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Immune Thrombocytopenia – Current Diagnostics and Therapy: Recommendations of a Joint Working Group of DGHO, ÖGHO, SGH, GPOH, and DGTI

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Introduction

Immune thrombocytopenia (ITP) is a rare disorder and meets the criteria for an orphan disease. Expertise in the management of these patients is not widely spread. The following recommendations are intended to provide guidance and support to physicians, dentists and other health professionals who do not regularly see ITP patients.

In 1996, the American Society of Hematology (ASH) published its first ITP guideline [1]. This so-called 'ASH guideline' set the standards of ITP treatment for many years. It is often cited as the first guideline on ITP. However, the first ITP guideline was published 4 years earlier in 1992 [2], but this was on pediatric ITP and, therefore, did not reach a comparable level of awareness. The last German-language ITP guideline was published in 2014 [3]. Because of numerous new findings, an update was necessary. The following recommendations were developed by an interdisciplinary working group of experts from the German Society for Hematology and Medical Oncology (DGHO), the Austrian Society for Hematology and Medical Oncology (ÖGHO), the Swiss Society for Hematology (SGH), the Society for Pediatric Oncology and Hematology (GPOH), and the German Society for Transfusion Medicine and Immunohematology (DGTI). They are based on all relevant publications until November 2017. Abstracts were considered only if they had been presented at meetings in 2015 and thereafter.

Terminology and Definition

Degree of recommendation: Expert consensus (EC)

ITP is an acronym for 'immune thrombocytopenia'. The term 'idiopathic thrombocytopenic purpura' should no longer be used.

ITP should only be diagnosed if the platelet count is repeatedly below 100×10^9/l.

The acronym ITP stands for 'immune thrombocytopenia' and has, by international agreement, replaced the term 'idiopathic thrombocytopenic purpura'. This is because ITP is no longer idiopathic. The Greek term 'ídios pathos' designates a disease without a tangible cause, but today we know that ITP is caused by a dysregulation of the immune system [4]. The term 'purpura' is also misleading since almost one-third of the newly diagnosed ITP patients have no bleeding but only low platelet counts [5, 6].

Based on international consensus again, ITP should only be diagnosed if the platelet counts are repeatedly below 100×10^9/l [4]. This value is different from the usual lower threshold for normal platelet counts (~150×10^9/l) but the risk of developing clinically relevant ITP in individuals with counts between 100×10^9/l and 150×10^9/l is negligible (<1%/year).

Table 1 lists the causes of thrombocytopenia. One distinguishes primary ITP, in which no causative agent or event can be identi-

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Table 1. Classification of thrombocytopenias

Decreased platelet production	Increased platelet consumption
Bone marrow damage (drugs, alcohol, cytostatic agents, etc.)	*Primary immune thrombocytopenia*
Infiltration and replacement of the bone marrow (hematologic malignancies, rarely solid tumors)	No trigger identifiable
Myelofibrosis	*Secondary immune thrombocytopenia*
Myelodysplastic syndromes	Drug-induced immune thrombocytopenia
Bone marrow hypo-/aplasia, paroxysmal nocturnal hemoglobinuria	Autoimmune diseases
Severe vitamin, iron deficiency	Antiphospholipid syndrome
Rare genetic defects: Bernard-Soulier syndrome, MYH9-associated syndromes and other hereditary thrombocytopenias	Immunodeficiency syndromes (common variable immunodeficiency syndrome, autoimmune lymphoproliferative syndrome (Canale-Smith syndrome), Wiskott-Aldrich syndrome)
In ITP thrombocytopoiesis in the bone marrow may also be impaired	Evans syndrome (e.g. with lymphomas, CLL)
	Hepatitis, HIV and other viral infections
	Vaccination-associated
	Other immune-mediated thrombocytopenias (not ITP)
	Heparin-induced thrombocytopenia
	Thrombocytopenia after GPIIb/IIIa inhibitor administration
	Post-transfusional purpura
	Pregnancy-associated thrombocytopenia
	Neonatal and fetal alloimmune thrombocytopenia
	Other consumption thrombocytopenias (not immune-mediated)
	Microangiopathic hemolytic anemia (TTP, HUS, aHUS, etc.)
	Disseminated intravascular coagulation
	von Willebrand disease type 2b
	Massive pulmonary embolism
	Large hemangiomas
	Large aneurysms
Other Thrombocytopenias	
Thrombocytopenia with splenomegaly	
Thrombocytopenia after massive bleedings	
Thrombocytopenia during severe infections (e.g. sepsis)	
Problems of laboratory analysis	
EDTA-induced pseudothrombocytopenia	

fied, from secondary types, where ITP is triggered by drugs or other diseases (~80% primary, 20% secondary) [7, 8].

History

A commonly used eponym for ITP is the term 'Werlhof's disease'. This refers to Paul Gottlieb Werlhof (1699–1767), personal physician to the king of Hanover. In 1735, he described the case of a 16-year-old girl who developed bleeding of the skin and mucous membranes after an infection (Morbus maculosus hemorrhagicus) [9]. In English-speaking countries one also refers to Robert Willan (1757–1812), an English physician and the founder of dermatology. In 1802, he described the simultaneous occurrence of cutaneous purpura with mucosal hemorrhages which are typical of ITP. It was not before 1883 that Eduard Krauss realized that the hemorrhagic symptoms were caused by thrombocytopenia (review in [10]).

Epidemiology

The incidence of ITP is 0.2–0.4 new cases per 10,000/year in adults and 0.2–0.7 per 10,000/year in children.

In adults, the ITP incidence is between 0.2 and 0.4 new cases per 10,000 per year [11, 12] and the prevalence is 0.9–2.6 per 10,000 [11, 13, 14].

In children and adolescents, the ITP incidence is 0.2–0.7 new cases per 10,000 per year [12, 15, 16] and the prevalence is 0.4–0.5 per 10,000 [17]. The prevalence is significantly lower in children than in adults because pediatric ITP rarely becomes chronic (see the section 'Prognosis and Risk').

Age: The median age of adult ITP patients is 50–55 years [14, 18].

Gender: In pediatric ITP, boys are more often affected than girls [19, 20]. In middle age, women are more likely to develop ITP than men. After age 60 years, men predominate again [8, 14, 21].

Seasonal variability: The ITP incidence in children is twice as high in spring as in summer. It is assumed that infections that can trigger ITP are more frequent in winter [16, 19].

Ethnic variability: Older studies find a lower incidence in African Americans while in the Asia-Pacific region ITP seems to be as frequent as in Europe.

Estimates for the German Federal Republic: Approximately 60% of adult and 20–30% of pediatric ITP patients develop a chronic course (see 'Prognosis and Risk'). Based on these numbers, an annual incidence of ~2,400 new cases and a prevalence of ~16,000 patients with chronic ITP can be expected in Germany. The proportion of ITP patients with low platelet counts ($<30 \times 10^9$/l) varies between 30 and 70% [5, 21]. For Germany, this translates into 5,000–13,000 patients potentially requiring treatment.

