Oncology Research and Treatment

Oncol Res Treat , DOI: 10.1159/000529662

Received: February 6, 2023

Accepted: February 7, 2023

Published online: February 14, 2023

Expert Report on Immune Thrombocytopenia - Current Diagnostics and Treatment

Recommendations from an Expert Group from Austria, Germany, and Switzerland

Matzdorff A, Alesci SR, Gebhart J, Holzhauer S, Hütter-Krönke ML, Kühne T, Meyer O, Ostermann H, Pabinger I, Rummel M, Sachs UJ, Stauch T, Trautmann-Grill K, Wörmann B

ISSN: 2296-5270 (Print), eISSN: 2296-5262 (Online)

https://www.karger.com/ORT

Oncology Research and Treatment

Expert Report on Immune Thrombocytopenia

- Current Diagnostics and Treatment

Recommendations from an Expert Group from Austria, Germany, and Switzerland

Axel Matzdorff[a], Sonja R. Alesci[b], Johanna Gebhart[c], Susanne Holzhauer[d], Marie Luise Hütter-Krönke[e], Thomas Kühne[f], Oliver Meyer[g], Helmut Ostermann[h], Ingrid Pabinger[i], Mathias Rummel[j], Ulrich J. Sachs[k], Thomas Stauch[l], Karolin Trautmann-Grill[m], Bernhard Wörmann[n]

[a] Department of Medicine II, Asklepios Clinic Uckermark, Schwedt, Germany

[b] IMD Blood Coagulation Centre, Bad Homburg, Germany

[c] Clinical Division of Hematology and Hemostaseology, Department of Medicine I, Medical University of Vienna, Vienna, Austria

[d] Charité University Medicine, Department of Paediatric Haematology and Oncology, Berlin, Germany.

[e] Department of Medicine, Hematology, Oncology, and Tumor Immunology, Charite-Universitätsmedizin Berlin, Berlin, Germany

[f] Department of Oncology/Hematology, University Children's Hospital Basel, Basel, Switzerland.

[g] DRK Blood Service NSTOB, Springe, Germany

[h] University Hospital of Munich, Munich, Germany

[i] Clinical Division of Hematology and Hemostaseology, Department of Medicine I, Medical University of Vienna, Vienna, Austria

[j] Department of Hematology, Clinic for Haematology and Medical Oncology, Justus Liebig University Hospital, Gießen, Germany

[k] Institute for Clinical Immunology, Transfusion Medicine and Hemostasis, Justus-Liebig-University, Giessen, Germany

[l] Department of Internal Medicine II, Hematology and Oncology, University Hospital Jena, Jena, Germany

[m] Department of Internal Medicine I, University Hospital Dresden, Dresden, Germany

[n] Department of Medicine, Hematology, Oncology, and Tumor Immunology, Charite-Universitätsmedizin Berlin, Berlin, Germany

Short title: Expert Report ITP

Corresponding author:

Axel Matzdorff

Department of Medicine II

Asklepios Clinic Uckermark

Am Klinikum 1

16303 Schwedt, Germany

a.matzdorff@asklepios.com

Tables: 26

Figures: 8

Words: 20,244 (without title page and without statements)

Introduction

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

Baseline Information

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 distiguishes 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 [0].

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

Table 1 here

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.

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 to26 per 100,000.

In recent years there seems to be a trend towards a higher age at onset (~ 60 years). Almost a third of patients are more than 70 years old [0, 0].

In children and adolescents, the annual incidence rate of ITP is 2 to 7 new cases per 100,000 and the prevalence 4 to 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 spring than in summer, possibly reflecting the higher incidence of viral infections in the spring.

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 [0]. 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 pre-existing ITP can be expected. Of these, about half i.e., 3,500 to 9,000 patients, might require treatment.

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 enrol 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.

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 **figure 1**, for review see 0, 0). 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**).

Table 2 here

Figure 1 here

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.

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 0**).

Typical bleeding symptoms of ITP:

petechiae on the legs, less frequently on the trunk and arms (on 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%) [0].

the bleeding tendency in ITP patients is not as severe as in patients with a similar degree of thrombocytopenia 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 [0]. **Note:** in patients with thrombocytopenia or severe bleeding at other sites, special MRI techniques often show asymptomatic (!) CNS microbleeds [0].

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 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 [0] (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**).

Diagnosis

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

Some ten years ago, the American Society of Hematology and the International Working Group proposed criteria to improve the diagnostic accuracy for ITP [0, 0]:

- 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:

- 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 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**).

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.

Table 3 here

Table 4 here

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.

Platelet autoantibody testing

[for review see 0-0]

Platelet autoantibody testing is not part of the routine work-up 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 towards 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% [0, 0]. Also, false positive tests can sometimes occur in myelodysplastic syndromes and with lymphomas.

Table 5 here

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 [0, 0].

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.

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**)

Table 6 here

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 analysisshould further testing be necessary.

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.

Immature Platelet Fraction (IPF)

Immature platelets are one-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 whether the IPF value distinguishes thrombocytopenias with reduced platelet production (low IPF) from those with increased platelet consumption (high IPF) [0, 0]. 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.

Next Generation Sequencing (NGS)

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 thrombocytopenias (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-generaion sequencing (NGS) 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 [0, 0].

Classification

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

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**) [0].

Table 7 here

Table 8 here

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 (**figure 2** and **table 9**).

Figure 2 here

Table 9 here

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

Prognosis

Self-limited vs. 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 [0].

Morbidity and Mortality

Despite therapeutic advances, life expectancy of patients with chronic ITP is still significantly reduced [0]. 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. [0].

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.

Table 10 here

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 [0].

Mechanisms underlying drug-induced ITP are:

molecular mimicry may be the main mechanism in vaccine-related thrombocytopenia (for vaccines, see **chapter19.2**),

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 here

Indication for Treatment

The indication for starting treatment of ITP is based primarily on the bleeding tendency, and secondarily on the severityof 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**, andfor 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.

Figure 3 here

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 is the platelet count 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 & 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**).

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 Haemostsis (ISTH) [0]:

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.

1st Line Therapy

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, nor longer than 6 to 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**).

Table 12 here

Table 13 here

Corticosteroids achieve an initial rise in platelet counts in 60% to 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 [0, 0].

Prednisone vs. 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 x 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 1st line dexamethasone than with prednisone. Other studies 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.

1st Line Corticosteroid Monotherapy vs. Corticosteroid Combinations

1st 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 [0] or with tacrolimus [0] in 1st 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 1st line ITP therapy. There are also data on the combination of corticosteroids with rituximab or TPO-RAs as 1st 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.

Emergency Treatment

Intravenous immunoglobulins (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.

Emergency Treatment with Intravenous Immunoglobulins (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 GPIb/IX. Nevertheless, a trial of IVIG is justified in these and other patients whose severe bleeding is uncontrolled by other measures [0].

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.

Emergency Treatment with Platelet Concentrates, Rituximab, Thrombopoetin-Receptor-Agonists (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.

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 that 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**).

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

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 [0]. 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 [0]. 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.

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**.

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 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.

Figure 4 here

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 & 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 & 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.

Thrombopoetin-Receptor-Agonists (TPO-RAs)

Thrombopoietin-receptor agonists (TPO-RAs) are the established second-line therapy when an ITP patient does not respond to 1st line corticosteroids or has a prompt relapse. TPO-RAs have different pharmacological properties and approval status. The SYK inhibitor fostamatinib is also approved for 2nd line, see **chapter 0**.

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 [0].

Both eltrombopag and romiplostim appear to be less effective in patients with elevated serum thrombopoietin levels. No data are yet available for avatrombopag. 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 throm-bopoietin 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.

Additional data on TPO-RAs and the SYK inhibitor fostamatinib are summarized in **table 15, table 16,** and **figure 5**.

Table 15 here

Table 16 here

Figure 5 here

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 1st 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.

Other Thrombopoietin-Receptor Agonists

TPIAO is a recombinant thrombopoietin molecule approved for 2nd-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.

A romiplostim biosimilar (trade name: Romy) is available in India [0].

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 [0].

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.

Inadequate response to 2nd 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**).

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% [0-0]. 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 [0].

Figure 6 here

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 tofor be sought to achieve a therapy-free remission. ASH recommends the administration of rituximab or splenectomy [0, 0], and patients generally prefer rituximab to surgery. However, health insurers might insist on splenectomy 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.

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 **figure 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 3rd line by many hematologists after failure of TPO-RAs, although the approval text also allows prescription in the 2nd 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 2nd line is significantly higher than when the drug is given 3rd line with the same durability of response [0, 0]. 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.

3rd Line Therapy

Table 17 here

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.

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 x 375 mg/m^2, 2 x 1000 mg fixed dose, 4 x 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 [0]. 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% [0].

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 6^{th}-7^{th} 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 [0].

The ASH explicitly recommends rituximab for patients who wish to become therapy-free. Despite not being approved for ITP, rituximab is the most common 2^{nd} line therapy in the USA, ahead of TPO-RAs [0].

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.

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 [0, 0, 0].

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 [0]. Risks and contraindications of splenectomy are summarized in **table 18**.

Table 18 here

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 splenectomyhas remained constant even though patients have been previously treated with TPO-RAs and rituximab [0].

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 [0] (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 [0, 0].

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 vs. 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.

Therapy of Persistent or Chronic ITP in Children and Adolescets

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.

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 0, 0)

All-Trans-Retinoic Acid (ATRA)

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 1st line therapy of newly diagnosed ITP (dose 20 mg/d; 68% therapy-free remissions) [0] and in combination with rituximab for chronic relapsed ITP (dose 20 mg/m^2/d for 12 weeks, 61% therapy-free remissions) [0]. ATRA is not currently licensed for the treatment of ITP.

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 [0]. 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 [0].

Bruton's Tyrosine Kinase (BTK)-Inhibitors

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) [0, 0]. A phase III trial (Luna 3) has been initiated, and another BTK inhibitor, orelabrutinib, is being investigated [0].

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 the long-lived autoreactive plasma cells in the bone marrow that account for the failure of conventional treatments in autoimmune cytopenias (Dart study) [0, 0].

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. [0]. Alternatively, bortezomib might prevent dendritic cells from presenting antigens to CD4 lymphocytes [0].

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 [0-0].

Inhibitors of the Neonatal Fc Receptor (FcRn)

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 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 [0, 0]. Their side effects include headache, fever, and abdominal discomfort. Positive phase III study results have currently been published for efgartigimod [0], but the ITP studies with rozanolixizumab have been discontinued for non-medical reasons.

Inhibitors of B cell activating factor (BAFF)

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 [0].

Sutimlimab

Complement fixed to the platelet surface by anti-platelet antibodies can induce cell injury and is another pathophysiologic mechanism in the setting of chronic ITP (see **chapter 3**) [0, 0]. 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 [0]. 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 c**hapter 19.9**) [0].

