteria to improve the diagnostic accuracy for ITP [13, 14]:

- thrombocytopenia <100,000/μL,
- no other apparent cause of thrombocytopenia.

Despite these criteria, another cause of the thrombocytopenia will be revealed in as many as 10% of patients with the diagnosis of primary ITP. Additional criteria are, therefore, as follows:

- normal values for leukocytes and erythrocytes (except iron deficiency anemia from bleeding),
- bleeding tendency not commensurate with the low platelet counts,
- a doubling of the platelet count from baseline and an increase to >30,000/μL after administration of corticosteroids or intravenous immunoglobulins (IVIG).

The diagnosis of ITP is usually established with a stepwise approach. At initial patient presentation, the recommendations of Table 3 should be followed. In many patients, this is sufficient to confirm the diagnosis or to exclude alternative diagnoses. If ITP persists or becomes chronic, further differential diagnoses must be considered (see Table 4). Immune-mediated thrombocytopenias that are associated with other diseases are usually secondary ITPs (see chapter 19.1).

Table 4. Advanced testing for persistent or chronic ITP or for ITP not responding adequately to standard therapies

Diagnostic test	Reasoning, consequence
Blood typing	For emergency card, before surgical procedures with high risk of bleeding
Bone marrow biopsy	Always with atypical findings, see chapter 5.2 and Table 6. Also recommended for older patients (>60 years) without atypical findings or in patients with no reponse to standard therapies
Blood glucose/urine glucose	Exclude subclinical diabetes before initiating corticosteroid therapy
Serum protein electrophoresis, serum immunoglobulins, lymphocyte typing test	Exclude immunodeficiency syndromes (primary, e.g., common variable immunodeficiency and secondary, e.g., due to HIV), exclude myeloma
Autoantibody panel (anti-citrullinated protein antibodies, ANA, ANCA, anti-DS-DNA, antiphospholipid antibodies, lupus anticoagulant)	Exclude secondary ITP from autoimmune disease (SLE or antiphospholipid syndrome)
Antiplatelet autoantibodies	In patients with persistent thrombocytopenia when there is doubt about the diagnosis of ITP (only helpful if positive)
Quantitative and functional analysis of von Willebrand factor including multimer analysis, in case of platelet-type von Willebrand syndrome molecular analysis of the GPIbα gene	Moderate to severe thrombocytopenia may occur in von Willebrand syndrome type 2b and in the rare platelet-type (pseudo) von Willebrand syndrome
Thyroid function tests	Up to 10% of ITP patients have autoimmune thyroid disease and may need treatment
H. pylori-testing	See chapter 5.3
Hepatitis B, C, HIV-serology	If positive, usually need specific treatment Risk of viral reactivation or worsening of symptoms with immunosuppressive therapy or splenectomy
Abdominal ultrasound, chest-X-ray, chest/abdominal CT.	Exclude solid tumors, lymphoma, or other hematologic diseases. If splenomegaly, consider Gaucher's disease

For the initial diagnosis of ITP or any other thrombocytopenia, the blood smear must be examined by a physician experienced in the diagnosis of hematological diseases in adults as well as in children and adolescents. Thrombotic thrombocytopenic purpura is an important differential diagnosis that must not be overlooked.

The detection of ANA, antiphospholipid antibodies, and lupus anticoagulant is important because these patients are predisposed to thrombosis (see chapters 19.1 and 19.6).

Testing for thyroid antibodies, which are detectable in approximately 5% of ITP patients, is only relevant if the patient's thyroid function is abnormal and this was not previously known. It does not affect the treatment of ITP.

If abdominal ultrasound shows an enlarged spleen, consider liver disease, lymphoma, or rarely Gaucher's disease or Niemann-Pick type B disease.

Note: Patients with newly diagnosed ITP might ask whether they should be tested for SARS-CoV-2 antibodies. However, a positive test would only denote that they have been vaccinated or exposed to the virus, and not that the thrombocytopenia is related to COVID-19. In addition, the thrombocytopenias associated with SARS-CoV-2 infection are usually transient and do not require therapy, so a positive test would have no therapeutic consequence (see also chapter 19.3). Therefore, SARS-CoV-2 antibody testing is not recommended.

5.1 Platelet Autoantibody Testing

Platelet autoantibody testing is not part of the routine workup for newly diagnosed ITP but should be reserved for patients with persistent or chronic ITP and an atypical disease course.

The clinically relevant IgG autoantibodies in ITP are directed toward glycoproteins on the platelet surface (mainly GP IIb/IIIa and Ib/IX, less frequently GP V, Ia/IIa) and lead to platelet phagocytosis by the spleen and liver. The direct glycoprotein-specific test in EDTA blood (MAIPA, Monoclonal Antibody Immobilization of Platelet Antigens Test) has a specificity of approximately 98%. A positive result can confirm the diagnosis of ITP or exclude other differential diagnoses (see Table 5). However, a negative result is of little help because the sensitivity of this method is only ~63% [15, 16]. Also, false-positive tests can sometimes occur in myelodysplastic syndromes and with lymphomas.

Table 5. Indications for platelet autoantibody testing to differentiate ITP from non-immune thrombocytopenias

Minimal or complete lack of response to corticosteroids or i.v. immunoglobulins (IVIG)
Thrombocytopenia due to bone marrow injury from drugs (e.g., with chronic alcohol abuse)
Hereditary thrombocytopenia syndromes
Thrombocytopenia due to liver disease or splenomegaly
Gestational thrombocytopenia in women with platelet counts in the "grey zone" between 50,000 and 100,000/μL (see chapter 19.5)

Table 6. Indications for bone marrow biopsy

Abnormal laboratory values in addition to thrombocytopenia, especially abnormal leukocyte and erythrocyte counts
Atypical findings on history (e.g., B symptoms, weight loss) and physical examination (e.g., enlarged lymph nodes, hepatosplenomegaly)
Only a very brief or no response to standard therapies
Patients >60 years of age because alternative diagnoses are more common: lymphomas, myelodysplastic syndromes, clonal cytopenias of undetermined significance (CCUS), multiple myeloma, etc.
Prior to splenectomy, to exclude other diagnostic possibilities

Older studies show that patients with anti-GP Ib/IX autoantibodies do not respond as well as patients with other antibody specificities to corticosteroids, IVIG, or TPO receptor agonists (TPO-RAs). It is also not uncommon for a patient to have antibodies to several platelet glycoproteins (epitope spread). Patients with two or three antibody specificities appear to have lower platelet counts and a poorer response to treatment [17, 18].

Tests for platelet-associated total IgG (PAIgG) should no longer be performed because they have low specificity and are not useful for the diagnosis of ITP. False-positive results occur because the platelet-bound, non-specific immunoglobulins that these tests recognize increase with decreasing platelet counts, regardless of the cause of the thrombocytopenia.

Only autoantibodies against specific glycoprotein receptor antigens support the diagnosis of primary or secondary ITP. Antibodies against platelet HLA antigens are much more common in clinical practice (e.g., after platelet transfusions), but they are not related to ITP.

Note: A false-negative test might occur if the laboratory receives a sample volume that is too small. If the thrombocytopenia is severe, a sample volume of 20 to 40 mL EDTA blood might be required to provide sufficient platelets to conduct the test.

5.2 Bone Marrow Biopsy

The main purpose of bone marrow biopsy is to exclude alternative diagnoses. Bone marrow biopsy can usually be omitted in patients with typical clinical findings and a good response to treatment.

However, those with less than an adequate response to standard ITP therapies should be offered bone marrow biopsy. Biopsy should also be considered in older patients because, with increasing age, thrombocytopenia might be due to myelodysplastic syndrome (see Table 6).

It is not necessary to raise the platelet count before a bone marrow biopsy. Bleeding is very rare, even in patients with very low platelet counts, and can usually be controlled by prolonged compression. Nevertheless, the patient should be provided with contact information and the location of emergency services if bleeding occurs, e.g., in the evening or on the weekend.

Practical advice: in order to spare the patient a second biopsy if the diagnosis turns out to be not ITP but another hematological disease, collect and set aside material for molecular and cytogenetic analysis should further testing be necessary.

5.3 Testing for Helicobacter pylori

All adult patients with ITP, especially those with persistent or chronic disease, should be tested for *H. pylori* and receive treatment if the results are positive. This test is less likely to be positive in Europeans than in patients from Asia or other geographic regions. Testing for *H. pylori* antigen in stool is simple and inexpensive.

5.4 Immature Platelet Fraction

Immature platelets are one- to two-day-old platelets. They are larger than mature platelets and contain more RNA. They are the thrombopoietic counterpart of the erythroid reticulocyte, which is why they are often referred to as reticulated platelets. Some blood counting devices can automatically detect these young platelets as so-called immature platelet fraction (IPF) and there is an ongoing discussion about whether the IPF value distinguishes thrombocytopenias with reduced platelet production (low IPF) from those with increased platelet consumption (high IPF) [19, 20]. However, all publications to date show a large variation in measured values. The test results in patients with ITP and those in patients with other thrombocytopenias overlap significantly. The determination of IPF/reticulated platelets does not exclude ITP or prove the diagnosis with sufficient certainty to support therapeutic decisions.

5.5 Next-Generation Sequencing

ITP is an acquired, not hereditary, thrombocytopenia. The diagnosis of ITP is in doubt if the patient states that other family members also have thrombocytopenia. Under these circumstances, one of the rare familial throm-

Table 7. Bleeding grades according to the WHO and the NCI Common Terminology Criteria for Adverse Events (CTCAE v5.0)

WHO bleeding grade	Definition
0	No signs of bleeding
I	Petechiae Small hematomas, ecchymoses (<10 cm) Bleeding from mucous membranes (mouth, nose) Epistaxis (<1 h duration, no medical intervention necessary) Subconjunctival hemorrhages Vaginal bleeding (independent of menstruation, no more than 2 sanitary napkins/day necessary)
II (no transfusion required)	Hematomas, ecchymoses (>10 cm) Epistaxis (>1 h. duration or tamponade necessary) Retinal bleeding without visual impairment Vaginal bleeding (independent of menstruation, more than 2 sanitary napkins/day necessary) Melena, hematemesis, hemoptysis, hematuria, hematochezia Bleeding from puncture sites Bleeding in muscles and joints
III (transfusion required)	Epistaxis Bleeding from mucous membranes (mouth, nose) Vaginal bleeding Melena, hematemesis, hemoptysis, hematuria, hematochezia Bleeding from puncture sites Bleeding in muscles and joints
IV (life-threatening, potentially permanent, functional impairment, fatal)	Retinal hemorrhage with visual impairment CNS bleeding Hemorrhages in other organs with functional impairment (joints, muscles, kidneys, lungs, etc.) Fatal bleeding (in the NCI CTCAE graded as V)

bocytopenias (MYH9-associated thrombocytopenia, platelet-type [pseudo] von Willebrand syndrome, Glanzmann thrombasthenia, Bernard-Soulier syndrome, and others) or another blood coagulation disorder should be considered. These hereditary thrombocytopenias usually manifest at or shortly after birth and are often syndromal.

Next-generation sequencing testing panels can detect many rare genetic causes of thrombocytopenias. This raises the question of whether a patient with unexplained thrombocytopenia, especially one who responds poorly or not at all to standard therapies, should be tested for a genetic etiology. However, testing only makes sense if it has a practical consequence, e.g., a new therapy or a change in the current therapy. Such panels should not be requested without the availability of genetic expertise to interpret the results. The requesting physician must either be a specialist in human genetics or have the additional qualification for specialist genetic counseling. He or she must consider the consequences for the patient, especially if a genetic variant with a germline predisposition to cancer or hematologic neoplasia is detected [21, 22].

6. Classification

The classification of ITP is based on disease phase and bleeding severity.

6.1 Bleeding Severity

The treatment of ITP is primarily based on clinical bleeding severity.

Numerous bleeding scores have been devised to assess bleeding severity. Although often used in scientific studies, they are time-consuming, which limits their application in a tightly scheduled daily practice. Instead, the WHO bleeding grades or the National Cancer Institute Common Terminology Criteria for Adverse Events are recommended (Table 7) and are familiar to physicians from all specialties. The modified Buchanan score is recommended for pediatric patients (Table 8) [23].

6.2 Disease Phases and Therapeutic Goals

Therapy type and goals change with disease duration and severity. Therefore, the dichotomy of "acute" and "chronic" ITP was abandoned, and a classification into three disease phases with changing therapeutic goals was developed (Fig. 2 and Table 9).

This classification is used by regulatory authorities to limit the use of therapies to specific disease phases. Every physician treating ITP patients needs to be familiar with these phases to avoid off-label treatment and claim denials from health insurance companies. The definition of "newly diagnosed," "persistent," and "chronic" should not be based on the duration of symptoms but on when

Table 8. Modified Buchanan bleeding score for pediatric ITP patients [23]

Grade		Bleeding sign
0	None	No new hemorrhage of any kind
1	Minor	Few petechiae (≤100) and/or ≤5 small bruises (≤3 cm diameter), no mucosal bleeding
2	Mild	Many petechiae (>100 total) and/or >5 large bruises (>3 cm diameter)
3a	Moderate low risk	Blood crusting in nares, painless oral purpura, oral/palatal petechiae, buccal ecchymoses along molars only, mild epistaxis ≤5 min
3b	Moderate high risik	Epistaxis >5 min, hematuria, hematochezia, painful oral purpura, significant menorrhagia
4	Severe	Mucosal bleeding or suspected internal hemorrhage (brain, lung, muscle, joint, etc.) that requires immediate medical attention or intervention
5	Life-threatening/fatal	Documented intracranial hemorrhage or life-threatening/fatal hemorrhage at any site

Table 9. Disease phases and treatment goals

Phase	Definition	Treatment goals
Newly diagnosed	Up to 3 months after diagnosis Spontaneous remissions common	Prevention or termination of bleeding, cure Because treatment might be of brief duration, side effects are more acceptable
Persistent	Between 3 and 12 months after diagnosis Spontaneous remissions less common	Prevention or termination of bleeding, cure Since therapy now extends over a longer interval the benefits and side effects must be carefully weighed
Chronic	More than 12 months after diagnosis Spontaneous remissions uncommon	Prevention or termination of bleeding, cure Recurrent episodes of thrombocytopenia should be anticipated Quality of life and avoidance of side effects become more important than platelet count A watch and wait strategy is acceptable for patients with no or few symptoms, and only severe bleeding will require therapy

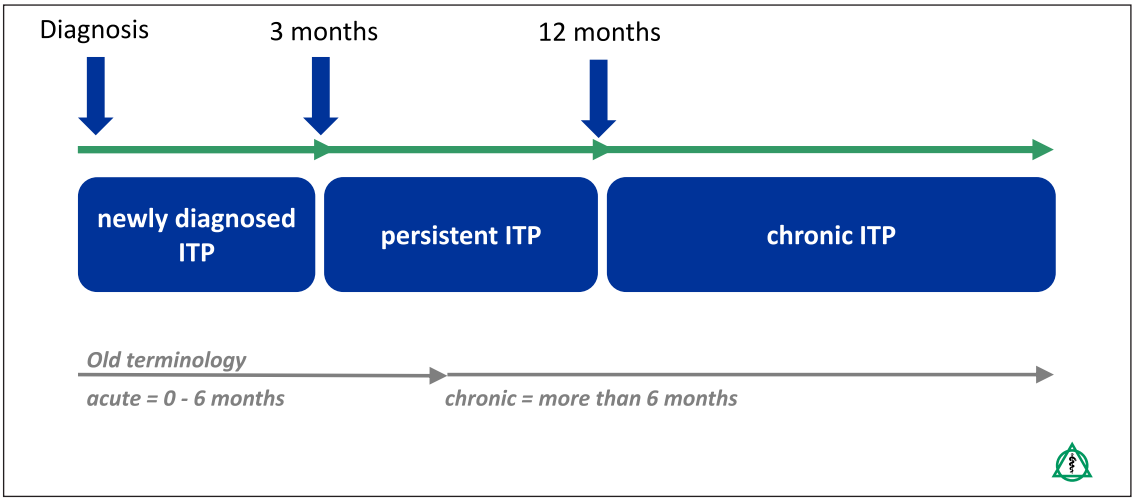


Fig. 2. Phases of ITP.