Since ITP patients are rare ('orphan disease') and because diagnostics and therapy become more and more expensive, the authors suggest the foundation of a competence network for ITP patients, comparable to hemophilia centers for hemophiliacs. See table 2 for ITP centers.

Table 2. Purpose of ITP centers

Purpose of ITP centers
ITP patient care in close cooperation with family physician, referring specialist or referring hospital
Initial examination, if necessary involving other medical specialties
Designing an individual treatment plan
Initiation of treatment incl. training in self-therapy
At least 6-month controls and check-ups
One ITP specialist is assigned to each patient with the option for regular telephone or web-based consultations on questions regarding further diagnostics and therapy
Telephone or web-based consultation service for other physicians and hospitals also outside normal working hours
Second opinion consultation for patients
Consultation on bleeding prophylaxis before surgery
Consultation on anticoagulation if required for concomitant disorders (coronary heart disease, stroke, thrombosis, etc.)
Consultation on the treatment of infections
Consultation on vaccinations
Consultation on international travel
Consultation on individual problems with work, social life, insurances, other family and psychological issues

Pathophysiology

The following pathomechanisms play a role in ITP:

1. Platelet autoantibodies
   - 1.1. Antibody-coated platelets bind to Fc receptors on macrophages in liver and spleen and are subsequently degraded.
   - 1.2. Damaged platelets bind to Ashwell-Morell receptors in the liver and are subsequently degraded.
   - 1.3. Autoantibodies damage platelets directly
   - 1.4. Autoantibodies interfere with platelet function
2. T lymphocytes
   - 2.1. Reduced numbers of regulatory T lymphocytes (Tregs) lead to immunodysregulation
   - 2.2. T lymphocytes directly damage platelets.
3. Impaired thrombopoiesis
   - 3.1. Autoantibodies damage megakaryocytes
   - 3.2. Relative deficiency of thrombopoietin
   - 3.3. Impaired thrombopoietin production.

ITP is not hereditary but an acquired form of thrombocytopenia and needs to be distinguished from congenital thrombocytopenias, which are much rarer (e.g., Bernard-Soulier syndrome, MYH9-associated syndromes (MYH9 = myosin, heavy chain 9), and others). However, there are also hereditary immunothrombocytopenia syndromes (Wiskott-Aldrich syndrome, autoimmune lymphoproliferative syndrome = Canale-Smith syndrome). For details of these rare conditions see textbooks of pediatric hematology. The cause of ITP is an autoimmune reaction against platelets and megakaryocytes [7, 22]. The immune response involves different pathogenetic mechanisms (for reviews, see [23–25]).

Platelet Autoantibodies

Degradation of antibody-coated platelets after binding to Fc receptors in spleen and liver: In the 1950s, it was shown that the transfusion of plasma from a patient with ITP into healthy subjects can trigger reversible thrombocytopenia [26]. The publication of Harrington et al. [26] was, however, not the first to show a pathogenic factor against platelets in the blood of ITP patients. In 1938, animal experiments already suggested that the spleen of ITP patients contains thrombocytopenia-inducing factors. Today, we know that these factors are autoantibodies against platelets. With modern laboratory methods one can detect such autoantibodies against platelet membrane proteins in ~60% of all ITP patients (e.g., against membrane glycoprotein (GP) Ib/IX, GP IIb/IIIa). The antibody-coated platelets bind to Fc receptors of macrophages and dendritic cells in the spleen and liver and are subsequently phagocytized and degraded.

Degradation of damaged platelets after binding to Ashwell-Morell receptors in the liver: Recently, a new degradation pathway has been described. Sialic acid residues on the platelet membrane are hydrolyzed when platelets age or when they are damaged by autoantibodies (desialylation). Desialylated platelets bind to the Ashwell-Morell receptor on hepatocytes and are filtered out of the blood stream, which then stimulates the formation of new thrombopoietin in the liver [27, 28].

Direct damage of platelets by autoantibodies and subsequent apoptosis: Antibodies can directly damage platelets and trigger complement lysis, independent of phagocytosis in the spleen.

Platelet function defect due to platelet autoantibodies: Platelet autoantibodies bind to receptors on the platelet membrane and interfere with adhesion or aggregation. This – in addition to thrombocytopenia – increases the bleeding tendency (e.g., some antibod-

ies bind to the GP IIb/IIIa receptor and cause acquired Glanzmann's thrombasthenia).

T Lymphocytes and Immune Dysregulation

Immune dysregulation: Treatment against B lymphocytes and their antibody production (e.g., steroids and rituximab) does not achieve a platelet response in all ITP patients. This indicates that there must be B lymphocyte-independent mechanisms. Abnormalities of T lymphocytes and particularly an imbalance between activating and regulatory T lymphocytes (Tregs) have been found in ITP.

Direct toxicity of T lymphocytes towards platelets: T lymphocytes are not only involved in immune dysregulation. A direct toxic effect of T lymphocytes on platelets and megakaryocytes has been described [29].

Insufficient Thrombopoiesis

Megakaryocyte damage from autoantibodies against membrane GPs: Autoantibodies against platelet membrane proteins also attack megakaryocytes in the bone marrow and disturb platelet production.

Relative thrombopoietin deficiency: ITP patients often show an insufficient thrombopoietin response to thrombocytopenia. Thrombopoietin levels are higher than in healthy people, but not as high as in other diseases with a comparable degree of thrombocytopenia (e.g., as in aplastic anemia or after chemotherapy) [30]. One reason could be that thrombopoietin binds to platelets and is then degraded in the liver and the spleen together with the platelet [31]. In addition, the increased numbers of megakaryocytes in the bone marrow of ITP patients also bind thrombopoietin. Altogether, this leads to a relative deficiency of thrombopoietin.

Reduced thrombopoietin synthesis: Another mechanism that keeps thrombopoietin levels relatively low is the platelet antibodies themselves. In animal experiments, it could be shown that the binding of antibody-coated platelets to Fc receptors of macrophages and dendritic cells in liver and spleen does not stimulate the Ashwell-Morell receptor and thrombopoietin synthesis [27].

Clinical Presentation

The central clinical symptom of ITP is the increased bleeding tendency. Petechiae and mucosal hemorrhages are typical. Many ITP patients also complain of exhaustion and fatigue, including depressive disorders.

Bleeding Symptoms

Typical bleeding symptoms are:
- Petechiae on the legs, less frequently on the trunk and arms
- Bleeding of mucous membranes from mouth and nose
- Urogenital bleeding and increased menstrual bleeding
- Increased bleeding and hematomas even with small traumas
- Bleeding into internal organs is rare (e.g., intracerebral bleeding)

Typical petechiae are flat and not palpable. Any palpable purpura would be more suggestive of a vasculitic purpura. Also atypical of ITP are extensive hematomas (small area: ecchymosis, large area: sugillations) and joint hemorrhages; those are more common in plasmatic coagulation disorders (e.g., hemophilia A and B).

Of all pediatric patients, 10% and 20–30% of all adult patients with newly diagnosed ITP have no bleeding symptoms at all [5, 32, 33]. In chronic ITP, the proportion of patients without any bleeding symptoms is 30–40% [32, 34, 35].