Atorvastatin

Atorvastatin has a stimulatory effect on megakaryocytes and thrombopoiesis in patients with steroid-refractory ITP [0]. A clinical trial examining the combination of dexamethasone and atorvastatin in newly diagnosed ITP is underway (NCT03692754).

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 [0].

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

Special Situations

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 1st line therapy with corticosteroids. Many patients require additional lines of therapy (for review see 0).

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 [0]. A recent study shows that 12% of all ITP cases initially classified as primary – even by experts – subsequently require reclassification as secondary ITP [0]. In the presence of certain key findings, one should search for an underlying disease (**figure 7**).

Figure 7 here

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 [0], 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, its can also enhance immunosuppression and increase the risk for infections. Therefore,, splenectomy should be avoided in secondary ITP.

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 three months between administration of the immunoglobulins and a live vaccine, and up to one 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 re-vaccination; 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.

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.) [0]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 [0].

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. [0, 0]. 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 [0].

Can COVID-19 infection trigger new cases of ITP?

There are numerous reports that COVID can trigger the first onset of ITP [0-0], 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 [0, 0, 0, 0].

It is unclear whether the COVID-19 infection non-specifically activates a preexisting immune dysregulation or induces antibodies specifically directed towards platelets. There is one report that discusses the possibility of molecular mimicry [0].

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) [0]. 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 [0, 0].

Can ITP increase the risk for COVID-19 infection?

ITP patients on immunosuppressive therapy (high-dose or long-term corticosteroids, azathioprine, rituximab) are atr 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 [0, 0]. 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 [0-0]. However, the risk seems to be extremely low, and the prognosis is very good, i.e., most patients recover [0]. 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 [0, 0].

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 [0]. There is no study that shows that the number of new ITP cases after vaccination significantly exceeds the expected background incidence [0].

Can COVID-19 vaccination worsen a pre-existing ITP?

It has been noted that in patients with pre-existing ITP, platelet counts can decline after COVID-19 vaccination [0, 0]. In most cases, the decrease is mild, and the incidence of clinically relevant bleeding appears to be in the lower single digit range [0]. 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 [0].

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. [0]. 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, andIf 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 [0, 0].

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 2nd or 3rd 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 [0]. There are no data yet for those 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 2nd or 3rd 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 [0].

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 3rd vaccination (booster) 4 weeks after the first two vaccinations.

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**).

Table 19 here

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.

Table 20 here

Pregnancy and ITP

(for review, see reference 0)

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 in1-4%. Antiphospholipid syndrome, thrombotic thrombocytopenic purpura, familial thrombocytopenias, and other syndromes are rare [0]. The incidence of ITP in pregnancy is approximately 1/1000 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 bleeding 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[0]. 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 work-up

The differential diagnosis is based on the time of occurrence of thrombocytopenia, and additional clinical and laboratory findings (see **table 21** and **figure 8**).

Insert table 21 and figure 8 here

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 work-up is similar to that performed in non-pregnant patients with suspected ITP, see **chapter 0**.

Table 21 here

Figure 8 here

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 [0].

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 2nd trimester.

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 [0, 0]. 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 2nd or 3rd 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 [135].

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.

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,

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) [0]. 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 vs. 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 [0]. 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.

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 [0, 0].

Table 22 here

Table 23 here

ITP vs. 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 (I) reduced thrombopoietin production, (II) increased sequestration in an enlarged spleen, (III) increased platelet consumption from decompensated hemostasis, and (IV) direct nutritive-toxic damage, e.g., from alcohol [0].

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**).

Table 24 here

Quality of Life and Fatigue

ITP patients have poor health-related quality of life, similar to that of cancer patients and sometimes even worse [0, 0, 0, 0]. This is also true for pediatric ITP [0, 0]. 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 [0]. A recent German study found a high incidence of fatigue in ITP patients [0]. 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.

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.

Travelling

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 cancelled.

Management Issues

Different Treatment Goals: Patients vs. 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 5th place for patients) [0].

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 [0].

This focus on 'good blood values' explains why a watch & wait strategy (as in **figure 3**) is not an option for many patients when platelet counts are low, despite minimal or no bleeding [0].

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 [0]. However, this is not reflected in physicians' daily practice. Steroids are still the most commonly used treatment for ITP [0, 0]; 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.

Do we need new Study Endpoints?

For ITP patients with bleeding, increasing the platelet count and stopping or preventing hemorrhages is a priority. 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 2nd 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 [0, 0]. A discussion is needed about whether future ITP studies need new primary endpoints [0]:

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).

Rehabilitation and Social Law

(only applicable for the Federal Republic of Germany)

The degree of disability (Grad der Behinderung GdB) according to 'Social Code Book IX' (Sozialgesetzbuch IX = SGB IX, - Rehabilitation and Participation of Disabled Persons) is based on the 'Medical Care Principles' (Versorgungsmedizinische Grundsätze = VMG) 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, and receives the following degrees of disability (**see table 25**):

Table 25 here

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 to 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).

ITP-Studies in AU/CH/D

Table 26 here

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.

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

United Kingdom: ITP Support Association

http://www.itpsupport.org.uk

Additional resources:

International ITP Alliance

http://www.globalitp.org

Conflicts of Interest Statement

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, Astra Zeneca, 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.

Statements

Funding Sources

The authors received no financial or nonfinancial support for authorship and publication of this article.

Author Contributions

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

Acknowledgement

A sincere thanks to Prof. David Green, Department of Medicine, Northwestern University-Feinberg School of Medicine, Chicago for his diligent proofreading of this manuscript.

References

Matzdorff A, Meyer O, Ostermann H, Kiefel V, Eberl W, Kühne T, et al. Immunthrombozytopenie - aktuelle Diagnostik und Therapie: Empfehlungen einer gemeinsamen Arbeitsgruppe der DGHO, ÖGHO, SGH, GPOH und DGTI. Oncol Res Treat. 2018;41 Suppl 2:5-36.

Matzdorff A, Holzhauer S, Kühne T, Meyer O, Ostermann H, Pabinger-Fasching I, et al. Onkopedia Leitlinie: Immunthrombozytopenie (ITP). ICD-10 D69.3. Stand März 2021 [cited 2022, Nov. 30th]. Available from: https://www.onkopedia.com

Ayad N, GraceRF, Kuter DJ, Al-Samkari H. Long-Term Risk of Developing Immune Thrombocytopenia and Hematologic Neoplasia in Adults with Persistent, Isolated Mild Thrombocytopenia. ASH Annual Meeting Ab-stract. Blood 2022;140 (Supplement 1):1-2, Abstr. 19. [cited 2022, Nov. 30th]. Available from: https://ash.confex.com/ash/2022/webprogram/Paper168000.html

Christiansen CF, Bahmanyar S, Ghanima W, Risbo N, Ekstrand C, Stryker S, et al. Chronic immune thrombocytopenia in Denmark, Sweden and Norway: The Nordic Country Patient Registry for Romiplostim. EClinicalMedicine. 2019 Aug 23;14:80-87.

Doobaree IU, Conway K, Miah H, Miah A, Makris M, Hill Q, et al.; UK adult ITP registry. Incidence of adult primary immune thrombocytopenia in England-An update. Eur J Haematol. 2022 Sep;109(3):238-249.

Kim TO, Grimes AB, Kirk SE, Gilbert MM, Reed HD, Staggers KA, et al. Racial variation in ITP prevalence and chronic disease phenotype suggests biological differences. Blood. 2020 Jul 30;136(5):640-643.

Semple JW, Rebetz J, Maouia A, Kapur R. An update on the pathophysiology of immune thrombocytopenia. Curr Opin Hematol. 2020 Nov;27(6):423-429.

Audia S, Mahévas M, Nivet M, Ouandji S, Ciudad M, Bonnotte B. Immune Thrombocytopenia: Recent Advances in Pathogenesis and Treatments. Hemasphere. 2021 Jun 1;5(6):e574.

Hallan DR, Simion C, Sciscent BY, Lee J, Rizk E. Immune Thrombocytopenic Purpura and Intracerebral Hemorrhage, Incidence, and Mortality. Cureus. 2022 Apr 24;14(4):e24447.

Zitek T, Weber L, Pinzon D, Warren N. Assessment and Management of Immune Thrombocytopenia (ITP) in the Emergency Department: Current Perspectives. Open Access Emerg Med. 2022 Jan 29;14:25-34.

Cooper N, Morrison MA, Vladescu C, Hart ACJ, Paul D, Malik A, et al. Identification of occult cerebral microbleeds in adults with immune thrombocytopenia. Blood. 2020 Dec 17;136(25):2875-2880.

Koca Yozgat A, Leblebisatan G, Akbayram S, Çınar Özel S, Karakaş Z, Erduran E, et al. Outcomes of Eltrombopag Treatment and Development of Iron Deficiency in Children with Immune Thrombocytopenia in Turkey. Turk J Haematol. 2020 Aug 28;37(3):139-144.

Rodeghiero F, Stasi R, Gernsheimer T, Michel M, Provan D, Arnold DM, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Blood. 2009 Mar 12;113(11):2386-93.

Neunert C, Lim W, Crowther M, Cohen A, Solberg L Jr, Crowther MA; American Society of Hematology. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood. 2011 Apr 21;117(16):4190-207.

Sachs UJ. Diagnosing Immune Thrombocytopenia. Hamostaseologie. 2019 Aug;39(3):250-258.

Gabe C, Sirotich E, Li N, Ivetic N, Nazy I, Smith J, et al. Performance characteristics of platelet autoantibody testing for the diagnosis of immune thrombocytopenia using strict clinical criteria. Br J Haematol. 2021 Jul;194(2):439-443.

Al-Samkari H, Rosovsky RP, Karp Leaf RS, Smith DB, Goodarzi K, et al. A modern reassessment of glycoprotein-specific direct platelet autoantibody testing in immune thrombocytopenia. Blood Adv. 2020 Jan 14;4(1):9-18.

Sachs U, Reich M, Qiu D, Cooper N, Bein G. Glycoprotein-specific Platelet Autoantibodies Predict Lower Platelet Counts in Thrombocytopenic Patients. ISTH 2022 Abstr. PB1209. [cited November 30th, 2022] Available from https://abstracts.isth.org/abstract/glycoprotein-specific-platelet-autoantibodies-predict-lower-platelet-counts-in-thrombocytopenic-patients/.

Li J, Li Y, Ouyang J, Zhang F, Liang C, Ye Z, et al. Immature platelet fraction related parame-ters in the differential diagnosis of thrombocytopenia. Platelets. 2020 Aug 17;31(6):771-776.

Pereira KN, de Carvalho JAM, Paniz C, Moresco RN, da Silva JEP. Diagnostic characteristics of immature platelet fraction for the assessment of immune thrombocytopenia. Thromb Res. 2021 Jun;202:125-127.