Table 10. Prognosis and risk indicators

Potential self-limited disease course	Potential for a chronic disease course	Risk of severe hemorrhage
Children, young adults	Adults, especially if >60 years old	Age >60 years
Abrupt onset	No preceding infection or other disorder	Platelet count <20,000–30,000/μL
Preceding infection	Insidious onset	Infection, fever
Preceding vaccination	Platelet count >20,000–30,000/μL	Hematuria
Acute bleeding symptoms	Onset with only minor bleeding symptoms or	Multiple hematomas
Rapid response to treatment	incidental thrombocytopenia without bleeding	Infection, Fever
	No or only minor response to first-line therapy	Mucosal hemorrhage ("wet purpura")
	Presence of ANA, rheumatoid factor or anti-CCP,	History of prior severe bleeding
	and/or antiphospholipid antibodies	No response to steroids
		Autoantibodies to more than one platelet antigen
		Children: modified Buchanan Score ≥3

the diagnosis was established because a review of medical records might reveal that thrombocytopenia preceded clinical bleeding by many months or years.

7. Prognosis

7.1 Self-Limited versus Chronic Course of ITP in Children, Adolescents, and Adults

Adult ITP is not considered a lifelong disease because one- to two-thirds of patients eventually achieve a partial or complete remission, although sometimes only after several years. This has implications for the choice of therapy, e.g., the decision to proceed to splenectomy (see chapter 16).

In adults, there is no marker that reliably predicts future remission or a chronic disease course, but in children, prognostic factors for spontaneous remission are younger age and sudden onset of symptoms with overt bleeding. The risk of a chronic course of disease is higher if bleeding symptoms are mild or absent.

Data on pediatric and adult ITP do not reflect the situation of adolescents and young adults (AYAS). AYAS have special needs and questions about physical activity (sports), therapy side effects (steroid acne, fatigue), career and family planning, and the risk of their ITP becoming chronic. To date, the only study that specifically addressed this age group observed that ITP became chronic in up to 50% of AYAS. Unfortunately, the study also shows that many AYAS are still being treated with corticosteroids for prolonged periods of time, while relatively few receive TPO-RAs [24].

7.2 Morbidity and Mortality

Despite therapeutic advances, life expectancy of patients with chronic ITP is still significantly reduced [25]. The chief causes are major hemorrhage including CNS bleeding, and infections associated with splenectomy or due to immunosuppressive therapy. The risk of cancer also is increased, which is why patients should get all age-appropriate cancer screening [26].

The prognosis of ITP has improved in recent years because of safer and more effective corticosteroid regimens and the use of TPO-RAs. ITP-related mortality is almost 0% in newer pediatric studies and 0–7% in adults. Prognostic factors and risk indicators are summarized in Table 10.

8. Differential Diagnosis

In patients with prolonged thrombocytopenia, several differential diagnoses must be considered; see Table 11 for details. Drug-induced thrombocytopenia, myelodysplastic syndromes, and liver disease are the three most common entities misdiagnosed as ITP [27].

Drug-induced ITP is the most important differential diagnosis of primary ITP. The incidence is approximately 0.1 per 10,000 per year. The course is usually acute, and after discontinuation of the drug, the platelet count recovers quickly. An updated list of drugs associated with immune thrombocytopenia has recently been published [28].

Mechanisms underlying drug-induced ITP are

- molecular mimicry may be the main mechanism in vaccine-related thrombocytopenia (for vaccines, see chapter 19.2),
- drugs bind to platelet surface proteins and induce antibodies against drug-protein complexes,
- checkpoint inhibitors disinhibit the immune system and may trigger autoimmune reactions, including cytopenias,
- alemtuzumab-induced thrombocytopenia usually develops after several months, possibly due to changes in regulatory lymphocyte (T-cell?) populations.

Many patients ask whether a drug they had taken might have caused the ITP, even if the drug has since been discontinued. Whether persistent glycoprotein-specific platelet autoantibodies can be induced in this way is controversial.

Table 11. Differential diagnosis of ITP

Differential diagnosis	History and laboratory evaluations
EDTA pseudothrombocytopenia	1–5% of all blood samples
Hereditary thrombocytopenia	Family history, examination of blood smear including mean platelet volume (large platelets in Bernard-Soulier syndrome, MYH9-asscoiated syndromes, and very small platelets with Wiskott-Aldrich syndrome)
Drug-induced thrombocytopenia	Medical history, test for drug-dependent platelet autoantibodies, see chapter 19.1
Thrombocytopenia from cytostatic drugs	Medical history (includes not only classical chemotherapy agents but also molecular/targeted or immunologic anti-cancer drugs, e.g., checkpoint inhibitors, see chapter 19.1
Antiviral drugs	Medical history
Heparin-induced thrombocytopenia (HIT)	Medical history and laboratory tests for HIT
Posttransfusion purpura	History of recent blood transfusions
Gestational thrombocytopenia	Usually platelets >80,000/µL
Lymphoma	Medical history, presence of B symptoms, enlarged lymph nodes or spleen, consider bone marrow biopsy
Infections (viral, bacterial, parasitic)	Tests for EBV, CMV, hantavirus, HIV, SARS-CoV-2, parvovirus B19, rubella and other microbiological examinations, blood cultures for sepsis, blood smear for suspected malaria
Liver disease	Liver enzymes, hepatitis antigen/antibody screen, ultrasound of liver and spleen
Splenomegaly and hypersplenism	Liver cirrhosis, infections, hematologic diseases (isolated splenomegaly in hairy cell leukemia, marginal zone lymphoma), Gaucher's disease
Alcohol	A direct toxic effect on bone marrow cells can cause thrombocytopenia independently of vitamin deficiency, liver cirrhosis, or splenomegaly. Alcohol abuse is often unsuspected and should be considered
Severe vitamin deficiencies (vitamin B12, folic acid) rarely profound iron deficiency	Laboratory analysis
Other autoimmune disorders	Test for SLE, rheumatoid arthritis, antiphospholipid syndrome, autoimmune thyroiditis, etc.
Evans syndrome	Signs of hemolytic anemia, positive anti-erythrocyte antibody tests
Cyclic thrombocytopenia	Cause unknown, mainly affects women, can usually only be diagnosed from disease course
Hematological disorders (acute leukemia, myelodysplasia, idiopathic thrombocytopenia of undetermined significance, lymphoma, CVID, autoimmune lymphoproliferative syndrome, aplastic anemia, paroxysmal nocturnal hemoglobinuria, graft-versus-host disease)	Thrombocytopenia plus changes in other blood cell lines and/or serum immunoglobulins; consider bone marrow biopsy with flow cytometry andcytogenetics The most important differential diganosis of new thrombocytopenia in children is acute lymphoblastic leukemia!
Thrombotic thrombocytopenia purpura and hemolytic uremic syndrome	Usually with additional symptoms: fever, hemolysis, renal insufficiency, neurological symptoms, etc.
Von Willebrand disease type 2b von Willebrand, platelet-type (pseudo) von Willebrand disease	von Willebrand factor function testing and multimer analysis
Disseminated intravascular coagulation	Changes in coagulation factors
Large hemangiomas (e.g., Kasabach-Merrit syndrome), large aneurysms	Clinical symptoms

9. Indication for Treatment

The indication for starting treatment of ITP is based primarily on the bleeding tendency and secondarily on the severity of the thrombocytopenia. There is no platelet threshold below which treatment is mandatory or above which treatment would be inappropriate. Disease phase, disease course, occupational bleeding risk, and numerous other individual factors must be considered.

A treatment algorithm for adult patients is shown in Figure 3, and for pediatric patients, see chapters 12 and 17. Many factors need to be taken into account, including the approval status of new drugs. Other considerations are

- bleeding symptoms, especially the occurrence of severe or life-threatening bleeding,
- platelet count,
- disease stage (newly diagnosed vs. persistent vs. chronic ITP),
- disease course and bleeding history,
- side effects of treatment,
- impact of ITP on education and occupation (risk of occupational disability),
- patient age, secondary diseases, concomitant medications (especially anticoagulants),
- access to outpatient and inpatient specialist care,
- experience of the attending physician/clinic in the management of ITP,
- patient preference, health literacy, psychosocial situation,
- children and adolescents have a greater need for physical activity, so special attention must be paid to the risk of injury with school and recreational activities.

The list does not imply any ranking; in principle, all factors should be considered when deciding on a treatment.

9.1 Platelet Threshold

The traditional assumption of a platelet threshold below which every patient must be treated and above which there is no need for treatment is not evidence-based.

The risk of bleeding and death increases when the platelet count falls below 20,000–30,000/μL, but there is wide individual variability. Defining a platelet threshold value may be helpful for the inclusion and exclusion criteria of clinical trials but is not applicable to individual therapy decisions in daily practice. The longer ITP persists, the less relevant the platelet count is as an indicator for treatment. When a patient still has very low counts despite several lines of therapy and only minor or no bleeding has occurred, then a "watch and wait" strategy is appropriate providing the patient feels comfortable with this approach.

This does not mean that platelet counts are irrelevant in advanced phases of the disease. Studies have shown that significant declines in the platelet count impair the quality of life (see chapter 19.9).

9.2 Severe and Life-Threatening Bleeding

A new standard definition of severe or life-threatening bleeding was proposed in 2021 by the International Society of Thrombosis and Haemostasis (ISTH) [29]:

- Bleeding into the following anatomic structures: intracranial, intraspinal, intraocular, retroperitoneal, pericardial, or intramuscular bleeding with compartment syndrome.
- Bleeding that leads to hemodynamic or respiratory instability.

Critical bleeding requires immediate treatment, including the use of off-label therapies. For patients already on some type of treatment, a change in treatment should be considered.

Patients and physicians often consider bleeding as severe even if they do not meet the ISTH definition for "critical" or require transfusion. A new therapy or a change of therapy may be justified if the patient requests it.

10. 1st-Line Therapy

10.1 Corticosteroids

Corticosteroids are immunosuppressive and the general opinion is that they inhibit the formation of platelet autoantibodies. They achieve an increase in platelet counts in most patients at least temporarily.

The dosage of predniso(lo)ne has not been standardized, and different guidelines give different recommendations (see Table 12). The initial dose is 1 to 2 mg predniso(lo)ne/kg/d for 1–2 weeks, then gradually tapered and eventually discontinued. Corticosteroids should not be given for less than 3 weeks or longer than 6–8 weeks. Prolonged treatment does not improve the remission rate and is associated with serious side effects (for prophylaxis of osteoporosis during corticosteroid therapy, see Table 13).

Corticosteroids achieve an initial rise in platelet counts in 60–80% of adult ITP patients, but counts decline when the dose is decreased or the agent discontinued, and only 30–50% of patients maintain a stable, steroid-free remission. Recent studies show that corticosteroids are prescribed too often and for too long periods [39, 40].

10.2 Prednisone versus Dexamethasone

The decision to give predniso(lo)ne or dexamethasone should be left to the physician's discretion. Dexamethasone is contraindicated for the treatment of ITP during pregnancy.

The usual dose of dexamethasone is 40 mg/d × 4 days every 2–4 weeks, 3 cycles (in studies, 1 to a maximum of 6 cycles).

Two randomized trials, though numbers of patients were small, showed more long-term remissions with first-line dexamethasone than with prednisone. Other studies

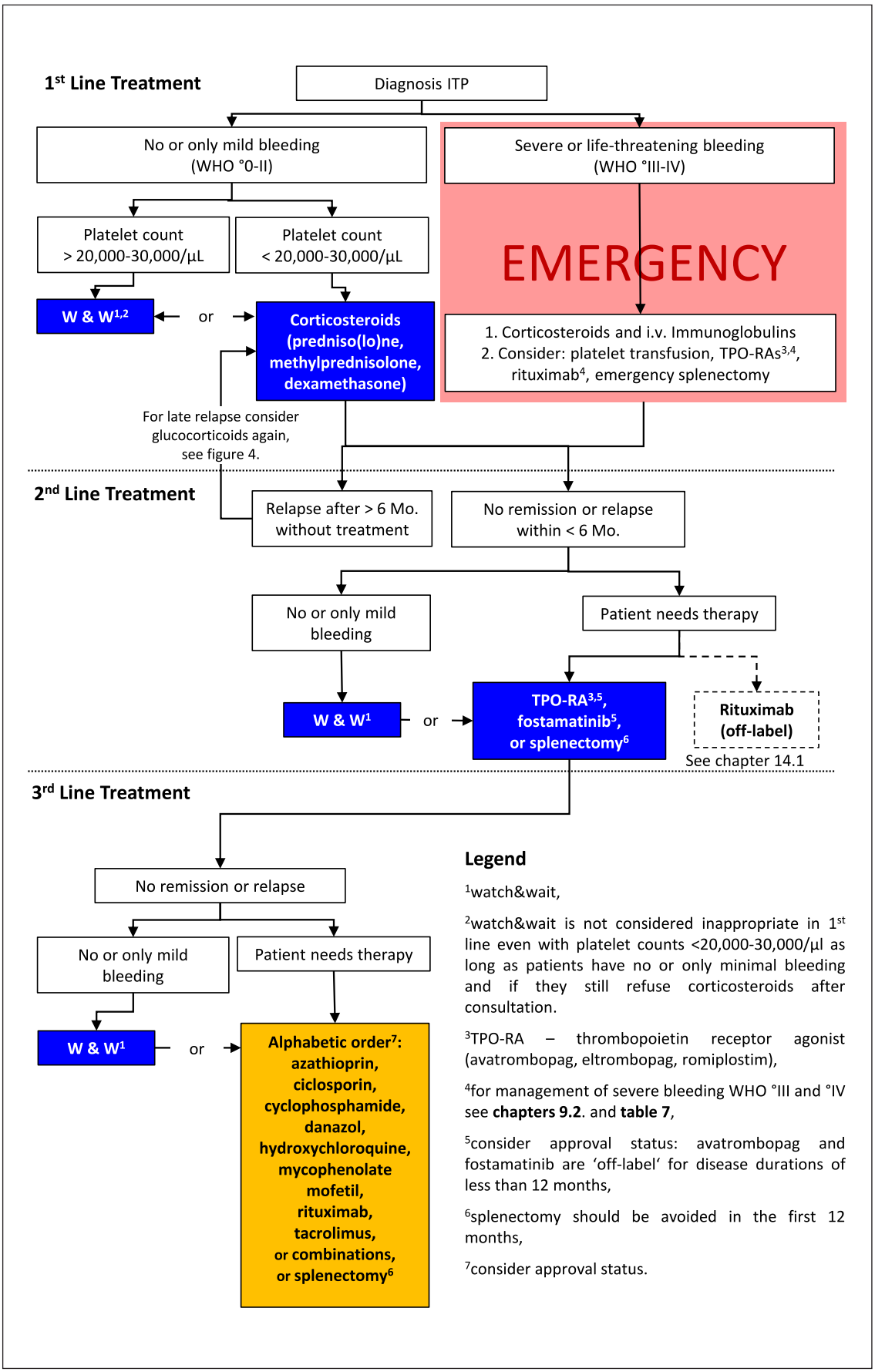


Fig. 3. ITP treatment algorithm.