The bleeding tendency in ITP patients is lower than in patients with a comparable thrombocytopenia from other causes (e.g., after chemotherapy or with myelodysplasia, leukemia). Some authors suggest that ITP platelets are 'younger' and more reactive than platelets in other diseases. The increased reactivity of ITP platelets not only explains the relatively low bleeding tendency, but also the increased risk of thrombosis (see section 'ITP as a Risk Factor for Venous and Arterial Thromboembolic Events').

Additional Symptoms
- ITP patients have an increased risk of infection from immunosuppressive therapies or splenectomy. It has recently been described that ITP per se also increases the risk of infection [36]. Platelets not only play a role in coagulation but also in the host defense against infections [37].
- Iron deficiency anemia may develop from increased blood loss. Microcytic iron deficiency anemia is therefore compatible with ITP, but macrocytic anemia is not.
- Many ITP patients complain of exhaustion and fatigue, including depressive disorders. A relationship between ITP and cognitive impairment has also been described [38, 39] (see section 'Quality of Life').

Grading the Severity of Bleeding

Degree of recommendation: EC

The severity of bleeding in adults should be graded according to the World Health Organization (WHO) bleeding scale or the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE).

ITP treatment depends on the bleeding severity. Numerous bleeding scores have been developed to assess the bleeding severity (for a review, see [40]). The disadvantage of all these scores is that they are usually time consuming, which limits their application in the busy daily routine. Therefore, the authors recommend using the World Health Organization (WHO) bleeding scale or the National Cancer Institute Common Terminology Criteria for Adverse

Table 3. Bleeding grades according to the WHO and the NCI Common Terminology Criteria for Adverse Events (CTCAE v4.0) [41–43]

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 bandages/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 bandages/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)	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)

Events (NCI-CTCAE) [41–43] (table 3). They are well established in clinical practice and familiar to most physicians including non-hematological specialists.

Phases of the Disease

Degree of recommendation: EC

In ITP, one distinguishes 3 phases: newly diagnosed versus persistent versus chronic ITP.

With longer duration of the ITP, the normalization of the platelet count becomes less important as the primary therapeutic goal while quality of life and the avoidance of side effects from treatment gain more relevance.

The therapy and therapeutic goals change with the duration and severity of the disease. Therefore, the traditional distinction of 'acute' and 'chronic' ITP was abandoned and a new division into 3 disease and treatment phases was developed and adopted from the guidelines (table 4) [4].

Older blood counts often show that adult ITP patients have slightly decreased platelet levels already months or years before ITP is eventually diagnosed, or the patients observed an increased bleeding tendency for quite some time but did not attach any importance to it. Despite all this, the definition 'newly diagnosed', 'persistent', or 'chronic' should be determined not by the prior duration of symptoms but by the time point of diagnosis.

Prognosis and Risk Factors

The risk of fatal bleeding is almost 0% in children and 0–7% in adults (especially older patients). One- to two-thirds of chronic ITP patients still achieve partial or complete remission after several years.

In adult ITP, a long-term, chronic course over several years or even a lifetime has been postulated. The ASH guideline of 1996 states that only ~5% of all chronic patients achieve remission [1]. Today it is known that one- to two-thirds of chronic ITP patients achieve partial or complete remission after several years [32, 44]. This affects the choice of therapy, such as the decision to recommend or wait for a splenectomy (see the section 'Splenectomy'). There is no marker that can reliably predict a chronic course.

Just over 10 years ago, the risk of severe bleeding was reported at 3% in children and over 70% in older adults (> 60 years), the risk of fatal bleeding, at 0% and 13%, respectively [45–47]. Due to reduced steroid prescriptions and the new thrombopoietin receptor agonists (TRAs), the prognosis has improved significantly in recent years. Mortality in current pediatric studies is unchanged at 0%; in adults it has halved to 0–7% [34, 48–52] (table 5).

Table 4. Disease phases and treatment goals [4]

Phase	Definition	Treatment goal
Newly diagnosed	Up to 3 months after diagnosis Spontaneous remissions common	Prevention or termination of bleeding, cure. Because treatment might only take a short time period 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 time period, the benefits and side effects must be weighed more strongly against each other.
Chronic	More than 12 months after diagnosis Spontaneous remissions uncommon.	Prevention or termination of bleeding, cure. Patient should accept that thrombocytopenia will most likely be chronic. Quality of life and avoidance of side effects become more important than platelet count. Therapy only mandatory for severe bleeding, in oligo- or asymptomatic patients also 'watch & wait' possible

Before 2009, there was only the distinction between 'acute' and 'chronic' ITP depending on whether the disease lasted less or more than 6–12 months.

Table 5. Prognosis and risk indicators [53–58]

Indicators for chance of self-limited disease course	Indicators for risk of chronic disease course	Indictors for risk of severe hemorrhage
Child, young adult	Adult, especially if >60 years old	Platelet count <20–30 × 10^9/l Multiple hematomas
Preceding infection	No preceding infection or other disorder	Mucosal hemorrhage ('wet purpura')
Abrupt onset	Insidious onset	History of prior severe bleedings, Hematuria
Initial presentation with acute bleeding symptoms	Onset with only minor bleeding symptoms or incidental thrombocytopenia without bleeding at all	No response to steroids, Infection, fever, Age > 60 years

Diagnosis

Degree of recommendation: EC

The detection of isolated thrombocytopenia in the presence of otherwise normal leukocyte and erythrocyte parameters is usually sufficient for an initial diagnosis. The extent of any further diagnostic workup depends on the severity and course of the disease.

A blood smear must always be examined.

The diagnosis of ITP should only be made by a physician experienced in thrombocytopenias.

ITP is a diagnosis by exclusion. There is no laboratory test or any other method that 'proves' ITP. Diagnosis and differential diagnosis usually occur in several steps.

Step 1: Detection of a Low Platelet Count by the General Practitioner or Any Other Doctor Not Specialized in the Diagnosis of Thrombocytopenias

ITP patients with bleeding usually present to their family doctor first or go to the emergency department of a hospital. ITP patients without bleeding are often detected by routine examinations (e.g., health checks) or in the context of preoperative clarifications. A doctor with limited experience in the diagnosis and therapy of thrombocytopenias should refer the patient to a specialist in hematology or to a hospital for further workup. Also, the diagnosis of ethylenediaminetetraacetate(EDTA)-induced pseudothrombocytopenia should not be made by the family doctor or general practitioner alone.

Step 2: Initial Testing for Suspected ITP

After referral to a hematology specialist or clinic, a basic diagnostic program as given in table 6 is recommended.

The diagnosis of ITP can be made if this basic program reveals no other differential diagnosis and if the platelet count is <100 × 10^9/l [4]. This threshold is lower than the usual lower limit of platelet counts (usually 150 × 10^9/l), because any thrombocytopenia above 100 × 10^9/l does not require treatment.