Perez Botero J, Di Paola J. Diagnostic approach to the patient with a suspected inherited platelet disorder: Who and how to test. J Thromb Haemost. 2021 Sep;19(9):2127-2136.

Greinacher A, Eekels JJM. Simplifying the diagnosis of inherited platelet disorders? The new tools do not make it any easier. Blood. 2019 Jun 6;133(23):2478-2483.

Holzhauer S, Bergmann F, Cario H, Dame C, Dickerhoff R, Klarmann D, et al. Leitlinie „S2k-Leitlinie 086-001: Neu diagnostizierte Immunthrombozytopenie im Kindes- und Jugendalter". Stand: 31.10.2018, gültig bis 31.01.2023 [cited November 30th, 2022], Available from https://www.awmf.org/leitlinien/detail/ll/086-001.html

Schifferli A, Moulis G, Godeau B, Leblanc T, Michel M, Aladjidi N, et al. Adolescents and Young Adults with Immune Thrombocytopenia (ITP): A Project of the Carmen-France and Parc-ITP Registry. ASH Annual Meeting Abstract. Blood. 2021 Nov;138 (Supplement 1):2079.

Mannering N, Hansen DL, Pottegård A, Frederiksen H. Long-term survival in patients with primary and secondary immune thrombocytopenia – a nationwide population-based cohort study. EHA Annual Meeting 2021. EHA Library. Mannering N. 06/09/21; 324704; S296. [cited November 30th, 2022], Available from https://library.ehaweb.org/eha/2021/eha2021-virtual-congress/324704/nikolaj.mannering.long-term.survival.in.patients.with.primary.and.secondary.html?f=menu%3D6%2Abrowseby%3D8%2Asortby%3D2%2Amedia%3D3%2Ace_id%3D2035%2Aot_id%3D25574.

Ekstrand C, Bahmanyar S, Cherif H, Kieler H, Linder M. Cancer risk in patients with primary immune thrombocytopenia - A Swedish nationwide register study. Cancer Epidemiol. 2020 Dec;69:101806.

Bussel JB, Tomiyama Y, Michel M, Provan D, Hou M, Santoro C, et al. Physicians' perceptions on causes of primary and secondary ITP and leading causes of misdiagnosis: results from the ITP World Impact Survey (I-WISH). EHA Annual Meeting 2019 Abstract, EHA Library. Bussel J. 06/14/19; 266511; PF712, no DOI, [cited November 30th, 2022] Available from https://library.ehaweb.org/eha/2019/24th/266511/j.bussel.physicians.perceptions.on.causes.of.primary.and.secondary.itp.and.html?f=listing%3D0%2Abrowseby%3D8%2Asortby%3D1%2Asearch%3Dbussel

Fuentes S, Chrétien B, Dolladille C, Alexandre J, Dumont A, Nguyen A, et al. An updated list of drugs suspected to be associated with immune thrombocytopenia based on the WHO pharma-covigilance database. Blood. 2022 Aug 25;140(8):922-927.

Sirotich E, Guyatt G, Gabe C, Ye Z, Beck CE, Breakey V, et al. Definition of a critical bleed in patients with immune thrombocytopenia: Communication from the ISTH SSC Subcommittee on Platelet Immunology. J Thromb Haemost. 2021 Aug;19(8):2082-2088.

Meyer O, Richter H, Lebioda A, Schill M. Treatment patterns in adults with immune thrombocytope-nia before, during and after use of thrombopoietin receptor agonists: a longitudinal prescription database study from Germany. Hematology. 2021 Dec;26(1):697-708.

Kubasch AS, Kisro J, Heßling J, Schulz H, Hurtz HJ, Klausmann M, et al. Disease management of patients with immune thrombocytopenia-results of a representative retrospective survey in Germany. Ann Hematol. 2020 Sep;99(9):2085-2093.

Neunert C, Terrell DR, Arnold DM, Buchanan G, Cines DB, Cooper N, et al. American Society of Hematology 2019 guidelines for immune thrombocytopenia. Blood Adv. 2019 Dec 10;3(23):3829-3866.

Choi PY, Merriman E, Bennett A, Enjeti AK, Tan CW, Goncalves I, e tal. Consensus guidelines for the management of adult immune thrombocytopenia in Australia and New Zealand. Med J Aust. 2022 Jan 17;216(1):43-52.

Thrombosis and Hemostasis Group, Chinese Society of Hematology, Chinese Medical Association. [Chinese guideline on the diagnosis and management of adult primary immune thrombocytopenia (version 2020)]. Zhonghua Xue Ye Xue Za Zhi. 2020 Aug 14;41(8):617-623.

Protocole National de Diagnostic et de Soins. Purpura thrombopénique immunologique l'enfant et de l'adulte 2017. [cited November 30th, 2022] Available from: https://www.has-sante.fr/upload/docs/application/pdf/2017-06/dir36/pnds-_purpura_thrombopenique_immunologique.pdf.

Provan D, Arnold DM, Bussel JB, Chong BH, Cooper N, Gernsheimer T, et al. Updated international consensus report on the investigation and management of primary immune thrombocytopenia. Blood Adv. 2019 Nov 26;3(22):3780-3817.

No authors listed. Linea guida "Trombocitopenia immune dell'adulto". [cited November 30th, 2022]. Available from: https://snlg.iss.it/wp-content/uploads/2021/05/LG-347-SIE_Trombocitopenia_immune_adulto.pdf

Kashiwagi H, Kuwana M, Hato T, Takafuta T, Fujimura K, Kurata Y, et al.; Committee for the Revision of "Reference Guide for Management of adult ITP" Blood Coagulation Abnormalities Research Team, Research on Rare and Intractable Disease supported by Health, Labour and Welfare Science Research Grants. Reference guide for management of adult immune thrombocytopenia in Japan: 2019 Revision. Int J Hematol. 2020 Mar;111(3):329-351.

Lozano ML, Sanz MA, Vicente V; Grupo Español de PTI (GEPTI). Guidelines of the Spanish ITP Group for the diagnosis, treatment and follow-up of patients with immune thrombopenia. Med Clin (Barc). 2021 Aug 27;157(4):191-198.

Hill QA, Grainger JD, Thachil J, Provan D, Evans G, Garg M, et al.; British Society of Haematology in conjunction with the UK ITP forum. The prevention of glucocorticoid-induced osteoporosis in patients with immune thrombocytopenia receiving steroids: a British Society for Haematology Good Practice Paper. Br J Haematol. 2019 May;185(3):410-417.

Bradbury CA, Pell J, Hill Q, Bagot C, Cooper N, Ingram J, et al. Mycophenolate Mofetil for First-Line Treatment of Immune Thrombocytopenia. N Engl J Med. 2021 Sep 2;385(10):885-895.

An ZY, Wu YJ, He Y, Zhu XL, Shi HX, Wang CC, et al. Tacrolimus Plus High-Dose Dexamethasone Versus High-Dose Dexamethasone Alone As First-Line Treatment for Adult Immune Thrombocytopenia: The Phase 2, Open Label, Random-ized Trial (TARGET 020). ASH Annual Meeting Abstract. Blood. 2021;138 (Supplement 1):13 [cited November 30th, 2022]. Available from: https://ashpublications.org/blood/article/138/Supplement%201/13/477483/Tacrolimus-Plus-High-Dose-Dexamethasone-Versus

Yu Y, Wang M, Hou Y, Qin P, Zeng Q, Yu W, et al. High-dose dexamethasone plus recombinant human thrombopoietin vs high-dose dexamethasone alone as frontline treatment for newly diagnosed adult primary immune thrombocytopenia: A prospective, multicenter, randomized trial. Am J Hematol. 2020 Dec;95(12):1542-1552.

Zhang L, Zhang M, Du X, Cheng Y, Cheng G. Safety and efficacy of eltrombopag plus pulsed dexamethasone as first-line therapy for immune thrombocytopenia. Br J Haematol. 2020 Apr;189(2):369-378.

Matzdorff A, Binder M, Nimmerjahn F, Meyer O, Rummel MJ, Tesanovic T, et al. A Phase II Study to Investigate the Efficacy and Safety of El-trombopag in Combination with Dexamethasone As First-Line Treatment in Adult Patients with Newly Diagnosed Primary ITP (XPAG-ITP). ASH Annual Meeting Abstract, Blood. 2020;136 (Supplement 1):36–37. [cited November 30th, 2022]. Available from: https://ashpublications.org/blood/article/136/Supplement%201/36/473251/A-Phase-II-Study-to-Investigate-the-Efficacy-and

Neunert CE. Management of newly diagnosed immune thrombocytopenia: can we change outcomes? Hematology Am Soc Hematol Educ Program. 2017 Dec 8;2017(1):400-405.

Yu Y, Hou Y, Zhao Y, Zhou H, Jing F, Liu Y, et al. Platelet autoantibody specificity and response to rhTPO treatment in patients with primary immune thrombocytopenia. Br J Haematol. 2021 Jul;194(1):191-194.

Schoettler ML, Graham D, Tao W, Stack M, Shu E, Kerr L, et al. Increasing observation rates in low-risk pediatric immune thrombocytopenia using a standardized clinical assessment and management plan (SCAMP®). Pediatr Blood Cancer. 2017 May;64(5):10.1002/pbc.26303.

Al-Samkari H, Jiang D, Gernsheimer T, Liebman H, Lee S, Wojdyla M, et al. Adults with immune thrombocytopenia who switched to avatrombopag following prior treatment with eltrombopag or romiplostim: A multicentre US study. Br J Haematol. 2022 May;197(3):359-366.

Al-Samkari H, Kuter DJ. Immune Thrombocytopenia in Adults: Modern Approaches to Diagnosis and Treatment. Semin Thromb Hemost. 2020 Apr;46(3):275-288.

Bhatwadekar SS, Deshpande SV, Khadse SV, Jani D, Lakhmapurkar U, Vasoya P, et al. Efficacy and Safety of Biosimilar Romiplostim in Immune Thrombocytopenic Purpura. Single Centre Retrospective Data Analysis. ASH Annual Meeting Abstract, Blood. 2020;136 (Supplement 1): 23. . [cited November 30th, 2022]. Available from: https://ashpublications.org/blood/article/136/Supplement%201/23/472341/Efficacy-and-Safety-of-Biosimilar-Romiplostim-in?searchresult=1

Syed YY. Hetrombopag: First Approval. Drugs. 2021 Sep;81(13):1581-1585.

Cooper N, Hill QA, Grainger J, Westwood JP, Bradbury C, Provan D, et al. Tapering and Discontinuation of Thrombopoietin Receptor Agonist Therapy in Patients with Immune Thrombocytopenia: Results from a Modified Delphi Panel. Acta Haematol. 2021;144(4):418-426.