Table 12. Predniso(lo)ne dosing recommendations in different guidelines

Guideline (alphabetic order)	Predniso(lo)ne dose
American Society of Hematology 2019 [30]	Prednisone 0.5–2 mg/kg/d, then dose reduction and discontinuation over 6 weeks
Australia and New Zealand 2022 [31]	Prednisone 1 mg/kg/d for 2 weeks (max. 75–80 mg), then dose reduction and discontinuation over 6 weeks
Chinese Guideline [32]	Prednisone 1 mg/kg/d (max. 80 mg/d), if response then dose reduction and discontinuation within 6, max. 8 weeks
French Guideline [33]	Prednisone at 1 mg/kg/d for 3 weeks with gradual reduction until discontinuation in 3–7 days. Prednisolone should be avoided because of poor bioavailability
International Consensus Report [34]	Predniso(lo)ne at 1 mg/kg/d (maximum dose 80 mg) for 2 weeks, to a maximum of 3 weeks. If response then taper, aiming to stop predniso(lo)ne by 6 weeks (maximum 8 weeks)
Italian Guideline [35]	Prednisone 0.5–2 mg/kg/d for a maximum of 2–3 weeks, then dose reduction aiming to stop by 8 weeks
Japanese Guideline [36]	Prednisolone 0.5–1 mg/kg/d for 2–4 weeks. Then the dose is tapered over 8–12 weeks until it is reduced to 10 mg/day or less
Onkopedia [2]	Predniso(lo)ne 1–2 mg/kg/d for 1–2 weeks, if response then dose reduction and discontinuation within 6 weeks
Spanish Guideline 2021 [37]	Prednisone 0.5–1 mg/kg/d (maximum 80 mg/day) should not be maintained for more than 3 weeks (2 weeks if no response) and should be discontinued within 8 weeks of initiation after tapering

Table 13. Recommendations for osteoporosis prophylaxis (adapted from British Society of Haematology Good Practice Paper) [38]

Assessment of fracture risk
High risk – ≥70 years – men aged ≥50 years and postmenopausal women receiving corticosteroids for ≥3 months – those with a prior fragility fracture – and those taking a high dose of glucocorticoids (≥7.5 mg prednisolone) for >3 months (> cumulative dose >682 mg prednisolone)
Example calculations for cumulative steroid dose – Prednisolone: 1 mg/kg (70 kg) for 1 week, then taper in weekly 10-mg steps (50 mg → 40 mg → 30 mg → 20 mg → 10 mg) and eventually stop after 6 weeks → cumulative dose 1,960 mg – Dexamethasone: 40 mg/d for 4 days, 2 cycles → equals prednisolone 2,133 mg
General recommendations – Adults should receive lifestyle counseling to reduce risk of osteoporosis – exercise, sports – smoking cessation, reduce alcohol intake – Measure serum calcium and vitamin D levels. Adults should have adequate daily intake of calcium (700–1,200 mg/d) and vitamin D (800 IU/d) through diet if possible or supplements if needed
Bone-protective therapy – For patients with high risk of osteoporotic fractures consider an oral bisphosphonate, such as alendronate or risedronate*
* Alendronate is licensed in Germany only for women, risedronate for men and women.

found no difference but a faster response with dexamethasone and thus a lower overall steroid burden. Cushingoid changes are not as common with dexamethasone as with predniso(lo)ne.

10.3 1st-Line Corticosteroid Monotherapy versus Corticosteroid Combinations

First-line corticosteroid monotherapy achieves 30–50% stable, therapy-free remission (see above). Attempts have been made to improve on this by combining corticosteroids with other agents. The combination of corticosteroids with mycophenolate mofetil [41] or with tacroli-

mus [42] in first-line achieve 60–70% therapy-free remissions (follow-up time 1 year and longer) and thus significantly greater than corticosteroids alone. However, mycophenolate and tacrolimus are not approved for ITP, and theirpotential side effects might negatively impact patients' quality of life. The authors do not anticipate that these new combinations will play a major role in first-line ITP therapy. There are also data on the combination of corticosteroids with rituximab or TPO-RAs as first-line therapy. However, these studies are small; phase III data with higher patient numbers are eagerly awaited ([43–45]; for review, see [46]).

The use of rituximab or TPO-RAs in first-line ITP treatment is "off-label" and should be restricted to clinical trials.

11. Emergency Treatment

IVIG can be given along with corticosteroids to achieve a prompt increase in the platelet count in patients with severe and life-threatening bleeding (WHO III/IV) (see chapter 6.1) or before urgent surgery. Another option is the transfusion of platelet concentrates, although the rise in platelet count will be only short-lived. If the above measures are ineffective in controlling severe hemorrhage, administration of rituximab and TPO-RAs may be considered, even if this approach is not evidence-based (see chapter 11.3). Emergency splenectomy is another option.

11.1 Emergency Treatment with IVIG

IVIG blocks phagocytosis of antibody-coated platelets and leads to a rapid but usually short-lived platelet increase. After 2–4 weeks, platelet counts usually return to baseline, and a sustained remission is not achieved. Thus, the use of IVIG is limited to situations in which a rapid platelet increase is needed (bleeding, non-deferrable surgery) or when high-dose corticosteroids must be avoided, e.g., pregnancy, see chapter 19.5. Approximately 10–20% of patients are relatively unresponsive to IVIG, particularly those with platelet autoantibodies directed against GP Ib/IX. Nevertheless, a trial of IVIG is justified in these, and other patients whose severe bleeding is uncontrolled by other measures [47].

11.2 Emergency Treatment with Anti-D Immune Globulin

The anti-D immune globulin preparation WinRho had been approved for ITP for the European market in the late 1990s but was withdrawn in 2009 due to reports of severe intravascular hemolysis. However, it is still available and used in other countries (e.g., USA). The marketing authorization for the anti-D preparations currently available in Germany, Austria, and Switzerland (Rhophylac®, Rhesonativ®, and others) is limited to Rh isoimmunization suppression, but these agents have occasionally also been used to treat ITP. Anti-D is only effective in Rh-positive patients with intact spleens.

11.3 Emergency Treatment with Platelet Concentrates, Rituximab, TPO-RAs

Platelet concentrates can be used for critical bleeding (WHO III, IV) to achieve a brief increase in platelet counts and to control bleeding. Generally, more than 1–2 concentrates will be required. In these rare emergency situations, corticosteroids and immunoglobulins are co-administered with the platelets. In the most severe bleeding cases, the use of rituximab and early administration of TPO-RAs may also be considered (though TPO-RAs need some days to take effect). The administration of platelet concentrates does not appear to stimulate the production of platelet autoantibodies.

12. Treatment of Newly Diagnosed ITP in Children and Adolescents

Pediatric ITP differs from adult ITP in that it becomes chronic less often. In addition, the prognosis and treatment of older adolescents and young adults (AYAs) differ from those of children and adults. Because of the rarity of ITP in pediatrics and age-related therapeutic considerations, most experts recommend that children and adolescents be treated in centers with pediatric hematologic expertise.

The younger the child, the more likely the onset of bleeding will be acute, and often after an infection. This is the scenario in about 60% of children younger than 10. The thrombocytopenia is transient in most children and chronic courses are less common than in adults. The older the child, the more similar the course is to that of adults (insidious onset, no history of infection, often chronic with minor bleeding). Indicators for therapy are individual bleeding signs, the platelet count, and other risk factors (Table 14).

First-line treatment includes either observation without medication or administration of corticosteroids and immunoglobulins. However, drug therapy is often unnecessary for newly diagnosed ITP in children and adolescents with only a mild bleeding tendency [23]. Mucosal bleeding and bleeding more intense than 3b according to the modified Buchanan bleeding score (see Table 8) are indications for treatment. Platelet counts are generally not the decisive factor for the treatment of newly diagnosed pediatric ITP with mild or no bleeding [23]. Individual considerations such as age, susceptibility to injury, and psychosocial aspects should be taken into account. According to international and American guidelines, drug therapy is only indicated for moderate and severe bleeding.

Table 14. 1st line therapy for children and adolescents with newly diagnosed ITP

Grade (risk)	Bleeding signs	Recommendation
0–2 – Low or mild	From no hemorrhage of any kind up to many petechiae (>100 total) and/or >5 large bruises (>3 cm diameter)	Watch and wait
3a[a] – Low risk moderate	Blood crusting in nares, painless oral purpura, oral/palatal petechiae, buccal purpura only along molars, mild epistaxis ≤5 min	No standardized recommendations available. Individualized treatment decision based on (1) platelet count, (2) risk of injury, (3) infection, fever, (4) health literacy, psychosocial situation
3b[a] – High risk moderate	Epistaxis >5 min, hematuria, hematochezia, painful oral purpura, menorrhagia	Prednisone 4 mg/kg/d for 4 days or/and IVIG 0.8–1 g/kg/d for 1 or 2 consecutive days If necessary, add tranexamic acid 20–25 mg/kg/d in 3 single doses p.o Hormonal therapy for menorrhagia and gynecological consultation if necessary
4 – Severe	Mucosal bleeding or suspected internal hemorrhage (brain, lung, muscle, joint, etc.) that requires immediate intervention	Prednisone 2–4 mg/kg/d for 4 days and IVIG 0.8–1 g/kg/d for 2 consecutive days If necessary, add tranexamic acid 20–25 mg/kg/d in 3 single doses p.o Hormonal therapy for menorrhagia and gynecological consultation if necessary
5 – Life threatening	Documented intracranial hemorrhage or life-threatening hemorrhage at any site. Need for emergency surgery	Concurrent: (1) Platelet concentrates will need to be given in high doses because of shortened platelet half-life (2) Methylprednisolone 30 mg/kg bw i.v. (max. 1 g) for 3 consecutive days (3) IVIG 0.8–1 g/kg/d on 2 consecutive days (4) If necessary, add tranexamic acid 20–25 mg/kg/d in 3 single doses p.o. or 10–20 mg/kg/d i.v (5) TPO-RA administration to be decided individually, analogous to the recommendations for adults Consider emergency splenectomy for refractory thrombocytopenia, and craniotomy to relieve increased intracranial pressure in patients with cerebral hemorrhage

[a] This modification of the Buchanan score in 3a and 3b originates from a study on a standardized bleeding assessment (Standardized Clinical Assessment and Management Plan [SCAMP®]), which has proven to be accurate and found wide acceptance [48].

Retrospective studies and registry data including both treated and untreated children report an incidence of ~3% severe to life-threatening bleeding. The incidence of intracranial hemorrhage is <1% and is particularly feared. Typically, platelet counts at the time of hemorrhage are 20,000/μL or below, and affected children usually have mucosal bleeding (mouth, nose, pharyngeal – wet purpura). Particular caution should be exercised if hematuria is also present because hematuria can be a harbinger of more severe bleeding at other sites (see Table 10). IVIG should be given for severe bleeding, and add corticosteroids and platelet concentrates if bleeding is life-threatening.

If there is little or no response to therapy, the diagnosis should be questioned and the patient referred to a center with hematologic expertise. Acute lymphoblastic leukemia (ALL) is the most important differential diagnosis of newly diagnosed ITP in childhood. For management of pediatric patients with persistent or chronic ITP and the relevance of bleeding symptoms and blood counts in these patients, see chapter 17.

13. 2nd-Line Therapy

If first-line treatment with corticosteroids does not achieve a response after 2–4 weeks, then second-line therapy should be initiated. Second-line therapy is also given if first-line therapy is poorly tolerated or if there is an initial but short-lived response.

There is no generally accepted threshold value below which second-line therapy must be offered or above which therapy would be inappropriate. The indication for treatment is always an individual decision.

If first-line therapy has achieved a response and recurrence occurs after more than 6 months, then first-line therapy can be repeated, see Figure 4. In contrast to first-line therapy, quality of life and avoidance of side effects

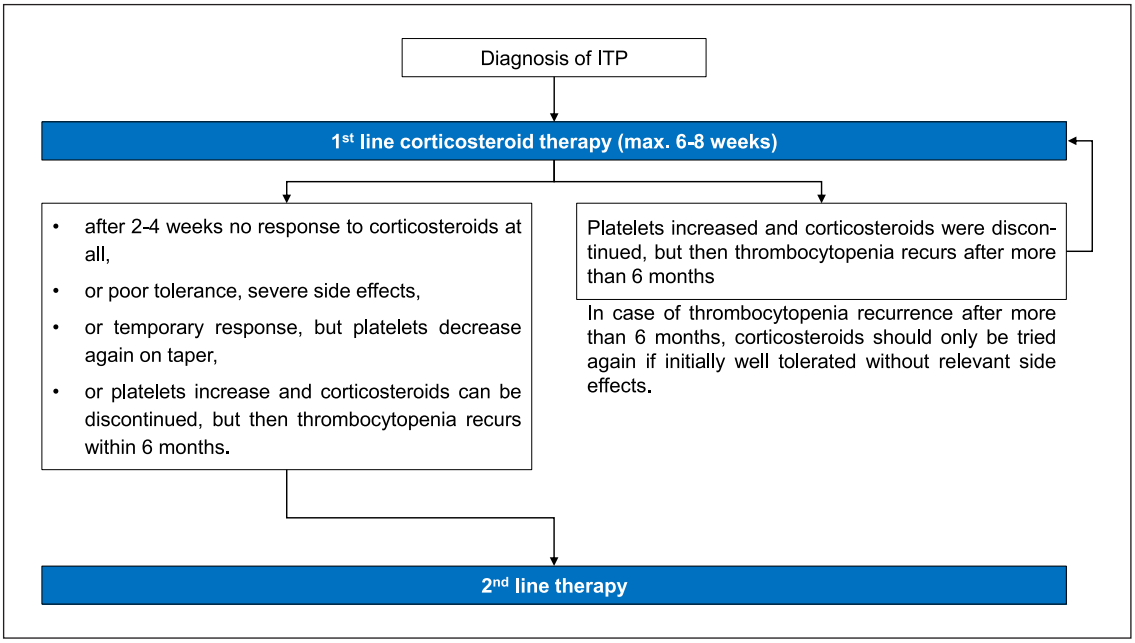


Fig. 4. Second-line treatment algorithm for thrombocytopenia recurrence.

become more relevant in second and further lines of therapy. While all therapy attempts should be aimed at achieving cure in newly diagnosed ITP, a durable remission is less likely with increasing disease duration, and the side effects of therapy need to be weighed against its benefits.

The following has proven helpful in daily practice:

- In patients with no or minimal bleeding (WHO 0 to I) (see Table 7), second-line therapy can be offered after failure of first-line therapy, but other options would be no therapy and watch and wait. Many patients will choose second-line therapy even when they have only very mild or no bleeding because they are afraid of more severe hemorrhages.
- In patients with moderate bleeding (WHO II), treatment may be offered, but watch and wait is not inappropriate. Most patients will opt for second-line therapy.
- In patients with WHO III or IV bleeding, therapy is indicated regardless of the platelet count, and hospital admission is recommended.

13.1 Thrombopoietin-Receptor Agonists

TPO-RAs are the established second-line therapy when an ITP patient does not respond to first-line corticosteroids or has a prompt relapse. TPO-RAs have different pharmacological properties and approval status. The SYK inhibitor fostamatinib is also approved for second line, see chapter 13.6.

In Europe, the three TPO-RAs, romiplostim, eltrombopag, and avatrombopag, have been approved for the treatment of ITP. All three agents can increase platelet counts to a safe range. Data from pivotal and ongoing studies can be summarized as follows:

- The target range of platelet count is 50,000-150,000/μL, and normalization of platelet count is not intended.
- The platelet count should not increase above 250,000/μL.
- Platelet counts should be checked every week initially, then every 4 weeks. If the values are stable and the patients have no other morbidities, quarterly or half-yearly checks may be sufficient.
- A short-term response is achieved in more than 90% of patients.
- Long-term responses (on treatment) vary between 30% and 90%.
- Approximately 50% of patients can discontinue all other ITP medications (e.g., corticosteroids) while on TPO-RAs.
- TPO-RAs are effective in patients that have had a splenectomy.
- TPO-RAs are effective in children as well as adults.
- Cross-resistance does not occur between avatrombopag, eltrombopag, and romiplostim, i.e., loss of efficiency of one does not preclude effectiveness of another [49].
- Both eltrombopag and romiplostim appear to be less effective in patients with elevated serum thrombopoietin levels. No data are yet available for avatrombopag.

Table 15. Routes of administration and adverse effects of TPO-RAs and the SYK inhibitor fostamatinib

	Romiplostim	Eltrombopag	Avatrombopag	Fostamatinib
Route	subcutaneous	oral	oral	oral
Headache, arthralgia, myalgias	X	X	X	X
Nausea, upper GI symptoms	X	X	X	X
Upper respiratory tract symptoms	X	X	X	X
Hypertension				X
Arterial and venous thromboses (see additional note #1)	X	X	X	
Elevated liver function tests		X		X
Gastrointestinal symptoms (constipation, nausea, diarrhrea)	X	X	(X)	X
Rash, itching, exanthema	Skin reaction at injection site	X	X	X
Steep decline in platelet count after stopping TPO-RA	X	X	X	
Neutropenia				X
Blasts in MDS	X	X	X	
Antibody formation	X			
Interaction with HMG-CoA-inhibitors		X		X
Reduced iron absorption, iron deficiency		X		
Increase in bone marrow reticulin (see additional note #2)	X	X	X	

Table 16. Comparison of TPO-RAs and the SYK inhibitor fostamatinib for the treatment of ITP refractory to other treatments (see also [50])

	Romiplostim	Eltrombopag	Avatrombopag	Fostamatinib
Structure	Peptide	Small molecule	Small molecule	Small molecule
Target	Extracellular domain of TPO receptor	Transmembrane domain of TPO receptor	Transmembrane domain of TPO receptor	Splenic tyrosine kinase
Food interactions	No effect	Calcium decreases absorption of drug	Should be taken with some food	No effect
Therapeutic indication	Treatment of primary ITP in adult patients who are refractory to other treatments (e.g., corticosteroids, immunoglobulins), a minimum duration of illness not specified Treatment of chronic ITP in pediatric patients 1 year of age and older who are refractory to other treatments (e.g., corticosteroids immunoglobulins)	Treatment of adult patients with primary ITP who are refractory to other treatments (e.g., corticosteroids, immunoglobulins), a minimum duration of illness not specified (does not apply to Switzerland, where approval is only after 6 months of illness) Treatment of pediatric patients aged 1 year and above with primary ITP lasting 6 months or longer and who are refractory to other treatments e.g., corticosteroids, immunoglobulins)	Treatment of chronic ITP in adult patients who are refractory to other treatments (e.g., corticosteroids, immunoglobulins)	Treatment of chronic ITP in adult patients who are refractory to other treatments

However, determining the TPO level before prescribing TPO-RAs is not recommended because threshold values have not been validated and depend on the test method. Even patients with high TPO levels might have therapeutic responses.