Examination of a Blood Smear

The initial diagnostic workup not only for ITP but for any thrombocytopenia in adults, children, and adolescents must include an examination of a blood smear by a physician expe-

Table 6. Basic diagnostic workup during initial presentation for clinically suspected ITP

	Diagnostic workup at initial presentation
History	Current and previous bleeding, infections, medication (anticoagulants!), alcohol, pregnancy, previous thrombosis, amily history, professional history
Physical examination	Bleeding symptoms, mucous membranes, lymph nodes, liver, spleen size, exanthemas etc.
Blood count	EDTA, citrate, if available use ThromboExact™ blood collection tubes to exclude pseudothrombocytopenia
Blood smear (always!)	Must be examined by a physician experienced in the diagnosis of hematological diseases
Coagulation profile	Prothrombin time (Quick, INR), aPTT, fibrinogen
Other	Blood group incl. testing for erythrocyte autoantibodies, especially in bleeding patients with concurrent anemia, stool and urine test for blood
Bone marrow examination	Always when there are atypical findings (see table 9) Consider in older patients (>60 years) also without atypical findings Include bone marrow testing for molecular and cytogenetic defects to spare the patient a second puncture (differential diagnosis: myelodysplastic syndrome or idiopathic cytopenia of indeterminate significance).

rienced in the diagnosis of hematological diseases. Thrombotic thrombocytopenic purpura is an important differential diagnosis and a hematological emergency that must not be overlooked!

Step 3: Specialized Further Testing for Persistent or Chronic ITP

For persistent or chronic ITP, further differential diagnoses must be considered (table 7). These additional diagnostic tests and their interpretations are listed in table 8.

The detection of antinuclear antibodies (ANA), antiphospholipid antibodies, and lupus anticoagulant is of prognostic relevance because thrombosis is more common in these patients (see the section 'ITP as a Risk Factor for Venous and Arterial Thromboembolism'). The detection of thyroid antibodies has no effect on the treatment of the ITP, but autoimmune thyroiditis should not be overlooked and thus left untreated.

In some patients, ultrasound shows an enlarged spleen, which is not typical of ITP. In addition to diseases of the liver and lymphomas (hairy cell leukemia, marginal zone lymphoma, and others), one must consider Gaucher's disease (ferritin ↑, angiotensin-converting enzymes (ACE) ↑; β-glucocerebrosidase activity ↓ with dry blood test).

Drug-Induced Thrombocytopenia

This is the most important differential diagnosis of ITP and can sometimes only be excluded by repeated (!) history taking. One should also ask for naturopathic and non-prescription medications, which are often not considered as medications by laymen and therefore not mentioned during history taking. The incidence of drug-induced thrombocytopenia is ~0.1 per 10,000 per year (ITP 0.2–0.4 per 10,000 per year) [59]. Drug-induced ITP usually has an acute course. After discontinuation of the drug, the platelet count recovers rapidly. A current list of drugs for which drug-induced thrombocytopenia has been described can be found at *www.ouhsc.edu/platelets/ditp.html*.

Testing for Platelet Autoantibodies

Testing for platelet autoantibodies is not part of the standard diagnostic program for newly diagnosed ITP but should be reserved for patients with persistent or chronic ITP and an atypical disease course.

Only bound antibodies against platelet GPs are relevant, HLA antibodies are not.

Bound autoantibodies against epitopes on GP Ib and IIb/IIIa can be detected in 60–80% of patients. Testing for platelet antibodies is not recommended as a routine test. Only bound antibodies are relevant, while free antibodies are not very sensitive. For patients with persistent or chronic ITP and atypical findings, however, detection of platelet antibodies may sometimes help to confirm the diagnosis of ITP or exclude other differential diagnoses (table 9).

Remember: Only autoantibodies against GP antigens support the diagnosis of primary or secondary ITP. Antibodies against human leukocyte antigens (HLAs) on platelets are much more common in clinical routine (e.g., after platelet transfusion) but they have nothing to do with ITP.

Bone Marrow Biopsy

Bone marrow biopsy cannot prove ITP, but it helps to exclude other diagnoses. Therefore, if all symptoms and other findings are consistent with ITP, bone marrow biopsy can be omitted. This is a great relief especially for pediatric patients.

Table 7. Differential diagnosis of ITP and typical findings

Differential diagnosis	Typical history and findings
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, etc., very small platelets with Wiskott-Aldrich syndrome, etc.)
Drug-induced thrombocytopenia	Medical history, test for drug-dependent platelet autoantibodies
Thrombocytopenia from cytostatic drugs	Medical history (includes not only classical chemotherapy agents but also modern molecular/targeted or immunologic anti-cancer drugs, e.g. checkpoint inhibitors)
Antiviral drugs	Medical history
Heparin-induced Thrombocytopenia (HIT)	Medical history and laboratory tests for HIT
Posttransfusion purpura	History of recent blood transfusions
Gestational thrombocytopenia	Only during pregnancy, usually platelets > 80×10^9/l
Lymphoma	Medical history, presence of B-symptoms, enlarged lymph nodes or spleen, consider bone marrow biopsy
Infections (viral, bacterial, parasitic)	Tests for HIV, CMV, EBV, Rubella, parvovirus B19, Hantavirus and other microbiological examinations, blood culture for sepsis, blood smear when malaria is suspected
Liver disease	Liver function tests, hepatitis screen, ultrasound of liver and spleen, with large spleen consider Gaucher's disease
Alcohol	Must be specifically and repeatedly asked for
Sarcoidosis	May enlarge spleen and infiltrate bone marrow
Severe vitamin deficiencies (vitamin B12, folic acid, rarely also with severe iron deficiency)	Laboratory analysis
Other autoimmune disorders	Test for SLE, rheumatoid arthritis, antiphospholipid-syndrome, autoimmune thyroiditis etc.
Evans syndrome	Anemia, positive anti-erythrocyte antibody tests
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 of other blood cell lines and/or serum immunoglobulins, consider bone marrow biopsy with flow cytometry, molecular and cytogenetics !The most important DD of newly diagnosed ITP in children is ALL!
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 factor function testing and multimer analysis
Disseminated intravascular coagulation	Changes of other coagulation parameters
Large hemangiomas (e.g. Kasabach-Merrit syndrome), large aneurysms	Clinical symptoms

Myelodysplastic syndromes (MDSs) and idiopathic cytopenias of indeterminate significance (ICUS; especially the subtype ICUS-T, see textbooks of hematology) can be mistaken as ITP. It is important to rule these out because in people over 60 years the incidence of MDS is as high as that of ITP [60].

Bone marrow biopsy is a simple procedure. It can be performed on the same day immediately after obtaining informed consent and the patient does not need to be called in a second time. They should be informed about the risk of bleeding, local pain, local infections, and the very rare risk of organ and nerve damage. In the authors' experience, it is not necessary to put anticoagulants on hold (e.g., acetylsalicylic acid, vitamin K antagonists) before the biopsy. New oral anticoagulants (NOACs) have their highest plasma concentration after 2–4 h and should therefore not be taken immediately before the biopsy, but a couple of hours afterwards. Even with severe thrombocytopenia, platelet concentrates need not be given before biopsy. Bleeding is very rare even with the lowest platelet counts and can usually be controlled by prolonged compression.