Cuker A, Despotovic JM, Grace RF, Kruse C, Lambert MP, Liebman HA, et al. Tapering thrombopoietin receptor agonists in primary immune thrombocytopenia: Expert consensus based on the RAND/UCLA modified Delphi panel method. Res Pract Thromb Haemost. 2020 Dec 8;5(1):69-80.

Lucchini E, Palandri F, Volpetti S, Vianelli N, Auteri G, Rossi E, et al; for Gruppo Italiano Malat-tie Ematologiche dell'Adulto (GIMEMA). Eltrombopag second-line therapy in adult patients with primary immune thrombocytopenia in an attempt to achieve sustained remission off-treatment: results of a phase II, multicentre, prospective study. Br J Haematol. 2021 Apr;193(2):386-396.

Zaja F, Carpenedo M, Baratè C, Borchiellini A, Chiurazzi F, Finazzi G, et al. Tapering and discontinuation of thrombopoietin receptor agonists in immune thrombocytopenia: Real-world recommendations. Blood Rev. 2020 May;41:100647.

Ghanima W, Gernsheimer T, Kuter DJ. How I treat primary ITP in adult patients who are unresponsive to or dependent on corticosteroid treat-ment. Blood. 2021 May 20;137(20):2736-2744.

Boccia R, Cooper N, Ghanima W, Boxer MA, Hill QA, Sholzberg M, et al; FIT Clinical Trial Investigators. Fostamatinib is an effective second-line therapy in patients with immune thrombocytopenia. Br J Haematol. 2020 Sep;190(6):933-938.

Kapur R. Fine-tuning the treatment toolbox of immune thrombocytopenia: fostamatinib as a second-line therapy. Br J Haematol. 2020 Sep;190(6):817-818.

Dong Y, Yue M, Hu M. The Efficacy and Safety of Different Dosages of Rituximab for Adults with Immune Thrombocytopenia: A Systematic Review and Meta-Analysis. Biomed Res Int. 2021 Oct 6;2021:9992086.

Tjønnfjord E, Holme PA, Darne B, Khelif A, Waage A, Michel M, et al. Long-term outcomes of patients treated with rituximab as second-line treatment for adult immune thrombocytopenia - Follow-up of the RITP study. Br J Haematol. 2020 Nov;191(3):460-465.

Ghanima W, Bussel JB, Provan D, Kruse A, Kruse C, Tomiyama Y, et al. Patients' reported perceptions on satisfaction with immune thrombocytopenia treatments: results from the ITP world impact survey (i-WISh). EHA

Library. Haenig J. 06/12/20; 294113; EP1631. [cited November 30th, 2022]. Available from: https://library.ehaweb.org/eha/2020/eha25th/294113/jens.haenig.patients.reported.perceptions.on.satisfaction.with.immune.html?f=listing%3D0%2Abrowseby%3D8%2Asortby%3D1%2Asearch%3Ditp+world+impact+survey.

McGrath LJ, Kilpatrick K, Overman RA, Reams D, Sharma A, Altomare I, et al. Treatment Patterns Among Adults with Primary Immune Thrombocytopenia Diagnosed in Hematology Clinics in the United States. Clin Epidemiol. 2020 May 5;12:435-445.

Miltiadous O, Hou M, Bussel JB. Identifying and treating refractory ITP: difficulty in diagnosis and role of combination treatment. Blood. 2020 Feb 13;135(7):472-490.

Vianelli N, Auteri G, Buccisano F, Carrai V, Baldacci E, Clissa C, et al. Refractory primary immune thrombocytopenia (ITP): current clinical challenges and therapeutic perspectives. Ann Hematol. 2022 May;101(5):963-978.

Engelhardt M, Eber S, Germing U, Schmugge-Liner M, Rieg S. Onkopedia Leitlinie: Asplenie und Hyposplenismus (früher: Prävention von Infektionen und Thrombosen nach Splenektomie oder funktioneller Asplenie). Stand Mai 2020. [cited November 30th, 2022]. Available from: https://www.onkopedia.com/de/onkopedia/guidelines/asplenie-und-hyposplenismus-frueher-praevention-von-infektionen-und-thrombosen-nach-splenektomie-oder-funktioneller-asplenie/@@guideline/html/index.html

Mageau A, Terriou L, Ebbo M, Souchaud-Debouverie O, Orvain C, Graveleau J, et al. Splenectomy for primary immune thrombocytopenia revisited in the era of thrombopoietin receptor agonists: New insights for an old treatment. Am J Hematol. 2022 Jan 1;97(1):10-17.

Cooper N, Kruse A, Kruse C, Watson S, Morgan M, Provan D, et al. Immune thrombocytopenia (ITP) World Impact Survey (I-WISh): Impact of ITP on health-related quality of life. Am J Hematol. 2021 Feb 1;96(2):199-207.

Caocci G, Efficace F, Mulas O, Cottone F, Maxia A, Costa A, et al. Health-related quality of life profile of patients with immune thrombocytopenia in the real life is impaired by splenectomy. Ann Hematol. 2022 Apr;101(4):749-754.

Zhou H, Fan J, He J, Hu S. Comparative efficacy of 19 drug therapies for patients with idiopathic thrombocytopenic purpura: a multiple-treatments network meta-analysis. Ann Hematol. 2022 May;101(5):953-961.

Mingot-Castellano ME. New treatments for primary immune thrombocytopenia. Blood Coagul Fibrinolysis. 2022 Jan 1;33(Suppl 1):S8-S11.

Huang QS, Liu Y, Wang JB, Peng J, Hou M, Liu H, et al. All-trans retinoic acid plus high-dose dexamethasone as first-line treatment for patients with newly diagnosed immune thrombocytopenia: a multicentre, open-label, randomised, controlled, phase 2 trial. Lancet Haematol. 2021 Oct;8(10):e688-e699.

Wu Y, Liu H, Zeng QZ, Liu Y, Wang JW, Wang WS, et al. All-trans retinoic acid plus low-dose rituximab vs low-dose rituximab in corticosteroid-resistant or relapsed ITP. Blood. 2022 Jan 20;139(3):333-342.

Colunga-Pedraza PR, Peña-Lozano SP, Sánchez-Rendón E, De la Garza-Salazar F, Colunga-Pedraza JE, Gómez-De León A, et al. Oseltamivir as rescue therapy for persistent, chronic, or refractory immune thrombocytopenia: a case series and review of the literature. J Thromb Thrombolysis. 2022 Aug;54(2):360-366.

Sun L, Wang J, Shao L, Yuan C, Zhao H, Li D, et al. Dexamethasone plus oseltamivir versus dexamethasone in treatment-naive primary immune thrombocytopenia: a multicentre, randomised, open-label, phase 2 trial. Lancet Haematol. 2021 Apr;8(4):e289-e298.

Kuter DJ, Efraim M, Mayer J, Trněný M, McDonald V, Bird R, et al. Rilzabrutinib, an Oral BTK Inhibitor, in Immune Thrombocytopenia. N Engl J Med. 2022 Apr 14;386(15):1421-1431.

Kuter DJ, Bussel JB, Cooper N, Gernsheimer T, Lambert MP, Liebman H, et al. LUNA3 Phase III Multicenter, Double-Blind, Randomized, Placebo-Controlled Trial of the Oral BTK Inhibitor Rilzabrutinib in Adults and

Adolescents with Persistent or Chronic Immune Thrombocytopenia. ASH Annual Meeting Abstract. Blood. 2021;138 (Supplement 1): 1010. [cited November 30th, 2022]. Available from: https://ashpublications.org/blood/article/138/Supplement%201/1010/480881/LUNA3-Phase-III-Multicenter-Double-Blind?searchresult=1

Yu T, Wang L, Ni X, Hou Y, Liu X, Hou M. Orelabrutinib, a Selective Bruton's Tyrosine Kinase (BTK) Inhibitor in the Treatment of Primary Immune Thrombocytopenia (ITP) ASH Annual Meeting Abstract. Blood. 2021;138 (Supplement 1): 3172. [cited November 30th, 2022]. Available from: https://ashpublications.org/blood/article/138/Supplement%201/3172/479487/Orelabrutinib-a-Selective-Bruton-s-Tyrosine-Kinase?searchresult=1

Crickx E, Audia S, Robbins A, Boutboul D, Comont T, Cheminant M, et al. Daratumumab, an original approach for treating multi-refractory autoimmune cytopenia. Haematologica. 2021 Dec 1;106(12):3198-3201.

Tsykunova G, Holme PA, Tuyet Tran HT, Anderson Tvedt TH, et al. Daratumumab as a treatment for adult immune thrombocytopenia: a phase II study with safety run-in (the dart study). EHA Annual Meeting Abstracts 2022. EHA Library. Tsykunova G. 06/10/22; 359164; PB2313. [cited November 30th, 2022]. Available from: https://library.ehaweb.org/eha/2022/eha2022-congress/359164/galina.tsykunova.daratumumab.as.a.treatment.for.adult.immune.thrombocytopenia.html?f=listing%3D4%2Abrowseby%3D8%2Asortby%3D2%2Amedia%3D3%2Aspeaker%3D907652.

Li G, Wang S, Li N, Liu Y, Feng Q, Zuo X, et al. Proteasome Inhibition with Bortezomib Induces Apoptosis of Long-Lived Plasma Cells in Steroid-Resistant or Relapsed Immune Thrombocytopaenia. Thromb Haemost. 2018 Oct;118(10):1752-1764.

Park SJ, Cheong HI, Shin JI. Antibody depletion by bortezomib through blocking of antigen presentation. N Engl J Med. 2013 Apr 4;368(14):1364-5.

Han P, Hou Y, Zhao Y, Liu Y, Sun Y, Wang H, et al. Low-dose decitabine modulates T cell homeostasis and restores immune tolerance in immune thrombocytopenia. Blood. 2021 Aug 26;138(8):674-688.

Ni X, Wang L, Wang H, Yu T, Xie J, Li G, et al. Low-dose decitabine modulates myeloid-derived suppressor cell fitness via LKB1 in immune thrombocytopenia. Blood. 2022 Aug 29:blood.2022016029. Epub ahead of print.

Zhou H, Qin P, Liu Q, Yuan C, Hao Y, Zhang H, et al. A prospective, multicenter study of low dose decitabine in adult patients with refractory immune thrombocytopenia. Am J Hematol. 2019 Dec;94(12):1374-1381.

Newland AC, Sánchez-González B, Rejtő L, Egyed M, Romanyuk N, Godar M, et al. Phase 2 study of efgartigimod, a novel FcRn antagonist, in adult patients with primary immune thrombocytopenia. Am J Hematol. 2020 Feb;95(2):178-187.