- Abrupt discontinuation of TPO-RAs may result in a steep decline in platelet count. Platelet counts should be recorded for at least 4 weeks after drug discontinuation.
- The TPO-RA can be decreased and eventually discontinued when patients have achieved a stable partial or complete remission. In approximately one-third of patients, the platelet count will remain above 50,000/μL, and no further treatment will be required (therapy-free remission) (see chapter 13.4).
- TPO-RAs are much better tolerated than corticosteroids. The most common side effects are headache, fatigue, upper respiratory tract infections, and inflammation. Liver function test elevations are less common with avatrombopag than with eltrombopag (see Table 15).
- Avatrombopag and eltrombopag both bind to the transmembrane domain of the thrombopoietin receptor. The main difference between the two compounds is that eltrombopag requires food abstinence (see prescribing information for details), whereas avatrombopag can be taken with food. In fact, the regulatory text for avatrombopag recommends taking it with a meal.

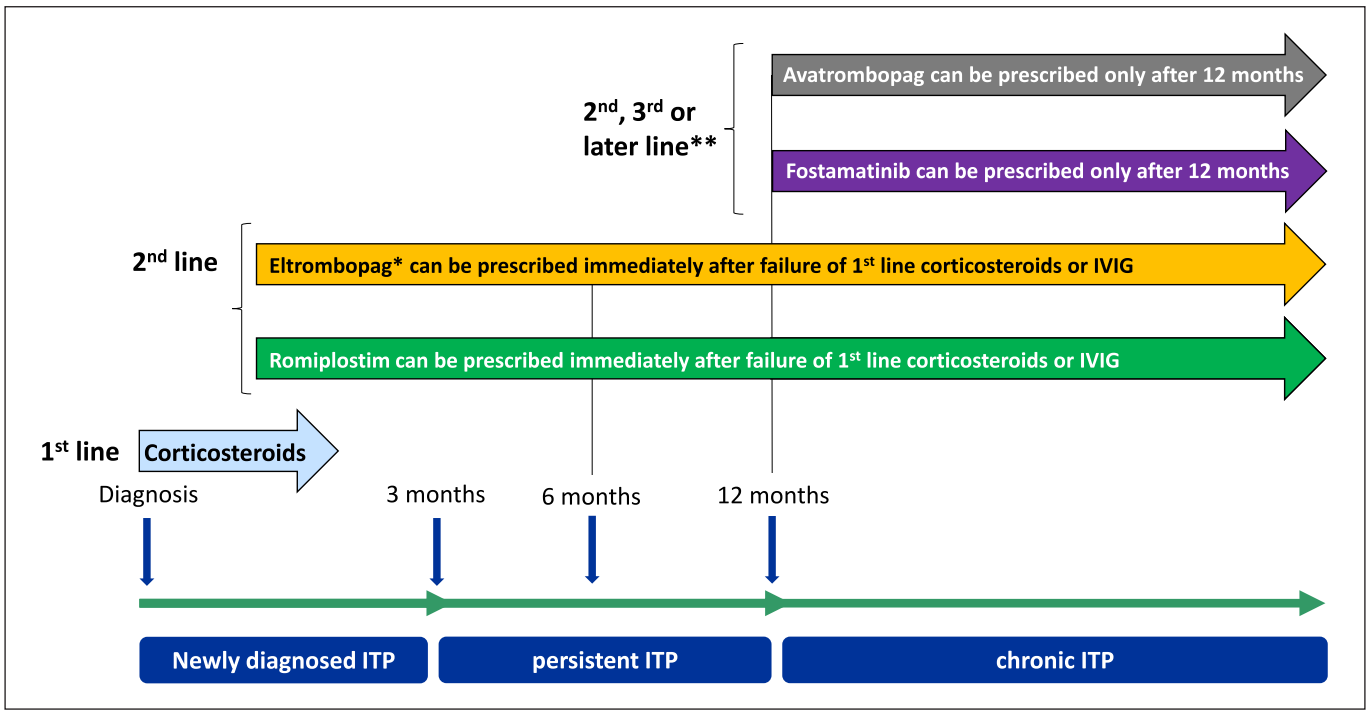


Fig. 5. Disease phases of ITP and approval status of various treatments. *In Switzerland, eltrombopag can only be prescribed after a disease duration of at least 6 months. **Avatrombopag and fostamatinib are usually given third line, but when the previous disease duration is more than 1 year (approval only for chronic ITP) and when the patient had only corticosteroids they can also be given second line.

Additional data on TPO-RAs and the SYK inhibitor fostamatinib are summarized in Tables 15, 16 and Figure 5. There are numerous studies showing that TPO-RAs are at least as effective and safe in newly diagnosed ITP as in persistent or chronic ITP. Thus, there is no medical reason to wait before giving these agents following failure of first-line corticosteroid therapy (e.g., 6 months for eltrombopag in Switzerland or 1 year for avatrombopag). Romiplostim can be prescribed immediately after failure of first-line therapy. The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) recommended in September 2022 that the marketing authorization for eltrombopag be extended to include adult patients with primary ITP who are refractory to other therapies (e.g., corticosteroids, immunoglobulins). A label update has been submitted to Swissmedic, the Swiss regulatory authority, and a decision is expected in mid/late 2023. Until then, the Swiss approval status is limited to chronic ITP with a minimal disease duration of 6 months.

Note 1: ITP patients might have a history of prior thrombosis or embolism or a known thrombophilia. Quite a few ITP patients also have antiphospholipid antibodies without meeting the criteria for antiphospholipid syndrome (i.e., no arterial or venous thrombosis to date, no gynecologic complications). If these patients receive a TPO-RA, it is theoretically possible that the thrombosis risk could be further increased (see chapter 19.6). To date, however, there are no prospective data that the risk of thrombosis with TPO-RAs in this group of patients outweighs the risk of bleeding. The administration of a TPO-RA should always be carefully considered in patients with risk factors for thrombosis, and the patient should be informed about what to do should symptoms appear. Thrombosis prophylaxis is not recommended; rather, if the risk of thrombosis is thought to be very high, offer fostamatinib (see chapter 13.6), which has not been shown to be thrombogenic.

Note 2: Bone marrow reticulin fiber proliferation associated with TPO-RAs is rarely clinically relevant. There are no evidence-based recommendations on whether or how often to perform bone marrow biopsies in patients receiving TPO-RAs. If a bone marrow biopsy is obtained for other purposes, the marrow fiber content could be determined.

13.2 Other Thrombopoietin-Receptor Agonists

- TPIAO is a recombinant thrombopoietin molecule approved for second-line therapy of ITP in China since 2010. It is the only TPO-RA that has ever been tested in a study in pregnant women to date and found to be safe. TPIAO is currently approved in China and the Philippines but is not available in Germany.

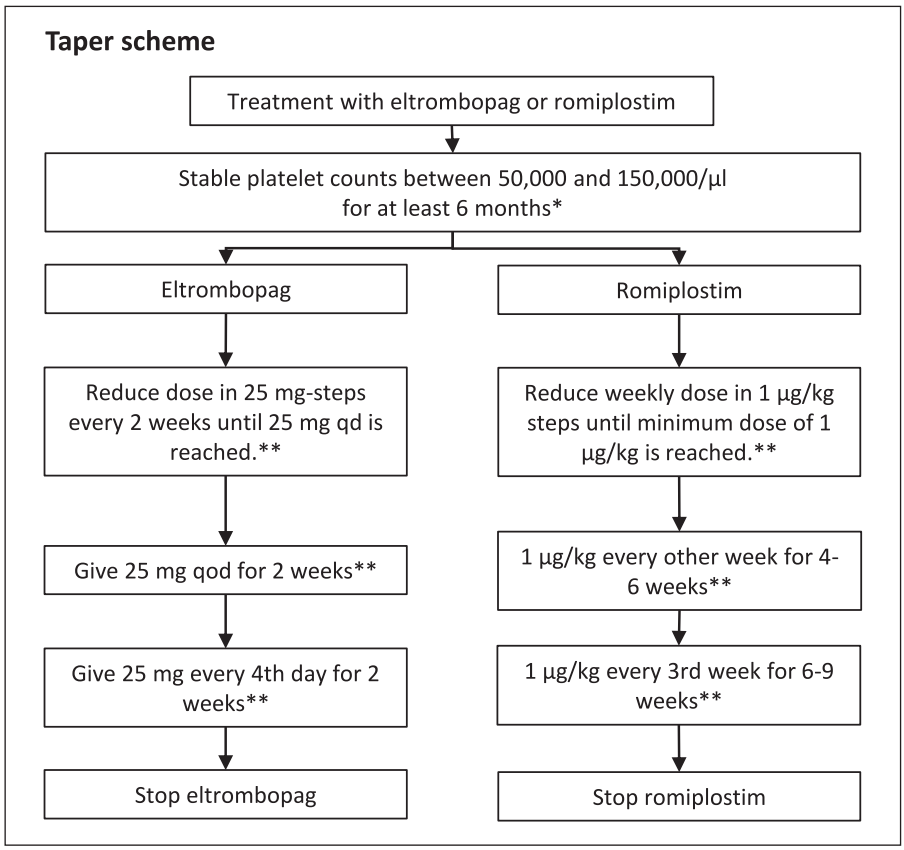


Fig. 6. Proposed scheme for eltrombopag and romiplostim taper and discontinuation. *There is no consensus on how long the platelet count should be stable and above 50×10^9/L before attempts at discontinuation. Literature gives a range of between 4 and 12 months. The 6 months given here is from the publication by Zaja et al. [51]. **Continue to reduce the dose as long as the platelet count does not fall below 30×10^9/L (not below 50×10^9/L in patients with bleeding). IVIG, intravenous immunoglobulin.

- A romiplostim biosimilar (trade name: Romy) is available in India [52].
- Hetrombopag (trade name: Hengqu) is an oral TPO-RA and was developed in China for the treatment of thrombocytopenias and aplastic anemia. Hetrombopag is not available in Europe [53].
- Lusutrombopag (trade name: Mulpleo) is another oral TPO-RA that was approved in Europe in 2019, for the treatment of thrombocytopenias in adult patients with chronic liver disease for whom invasive surgery is planned. Lusutrombopag is not approved for ITP and is currently not available in Germany.

13.3 Inadequate Response to Second-Line TPO-RAs

If TPO-RAs fail to raise the platelet count, they may be combined with low-dose steroids for greater efficacy. This is because each agent addresses a different mechanism that contributes to the thrombocytopenia of ITP (impaired platelet production: TPO-RAs; increased platelet phagocytosis: steroids (see chapter 3).

13.4 Achieving a Therapy-Free Remission with TPO-RAs

Discontinuation of TPO-RAs should be attempted if the platelet count has been above 50,000/µL for 6 months or longer. The TPO-RA dose is gradually decreased over several weeks. This strategy will be successful in approximately one-third of patients, and further therapy will not be required.

If patients do not bleed and platelets remain stable above 50,000/µL for at least 6 months, discontinuation of the TPO-RA can be attempted, even if the platelet count is not in the normal range. Reviews cite remission rates of up to 30% [54–56]. It is important that TPO-RA be phased out slowly over several weeks and not abruptly. The remission rate seems to be higher if TPO-RAs have been prescribed early in the course of ITP, whereas later-line or splenectomized patients have a lower rate of therapy-free remissions. No other predictive factors have been identified. Figure 6 suggests a discontinuation scheme for eltrombopag and romiplostim following the recommendations of the Italian ITP Expert Group [51].

13.5 Achieving a Therapy-Free Remission with Splenectomy or Rituximab

Unfortunately, most patients do not achieve a drug-free remission, and the need for continuous therapy poses a particular risk for women of reproductive potential. Since some TPO-Ras and SYK inhibitors should not be given during pregnancy, alternative approaches need to be sought to achieve a therapy-free remission. ASH recommends the administration of rituximab or splenectomy [30, 57], and patients generally prefer rituximab to surgery. However, health insurers might insist on sple-

nectomy before rituximab because it is more cost effective. It is the authors' experience that health insurers do not refuse coverage for rituximab in women who are planning to become pregnant and who have not achieved treatment-free remission with corticosteroids and TPO-RAs.

13.6 Fostamatinib

Fostamatinib is the "first-in-class" SYK (spleen tyrosine kinase) inhibitor. SYK plays an important role in signal transduction, phagocytosis, and degradation of erythrocytes (autoimmune hemolysis) and platelets (ITP) in the spleen. Fostamatinib achieves a sustained platelet increase in approximately half of ITP patients.

Fostamatinib is approved for the treatment of chronic ITP in adult patients who are refractory to other types of treatment. The approval is not limited to primary ITP but, unlike TPO-RAs, also includes secondary ITP (see also Table 16 and Fig. 5).

The most common side effects in the pivotal trials were diarrhea, arterial hypertension, nausea, elevation of liver enzymes, and neutropenia. No other side effects have been reported for long-term treatment. Because fostamatinib is metabolized primarily by CYP3A4, CYP3A4 inhibitors and inducers affect its efficacy.

Fostamatinib is given third line by many hematologists after failure of TPO-RAs, although the approval text also allows prescription in the second line. This is because approval has been restricted to chronic ITP, i.e., ITP that has been present for at least 1 year; by that time most patients have undergone 2 or 3 lines of therapy, including TPO-RAs. A post hoc analysis of the pivotal studies – although with a small number of patients – showed that the response rate in the second line is significantly higher than when the drug is given in the third line with the same durability of response [58, 59]. Fostamatinib has not been shown to increase the incidence of thromboembolism. It is, therefore, a good choice for high-risk patients, e.g., patients with a history of venous thromboembolism.

14. 3rd-Line Therapy

The drugs listed in Table 17 have shown efficacy in ITP. The order of therapies does not imply an order of preference. Many of these agents are off-label or have old approvals. This means that these compounds have not been studied according to current good clinical practice and evidence-based medicine standards, and their approval might be based on tradition rather than evidence. They should be given only when contemporary, more thoroughly studied agents such as TPO-RAs, SYK inhibitors, and rituximab are not effective. Rituximab is the best-studied agent on the list and will be discussed in more detail.

14.1 Rituximab

Rituximab induces selective lymphocyte depletion which leads to a decrease in platelet autoantibody production. Rituximab has not been approved in any country for the treatment of ITP. Nevertheless, it is recommended as a valid therapeutic option in guidelines and by experts.

Different dose recommendations can be found in the literature (4 × 375 mg/m^2, 2 × 1,000 mg fixed dose, 4 × 100 mg fixed dose, etc.), but a clear superiority of one dosage over the other is not apparent. Lower cost is often given as an argument for lower doses [60]. From published studies, the following conclusions can be drawn regarding efficacy and tolerability:

- On average, rituximab achieves a short-term increase in platelet counts in 60% of patients. However, relapses do occur.
- Longer-term remission rates are 20–30% [61].
- Rituximab is effective before and after splenectomy.
- Children seem to respond somewhat better than adults. Relapses occur mainly in the first few years in children while they occur later in adults.
- Women and girls seem to respond better to rituximab than men and boys. This may be due to gender-related differences in the blood levels of the agent.
- ITP patients in earlier phases of the disease seem to respond better.