Table 8. Additional diagnostic workup for patients with persistent or chronic ITP

Diagnostic test	Rationale
Blood group	For emergency passport, before surgery with high bleeding risk
Bone marrow biopsy	see table 9
Blood glucose/urine glucose	Detect (subclinical) diabetes as a side effect of corticosteroid treatment
Serum electrophoresis and/or serum immunoglobulins	Detect immunodeficiency syndromes (e.g. common variable immunodeficiency), myeloma
Autoimmune markers (anti-CCP, ANA, ANCA, anti-DS-DNA, antiphospholipid-antibodies, Lupus anticoagulant)	Exclude ITP secondary to other autoimmune disorders
Antibodies against platelet glycoproteins	For patients with persistent thrombocytopenia when there is any doubt about the diagnosis of ITP (only helpful when positive, negative test does not exclude ITP). Only bound antibodies are relevant
Von Willebrand factor analysis	Von Willebrand disease type 2b can present with mild to severe thrombocytopenia
Thyroid function tests	Up to 10% of ITP patients have signs of thyroid autoimmune disease and may require therapy
Helicobacter pylori testing	see chapter '*Helicobacter pylori*'
Hepatitis B, C, HIV	Risk of progression or reactivation with immunosuppressive therapies or after splenectomy
Ultrasound, X-Ray, computed tomography	Exclude solid tumor, lymphoma or any other hematologic malignancy. With enlarged spleen consider Gaucher's disease.

Table 9. Indications for platelet antibody testing and bone marrow biopsy

Indications for platelet antibody testing (only helpful when positive)
Minimal or no response to corticosteroids or i.v. immunoglobulins
Differential diagnosis ITP vs. drug-induced or toxic bone marrow damage (e.g. chronic alcohol abuse)
Differential diagnosis ITP vs. hereditary thrombocytopenia
Confirm the diagnosis of ITP in patients with concomitant liver diseases, splenomegaly
Indications for bone marrow biopsy
Besides thrombocytopenia, also abnormal leukocyte and erythrocyte parameters
Atypical history (e.g. B-symptoms, weight loss) and physical findings (e.g. enlarged lymph nodes, hepatosplenomegaly)
>60 years because of the increasing frequency of alternative diagnoses: lymphomas, myelodysplastic syndromes, idiopathic cytopenia of uncertain significance, myeloma and others
Before splenectomy to rule out alternative diagnoses with the greatest certainty before this irreversible procedure

Helicobacter pylori

Level of recommendation: A
Level of evidence: 3

All adult patients with ITP, especially those with persistent or chronic ITP, should be tested for *Helicobacter pylori* and receive eradication if positive.

Numerous publications describe an association between ITP and *Helicobacter pylori* infections of the gastric mucosa [61]. This association seems to be more relevant in Asia than in Europe and North America. Current guidelines recommend testing *for H. pylori* in adult ITP patients (but not in children) and eradication if positive [62, 63]. This is reasonable because ITP patients often receive corticosteroids and have a higher risk for ulcers. Moreover, *H. pylori* therapy is simple and inexpensive. With an *H. pylori* breath or stool test, thrombocytopenic patients can avoid the risk of bleeding from gastroscopy and biopsy.

When to Treat

Level of recommendation: EC
Level of evidence: 3

The decision to initiate treatment should not be based only on the bleeding tendency and the platelet count. The stage and course of the disease and several other individual factors must be considered.

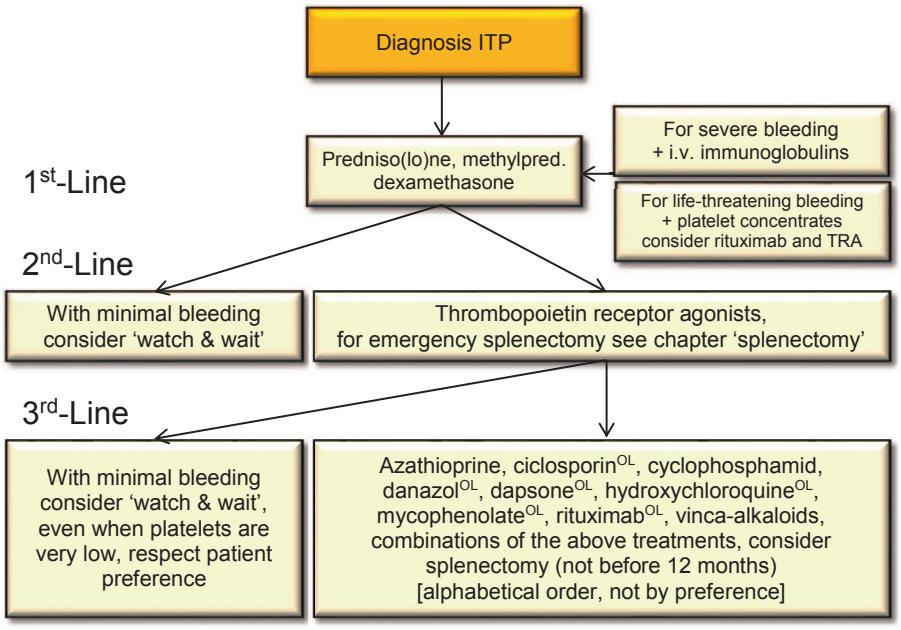

Fig. 1. Treatment algorithm (for details and special situations, see text). OL = Off-label.

A treatment algorithm is shown in figure 1.

Drugs and dosages are listed in table 10. Information on the approval status can be found in table 11.

Treatment Indications

Several factors need to be considered when deciding on treatment:

- Clinical bleeding tendency
- Platelet count
- Disease stage (newly diagnosed vs. persistent vs. chronic)
- Previous course of the disease and history of bleeding
- Side effects of treatment
- Consequences for work and school (avoid occupational disability)
- Patient age, concomitant disorders and medications (especially anticoagulants)
- Access to outpatient and inpatient specialist care
- Experience of the attending physician/clinic in ITP
- Patient preference, health literacy, psychosocial situation
- Children and adolescents are more active; special consideration needs to be given to the risk of injury in kindergarten, school, during leisure activities

This list is not ranked in the order of relevance; all factors must be considered when deciding for or against a treatment.

Platelet Threshold

The risk of bleeding and mortality increases if the platelet count falls below 30×10^9/l, but there are large individual variations. The traditional concept of a platelet threshold below which every patient must be treated and above which therapy would not be indicated is not evidence based.

The ASH ITP guideline of 1996 considered withholding treatment as inappropriate for patients with a platelet count < 20×10^9/l, even if the patient was completely asymptomatic [1]. As a result, many patients were treated with corticosteroids for months or even years, and in some cases most severe side effects (Cushing's syndrome, infections, diabetes) were accepted just to 'keep the values high'. The International Consensus Report of 2009 [64] stated that therapy was not necessary in case of values above 50×10^9/l; however, it left open whether it was obligatory to treat at lower values or not. The experts of the 2010 ASH guideline then again recommend a threshold value of 30×10^9/l and justified this by stating that this value is 'used by the majority of clinicians' [63]. There is no higher level of evidence to support this threshold. The main reason for defining a threshold is protection against malpractice suits in the Anglo-American healthcare system. A treatment indication based solely on platelet count without taking individual patient factors into account should be obsolete today.