Robak T, Kaźmierczak M, Jarque I, Musteata V, Treliński J, Cooper N, et al. Phase 2 multiple-dose study of an FcRn inhibitor, rozanolixizumab, in patients with primary immune thrombocytopenia. Blood Adv. 2020 Sep 8;4(17):4136-4146.

Broome CM, McDonald V, Miyakawa Y, Carpenedo M, Kuter DJ, Al-Samkari H, et al. Efficacy and Safety of Intravenous Efgartigimod in Adults with Primary Immune Thrombocytopenia: Results of a Phase 3, Multicenter, Double-Blinded, Placebo-Controlled, Randomized Clinical Trial (ADVANCE IV). ASH Annual Meeting Abstract. Blood 2022 Nov;140 (Supplement 1):1-2, Abstr. 3. [cited November 30th, 2022]. Available from: https://ash.confex.com/ash/2022/webprogram/Paper167838.html

Mahévas M, Azzaoui I, Crickx E, Canoui-Poitrine F, Gobert D, Languille L, et al. Efficacy, safety and immunological profile of combining rituximab with belimumab for adults with persistent or chronic immune thrombocytopenia: results from a prospective phase 2b trial. Haematologica. 2021 Sep 1;106(9):2449-2457.

Castelli R, Lambertenghi Delilliers G, Gidaro A, Cicardi M, Bergamaschini L. Complement activation in patients with immune thrombocytopenic purpura according to phases of disease course. Clin Exp Immunol. 2020 Sep;201(3):258-265.

Cheloff AZ, Kuter DJ, Al-Samkari H. Serum complement levels in immune thrombocytopenia: Characterization and relation to clinical features. Res Pract Thromb Haemost. 2020 Jun 21;4(5):807-812.

Broome CM, Röth A, Kuter DJ, Scully M, Smith R, Wang J, Reuter C, Hobbs WE, Daak AAA. Safety and Efficacy of Classical Complement Pathway Inhibition with Sutimlimab in Chronic Immune Thrombocytopenia. Blood Adv. 2022 Aug 16:bloodadvances.2021006864.

Roth A, Barcellini W, D'Sa S, Miyakawa Y, Broome CM, Michel M, et al. Complement C1s inhibition with sutimlimab results in durable response in cold agglutinin disease: CARDINAL study 1-year interim follow-up results. Haematologica. 2022 Jul 1;107(7):1698-1702.

Qian J, Shen Q, Yan CX, Yin H, Cao X, Lin ZH, et al. Atorvastatin improves bone marrow endothelial progenitor cell function from patients with immune-related hemocytopenia. Ann Transl Med. 2021 Jul;9(14):1142.

Ritter CA. Arzneimittelinteraktionen zwischen oralen TKI und pflanzlichen Präparaten. InFo Hämatologie + Onkologie 2021 Feb;24(1-2):18-24.

Michel M, Lega JC, Terriou L. Les purpuras thrombopéniques immunologiques secondaires de l'adulte [Secondary ITP in adults]. Rev Med Interne. 2021 Jan;42(1):50-57. French.

Schifferli A, Heiri A, Imbach P, Holzhauer S, Seidel MG, Nugent D, et al. Misdiagnosed thrombocytopenia in children and adolescents: analysis of the Pediatric and Adult Registry on Chronic ITP. Blood Adv. 2021 Mar 23;5(6):1617-1626.

Arnold DM, Nazy I, Clare R, Jaffer AM, Aubie B, Li N, et al. Misdiagnosis of primary immune thrombocytopenia and frequency of bleeding: lessons from the McMaster ITP Registry. Blood Adv. 2017 Nov 28;1(25):2414-2420.

Patwardhan P, Landsteiner A, Lal LS, Geevarghese L, Le L, Nandal S, et al. Eltrombopag treatment of patients with secondary immune thrombocytopenia: retrospective EHR analysis. Ann Hematol. 2022 Jan;101(1):11-19.

Raadsen M, Du Toit J, Langerak T, van Bussel B, van Gorp E, Goeijenbier M. Thrombocytopenia in Virus Infections. J Clin Med. 2021 Feb 20;10(4):877.

Yang X, Yang Q, Wang Y, Wu Y, Xu J, Yu Y, et al. Thrombocytopenia and its association with mortality in patients with COVID-19. J Thromb Haemost. 2020 Jun;18(6):1469-1472.

Mellema RA, Crandell J, Petrey AC. Platelet Dysregulation in the Pathobiology of COVID-19. Hamostaseologie. 2022 Aug;42(4):221-228.

Xu P, Zhou Q, Xu J. Mechanism of thrombocytopenia in COVID-19 patients. Ann Hematol. 2020 Jun;99(6):1205-1208.

Pantic N, Suvajdzic-Vukovic N, Virijevic M, Pravdic Z, Sabljic N, Adzic-Vukicevic T, et al. Coronavirus disease 2019 in patients with chronic immune thrombocytopenia on thrombopoietin receptor agonists: new perspectives and old challenges. Blood Coagul Fibrinolysis. 2022 Jan 1;33(1):51-55.

Ahmed MZ, Khakwani M, Venkatadasari I, Horgan C, Giles H, Jobanputra S, et al. Thrombocytopenia as an initial manifestation of COVID-19; case series and literature review. Br J Haematol. 2020 Jun;189(6):1057-1058.

Bomhof G, Mutsaers PGNJ, Leebeek FWG, Te Boekhorst PAW, Hofland J, Croles FN, et al. COVID-19-associated immune thrombocytopenia. Br J Haematol. 2020 Jul;190(2):e61-e64.

Lévesque V, Millaire É, Corsilli D, Rioux-Massé B, Carrier FM. Severe immune thrombocytopenic purpura in critical COVID-19. Int J Hematol. 2020 Nov;112(5):746-750.

Mahévas M, Moulis G, Andres E, Riviere E, Garzaro M, Crickx E, et al. Clinical characteristics, management and outcome of COVID-19-associated immune thrombocytopenia: a French multicentre series. Br J Haematol. 2020 Aug;190(4):e224-e229.

Zulfiqar AA, Lorenzo-Villalba N, Hassler P, Andrès E. Immune Thrombocytopenic Purpura in a Patient with Covid-19. N Engl J Med. 2020 Apr 30;382(18):e43.

Lee EJ, Liu X, Hou M, Bussel JB. Immune thrombocytopenia during the COVID-19 pandemic. Br J Haematol. 2021 Jun;193(6):1093-1095.

Merli M, Ageno W, Sessa F, Salvini M, Caramazza D, Moraet B, et al. Recurrence of immune thrombocytopenia at the time of SARS-CoV-2 infection. Ann Hematol. 2020 Aug;99(8):1951-1952.

Weiner M, Rodriguez-Vigouroux R, Masouridi-Levrat S, Samii K. Very severe immune thrombocytopenia following SARS-CoV-2 vaccination requiring splenectomy: a case report. Thromb J. 2022 Aug 23;20(1):45.

Boehm BA, Packer CD. Persistent Relapsing Immune Thrombocytopenia Following COVID-19 Infection. Cureus. 2022 Jul 22;14(7):e27133.

Frankel AE, Wylie D, Peters B, Marrama D, Ahn C. Bioinformatic Analysis Underpinning the Frequent Occurrence of Immune Thrombocytopenic Purpura in COVID-19 Patients. Isr Med Assoc J. 2022 May;24(5):320-326.

Chen W, Li Z, Yang B, Wang P, Zhou Q, Zhang Z, et al. Delayed-phase thrombocytopenia in patients with coronavirus disease 2019 (COVID-19). Br J Haematol. 2020 Jul;190(2):179-184.

de la Cruz-Benito B, Rivas-Pollmar MI, Álvarez Román MT, Trelles-Martínez R, Martín-Salces M, Lázaro-Del Campo P, et al. Paradoxical effect of SARS-CoV-2 infection in patients with immune thrombocytopenia. Br J Haematol. 2021 Mar;192(6):973-977.

Beltrami-Moreira M, Bussel JB. A narrative review of anti-SARS-CoV-2 vaccines and immune thrombocytopenia: be aware, but reassured. Clin Adv Hematol Oncol. 2022 Sep;20(9):572-578.

Lee EJ, Cines DB, Gernsheimer T, Kessler C, Michel M, Tarantino MD, et al. Thrombocytopenia following Pfizer and Moderna SARS-CoV-2 vaccination. Am J Hematol. 2021 May 1;96(5):534-537.

Lee EJ, Beltrami-Moreira M, Al-Samkari H, Cuker A, DiRaimo J, Gernsheimer T, et al. SARS-CoV-2 vaccination and ITP in patients with de novo or preexisting ITP. Blood. 2022 Mar 10;139(10):1564-1574.

Kuter DJ. Exacerbation of immune thrombocytopenia following COVID-19 vaccination. Br J Haematol. 2021 Nov;195(3):365-370.

Saluja P, Amisha F, Gautam N, Goraya H. A Systematic Review of Reported Cases of Immune Thrombocytopenia after COVID-19 Vaccination. Vaccines (Basel). 2022 Sep 1;10(9):1444.

Simpson CR, Shi T, Vasileiou E, Katikireddi SV, Kerr S, Moore E, et al. First-dose ChAdOx1 and BNT162b2 COVID-19 vaccines and thrombocytopenic, thromboembolic and hemorrhagic events in Scotland. Nat Med. 2021 Jul;27(7):1290-1297.

Welsh KJ, Baumblatt J, Chege W, Goud R, Nair N. Thrombocytopenia including immune thrombocytopenia after receipt of mRNA COVID-19 vaccines reported to the Vaccine Adverse Event Reporting System (VAERS). Vaccine. 2021 Jun 8;39(25):3329-3332.

Moulis G, Crickx E, Thomas L, Massy N, Mahévas M, Valnet-Rabier MB, et al.; and the French Covigilance COVID-19 Vaccine-ITP Study Group. De novo and relapsed immune thrombocytopenia after COVID-19 vaccines: results of French safety monitoring. Blood. 2022 Apr 21;139(16):2561-2565.

Crickx E, Moulis G, Ebbo M, Terriou L, Briantais A, Languille L, et al. Safety of anti-SARS-CoV-2 vaccination for patients with immune thrombocytopenia. Br J Haematol. 2021 Dec;195(5):703-705.

Visser C, Swinkels M, van Werkhoven ED, Croles FN, Noordzij-Nooteboom HS, Eefting M, et al. COVID-19 vaccination in patients with immune thrombocytopenia. Blood Adv. 2022 Mar 22;6(6):1637-1644.

Hippisley-Cox J, Patone M, Mei XW, Saatci D, Dixon S, Khunti K, et al. Risk of thrombocytopenia and thromboembolism after covid-19 vaccination and SARS-CoV-2 positive testing: self-controlled case series study. BMJ. 2021 Aug 26;374:n1931.