Important side effects to be aware of

- Infusion reactions with weakness, nausea, fever, chills, and headache are common (about 60%), usually mild and mostly during the first infusion (consider premedication with corticosteroid),
- Anaphylactic reactions are rare and should not be confused with the cytokine-release syndrome
- The risk of infection is increased, so that every 6th–7th patient may develop an infection requiring treatment.
- Vaccinations are ineffective for up to 6 months after rituximab. If the timing of therapy is optional, give rituximab in the spring so that the annual flu shot in the fall will be effective.
- In addition, rituximab poses a risk because it may adversely affect the response to COVID-19 vaccination or the course of this viral infection.
- Treatment with rituximab is generally well tolerated. A recent study found rituximab therapy to be at least as well tolerated as TPO-RAs [62].

The ASH explicitly recommends rituximab for patients who wish to become therapy-free. Despite not being approved for ITP, rituximab is the most common second-line therapy in the USA, ahead of TPO-RAs [63].

Table 17. Drugs for third line therapy in ITP

Drug	
Azathioprine	Azathioprine and steroids are usually given toggether and after a few weeks the steroid dose is slowly reduced (steroid-sparing agent) Neutropenia is common (about 30%), and the leukocyte count must be checked regularly (e.g., every 2–4 weeks initially) The response to treatment is slow and efficacy should not be assessed before at least 3–4 months Azathioprine does not need to be discontinued during pregnancy
Cyclosporin A (CSA)	CSA is used as monotherapy or in combination with prednisone. Lower doses seem to be better tolerated and not less effective. A CSA level of 150 to 400 ng/mL is targeted Common side effects include fatigue, weakness, renal insufficiency, hypertension, neuropathy Therapy response is slow and efficacy should not be assessed before 3–4 months
Cyclophosphamide	Cyclophosphamide is used as monotherapy or in combination with prednisone. The dose must be adjusted to the leukocyte count In addition to hematologic side effects and nausea and vomiting, rare cases of bladder cancer and secondary leukemia have been described. Fertility may be impaired
Danazol [off-label]	Danazol is a modified androgen and affects liver function during prolonged therapy. It should not be given to women (virilization) Other side effects include weight gain, myalgias, hair loss Therapy response is slow and efficacy should not be assessed before 3–4 months
Dapsone [off-label]	Dapsone is a sulfone (synthesized over 100 years ago) Before administering, exclude a deficiency or defect of glucose-6-phosphate dehydrogenase in patients from Mediterranean countries and in Africans and African-Americans The response to therapy is slow but can usually be expected after 4–6 weeks, and then an attempt should be made to reduce the dose
Hydroxychloroquine [off-label]	Hydroxychloroquine has multiple effects on the immune system. It has been given in studies of ITP patients who were also positive for ANA or had SLE. Therapy response is slow and the drug should be given for at least 2–3 months before assessing efficacy. Usually, hydroxychloroquine is combined with steroids and then the steroid dose is slowly reduced over a few weeks (steroid-sparing agent) Hydroxychloroquine is often prescribed for the therapy of ITP in countries with limited health care system resources
Mycophenolate mofetil [off-label]	Start with a low dose and then slowly increase it for better tolerability Gastrointestinal side effects such as nausea, loss of appetite, diarrhea, and vomiting are common (for combination with corticosteroids in the first line, see chapter 10.3)
Rituximab [off-label]	Rituximab has the best evidence-base of all the agents mentioned in this table. In many countries it is offered as second-line treatment. Therefore, rituximab will be discussed in more detail in chapter 14.1
Tacrolimus [off label]	Tacrolimus (FK506 or FK-506) is a macrolide lactone from the group of immunomodulators or calcineurin inhibitors, and is used in organ transplantation. For ITP, it is given as monotherapy or in combination with prednisone. The starting dose is 1 mg BID (in transplant medicine much higher doses of 0.1–0.2 mg/kg/day are given), targeting for a trough level of 4–10 ng/mL [42] The following side effects have been described in the transplant setting: renal insufficiency, cardiomyopathies, intestinal perforation, secondary tumors including lymphomas, and encephalopathy syndromes. Only mild side effects have been reported in ITP patients

15. Therapy of Refractory/Multiply Relapsed ITP

Approximately 15% of ITP patients fail to have a durable response after 3 lines of therapy. ITP in which patients have repeated clinically relevant hemorrhages and do not respond to multiple lines of therapy is a serious disease with high morbidity and mortality.

In this situation, combinations of thrombopoiesis-stimulating and immune system-inhibiting agents are usually offered (for review, see [64–66]):

- TPO-RA + fostamatinib
- TPO-RA + azathioprine or corticosteroid
- TPO-RA + azathioprine, cyclosporine, everolimus, or cyclophosphamide.

Further counseling and management of multidrug-resistant patients must consider four aspects.

What Is the Risk of Bleeding, Especially CNS Bleeding?

There are no generally accepted definitions for the severity of bleeding in ITP. Also, there is a lack of data about the frequency and severity of hemorrhages. Consequently, prognostic statements from registries, observational studies, and case series about bleeding risk in refractory/multiply relapsed ITP are not very reliable. Severe bleeding seems to occur more frequently in the early phases of ITP, i.e., in newly diagnosed individuals. In chronic ITP, the focus is more on milder bleeding that is not life-threatening but still affects the quality of life. In addition, refractory/multiply relapsed patients are difficult to manage surgically (e.g., for splenectomy) or when they need anticoagulation for other indications.

Table 18. Risks and contraindications of splenectomy

Risk	Comment
Operative morbidity	Complication rate 10%, mainly wound infections and pneumonia
Operative mortality	<1% may be higher in elderly patients
Overwhelming postsplenectomy infection syndrome (OPSI)	3-fold risk of septicemia compared to patients with spleen
Postsplenectomy thrombocytosis	When platelets rise to $>10^6$/μL consider aspirin or low-molecular-weight heparin
Venous thromboembolism	ITP patients have a higher than average risk for VTE (see chapter 19.6), which can be further increased by splenectomy
Pulmonary hypertension	Incidence after splenectomy 0.4% in 5 years. However, may be less common with splenectomy for ITP than for other hematologic disorders (sickle cell anemia, thalassemia, hemolytic anemia)
Contraindication with active infection	E.g., tuberculosis

Is It Possible to Achieve a Lasting Remission with a Fourth or Further Line of Therapy?

30% of multidrug-resistant patients eventually achieve a response to therapy. Current clinical trials of new drugs, which usually include patients with multiple prior therapies, also report responses in up to 50%. Therefore, therapeutic fatalism is not justified.

How Can Quality of Life be Improved?

Many patients with chronic ITP learn to cope with bleeding and hematomas. However, concerns about fluctuating platelet counts usually persist (see chapter 20.1).

Could It Be Another Form of Thrombocytopenia and Not Primary ITP?

Refractory or multiply relapsed thrombocytopenia should raise the question of whether the patient has primary ITP or another disorder. Recent work shows that 20–50% of multidrug-resistant patients eventually are found to have a secondary ITP and are diagnosed with hereditary thrombocytopenia, lymphoma, bone marrow insufficiency syndromes (more common in pediatrics), myelodysplasia, or an initially overlooked drug toxicity [57, 64, 65].

16. Splenectomy

Splenectomy is the treatment with the highest rate of durable remissions in ITP and two-thirds of patients achieve a partial or complete remission.

Splenectomy is an attractive option for patients who do not wish to take medicines over the long term. However, it is not performed during the first year of the disease because spontaneous remissions often occur during this period.

TPO-RAs achieve even higher remission rates than splenectomy when only platelet count response is considered, but they must be taken indefinitely. Platelet counts usually decline when TPO-RAs are discontinued.

Splenectomy should be considered for patients with persistent or chronic thrombocytopenia, severe bleeding WHO III of IV, and an inadequate response to other therapeutic modalities. In emergencies, such as life-threatening hemorrhage unresponsive to corticosteroids and/or i.v. immunoglobulins, splenectomy is the therapy of choice because alternative options, such as TPO-RAs or rituximab, usually do not provide an immediate increase in platelet numbers but raise counts gradually (often >1 week).

There is not a compelling indication for splenectomy in patients with chronic, therapy-resistant ITP who have no, mild, or only moderate bleeding (WHO 0, I, II), even if their platelet counts are <30,000/μL. In these patients, decisions should be made on an individual basis with consideration of patients' preferences.

Preoperatively, patients should be vaccinated against pneumococcus, haemophilus influenzae B, and meningococcus. After splenectomy, yearly influenza vaccination should be encouraged, even for younger individuals [66]. Risks and contraindications of splenectomy are summarized in Table 18.

Splenectomy is performed today much less frequently than some years ago. This is due to concerns about the risks and side effects associated with this operation. Other reasons include:

- Only approximately 60% of patients achieve a durable remission. However, the remission rate after splenectomy has remained constant even though patients have been previously treated with TPO-RAs and rituximab [67].
- Patient characteristics that predict a response to splenectomy have not been established, but older age, poor response to previous therapies, or secondary ITP are associated with lower response rates. The International Consensus Report recommends splenectomy if removal

of radiolabeled autologous platelets occurs predominantly in the spleen [34] (Note: these must be autologous platelets, not allogeneic platelets from healthy donors). In the Federal Republic of Germany, there are only a few nuclear medicine departments that still offer this study.
- For unclear reasons, a response to splenectomy is not automatically associated with an improvement in quality of life for some patients [68, 69].

16.1 Splenectomy-Deferring Therapy

Patients who have failed all approved therapies might refuse splenectomy and should be considered candidates for off-label treatment with rituximab. Splenectomy and rituximab are not medically equivalent, interchangeable treatment options. A decision on the selection of surgery versus infusions should only be made after counseling and educating the patient. Consideration of the patient's preference is mandatory. Patients who value the avoidance of long-term drug therapy should be offered splenectomy while those who wish to avoid surgery should receive rituximab after trials of TPO-RAs and fostamatinib (see Fig. 3). Preference for one treatment over the other for economic reasons should be refused.

17. Therapy of Persistent or Chronic ITP in Children and Adolescents

Eltrombopag and romiplostim are effective in children and adolescents with chronic ITP. The formal approval text varies by country based on age, duration of ITP, and treatment criteria. Avatrombopag has not yet been approved for children and adolescents, but pediatric studies are in progress. An increase in transaminases may occur with eltrombopag, particularly at higher doses. No serious adverse events such as neutralizing antibodies or myelodysplasia have been reported as of this writing. Mild and reversible reticulin fiber proliferation 1–2 was found in a few children, but systematic studies have not been performed. Other side effects include upper respiratory tract infections and fever.

Pediatricians often use the same approach in children with refractory ITP as in adults. Combination therapies, such as TPO-RAs and anti-T-cell drugs, have proven effective in childhood and adolescence. Therapy must be individualized.

Splenectomy should generally be avoided in children, but can be discussed and considered as a last resort in patients with refractory ITP complicated by persistent and clinically relevant bleeding. Antifibrinolytic therapy with tranexamic acid may be effective in some children, especially for oral and other mucosal bleeding, minor dental surgery, and menorrhagia.

18. New Therapies, Not Yet Licensed

The substances described below have not yet been licensed for ITP. They should only be used after all established therapeutic options have been exhausted (for review, see [70, 71]).

18.1 All-Trans-Retinoic Acid

All-trans-retinoic acid (ATRA), also known as tretinoin, is a vitamin A metabolite developed for the treatment of acute promyelocytic leukemia. Because ATRA supports the function of T helper and T regulatory lymphocytes, it might correct immune dysregulation in patients with ITP. ATRA has been evaluated both in combination with dexamethasone as first-line therapy of newly diagnosed ITP (dose 20 mg/d; 68% therapy-free remissions) [72] and in combination with rituximab for chronic relapsed ITP (dose 20 mg/m^2/d for 12 weeks, 61% therapy-free remissions) [73]. ATRA is not currently licensed for the treatment of ITP.

18.2 Oseltamivir

The chance observation that platelet counts increased in some ITP patients with influenza receiving the neuraminidase inhibitor, oseltamivir, led to studies of the effect of this antiviral on platelets [74]. It was discovered that oseltamivir inhibits the enzyme sialidase, resulting in fewer platelets becoming desialyzed and cleared by the liver (see chapter 3). One study showed that the combination of dexamethasone and oseltamivir was effective in achieving therapy-free remissions in newly diagnosed ITP patients. Unfortunately, relapses were also reported in these patients [75].

18.3 Bruton's Tyrosine Kinase Inhibitors

Bruton's tyrosine kinase (BTK) inhibitors are used to treat B-cell lymphomas, but because they also inhibit plasma cell antibody production and phagocytosis by macrophages, they might also be effective in immune diseases. However, ibrutinib, acalabrutinib, and zanabrutinib, the BTK inhibitors currently approved for lymphoma treatment, inhibit platelet aggregation and cause a mild bleeding tendency. Therefore, these drugs are usually contraindicated in patients with thrombocytopenia. Another BTK inhibitor, rilzabrutinib, has been studied in patients with chronic ITP and has no antiplatelet activity. A recent phase I/II study showed a greater than 50% response rate and only mild side effects (nausea, diarrhea, bloating, and fatigue) [76, 77]. A phase III trial (Luna 3) has been initiated, and another BTK inhibitor, orelabrutinib, is being investigated [78].

18.4 Daratumumab

Daratumumab is an anti-CD38 antibody that targets plasma cells and is licensed for the treatment of multiple

myeloma. Clinical trials of daratumumab in ITP have been launched based on the concept that this agent might disable the long-lived autoreactive plasma cells in the bone marrow that account for the failure of conventional treatments in autoimmune cytopenias (Dart study) [79, 80].

18.5 Bortezomib

There are case reports describing bortezomib-induced increases in platelet counts in patients with multidrug-resistant ITP. One theory is that bortezomib, as compared with rituximab and other immunosuppressants, has greater access to the long-lived plasma cells that produce platelet autoantibodies [81]. Alternatively, bortezomib might prevent dendritic cells from presenting antigens to CD4 lymphocytes [82].

18.6 Decitabine

Decitabine is a cytostatic drug that acts as a DNA methyltransferase inhibitor and, at low doses, promotes cell differentiation and maturation. It is used for the treatment of myelodysplastic syndromes. Decitabine also supports T helper and T regulatory lymphocyte function. There are some case reports suggesting that decitabine might correct immune dysregulation in ITP and promote megakaryocyte maturation [83–85].

18.7 Inhibitors of the Neonatal Fc Receptor

IgG and other serum proteins are continuously ingested by endothelial and bone marrow cells, transported to the lysosome, and degraded. The neonatal Fc receptor (FcRn) binds IgG and protects it from lysosomal degradation. The IgG is recirculated to the cell surface and released back into the bloodstream. Through this protective mechanism, FcRn prolongs the half-life of normal IgG, as well as that of pathological autoantibodies. Rozanolixizumab and efgartigimod are FcRn antagonists that interfere with the IgG-FcRn binding and increase lysosomal degradation of normal IgG and disease-causing IgG autoantibodies. Both agents have been studied in patients with chronic ITP and produce an increase in platelet counts [86, 87]. Their side effects include headache, fever, and abdominal discomfort. Positive phase III study results have currently been published for efgartigimod [88], but the ITP studies with rozanolixizumab have been discontinued for non-medical reasons.

18.8 Inhibitors of B-Cell Activating Factor

B-cell activating factor (BAFF) is important for proliferation and survival of activated B cells. High BAFF levels are associated with autoimmune diseases. Belimumab is a monoclonal antibody directed against BAFF and used in the treatment of systemic lupus erythematosus (SLE). Belimumab also shows activity in chronic ITP. In the few patients treated to date, the response rate is 80%, including 66% complete remissions. Side effects include infusion reactions, mild symptoms of serum sickness, and mild infections [89].

18.9 Sutimlimab

Complement fixed to the platelet surface by antiplatelet antibodies can induce cell injury and is another pathophysiologic mechanism in the setting of chronic ITP (see chapter 3) [90, 91]. Sutimlimab is a humanized monoclonal antibody against C1s. It prevents both complement-induced cell injury and long-term autoimmune B-cell activation and autoantibody production. In a phase I study of multi-refractory ITP patients, sutimlimab achieved a rapid increase in platelet counts in approximately half of the patients [92]. Platelet counts declined when sutimlimab was discontinued. It is noteworthy that sutimlimab can rapidly and sustainably suppress fatigue in patients with autoimmune hemolysis and might also be beneficial for the fatigue suffered by many ITP patients (see chapter 19.9) [93].

18.10 Atorvastatin

Atorvastatin has a stimulatory effect on megakaryocytes and thrombopoiesis in patients with steroid-refractory ITP [94]. A clinical trial examining the combination of dexamethasone and atorvastatin in newly diagnosed ITP is underway (NCT03692754).