The following approach appears to be useful in newly diagnosed ITP patients:

In the case of newly diagnosed ITP, without or with only mild bleeding (WHO 0–II, see table 4) and platelet counts below 20×10^9–30×10^9/l, treatment will usually be offered, if only because the patient is afraid of bleeding and denying treatment would hardly be acceptable.

In the case of newly diagnosed ITP, without or with only mild bleeding (WHO 0–II) and platelet values above 20×10^9–30×10^9/l, a 'watch-&-wait' strategy would not be inappropriate; however, if the patient wishes treatment, then it should not be denied. All the factors mentioned in the section 'When to Treat' should be considered when deciding for or against a therapy.

Table 10. Frequently used drugs and dosages for ITP

Corticosteroids in adults	
Predniso(lo)ne	1–2 mg/kg/day p.o. or i.v. for 1–2 weeks After response weekly dose reductions in 10 mg steps until a dose of 0.5 mg/kg body weight/day is reached, then dose reduction by 5 mg/week [67]
Methylprednisolone	125–1,000 mg i.v. for 1-5 days (followed by prednisone 1 mg/kg/day p.o. and subsequent dose reduction as above)
Dexamethasone	40 mg p.o. daily × 4 days, 4-6 cycles every 14–28 days
Corticosteroids in children	
Predniso(lo)ne	0,25–4 mg/kg body weight/day divided in two doses, recommended dose 2 mg/kg × 4 days, not longer than 2 weeks
Methylprednisolone	30 mg/kg (max. 1,000 mg) i.v.
Dexamethasone	0,7 mg/kg/day (max. dose 40 mg/day) for 4 days
Other treatments	
i.v. Immunoglobulins	0.4–1 g/kg body weight/day, if no response this dose can be repeated once after 3 days
Romiplostim	1–10 µg/kg s.c. 1× per week, continuous therapy
Eltrombopag	25–75 mg p.o. daily, continuous therapy
Azathioprine	2 mg/kg p.o. daily, response may take several months
Rituximab[1]	375 mg/m^2 1× per week i.v. for 4 weeks
Cyclophosphamid[1]	1–2 mg/kg p.o. daily
Ciclosporin[1]	Dosage by blood level, target 100-400 ng/ml
Danazol[1]	400–800 mg p.o. daily
Dapsone[1]	75–100 mg p.o. daily
Mycophenolate[1]	2 × 250 bis 2 × 1,000 mg p.o. daily
Anti-D	The only anti-D product approved for ITP (WinRho® SDF) was withdrawn from the European market in 2009, but is still available in the US and other non-European countries[2]

[1]No regulatory approval for the treatment of ITP. In the case of non-approved therapies, detailed patient information should be provided and documented in the patient file.
[2] Other anti-D immunoglobulins (e.g. Rhophylac®, Rhesonativ®) are not approved for ITP, but only for the prophylaxis of hemolytic disease of the newborn.

The longer the disease persists, the less relevant the platelet counts become for deciding pro or contra therapy. The side effects of treatment must be weighed against the benefits. Although a treatment is usually offered in later therapy lines, it would not be inappropriate to follow a 'watch-&-wait' strategy even with lowest platelet values as long as the patient does not bleed or has only mild bleedings, and, of course, if he/she agrees to this approach after detailed information about risks and benefits. Conversely, if the patient wishes treatment he/she should not be urged for a 'watch-&-wait' strategy. Any denial of treatment and conflict should be avoided.

First-Line Therapy

Corticosteroids

Level of recommendation: A
Level of evidence: 3
Corticosteroids should be used for first-line therapy.
The patient needs a treatment time table stating for how long and in which doses to take the steroids and until when they should be completely tapered.

Corticosteroids are immunosuppressive and the concept is that they inhibit the formation of platelet autoantibodies. Numerous older studies have shown that corticosteroids achieve an increase in platelet count in the vast majority of adult ITP patients. However, platelet counts in adults usually decrease again when steroids

Table 11. Approval status of ITP treatments in Germany and Austria

Treatment	Approval status	Comments
Anti-D immunoglobulin	no	The only product approved for ITP (WinRho® SDF) was withdrawn from the EU market in 2009 and is only available in the US and other non-European countries. Other anti-D-immunoglobulins are not approved for ITP therapy
Azathioprine	yes	Chronic, refractory ITP
Ciclosporin	no	Case reports
Cyclophosphamide	yes	Approved only for 'serious immune diseases'
Danazol	no	Case reports only; Danazol is not approved in Germany but it is available in Austria and Switzerland
Dapsone	no	Case reports
Dexamethasone	yes	Approved for initial therapy of autoimmune diseases.
Eltrombopag	yes	Treatment of patients with chronic immune thrombocytopenia who have had an insufficient response to corticosteroids and immunoglobulin therapy.
Hydroxychloroquine	no	Case reports
Immunoglobulins	yes	Most intravenous immunoglobulins explicitly mention ITP in their list of approved indication
Methylprednisolone	yes	Diseases requiring systemic therapy with glucocorticoids
Mycophenolate	no	Case reports
Predniso(lo)ne	yes	Hematological diseases requiring systemic treatment with glucocorticoids
Rituximab	no	Has been tested in phase I, II, and III studies.
Romiplostim	yes	Treatment of patients with chronic immune thrombocytopenia who have had an insufficient response to corticosteroids and immunoglobulin therapy
Vinblastin	no	Case reports
Vincristin	yes	Approved for ITP but not as primary therapy (no longer considered by experts to play a role in ITP therapy)

are stopped; permanent remissions are uncommon (5–6% in older publications) [1, 65]. The high relapse rate suggests that corticosteroids only alleviate the severity of the disease but do not shorten the course.

The duration of corticosteroid therapy should not be too short (not less than 3 weeks) [66]. However, prolonged steroid treatment does not improve the response rate. For dosages, see table 10. First-line prednisone therapy lasts several months if the recommended dosages are followed (e.g., 'McMillan scheme') [67] and almost all patients will develop side effects during this time (see table 12 for side effects).

Prednisone versus Dexamethasone

Dexamethasone was introduced in the second-line therapy of refractory chronic ITP in the 1990s [68]. Several non-randomized studies showed subsequently that dexamethasone is also effective in newly diagnosed ITP. Specific effects on Tregs and myeloid suppressor cells have been noted. Several comparative studies describe higher long-term remission rates when dexamethasone instead of prednisone is given in the first line [69–71], while others do not find an advantage [72, 73]. Cushingoid changes are not as frequent with dexamethasone as with prednisone [70]. The decision for prednisone or dexamethasone should be left to the expertise of the physician.

First-Line Treatment of Children and Adolescents

Level of recommendation: B
Level of evidence: 3

Treatment is usually not recommended for newly diagnosed ITP in children and adolescents with no or only mild bleeding. Also, hematomas and sugillations alone are not an indication to start therapy. However, mucosal hemorrhages ('wet purpura') can be an indication.