Matzdorff A, Sachs UJ. Immunthrombozytopenie (ITP) und andere Thrombozytopenien in der Schwangerschaft. Transfusionsmedizin. 2020;10(02):97-112.

Habas E Sr, Rayani A, Alfitori G, Eldin Ahmed G, Elzouki AY. Gestational Thrombocytopenia: A Review on Recent Updates. Cureus. 2022 Mar 16;14(3):e23204.

Guillet S, Loustau V, Boutin E, Zarour A, Comont T, Souchaud-Debouverie O, et al. Immune thrombocytopenia and pregnancy: an exposed/non-exposed cohort study. Blood. 2022 Sep 2:blood.2022017277.

Zhu XL, Feng R, Huang QS, Liang MY, Jiang M, Liu H, et al. Prednisone plus IVIg compared with prednisone or IVIg for immune thrombocytopenia in pregnancy: a national retrospective cohort study. Ther Adv Hematol. 2022 Apr 29;13:20406207221095226.

Bussel JB, Cooper N, Lawrence T, Michel M, Vander Haar E, Wang K, et al. Romiplostim use in pregnant women with immune thrombocytopenia. Am J Hematol. 2022 Sep 26. Epub ahead of print.

Michel M, Ruggeri M, Gonzalez-Lopez TJ, Alkindi S, Cheze S, Ghanima W, et al. Use of thrombopoietin receptor agonists for immune thrombocytopenia in pregnancy: results from a multicenter study. Blood. 2020 Dec 24;136(26):3056-3061.

Point F, Terriou L, Rakza T, Drumez E, Alluin G, Garabedian C, et al. Risk factors for severe neonatal thrombocytopenia in cases of maternal immune thrombocytopenia. Acta Paediatr. 2022 May;111(5):985-991.

Lozano ML, Mingot-Castellano ME, Perera MM, Jarque I, Campos-Alvarez RM, González-López TJ, et al. A decade of changes in management of immune thrombocytopenia, with special focus on elderly patients. Blood Cells Mol Dis. 2021 Feb;86:102505.

Swan D, Newland A, Rodeghiero F, Thachil J. Thrombosis in immune thrombocytopenia - current status and future perspectives. Br J Haematol. 2021 Sep;194(5):822-834.

Voigtlaender M, Langer F. Management of Vascular Thrombosis in Patients with Thrombocytopenia. Hamostaseologie. 2022 Feb;42(1):19-28.

Falanga A, Leader A, Ambaglio C, Bagoly Z, Castaman G, Elalamy I, et al. EHA Guidelines on Management of Antithrombotic Treatments in Thrombocytopenic Patients With Cancer. Hemasphere. 2022 Jul 13;6(8):e750.

Scharf RE. Thrombocytopenia and Hemostatic Changes in Acute and Chronic Liver Disease: Pathophysiology, Clinical and Laboratory Features, and Management. J Clin Med. 2021 Apr 6;10(7):1530.

Kruse C, Kruse A, DiRaimo J. Immune thrombocytopenia: the patient's perspective. Ann Blood. 2021 March;6:9.

Cooper N, Kruse A, Kruse C, Watson S, Morgan M, Provan D, et al. Immune thrombocytope-nia (ITP) World Impact Survey (iWISh): Patient and physician perceptions of diagnosis, signs and symptoms, and treatment. Am J Hematol. 2021 Feb 1;96(2):188-198.

Lassandro G, Palmieri VV, Barone A, Farruggia P, Giona F, Licciardello M, et al. Fatigue per-ception in a cohort of children with chronic immune thrombocytopenia and their caregivers u-sing the PedsQL MFS: Real-life multicenter experience of the Italian Association of Pediatric Hematology and Oncology (AIEOP). Pediatr Blood Cancer. 2021 Mar;68(3):e28840.

Grace RF, Klaassen RJ, Shimano KA, Lambert MP, Grimes A, Bussel JB, et al. Fatigue in children and adolescents with immune thrombocytopenia. Br J Haematol. 2020 Oct;191(1):98-106.

Meyer O, Schlag R, Stauch T, Fleischmann B, Reiser M, Kämpfe D, et al. Treatment of immune thrombo-cytopenia (ITP) with eltrombopag - results of the 4th interim analysis of the German non-interventional trial RISA. Focussing on steroid-pretreatment and fatigue. Oncol Res Treat 2021 October;44 (suppl.4):173, DGHO Jahrestagung 2021, Abstr. Ep48

Cuker A, Liebman HA. Corticosteroid overuse in adults with immune thrombocytopenia: Cause for concern. Res Pract Thromb Haemost. 2021 Aug 25;5(6):e12592.

Neunert C. Looking long-term: an unmet need in immune thrombocytopenia. Lancet Haematol. 2021 Apr;8(4):e245-e246.

Figures

Figure 1: Pathomechanisms of ITP and corresponding treatments (* off-label, see also **chapter 18**; ** T-Reg = Regulatory T-lymphocytes)

Figure 2. Phases of ITP

Figure 3: ITP treatment algorithm.

Figure 4: 2nd line treatment algorithm for thrombocytopenia recurrence

*In Switzerland, eltrombopag can only be prescribed after a disease duration of at least 6 months.

**Avatrombopag and fostamatinib are usually given 3rd 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 2nd line.

Figure 5: disease phases of ITP and approval status of various treatments (IVIG = intravenous immunoglobulin).

*There is no consensus on how long the platelet count should be stable and above 50 x10^9/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 [56].

** 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).

Figure 6: proposed scheme for eltrombopag and romiplostim taper and discontinuation

Figure 7: Clinical signs and recommended tests for secondary ITP.

[1] EDTA - Ethylenediaminetetra-acetic acid

[2] GT - Gestational thrombocytopenia

[3] ITP – Immune thrombocytopenia

[4] HIV - Human Immunodeficiency Virus

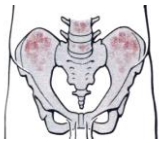
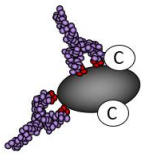
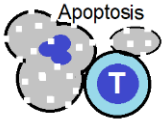
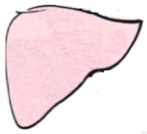
[5] HELLP - syndrome (hemolytic anemia, elevated liver enzymes, low platelets)

[6] TTP - Thrombotic thrombocytopenic purpura

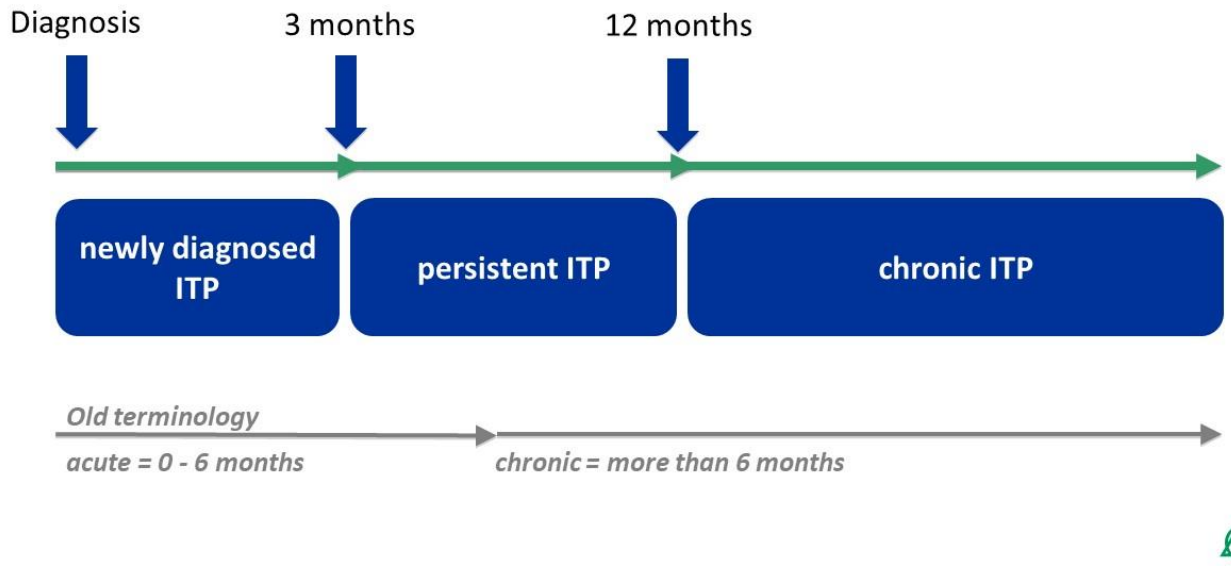
[7] HIT - Heparin-induced thrombocytopenia

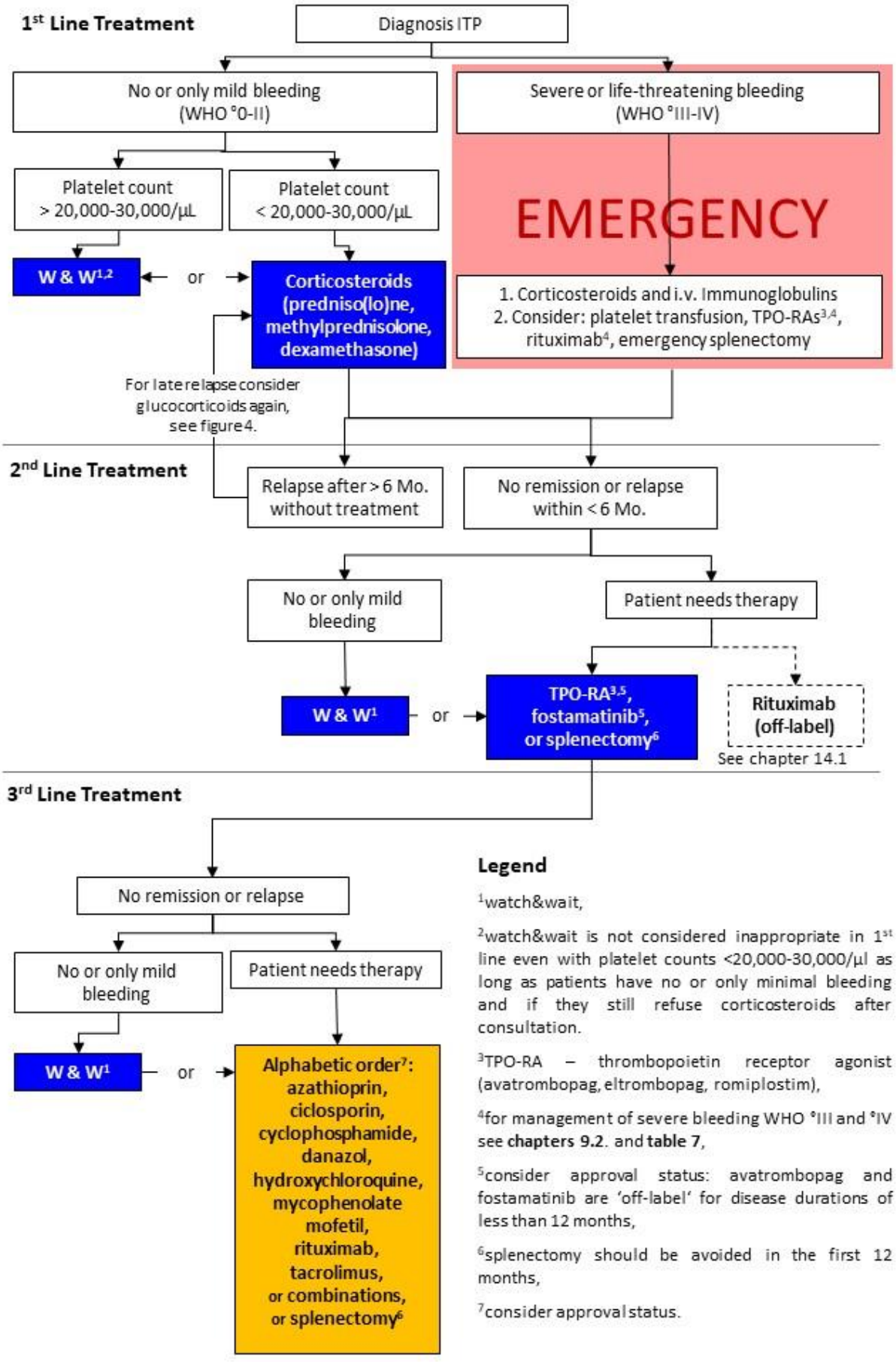
[8] e.g. Myelodysplastic syndrome, myeloproliferative neoplasms