18.11 Complementary and Alternative Treatments

More than half of all patients with chronic ITP use complementary and alternative treatments. There is no evidence that any are effective. The physician should ask patients about complementary treatments because they might interact with ITP medications and alter their effectiveness. Particularly relevant in this regard are frankincense, St. John's wort, Korean ginseng, milk thistle, and echinacea [95].

18.12 ITP Prevention and Screening

ITP patients often ask whether other family members, including children, have an increased risk of developing ITP and whether they should have platelet counts. Although immune diseases (e.g., asthma, hay fever) can occur in familial clusters, ITP is rare, and familial clustering is even more infrequent (see note in chapter 3), that screening relatives for thrombocytopenia is not recommended.

After they have achieved remission, many patients want to know if they should make dietary or lifestyle changes to prevent a recurrence of thrombocytopenia. To the authors' knowledge, there is no diet that can increase platelet counts. However, alcohol might cause transient thrombocytopenia through a direct toxic effect on megakaryocytes, and chronic consumption may lead to hepatic dysfunction, cirrhosis and splenomegaly with associ-

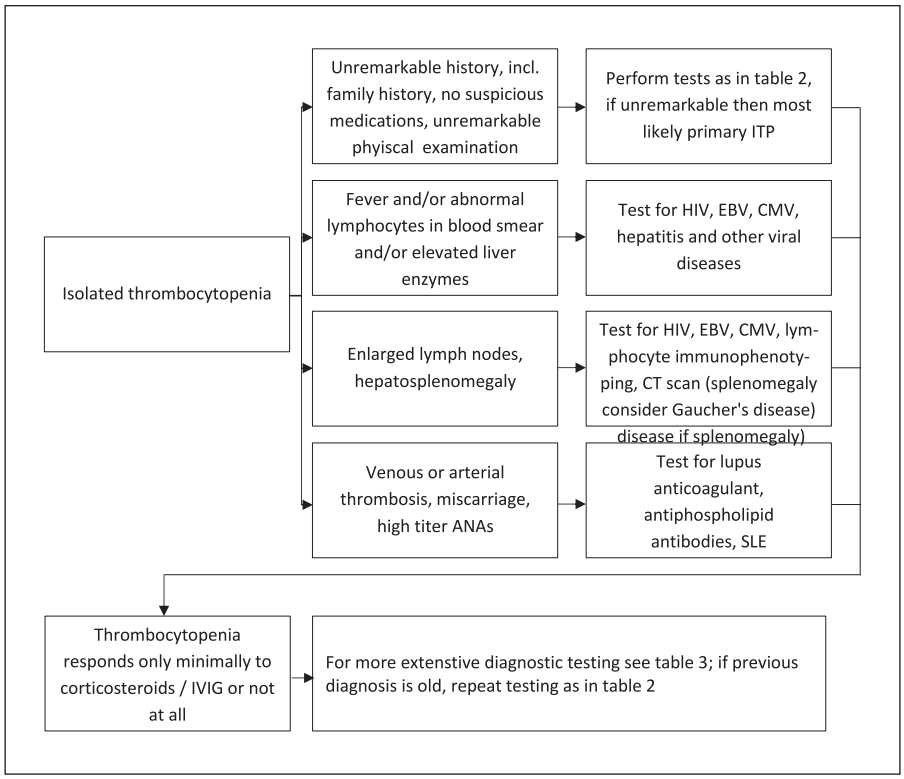


Fig. 7. Clinical signs and recommended tests for secondary ITP.

ated thrombocytopenia (see chapter 19.8). Therefore, it is recommended that alcohol be avoided or imbibed in only small amounts.

19. Special Situations

19.1 Secondary ITP

When ITP occurs in the setting of another underlying disease, it is secondary ITP. Secondary ITP is not uncommon and often does not respond well to first-line therapy with corticosteroids. Many patients require additional lines of therapy (for review, see [96]).

Common triggers of secondary ITP are

- medications,
- infections, e.g., HIV, hepatitis C, *H. pylori*, COVID, other viral diseases,
- systemic autoimmune diseases (Sjögren's syndrome, SLE, rheumatoid arthritis, autoimmune thyroiditis) and autoimmune inflammatory bowel diseases (ulcerative colitis, Crohn's disease),
- primary and secondary immunodeficiency syndromes (e.g., common variable immunodeficiency),
- hematologic neoplasms such as myelodysplastic syndromes and lymphomas (1–2% of all lymphoma and 2–5% of CLL patients develop secondary ITP).

The use of checkpoint inhibitors to treat patients with solid tumors has led to a rising incidence of secondary immune thrombocytopenias. These have been reported in ~1% of patients treated with checkpoint inhibitors, mostly during the first months of therapy.

As compared with primary ITP, secondary ITP has a relatively lower incidence in children and adolescents and then increases with increasing age [97]. A recent study shows that 12% of all ITP cases initially classified as primary – even by experts – subsequently require reclassification as secondary ITP [98]. In the presence of certain key findings, one should search for an underlying disease (Fig. 7).

Secondary ITP often does not respond well to first-line corticosteroid therapy. There are no specific treatment recommendations as treatment is based on both the underlying disease and the severity of thrombocytopenia. If thrombocytopenia is the primary clinical problem, then follow the usual approach as for primary ITP.

Secondary ITP frequently relapses after corticosteroid therapy but seems to respond well to TPO-RAs [99], although most of these agents are approved only for primary ITP. An uncomplicated and timely commitment for health insurance to cover the cost of off-label TPO-RAs would be desirable.

Splenectomy has lower long-term remission rates in secondary ITP than in primary ITP. Furthermore, it can also enhance immunosuppression and increase the risk for infections. Therefore, splenectomy should be avoided in secondary ITP.

19.2 Vaccinations

Vaccination in Patients with Known ITP

ITP patients should receive all standard vaccinations recommended by national health authorities. However, vaccinations with live viruses (e.g., measles, rubella, mumps, chickenpox, yellow fever, certain shingle vaccine preparations) are contraindicated in ITP patients on immunosuppressive therapies such as higher dose corticosteroids, rituximab, etc. This restriction does not apply to patients taking TPO-Ras, and there are no data yet for fostamatinib.

IVIG may interfere with the efficacy of live vaccines. The manufacturers recommend intervals of at least 3 months between administration of the immunoglobulins and a live vaccine, and up to 1 year for measles vaccination.

In patients with a history of ITP now in remission, or in patients currently suffering from ITP, vaccination does not appear to induce clinically relevant relapse or exacerbation of thrombocytopenia. If vaccination is omitted and the patient becomes infected, there is a risk that the thrombocytopenia might be exacerbated. Therefore, the measles-mumps-rubella (MMR) and chickenpox vaccines should be offered to all unvaccinated children with ITP.

Newly Diagnosed ITP in Association with Vaccinations

The incidence of short-term thrombocytopenia is 1:40,000 after MMR vaccination, but studies find no clustering of chronic thrombocytopenias. In the rare patient in whom an association between the occurrence of vaccination and new ITP is suspected, the benefit of further vaccinations with the same or related vaccine preparations should be weighed against the risks.

As noted above, short-term thrombocytopenias are not uncommon with MMR vaccines. Usually, at least two MMR vaccinations are recommended to achieve full vaccine protection, so the question arises whether a second vaccination is advisable if a patient has developed transient thrombocytopenia after the first vaccination. There are some reports that thrombocytopenia has not recurred after revaccination; should thrombocytopenia recur, the possibility of infection with wild viruses cannot be dismissed. Therefore, one should test whether the child has developed antibodies, and if the test is positive, vaccination should not be repeated. If antibody is absent or present in only low titers, the risk of developing thrombocytopenia after re-vaccination is considered less than the danger of infection with a wild virus.

Vaccinations before Splenectomy and before Rituximab

ITP patients with frequent or severe bleeding or refractoriness to treatment might be candidates for future splenectomy and should be vaccinated against pneumococci, meningococci and *Haemophilus influenzae* B (see chapter 16). The same applies to patients who are to receive rituximab because the vaccination responses are suppressed for several months after treatment with this agent.

19.3 COVID-19

COVID-19 and Thrombocytopenia Not Associated with Platelet Autoantibodies

Thrombocytopenia is not uncommon in the context of viral infections (HIV, HCV, EBV, CMV, herpes, parvovirus, measles, rubella, Zika, SARS-CoV-1, etc.) [100], including COVID-19. Declines in platelet counts to <150,000/μL occurs in about 20–30% of patients; however, the thrombocytopenia is usually mild. More severe thrombocytopenia and bleeding is uncommon, but when it occurs, it is an ominous prognostic sign heralding a severe and potentially fatal course of the COVID-19 infection [101].

The thrombocytopenia in COVID-19 disease could be due to concurrent bacterial infection (e.g., pneumonia, septicemia), and the suppressive effect by some therapeutic agents on platelet formation in the bone marrow. In addition, coagulation may be activated, which further consumes platelets. Low platelet counts are common in many patients treated in an intensive care unit – not only in those with COVID-19 but also with other diseases [102, 103]. Although the thrombocytopenias in these disorders are not caused by platelet autoantibodies and therefore are distinct from ITP, their pathophysiology may add to and exacerbate a preexisting ITP. Of note, COVID-19 infection can also cause thrombocytosis [104].

Can COVID-19 Infection Trigger New Cases of ITP?

There are numerous reports that COVID can trigger the first onset of ITP [105–113], which would then be classified as newly diagnosed secondary ITP. In some COVID-19 patients, the platelet count may be very low, and severe hemorrhage, including CNS bleeding, has been described [106, 107, 109, 112].

It is unclear whether the COVID-19 infection nonspecifically activates a preexisting immune dysregulation or induces antibodies specifically directed toward platelets. There is one report that discusses the possibility of molecular mimicry [114].

Secondary ITP typically occurs not at the onset of COVID-19 but after 1 week or even following recovery from the infection (late-phase thrombocytopenia) [115]. In most cases, the immune thrombocytopenia is transient and eventually platelet counts return to normal. Recurrences have been described, suggesting that COVID-19 can also induce persistent or even chronic ITP [108, 113].

Can ITP Increase the Risk for COVID-19 Infection?

ITP patients on immunosuppressive therapy (high-dose or long-term corticosteroids, azathioprine, rituximab) are at risk of developing symptomatic and more severe COVID-19. ITP patients who are not on these therapies or who are treated with TPO-RAs do not have this risk because TPO-RAs do not inhibit the immune system. The new ITP agent fostamatinib also appears to have no relevant immune inhibitory effect. Splenectomized ITP patients are not more likely to get infected with COVID-19 or develop more severe symptoms.

Counseling and Treatment of ITP Patients Infected with COVID-19

In general, ITP therapy does not have to be altered in patients infected with COVID-19. If bleeding occurs, corticosteroids or immunoglobulins can be given or the dose of the current treatment temporarily increased.

Many patients are concerned that COVID-19 infection will cause their platelets to decline, inciting bleeding. It has been previously mentioned that in the context of an infection, platelet counts might fall (see chapter 19.1), but in some patients platelets increase [104, 116]. Patients who are infected but have no new bleeding symptoms do not need platelet count monitoring. Patients who are infected and develop new bleeding should contact their physician and be evaluated. Most patients do not need monitoring and if bleeding occurs, corticosteroids or immunoglobulins are administered or the dose of the current therapeutic agents temporarily increased.

Although the risk of thrombosis with TPO-RAs might be increased by COVID-19 infection, this is not a reason to avoid or discontinue TPO-RAs. It is better to educate the patient about the symptoms of thrombosis and provide a contact who can be reached after hours or on weekends. ITP patients hospitalized with COVID-19 infection should be offered thromboprophylaxis if their bleeding tendency and platelet counts permit.

Can COVID-19 Vaccination Trigger New Cases of ITP?

A few patients without a prior history of ITP have been diagnosed with ITP after COVID-19 vaccination [117–124]. However, the risk seems to be extremely low, and the prognosis is very good, i.e., most patients recover [121]. A study from Scotland finds an increase in the number of new ITP cases from 1/200,000 to 2/200,000 given the AstraZeneca vaccine [117, 122].

It should be noted that the incidence of ITP is 2-4 new cases per 100,000 per year. Thus, one can expect 1.6–3.3 new cases in one million persons in the 4 weeks following vaccination, and a recent French study describes 1.6 new cases in the 6 weeks after vaccination [124]. There is no study that shows that the number of new ITP cases after vaccination significantly exceeds the expected background incidence [123].

Can COVID-19 Vaccination Worsen a Preexisting ITP?

It has been noted that in patients with preexisting ITP, platelet counts can decline after COVID-19 vaccination [125, 126]. In most cases, the decrease is mild, and the incidence of clinically relevant bleeding appears to be in the lower single digit range [126]. The fall in platelet count occurs in most patients within the first 2 weeks after vaccination. There are reports that platelets may also increase after vaccination [126].

When assessing the risk of vaccination, remember that COVID-19 infection in unvaccinated ITP patients might further decrease platelets and result in more frequent bleeding [127]. Therefore, all ITP patients should be vaccinated against COVID-19. The choice of vaccine does not appear to be relevant.

Should the Platelet Count Be Monitored in ITP Patients after Vaccination?

The platelet decline after vaccination is uncommon and usually mild. It does not provoke bleeding and needs no therapy. Therefore, monitoring the platelet count after vaccination is not helpful for the majority of ITP patients and might only trigger uncertainty and anxiety. The patient should be watch for new bleeding signs, and if present, the platelet count should be checked. Treatment can be initiated if the count has significantly declined. However, platelet count measurements can be offered to the following risk groups:

- Patients who have a history of severe bleeding
- Patients on anticoagulants
- Patients who have had a previous severe platelet decline and bleeding after vaccination
- Patients who have been splenectomized
- Patients with multiple prior ITP therapies who are difficult to manage
- Patients who are very worried and for whom monitoring would give reassurance.

Monitoring should be limited to the first and second week after vaccination [120, 126].

Do ITP Patients Who Develop a Decline in Platelet Count or Bleeding after a First COVID-19 Vaccination Have a Higher Risk for Complications after the Second or Third Vaccination (Booster)?

A recent study shows that only about half of ITP patients who had a decline in platelet count after their first vaccination also have a fall in count with the second vaccination [125]. There are no data yet for those

Table 19. Target platelet counts for surgery and other invasive procedures

Procedure	Target platelet count
Dental cleaning, tartar removal	≥20–30,000/μL
Tooth extraction (simple)	≥30,000/μL
Tooth extraction (complex, z.B. molar)	≥50,000/μL
Local anesthesia for tooth extraction	≥30,000/μL
Spinal tap (elective)	≥50,000/μL
Spinal tap (emergency)	≥20,000/μL
Spinal anesthesia	≥50,000/μL
Spinal anesthesia with epidural administrations	≥80,000/μL
Central line placement	≥20,000/μL
GI endoscopy without biopsy	No threshold
GI endoscopy with biopsy	≥20,000/μL
Bronchoscopy, bronchial lavage	≥20,000/μL
Bronchoscopy with transbronchial biopsy	≥50,000/μL
Joint aspiration	≥20,000/μL
Transjugular liver biopsy	≥10,000/μL
Percutaneous liver biopsy	≥50,000/μL
Bone marrow biopsy	No threshold
Other organ biopsies	≥50,000/μL
Minor surgery[a]	≥50,000/μL
Minor surgery where hemostasis can be achieved by compression	≥20,000/μL
Major surgery[b]	≥80,000/μL
Neurosurgery	≥70–100,000/μL
Surgery to the posterior segment of the eye	≥70–100,000/μL

These thresholds were developed for patients with non-ITP thrombocytopenias. There are no corresponding data for ITP patients. The individual bleeding history must be taken into account, e.g., whether a patient has already bled at a given platelet count. [a] Minor surgeries are surgical procedures with a low risk of bleeding, which includes most peripheral limb surgeries. [b] Major surgeries include abdominal or thoracic surgery and surgeries in regions that cannot be compressed in the event of postoperative bleeding.

having a third, booster vaccination. Patients who had a modest platelet decline and/or only mild bleeding after the first vaccination should receive the recommended second or third vaccination with monitoring. The authors would avoid revaccination with patients who had severe bleeding after the first vaccination, i.e., bleeding for which they had to be hospitalized or for which they needed an intensification of their ITP therapy [120].

What Else Needs to Be Considered when Vaccinating ITP Patients? Are There Any Differences to Non-ITP Patients?