Low platelet counts alone are not an indication to start treatment of newly diagnosed ITP.

An update of the German guideline on ITP in childhood and adolescence is currently in preparation and expected to be published in 2018. The clinical course and prognosis of pediatric ITP

Table 12. Side effects of corticosteroids and preventive measures

Side effects
Acne
Hypertension
Cushingoid appearance (moon face)
Thinning, fragile skin, stretch marks (striae)
Blood glucose elevations
Weight gain
Infections
Stomach pain
Muscular atrophy
Osteoporosis
Sleeplessness
Loss of emotional control
Preventive measures
Inform the patient about the above-listed side effects and provide a time table as to how long this therapy should be taken.
Osteoporosis prophylaxis: 600–1,000 units vitamin D3/day and 1,000 mg calcium/day
Protect stomach with proton pump inhibitor
Antibiotics as infection prophylaxis usually not indicated

differs from adult ITP. ITP in young children usually presents with acute bleeding symptoms, often after an infection. However, in most cases, thrombocytopenia is only temporary and chronic courses are uncommon. Older children are more likely to present with an adult type of ITP (oligosymptomatic, no history of infection, often chronic course with only mild bleeding) [5, 74, 75].

Most children and adolescents with newly diagnosed ITP do not require treatment. Hematomas and sugillations are not sufficient to start treatment. However, mucosal hemorrhages that cannot be controlled by local measures can lead to treatment. As a general principle, thrombocyte counts are not a decision criterion for the treatment of newly diagnosed pediatric ITP [76, 77]. Individual circumstances such as age, susceptibility to injury or psychosocial aspects should also be considered.

Retrospective studies and registry data (covering both treated and untreated children) find an incidence of ~3% for severe to life-threatening bleeding [47]. Intracranial bleedings are particularly feared. Their incidence is <1% [54, 78, 79]. As a rule, the platelet counts at the time of bleeding are $<20 \times 10^9$/l. The affected children often have heralding bleeds from the mouth and nose ('wet purpura').

Intravenous immunoglobulins (IVIGs) should be used for heavy bleeding, and additional platelet concentrates, for very heavy bleeding, because this achieves a faster rise in platelet counts than corticosteroids alone [79].

If there is little or no treatment response, the diagnosis should be questioned and the patient presented to a center with expertise in pediatric hematology (see also the section 'Therapy of Chronic ITP in Children and Adolescents'). The most important differential diagnosis of newly diagnosed childhood ITP is acute lymphocytic leukemia (ALL).

Emergency Treatment

Level of recommendation: A

Level of evidence: 3

In case of severe and life-threatening bleeding (WHO III/IV) or before surgery that cannot be delayed, intravenous immunoglobulins (IVIGs) should be administered in addition to steroids to increase the platelet count more rapidly.

In the case of life-threatening bleeding, one may also give platelet concentrates.

In life-threatening bleeding and if the above measures do not achieve hemostasis, consider administration of rituximab and thrombopoietin receptor agonists (TRAs).

For splenectomy, see the section 'Splenectomy'.

Emergency Treatment with IVIGs

IVIGs inhibit the phagocytosis of antibody-coated platelets and usually achieve a rapid but short-lived platelet increase. They do not induce permanent remissions. After 2–4 weeks, the values usually decrease to the initial level again. This limits the use of IVIGs to emergency situations in which a rapid platelet increase must be achieved (bleeding, surgery that cannot be delayed) or when higher doses of steroids are to be avoided (e.g., pregnancy, see the section 'ITP and Pregnancy'). See table 10 for dosing.

Emergency Treatment with Anti-D Immunoglobulins

Anti-D immunoglobulins have been used for the treatment of chronic ITP since the 1980s [80]. Anti-D binds to rhesus (Rh)-positive erythrocytes. The antibody-loaded erythrocytes are phagocytized in the spleen. In ITP patients this seems to inhibit the degradation of antibody-loaded platelets and the platelet count increases. This also explains why anti-D is only effective in Rh-positive patients and only if the spleen has not yet been removed. A clinically relevant side effect can be intravascular hemolysis.

The anti-D preparations available in Germany, Austria, and Switzerland (Rhophylac®, Rhesonativ®, and others) have been used for ITP treatment in the past although they are only licensed for hemolytic disease of the newborn.

Monoclonal Anti-D

Because anti-D is a plasma product and therefore has a risk of infection, attempts were made to manufacture recombinant anti-D immunoglobulin. Rozrolimupab is a mixture of 25 different recombinant anti-D antibodies. Initial results show good efficacy in ITP [81]. Regulatory drug approval is expected.

Table 13. Eltrombopag and romiplostim dosing

Romiplostim
The starting dose of romiplostim recommended in the prescribing information is 1 μg/kg once weekly based on the actual body weight. The weekly dose should be increased in steps of 1 μg/kg until a stable platelet count (≥50 × 10^9/l) is reached.
The maximum dose should not exceed 10 μg/kg/week.
The target range for the platelet count is 50–150 × 10^9/l, normalization of platelet count is not necessary
With romiplostim the platelet count should not exceed 250 × 10^9/l
Initially the platelet count should be checked weekly, then every 4 weeks Note: if the patient is bleeding a higher starting dose is often used (e.g. 3–5 μg/kg), for severe bleeding, start with the maximum dose to avoid long titrations
Eltrombopag
The recommended starting dose for eltrombopag is 50 mg once daily (25 mg for patients of East Asian descent). The dose should be adjusted until a stable platelet count (≥50 × 10^9/l) is reached
The maximum dose should not exceed 75 mg p.o. daily
The target range for the platelet count is 50–150 × 10^9/l
With eltrombopag the platelet count should not exceed 250 × 10^9/l
Initially the platelet count should be checked weekly, then every 4 weeks

Emergency Treatment with Platelet Concentrates

Transfusion of platelet concentrates can achieve a short-term increase in platelet counts and stop of bleeding in patients with severe hemorrhages (WHO III/IV) when given in addition to steroids and immunoglobulins. Most patients require more than the usual 1–2 platelet concentrates to achieve sufficient hemostasis. In severe bleeding, additional use of rituximab and early administration of TRAs may also be considered.

So far, there is no evidence that platelet transfusions stimulate the formation of platelet autoantibodies in ITP.

Second-Line Treatment

Degree of recommendation: EC
Level of evidence: 3
There is no thrombocyte count threshold below which a second-line treatment is obligatory or above which treatment becomes inappropriate. The decision for or against treatment must be individualized.

Second-line therapy is indicated if the patient only partially responds to first-line steroids or not at all, or if the platelet counts fall again after an initial response. As with first-line therapy, there is no thrombocyte threshold below which treatment is obligatory or above which it becomes inappropriate. The indication for treatment is always an individual decision. The same factors as for first-line therapy must be taken into account (see the section 'When to Treat').

In contrast to first-line therapy, quality of life and the avoidance of side effects become increasingly more important in the second and any further therapy lines. While with newly diagnosed ITP all therapeutic attempts should be aimed at achieving cure, with increasing disease duration a persistent remission becomes less likely and the potential benefit of any treatment must be weighed against its side effects. Basically, all treatment options can be offered, including a 'watch-&-wait' strategy. The patient's preferences must also be considered.