Figure 8: Differential diagnosis of thrombocytopenia in pregnancy.

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 ↓			

Neuraminida-se- Inhibitors*					Reduced desialylation and phagocytosis ↓
Daratmumab*		Platelet autoantibodies ↓			
Bortezomib*		Platelet autoantibodies ↓			
Complement-Inhibitors*		Complement activity ↓			
All-Trans-Retinoic Acid*		Immundysregulation ↓ T-Regs**-↑		Immunedysregulation ↓ T-Regs** ↑	
Decitabine*		Immundysregulation ↓, autoreactive T-lymphocytes ↓, T-Regs** ↑			





Legend

[1]watch&wait,

[2]watch&wait is not considered inappropriate in 1st line even with platelet counts <20,000-30,000/µl as long as patients have no or only minimal bleeding and if they still refuse corticosteroids after consultation.

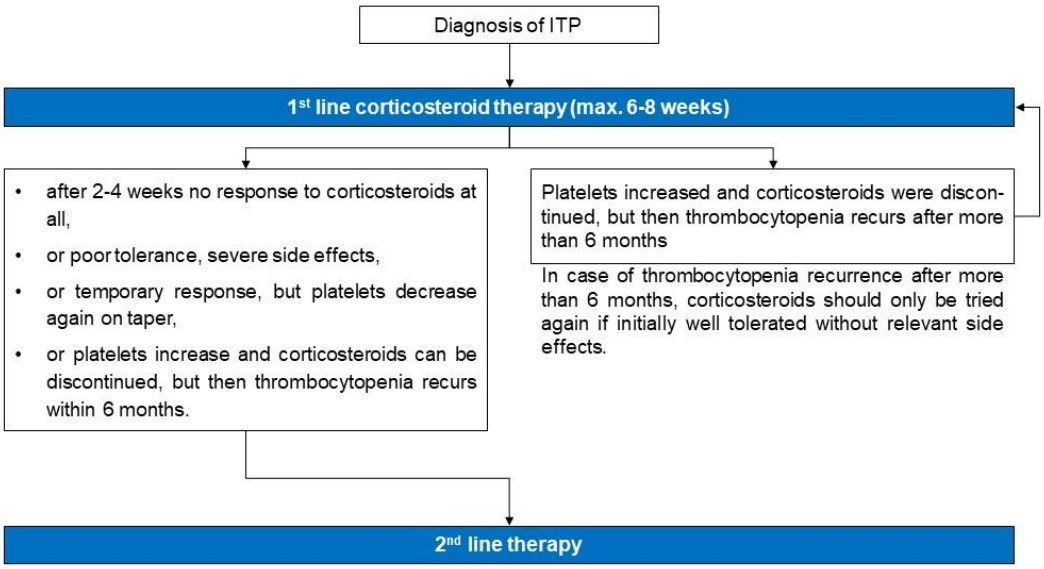
[3]TPO-RA – thrombopoietin receptor agonist (avatrombopag, eltrombopag, romiplostim),

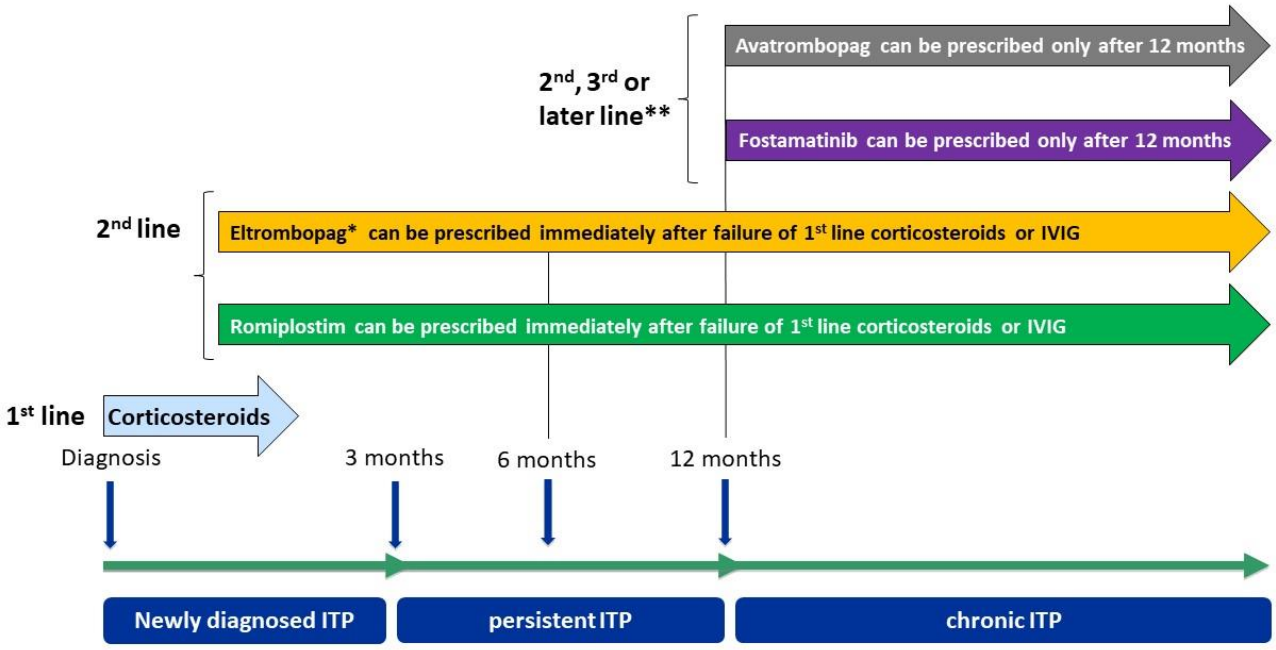
[4]for management of severe bleeding WHO °III and °IV see **chapters 9.2**. and **table 7**,

[5]consider approval status: avatrombopag and fostamatinib are 'off-label' for disease durations of less than 12 months,

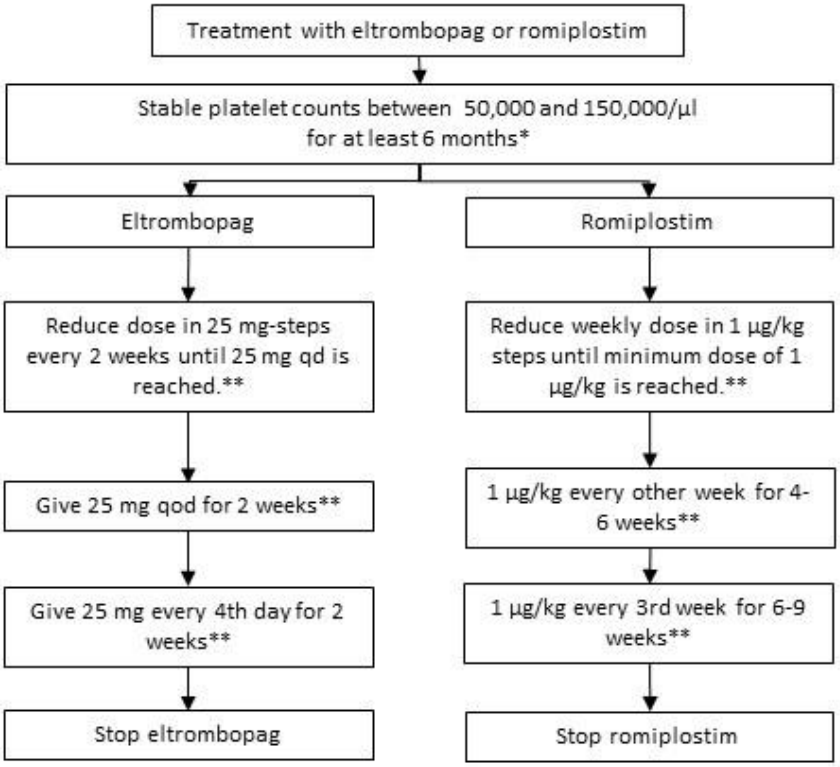
[6]splenectomy should be avoided in the first 12 months,