ITP patients are vaccinated at the same intervals as non-ITP patients, but those patients receiving immunosuppressive therapy, e.g., long-term or high doses of corticosteroids, azathioprine, or rituximab, should receive their third vaccination (booster) 4 weeks after the first two vaccinations.

Table 20. Treatment options to increase preoperative platelet counts in ITP patients (eltrombopag and romiplostim dose recommendations apply only to patients not already on TPO-RAs)

Drug	Dose
Eltrombopag	50 mg daily (or 25 mg daily for patients of East Asian descent) starting 21 days before surgery until 7 days post-op. The dose must be adjusted to the platelet count (minimum 25 mg, maximum 75 mg)
IVIG	IVIG infusion (1–2 g/kg) 7 (±2) days prior to surgery; if needed, another dose is allowed within 1 week of achieving the target platelet count
Romiplostim	A dose of 3 μg/kg per week in 2 divided doses increases platelet counts to >100 × 10^9/L in 79% of patients within 14 days

If the patient has never had any ITP therapy before, then TPO-RAs would be considered as first-line treatment and be off-label; IVIG is an alternative.

19.4 Surgery and Dental Procedures

When planning for surgery or invasive diagnostic procedures in ITP patients, what are the minimum platelet counts considered for safe surgery (see Table 19). If ITP patients need to undergo emergency surgery, they can be given IVIG, which is fast-acting. However, if surgery can be planned in advance, other options should be considered such as TPO-RAs, which can also achieve a safe platelet count (see Table 20). The administration of corticosteroids should be avoided because they interfere with wound healing and increase the risk of infection.

19.5 Pregnancy and ITP

For review, see reference [128].

Epidemiology

Mild thrombocytopenia (platelets 100,000–150,000/μL) developes in 5–10% of pregnancies. Gestational thrombocytopenia occurs in 70–80%, preeclampsia and HELLP syndrome in15–20%), and ITP in 1–4%. Antiphospholipid syndrome, thrombotic thrombocytopenic purpura, familial thrombocytopenias, and other syndromes are rare [129]. The incidence of ITP in pregnancy is approximately 1/1,000 to 1/10,000. ITP had been previously diagnosed in 70–90% of women and was a first-time diagnosis during pregnancy in the remaining 10–30%.

Course of ITP during Pregnancy and Monitoring

The platelet count is not static during pregnancy. In approximately 50%, counts will decline further during the pregnancy and 25% will need treatment. Many of these women are concerned that they will develop bleed-

Table 21. Clinical indicators for differential diagnosis of thrombocytopenia in pregnancy

ITP	Bleeding and thrombocytopenia <100,000/μL in any trimester are more indicative of ITP than gestational thrombocytopenia
Gestational thrombocytopenia	Usually observed in second and third trimesters, platelet counts <100,000/μL unusual
Preeclampsia/ HELLP syndrome	Usually third trimester, sudden weight gain, hypertension with/without organ dysfunction with/without proteinuria
Acute fatty liver of pregnancy	Mainly in third trimester; usually weight loss, jaundice, massive elevation of liver enzymes, prolonged prothrombin time (quick)
TTP	In second or third trimester; severe thrombocytopenia and hemolysis, very high LDH, LDH/AST ratio >22, neurologic symptoms, absence of coagulopathy

ing as the counts decline. The platelet count is monitored every 4 weeks in women with stable thrombocytopenia, usually during gynecological checkups. However, in those whose counts are declining or below 80,000/μL, monitoring should be performed at least weekly during the last 4 weeks before the expected delivery date. In some ITP patients, counts do not fall but rather rise during pregnancy.

Bleeding and Other Risks

The risk of bleeding during pregnancy in women with ITP is between 16% and 22%, which is lower than in non-pregnant women with ITP. The activation of coagulation during pregnancy may account for this lower bleeding tendency.

The fetus can be affected by the mother's ITP, and there is an approximately 5–14% risk that the placental transfer of platelet antibodies will cause thrombocytopenia in the newborn [130]. Intracerebral hemorrhage occurs in <1.5% and neonatal mortality is <1%. The hemorrhages do not develop in utero as in neonatal alloimmune thrombocytopenia but rather peripartum and during the week thereafter. The only predictive marker is a history of neonatal thrombocytopenia with a previous pregnancy.

Diagnostic Workup

The differential diagnosis is based on the time of occurrence of thrombocytopenia, and additional clinical and laboratory findings (see Table 21 and Fig. 8). If thrombocytopenia is newly diagnosed during pregnancy and counts are above 100,000/μL, additional testing is not required because gestational thrombocytopenia is the likely diagnosis. For thrombocytopenia <100,000/μL, the basic diagnostic workup is similar to that performed in non-pregnant patients with suspected ITP, see chapter 5.

Approximately half of pregnant women with ITP require treatment. While the platelet threshold value mandating treatment was abandoned in non-pregnant patients, it lives on in the management of pregnant ITP patients. Guidelines and many experts recommend treatment for pregnant women with ITP as soon as counts fall below 20,000 to 30,000/μL, regardless of the clinical bleeding tendency or any other factors. At term, platelet counts >50,000 platelets/μL are recommended for vaginal delivery and at least 70,000–80,000/μL for caesarean section or epidural anesthesia.

Treatment

- **Corticosteroids [predniso(lo)ne]:** start with 20–30 mg/d unless an emergency requires the use of higher doses and try to reduce the dose rapidly to the point where a platelet count of 20,000–30,000/μL can be maintained (10–20 mg/d is usually sufficient).
- **Dexamethasone,** which is often used in non-pregnant women, is contraindicated in pregnancy (see prescribing information). Fetal development defects have been reported.
- It is not recommended to administer corticosteroids (or IVIG, see below) only for the purpose of increasing the platelet count of the fetus.
- **IVIG** is used as an alternative when steroid requirements are high or therapy-limiting side effects such as hypertension, diabetes, osteoporosis, severe weight gain, and psychosis occur. IVIG can be given repeatedly, especially at term, to further raise the platelet count before delivery (and PDA).
- The combination of steroids and IVIG is particularly helpful when one does not want to give steroids for too long or if a rapid increase in platelet count is required [131].
- **Cyclosporine and azathioprine** have been used for many years to treat ITP. Their use is entirely empirical; there are only case reports and no large studies in pregnancy that would meet modern quality criteria. However, either agent can be used if justified by the benefit to the mother. They need several weeks to become effective and are unsuitable when the patient needs a short-term rise in platelet count. They are generally given when pregnancy can be planned and the current medications (e.g., TPO-RAs) need to be discontinued. Neonates exposed to azathioprine in breast milk can develop anemia or pancytopenia, so this agent should not be prescribed for nursing mothers.
- **Splenectomy:** splenectomy is indicated for severe thrombocytopenia and bleeding that cannot be controlled by any other means. If possible, splenectomy should be performed laparoscopically during the second trimester.

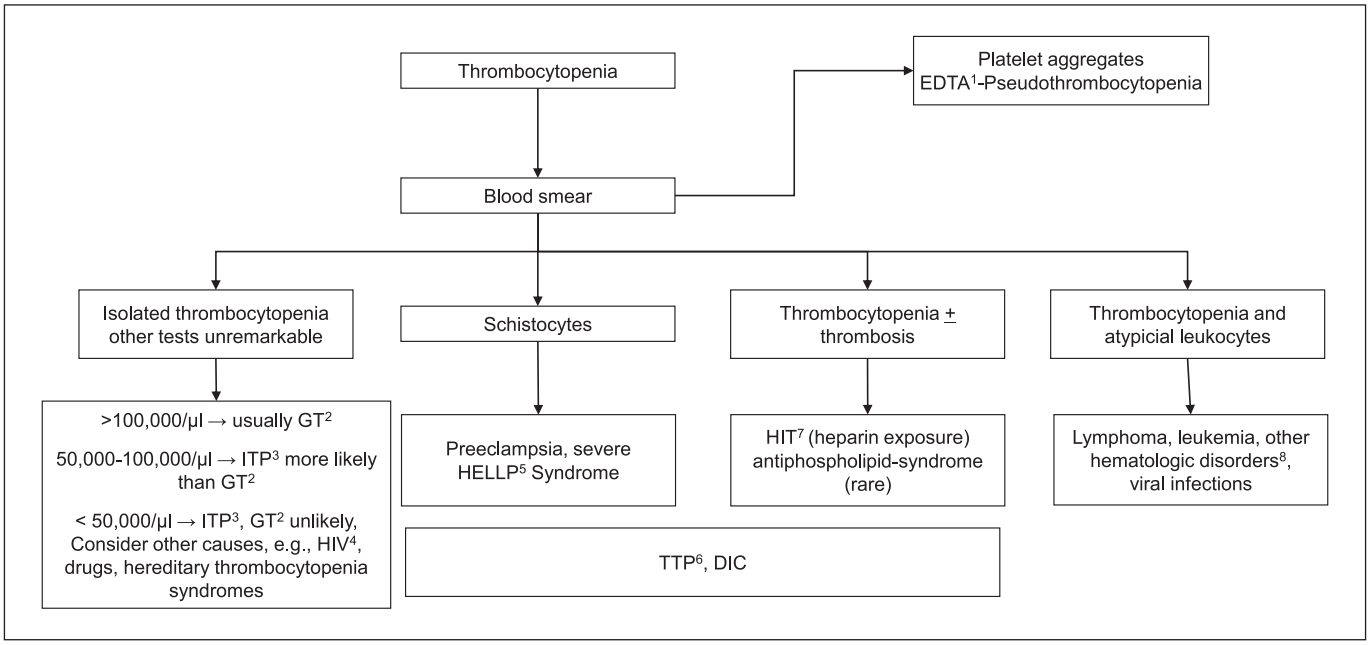


Fig. 8. Differential diagnosis of thrombocytopenia in pregnancy. [1]EDTA, ethylenediaminetetra-acetic acid; [2]GT, gestational thrombocytopenia; [3]ITP, immune thrombocytopenia; [4]HIV, human immunodeficiency virus; [5]HELLP syndrome (hemolytic anemia, elevated liver enzymes, low platelets); [6]TTP, thrombotic thrombocytopenic purpura; [7]HIT, heparin-induced thrombocytopenia; [8]E.g., myelodysplastic syndrome, myeloproliferative neoplasms.

- **Platelet concentrates** are given to women with clinically relevant bleeding and therapy-resistant thrombocytopenia.
- **TPO-RAs** are usually not given during pregnancy because of a lack of safety data and fear of inducing fetal thrombocytosis. However, two studies have recently been published which show that TPO-RAs are an option at the end of pregnancy [132, 133]. If the delivery date is approaching, if no therapy has achieved a satisfactory response, and if the treatment team has its "back against the wall," giving an TPO-RA could be considered.
- **Rituximab** is an established second or third line treatment in all current guidelines for non-pregnant ITP patients. Rituximab is usually avoided in pregnancy because of its off-label status; furthermore, it can cross the placental barrier and cause lymphocytopenia in the newborn.

Peri- and Postpartum Management

Obstetrical indications, and not ITP, should determine whether a caesarean section is appropriate. The incidence of severe postpartum hemorrhage in ITP patients varies between 8% and 21%.

Thrombocytopenia, with platelet counts below 100,000/µL, occurs in up to one-third of newborns of ITP mothers, and about half have values below 50,000/µL. If the newborn has a platelet count of <20,000/µL or if there are signs of bleeding, IVIG and corticosteroids are indicated. The newborn should be monitored for an appropriate length of time since the platelet nadir may not occur for several days (up to 1 week after delivery).

The risk of the child being born thrombocytopenic or developing thrombocytopenia after delivery is higher when the mother has had a splenectomy (splenectomy does not remove platelet autoantibodies, only the site of platelet degradation) or had to be treated for low platelet counts during her pregnancy. Also, if neonatal thrombocytopenia occurred in a previous pregnancy, the risk is increased [134].

After delivery, the mother's platelet count might rise to >50,000/µL or even into the normal range. However, ITP is not only a hemorrhagic, but also a thrombophilic disorder (see chapter 19.6). Thromboprophylaxis with low-molecular-weight heparin should be considered if the platelet count is >50,000/µL and the mother is less mobile postpartum.

19.6 Older Patients, Patients with Comorbidities, Thrombosis, and Anticoagulation

The incidence of ITP in older patients is almost twice as high as in younger patients. One-third of all ITP patients are over 70. ITP in older patients differs in certain aspects from ITP in younger patients:

- bleeding is more common in older patients,
- older patients take more medications and have a higher incidence of drug-induced thrombocytopenia, which might be difficult to distinguish from primary ITP,

Table 22. Anticoagulation with thrombocytopenia

Platelets	Indication for anticoagulation		
	venous thromboembolism	atrial fibrillation	mechanical heart valve
50–100,000/μL	Continue anticoagulation with usual dose. Consider LMWH if platelet levels fluctuate widely, even dropping below 50,000/μL		
25–50,000/μL	**Prophylactic anticoagulation** with LMWH only with high thrombotic risk. If platelet count cannot be raised → consider 50% of the regular prophylactic dose		
	Therapeutic anticoagulation for **acute VTE** with prophylactic or 50% dose-reduced LMWH	If platelet count cannot be raised and CHA2DS2VASC score ≥4 → consider left atrial appendage occlusion	Platelet counts 40–50,000/μL → adjust warfarin dose to target INR of 2, if feasible (low therapeutic range) Platelet counts 25–40,000/μL → half therapeutic dose of LMWH
<25,000/μL	**If platelet count cannot be raised → stop anticoagulation**		
	Consider IVC filter	Consider left atrial appendage occlusion	

INR, international normalized ratio; IVC, inferior vena cava; LMWH, low-molecular-weight heparin; VTE, venous thromboembolism.

- older patients have more often diseases that can be misdiagnosed as ITP (e.g., myelodysplastic syndromes, lymphomas, and other hematological disorders),
- older patients have more comorbidities and other factors that need to be considered when selecting an ITP treatment, e.g., concomitant anticoagulant therapy.

The incidence of venous thromboembolism is higher in older ITP patients (11.1% when >65 vs. 4.5% in younger patients) [135]. Registry data show that older patients are more likely to be treated with TPO-RAs than younger ones, so the slightly higher risk of venous thromboembolism with TPO-RAs (see chapter 13.1) might account for some of this increased incidence. Arterial thrombosis is not more common in older versus younger patients, but bleeding events are more frequent in the elderly. TPO-RAs should be offered to older patients, along with a discussion of the risks and benefits of these agents. All ITP patients should be informed about the symptoms of VTE and know who to contact if these symptoms appear.

Comorbidities

Nearly 2/3 of all ITP patients over the age of 60 have comorbidities that affect the course and treatment of ITP. Common comorbidities are hypertension, diabetes, coronary artery disease, neuropsychiatric disorders, pneumonia, anemia, and cataracts. Compared to non-ITP patients, ITP patients have a 3-fold higher risk of developing malignancies, especially lymphomas.

ITP as a Risk Factor for Venous and Arterial Thromboembolism

ITP patients not only carry the risk of bleeding, they also have an approximately 2-fold higher risk for venous and arterial thromboembolism compared to non-ITP patients [136]. Thus, ITP is both a hemorrhagic and a thrombophilic disorder. Patients are not protected from myocardial infarction, stroke, or thrombosis even with platelet counts <50,000/μL.

The risk is particularly high

- after splenectomy,
- after prior venous or arterial thromboembolism,
- when the platelet count rapidly increases (e.g., after IVIG or with TPO-RAs),
- in those who are overweight, and after general surgery,
- with antiphospholipid antibodies or lupus anticoagulant.

The reason for the increased venous and arterial thromboembolic tendency in ITP is unclear. Alterations in coagulation and fibrinolysis and release of microparticles are being examined. It is recommended that all ITP patients be informed about the risk of venous and arterial thromboembolism as well as bleeding. They should be educated about symptoms and know where to obtain assistance after hours and on weekends. Risk factors (e.g., smoking, high blood pressure, blood lipid levels, etc.) should be addressed and, if necessary, patients should be advised to seek specialist co-care.

Table 23. Antiplatelet therapy in patients with thrombocytopenia

Platelet count	Indication for antiplatelet therapy	
	single antiplatelet therapy with aspirin (or clopidogrel), e.g., after myocardial infarction, stroke, TIA, etc.	dual antiplatelet therapy, e.g., after coronary stent placement
75–100,000/μL	Continue low-dose aspirin (or clopidogrel)	Dual antiplatelet therapy with aspirin and clopidogrel for 3–6 months. Avoid ticagrelor or prasugrel
50–75,000/μL	Continue low-dose aspirin (or clopidogrel) only in the absence of major bleeding risk factors	
25–50,000/μL	Withhold single agent antiplatelet therapy unless major/multiple cardiovascular risk factors without major bleeding risk factors	Low-dose aspirin only (no clopidogrel) unless major cardiovascular risk factors without other major bleeding risk factors
<25,000/μL	**Stop single agent antiplatelet therapy**	**Avoid coronary intervention if possible. Low-dose aspirin only under very high-risk conditions and if platelets >10,000/μL**

For further information on thrombosis and bleeding risk factors, please refer to the original publications [138, 139].

19.7 ITP and Anticoagulation

Many ITP patients are older and have cardiac or vascular comorbidities that require anticoagulation. On the other hand, anticoagulants are usually contraindicated in thrombocytopenia. Therefore, Table 22 and Table 23 are based on the recommendations for oncology patients with thrombocytopenia who require anticoagulation [137, 138].

19.8 ITP versus Thrombocytopenia of Liver Disease

Patients with liver disease often have mild thrombocytopenia, with platelet counts typically between 50,000 and 100,000/μL. The mechanisms are (1) reduced thrombopoietin production, (2) increased sequestration in an enlarged spleen, (3) increased platelet consumption from decompensated hemostasis, and (4) direct nutritive-toxic damage, e.g., from alcohol [139].

The distinction from ITP should not be difficult. However, the diagnosis may be unclear if patients do not disclose risk factors such as alcohol abuse or that they have a history of liver disease. Liver cirrhosis might not be immediately apparent, even on imaging.

Patients with chronic liver disease and thrombocytopenia can be treated with TPO-RAs, just like ITP patients. Eltrombopag, avatrombopag, and lusutrombopag are all approved for liver disease, but the exact approval text differs slightly (see prescribing information). The dosing is also different from that in uncomplicated ITP (see Table 24).

19.9 Quality of Life and Fatigue

ITP patients have poor health-related quality of life, similar to that of cancer patients and sometimes even worse [62, 68, 140, 141]. This is also true for pediatric ITP [142, 143]. The quality of life is worse at the beginning of the disease, when bleeding symptoms are frequent and the patient and family members are still learning how to cope with the disorder, but it improves with time and experience. Treatment efficacy should be judged not only by looking at platelet counts and the bleeding tendency but also by the quality of life.

In addition to bleeding and the side effects of treatment, many ITP patients complain about symptoms of exhaustion, fatigue, and even depression. An association between ITP, CNS microbleeds, and cognitive dysfunction has been suggested [11]. A recent German study found a high incidence of fatigue in ITP patients [144]. The cause of ITP-associated fatigue is not clear but is probably multifactorial. Restrictions on physical activity due to the thrombocytopenia, reduced social contacts, stigmatization due to bleeding, sleep disturbances, and mood swings might all play a role.

Treating physicians should pay greater attention to symptoms of fatigue and depression in order to detect them at an early stage. There are few data on treatment. Increasing the platelet count and decreasing the bleeding tendency improves the quality of life for many patients. While there might be a direct correlation between platelet count and fatigue, many patients continue to complain of fatigue even after improvement of thrombocytopenia.

19.10 Sport

Most ITP patients can participate in sports. The individuals' risk of bleeding and the type of sport should be discussed with the physician. In analogy to patients with hemophilia or those taking anticoagulants, combat and contact sports such as rugby, soccer, and ice hockey, should be avoided if the platelet count is <50,000/μL. Swimming, cycling, and exercise workouts are safe and usually without problems. However, no sport is 100% safe or unsafe.

Table 24. Treatment with TPO-RAs for thrombocytopenia in patients with liver disease (not ITP)

TPO-RA	Approval status	Dosing
Romiplostim	Not licensed	
Eltrombopag	Thrombocytopenia in adults with chronic hepatitis C, when the thrombocytopenia is too severe to allow interferon-based therapy	Individual dosing
Avatrombopag[a]	Doptelet is indicated for the treatment of severe thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo an invasive procedure	<40,000 platelets/μL → 60 mg (three 20 mg tablets) for 5 days ≥40,000 to <50,000 platelets/μL 40 mg (two 20 mg tablets) for 5 days Dosing should begin 10–13 days prior to the planned procedure
Lusutrombopag[a,b]	Treatment of severe thrombocytopenia in adult patients with chronic liver disease undergoing invasive procedures	3 mg once daily for 7 days The procedure should be performed on day 9 after the start of lusutrombopag treatment

[a] With avatrombopag and lusutrombopag platelet count should be measured prior to the procedure. [b] Lusutrombopag is licensed for chronic liver disease only, not for ITP. Lusutrombopag is not currently available in Germany.

19.11 Traveling

The patient should receive advice about which emergency medications to take before traveling to countries with limited or costly (USA) medical care. Vaccinations should also be checked and completed (see recommendations on vaccinations chapter 19.2). In this context, many patients ask for an ITP emergency passport. Forms can be downloaded from the internet:

https://www.leben-mit-itp.de/sites/leben_mit_itp_de/files/2021-05/itp-notfall-ausweis.pdf.

https://www.amgen.de/downloads/003/60054/19/60054__191202_03_ITP_Notfallpass_85x55.pdf.

https://www.onkodin.de/e8/e63554/e63558/e64166/e66475/2011-02-13_ITP-Pass-Vorlage.pdf.

For patients who have had splenectomy, see http://www.asplenie-net.org/.

Patients should consult with their physician before (!) booking a trip regarding whether travel would be safe considering their symptoms and platelet counts. If not, travel insurers could fortfeit claims for reimbursement in case the trip must be canceled.

20. Management Issues

20.1 Different Treatment Goals: Patients versus Physicians and Other Stake Holders in the Health-Care System

Studies show that patients and doctors have different goals and expectations for the management of their disease. For patients, the most important therapeutic goal – apart from cure – is that their blood values "return to normal." Physicians often state "prevention of bleeding" as the most important therapeutic goal (which only ranks in fifth place for patients) [68].

Table 25. Degrees of disability

Severity of bleeding	Degree of disability
Not clinically relevant	10
Mild	20–40
Severe (e.g., severe bleeding with minor trauma)	50–70
Permanent high bleeding risk (spontaneous bleeding, risk of life-threatening bleeding)	80–100

It must be kept in mind that for most patients ITP is a chronic illness. At the time of diagnosis, patients view symptoms differently than after they have gained more experience with the disease. Bleeding (petechiae, hematomas, menorrhagia) and fatigue are at the center of the patient's attention initially, whereas with longer disease duration bleeding fades into the background and fatigue and the fear of fluctuating platelet levels are the primary burden. Physicians, on the other hand, consistently see bleeding as the primary factor reducing patients' quality of life, with fatigue and fear of fluctuating platelet counts listed as secondary [141].

This focus on "good blood values" explains why a watch and wait strategy (as in Fig. 3) is not an option for many patients when platelet counts are low, despite minimal or no bleeding [68]. Patients report that the various ITP therapies have different levels of burden. Rituximab and TPO-RAs are tolerated best, while corticosteroids and splenectomy score poorly [68]. However, this is not reflected in physicians' daily practice. Steroids are still the

Table 26. Currently active ITP studies in Austria, Germany, Switzerland

Study identifier	Title	Acronym
--	German Immune Thrombocytopenia Register Contact: https://d-itp.de/	D.ITP-Register
EUPAS42043	Post-Authorization Long Term Safety Surveillance Study of Fostamatinib in Adult Patients with Chronic Immune Thrombocytopenia (cITP) who Are Refractory to Previous Treatments	
NCT03576742	Severe Immune Cytopenia Registry www.sic-reg.org (sic-reg)	SIC-REG
NCT04188379	A Study to Assess the Efficacy and Safety of Efgartigimod in Adult Patients with Primary Immune Thrombocytopenia (ITP)	ADVANCE
NCT04225156	A Long-Term Study to Assess the Safety and Efficacy of Efgartigimod in Adult Patients with Primary Immune Thrombocytopenia (ITP)	ADVANCE+
NCT04278924	A Study of TAK-079 in Adults with Persistent/Chronic Primary Immune Thrombocytopenia	
NCT04346654	A Study to Assess Efficacy and Safety of Eltrombopag in Combination with a Short Course of Dexamethasone in Patients with Newly Diagnosed ITP	XPAG-ITP
NCT04516967	Avatrombopag for the Treatment of Thrombocytopenia in Pediatric Subjects with Immune Thrombocytopenia for ≥6 Months	
NCT04562766	Study to Evaluate Rilzabrutinib in Adults and Adolescents with Persistent or Chronic Immune Thrombocytopenia (ITP)	LUNA 3
NCT05086744	Basket Study to Assess Efficacy, Safety and PK of Iptacopan (LNP023) in Autoimmune Benign Hematological Disorders	LNP023
NCT04596995	A Study to Investigate the Long-Term Safety, Tolerability, and Efficacy of Rozanolixizumab in Study Participants with Persistent or Chronic Primary Immune Thrombocytopenia (ITP)	myOpportunITy3
NCT04669600	A Phase 2a Study Evaluating BIVV020 in Adults with Persistent/Chronic Immune Thrombocytopenia (ITP)	
NCT04812483	Immunomodulation with Eltrombopag in ITP.	iROM2
NCT04812925	A Phase 3 Study to Evaluate the Safety and Efficacy of Efgartigimod PH20 Subcutaneous in Adult Patients with Primary Immune Thrombocytopenia	Advance sc
NCT04943042	An Observational, Multicenter Study to Evaluate the Use and Effectiveness of Doptelet® in Patients With ITP.	ADOPT

most commonly used treatment for ITP [40, 145]; this is likely due to the rarity of the disease and limited personal expertise with other therapies. While physicians with many ITP patients promptly switch to TPO-RAs, those with few ITP patients are more likely to prolong corticosteroid treatment.

20.2 Do We Need New Study Endpoints?

For ITP patients with bleeding, increasing the platelet count and stopping or preventing hemorrhages are priorities. These goals were the primary endpoints selected by many older studies, but today, many patients with newly diagnosed ITP have no or only minimal bleeding symptoms, and the proportion is only 30–40% in chronic ITP (see chapter 4). In addition, current second-line therapies (TPO-RA, SYK inhibitors, etc.) are given long-term, which many patients find burdensome; only a minority achieve a complete remission and can discontinue these drugs.

The platelet count and bleeding events are still the primary endpoints in contemporary studies of new ITP agents. At the same time, however, a rethinking and paradigm shift has taken place. Two studies have been published recently that did not choose the platelet count response or prevention of bleeding as the main study endpoints but rather the number of treatment-free remissions [41, 42]. A discussion is needed about whether future ITP studies need new primary endpoints [146]:

- achievement of a therapy-free remission,
- delay of second-line therapies,
- avoidance of splenectomy,
- long-term improvement of health-related quality of life,
- reduction of total treatment costs including indirect costs (avoidance of hospitalizations, loss of working hours, patients' co-payments, less time spent on check-up visits).

21. Rehabilitation and Social Law

The law is only applicable for the Federal Republic of Germany. The degree of disability (Grad der Behinderung GdB) according to "Social Code Book IX" (SGB IX, Sozialgesetzbuch IX, Rehabilitation and Participation of Disabled Persons) is based on the "Medical Care Principles" (VMG, Versorgungsmedizinische Grundsätze) Part B. There are no specific recommendations for patients with thrombocytopenia. Instead, ITP is subsumed under the category of "other bleeding disorders"; according to

No. 16.10 of the VMG, it receives the following degrees of disability (see Table 25):

The VMG base the classification of functional impairment on the actual functional impairment. The assessment of the degree of disability must therefore be based on the actual impairment of the disabled person, without regard to the cause of the health impairment or possible future risks. This means that in the case of thrombocytopenia, only bleeding that has actually occurred is relevant and not the abstract possibility that severe bleeding may occur in the future. Thrombocytopenia in which severe bleeding is only a risk but has not yet occurred is therefore associated with moderate impairment according to VMG and receives a GdB of "only" 20–40. For comparison: myelodysplastic syndromes with moderate effects on daily acitivities (e.g., occasional transfusions) receive a degree of disability of 30–40, and for more severe effects (e.g., continuous need for transfusions, recurrent infections), a degree of disability of 50 to 80 (Versorgungsmedizinische Grundsätze, Part B, No. 16.7).

22. ITP Studies in AU/CH/D

This list of ITP studies (Table 26) was compiled to the best of the authors' knowledge. Study directors who do not find their study listed are encouraged to contact the corresponding author (AM) for updates.

23. Self-Support Groups

ITP-SHG Gießen:
http://www.itp-information.de.
Contact: Mrs. G. Arnold.

ITP-SHG Sömmerda:
Contact: Mrs. K. Riese (s-riese@t-online.de).

USA: Platelet Disorder Support Organisation
www.pdsa.org.

UK: ITP Support Association
http://www.itpsupport.org.uk.

Additional resources:
International ITP Alliance
http://www.globalitp.org.

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A. Matzdorff: advisory role or expert testimony: Amgen, Argenx, Grifols, Novartis, Sanofi, Swedish Orphan Biovitrium, Roche, UCB Biopharma; stock ownership: Roche, Johnson&Johnson; other financial relations: Amgen, CSL Behring, Novartis, Roche, Sanofi. RS Alesci: advisory role or expert testimony: Amgen, Bayer, Biontech/Pfizer, BMS/Pfizer, Grifols, Novartis, Sanofi, Swedish Orphan Biovitrium, Octapharma, Takeda; financing of scientific research: CSL Behring, Novartis, Octapharma, Swedish Orphan Biovitrium, Takeda; other financial relations: Amgen, BMS/Pfizer, Novartis, NovoNordisk, Sanofi, Swedish Orphan Biovitrium. J. Gebhart: advisory role or expert testimony: Amgen, Novartis, Swedish Orphan Biovitrium, CSL Behring, Honorare: Amgen, Novartis, Swedish Orphan Biovitrium, CSL Behring; financing of scientific research: Amgen, Novartis, Swedish Orphan Biovitrium, CSL Behring. S. Holzhauer: advisory role or expert testimony: Novartis. L. Hütter-Krönke: advisory role or expert testimony: Grifols; Honoraria: Jazz Pharmazeuticals. Th. Kühne: advisory role or expert testimony: UCB, Swedish Orphan Biovitrium; financing of scientific research: Amgen, Novartis. O. Meyer: Employment or Leadership Position: DRK-Blutspendedienst NSTOB; Honoraria: AMGEN, Grifols, Novartis, Swedish Orphan Biovitrum. H. Ostermann: advisory role or expert testimony: Novartis, UCB, Argenx, Swedish Orphan Biovitrium, Cerus, Servier, AstraZeneca, Johnson&Johnson, Grifols; Honoraria: Novartis, Cerus, Vertex, MSD, AstraZeneca. Ingrid Pabinger-Fasching: advisory role or expert testimony, Referentenhonorare: AMGEN, CSL-Behring, Novartis, Swedish Orphan Biovitrium. M. Rummel: advisory role or expert testimony: Amgen, Novartis, Swedish Orphan Biovitrium, CSL Behring; Honoraria: Amgen, Novartis, Sandoz, Swedish Orphan Biovitrium. U. Sachs: advisory role or expert testimony: Swedish Orphan Biovitrium, CSL Behring, Bayer; Other financial relations: Amgen, Bayer, Biotest, CSL Behring, Octapharma, Swedish Orphan Biovitrium, Roche. Th. Stauch: Employment or Leadership Position: University Hospital Jena, Median Bad Berka; advisory role or expert testimony: Grifols, Swedish Orphan Biovitrium, Novartis, Argenx; Honoraria: Amgen, Grifols, Swedish Orphan Biovitrium, Novartis, Deutsche Krebsgesellschaft; financing of scientific research: Grifols, Swedish Orphan Biovitrium, Amgen, Novartis, Argenx. K. Trautmann: advisory role or expert testimony: GSK, Takeda, Grifols, Swedish Orphan Biovitrium, Amgen, Sanofi, Roche; Honorare: Novartis, GSK, Grifols; financing of scientific research: Swedish Orphan Biovitrium, Grifols, Amgen, Novartis. B. Wörmann: Employment: Charité Universitätsmedizin, Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie; other: member of ASH, DGHO, DGIM.

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Author Contributions

Coordinating author: AM. All authors were equally involved in the literature search, critical appraisal of the evidence, and preparation of the manuscript.

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