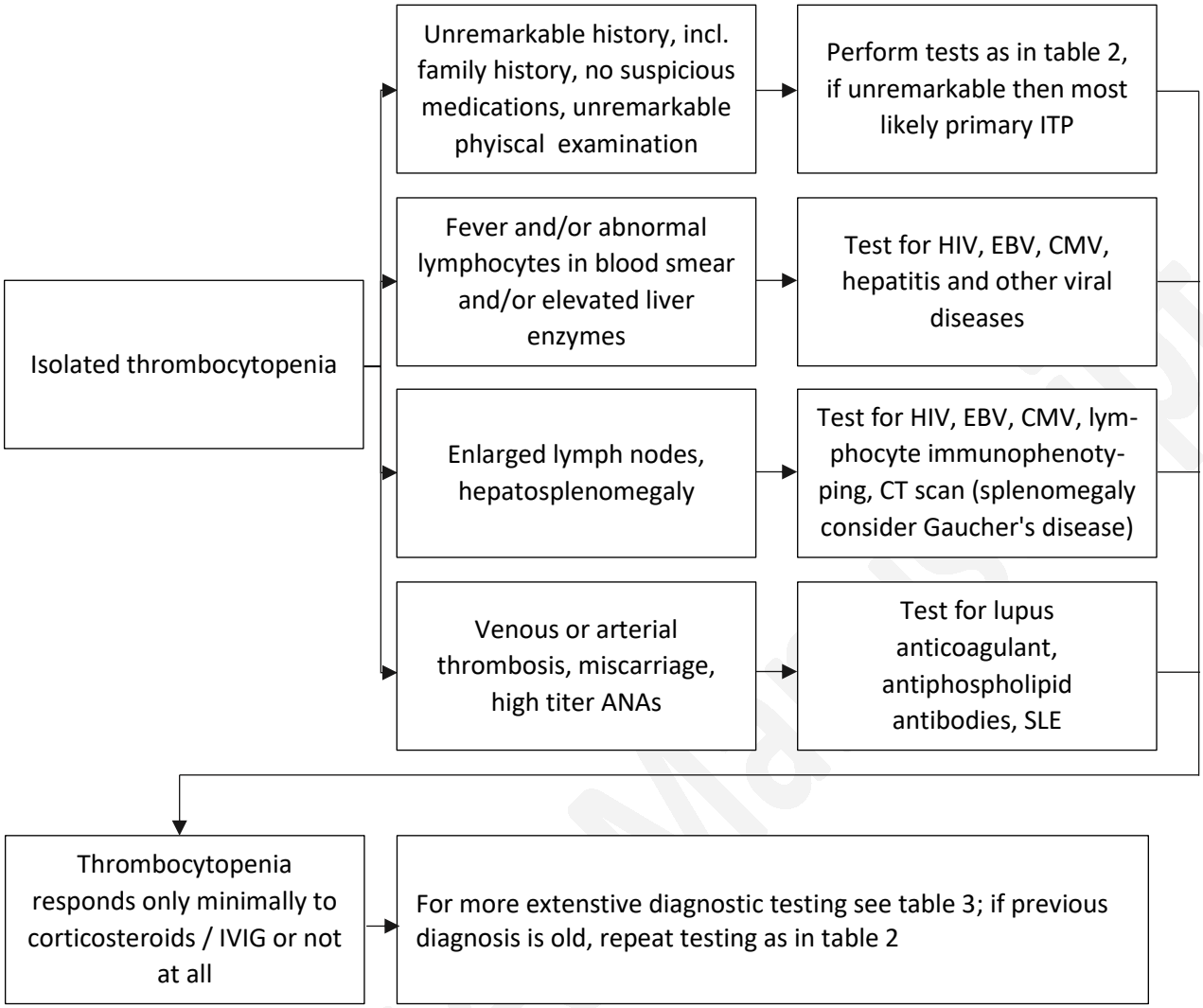
[7]consider approval status.

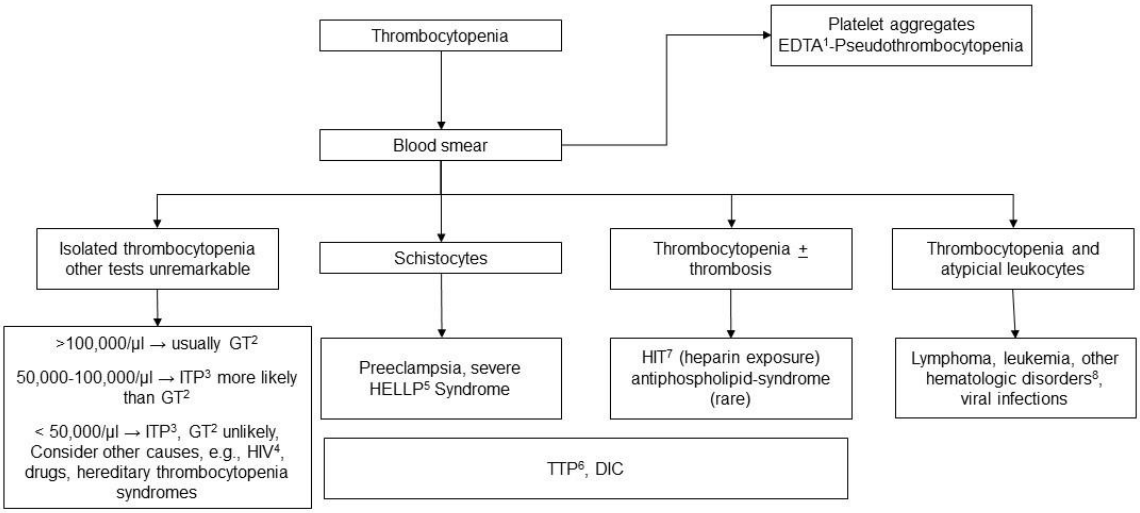




Taper scheme







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 Post-transfusion 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)	

Table 1: classification of thrombocytopenias

et 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).

Table 2: pathomechanisms of ITP (see also **figure 1**)

Diagnostic test	
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.

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

Diagnostic test	
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.

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

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 to 100,000/µl (see **chapter 19.5**).

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

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.

Table 6: indications for bone marrow biopsy.

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)

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

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

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 & wait strategy is acceptable for patients with no or few symptoms, and only severe bleeding will require therapy.

Table 9: Disease phases and treatment goals.

Potential self-limited disease course	Potential for a chronic disease course	Risk of severe hemorrhage
Children, young adults Abrupt onset Preceding infection Preceding vaccination Acute bleeding symptoms Rapid response to treatment	Adults, especially if >60 years old No preceding infection or other disorder Insidious onset Platelet count > 20,000-30,000/µl Onset with only minor bleeding symptoms or incidental thrombocytopenia without bleeding No or only minor response to 1st line therapy Presence of ANA, rheumatoid factor or anti-CCP, and/or antiphospholipid antibodies	Age > 60 years Platelet count < 20,000-30,000/µl Infection, fever Hematuria Multiple hematomas Infection, Fever, Mucosal hemorrhage ('wet purpura') History of prior severe bleeding No response to steroids Autoantibodies to more than one platelet antigen Children: modified Buchanan Score ≥3

Table 10: Prognosis and risk indicators

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.

Differential diagnosis	History and laboratory evaluations
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

Table 11: Differential diagnosis of ITP.

alphabetic order)	Predniso(lo)ne dose
American Society of Hematology 2019 [32]	Prednisone 0,5-2 mg/kg/d, then dose reduction and discontinuation over 6 weeks.
Australia and New Zealand 2022 [33]	Prednisone 1 mg/kg/d for 2 weeks (max. 75-80 mg), then dose reduction and discontinuation over 6 weeks.
Chinese Guideline [34]	Prednisone 1 mg/kg/d (max. 80 mg/d), if response then dose reduction and discontinuation within 6, max. 8 weeks.
French Guideline [35]	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 [36]	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 [37]	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 [38]	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 [39]	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. 12: Predniso(lo)ne dosing recommendations in different guidelines

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 1960 mg □ Dexamethasone: 40 mg/d for 4 days, 2 cycles → equals prednisolone 2133 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 (700–1200 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.

Table 13: Recommendations for osteoporosis prophylaxis (adapted from British Society of Haematology Good Practice Paper) [40].

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 & wait
3a* - Low risk moderate	Blood crusting in nares, painless oral purpura, oral/palatal petechiae, buccal purpura only along molars, mild epistaxis ≤ 5min	No standardized recommendations available. Individualized treatment decision based on (i) platelet count, (ii) risk of injury, (iii) infection, fever, (iv) health literacy, psychosocial situation.
3b* - High risk moderate	Epistaxis > 5min, hematuria, hematochezia, painful oral purpura, menorrhagia	Prednisone 4 mg/kg/d for 4 days or/ and IVIG 0.8-1g/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 0.8-1g/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 - 1g/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. (6) Consider emergency splenectomy for refractory thrombocytopenia, and craniotomy to relieve increased intracranial pressure in patients with cerebral hemorrhage.
* 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].		

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

	Romi-plostim	Eltrombo-pag	Avatrombo-pag	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 15: Routes of administration and adverse effects of TPO-RAs and the SYK inhibitor fostamatinib.

	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 one 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.

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

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 1st 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 2nd 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.

Table 17: Drugs for 3rd line therapy in ITP.

Risk	Comment
Operative morbidity	Complication rate 10%, mainly wound infections and pneumonia
Operative mortality	<1%, may be higher in elderly patients
Overwhelming post-splenectomy 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

Table 18: risks and contraindications of splenectomy

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[1]	≥ 50,000/µl
Minor surgery where hemostasis can be achieved by compression	≥ 20,000/µl
Major surgery[2]	≥ 80,000/µl
Neurosurgery	≥70-100,000/µl
Surgery to the posterior segment of the eye	≥70-100,000/µl

[1]minor surgeries are surgical procedures with a low risk of bleeding, which includes most peripheral limb surgeries.

[2]major surgeries include abdominal or thoracic surgery and surgeries in regions that cannot be compressed in the event of postoperative bleeding.

	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 one 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.

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. Note approval status: if the patient has never had any ITP therapy before, then TPO-RAs would be considered as 1st line treatment and be off-label; IVIG is an alternative).

ITP	Bleeding and thrombocytopenia < 100,000/µl in any trimester are more indicative of ITP than gestational thrombocytopenia
Gestational thrombocytopenia	Usually observed in 2nd and 3rd trimesters, platelet counts < 100,000/µl unusual
Preeclampsia/HELLP syndrome	Usually 3rd trimester, sudden weight gain, hypertension with/without organ dysfunction with/without proteinuria.
Acute fatty liver of pregnancy	Mainly in 3rd trimester; usually weight loss, jaundice, massive elevation of liver enzymes, prolonged prothrombin time (Quick).
TTP	In 2nd or 3rd trimester; severe thrombocytopenia and hemolysis, very high LDH, LDH/AST ratio > 22, neurologic symptoms, absence of coagulopathy.

Table 21: clinical indicators for differential diagnosis of thrombocytopenia in pregnancy.

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	

Table 22: Anticoagulation with thrombocytopenia (INR = international normalized ratio; IVC = inferior vena cava; LMWH = low-molecular weight heparin; VTE = venous thromboembolism).

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**

Table 23: Antiplatelet therapy in patients with thrombocytopenia. For further information on thrombosis and bleeding risk factors, please refer to the original publications [138, 139].

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*	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 to 13 days prior to the planned procedure.
Lusutrombopag*,**	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.
* With avatrombopag and lusutrombopag platelet count should be measured prior to the procedure. . ** Lusutrombopag is licensed for chronic liver disease only, not for ITP. Lusutrombopag is not currently available in Germany.		

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

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

Table 25. Degrees of disability

Study identifier	Titel	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

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