The following approach has proved to be practical:
In patients with no or only minimal bleeding (WHO 0–I) (see table 4), a second-line treatment can be offered after failure of the first line. A 'watch-&-wait' strategy would also be possible. However, in daily practice, many patients with little or no bleeding tendency will opt for a second-line therapy because they are afraid of hemorrhages. If they agree to the 'watch-&-wait' approach, it is neither inappropriate nor medical malpractice to pursue this strategy, even at the lowest platelet counts.

Therapy may be offered to patients with moderate bleeding (WHO II) because of the individual symptom burden from the bleeding symptoms. As above, many of these moderately bleeding patients will opt for therapy. However, a 'watch-&-wait' strategy would not be inappropriate either.

Patients with WHO III or IV bleedings always need treatment, regardless of the platelet count. Hospital admission is recommended.

Second-Line Treatment with TRAs

TRAs – Efficacy

Level of recommendation: A
Level of evidence: 2
TRAs should be offered as second-line therapy.

Until the early 1990s, there was the opinion that further stimulation of thrombocytopoiesis makes no sense in a disease like ITP with already increased platelet turnover. Then it was found that the thrombopoietin levels in ITP patients are higher than in healthy people, but not as high as in other diseases with a comparable degree of thrombocytopenia. This led to the concept that there was a relative thrombopoietin deficiency in ITP [30, 82]. Based on this observation, the TRAs romiplostim and eltrombopag were developed. Romiplostim (Nplate®) was approved in the European Union (EU) in 2009 and eltrombopag in 2010 (in the EU under the trade name Revolade®, in the USA and other countries under Promacta™) (table 13). Extensive studies have shown that both agents can increase the platelet counts to safe levels in many patients with chronic ITP.

- In over 90% of patients a short-term response is achieved.
- The number of patients with long-term response is not quite as high. Data on long-term response range from 30 to 90%, considering that patients and definitions of 'long-term response' vary between studies [50, 83–87].
- TRAs are effective in patients with and without splenectomy [88].
- TRAs are equally effective in old and young patients [89].
- The 2 TRAs, eltrombopag and romiplostim, are not cross-resistant, i.e., if one TRA fails, the other one can still achieve a response [90, 91].
- Romiplostim seems to be less effective when the serum thrombopoietin levels are high [92].
- With TRAs, about half of the patients can discontinue all other ITP drugs (e.g., steroids).

The manufacturer recommends taking eltrombopag at least 4 h after a meal containing calcium, magnesium, aluminum, or iron (antacids, dairy products, vitamin tablets, iron supplements for anemia). Intake on an empty stomach or at night, before going to bed, is best practicable for many patients. Patients of Asian origin respond more strongly to eltrombopag; a lower starting dose, usually 25 mg, should be chosen here.

TRAs – Side Effects

In the authors' experience, TRAs are significantly better tolerated than corticosteroids or other ITP treatments. The following side effects are frequently mentioned in the literature:

Headaches, joint pains, muscle pains and *stomach complaints*, but this might not be specific for TRAs since similar side effects are also described for other growth factors.

Upper-airway symptoms: Many patients (10–26%) have cold and upper-airway symptoms, but in ITP patients without TRAs these complaints are also common.

Venous and arterial thromboses were observed both under treatment with romiplostim and eltrombopag (see the section 'ITP as a Risk Factor for Venous and Arterial Thromboembolism'). There is no clear correlation with the platelet counts [93]. Patients with a history of thrombosis should be informed about this risk and its symptoms. In these patients, an antiphospholipid syndrome should also be excluded.

Gastrointestinal side effects and elevated liver function tests: Elevated liver function tests have been reported for eltrombopag. Other abdominal complaints (constipation, nausea, vomiting, diarrhea, pancreatitis) also seem to be more frequent with eltrombopag than with romiplostim [94].

Portal vein thrombosis: Portal vein thrombosis has been described in patients with chronic liver disease (e.g., cirrhosis).

Skin changes: Skin changes (itching, redness, maculopapular exanthema) have been described with eltrombopag. Then, patients can be switched to romiplostim.

Cataracts: Cataracts were found in ITP patients with eltrombopag, but also with placebo. It could well be that this is due to other causes, e.g., age or previous steroid therapies. It is recommended that patients undergo an ophthalmological examination.

Excessive platelet drop after stopping a TRA: If romiplostim or eltrombopag are abruptly discontinued, the platelet count may drop below the initial values. Therefore, the platelet count should be checked for at least 4 weeks after discontinuation.

Pro-leukemic effect: Blast transformation has been described in patients with MDS who received TRAs [95]. There are other publications that do not find a pro-leukemic effect [96]. In more recent MDS studies, TRAs had no effect on the rate of leukemic transformations [97]. Some authors recommend a bone marrow biopsy to exclude MDS (and fibrosis, see below) before the administration of TRAs. In any case, white blood cell count differentials should be checked regularly.

Bone marrow fibrosis: About 2–11% of patients on TRAs have a mild increase of reticulin fibers in the bone marrow [98–100]. However, reticulin fiber formation was also found in the bone marrow of ITP patients without TRAs [99]. Overt myelofibrosis has so far only been described in few individual cases.

Antibodies against TRAs: In some patients treated with romiplostim, neutralizing anti-romiplostim antibodies were observed, which disappeared again after discontinuation of romiplostim. The antibodies were only active against romiplostim and did not neutralize human thrombopoietin. The same has not yet been described for eltrombopag.

Off-Label Treatment of Newly Diagnosed or Persistent ITP with TRAs

TRAs have been approved only for chronic ITP, i.e., for patients with disease duration of more than 12 months. Nevertheless, patients with newly diagnosed or persistent ITP may not respond adequately to standard therapies and present with clinically relevant bleedings. Case reports describe that TRAs are increasingly used also for these patients with newly diagnosed or persistent ITP and refractory thrombocytopenia, usually in combination with other ITP drugs.

One must not forget that the definition for chronic ITP has been changed. The limitation to patients with disease courses of 12 months or longer [4] was introduced later, after TRAs had already come onto the market. Many patients with significantly shorter disease courses had been enrolled in the original TRA approval studies before this change in definition. The authors therefore consider the use of TRAs justified in all patients who do not respond to first-line therapy, even if the overall duration of the disease is not yet a whole year and the formal criterion according to the current definition of chronic ITP is not fulfilled. The objection of health insurances and other cost bearers to wait for 12 months before prescribing a TRA is neither medically reasonable nor comprehensible.

Persistent Remission under TRAs

In recent years, numerous individual cases have been reported in which the platelet count has not fallen again after stopping

Table 14. Tapering romiplostim and eltrombopag

Protocol for tapering romiplostim
Patients who maintained platelet counts >50 × 10^9/l for at least 12 months were eligible for dose-tapering. Romiplostim dose was reduced by 1 μg/kg every 2 weeks as long as platelet counts remained >50 × 10^9/l [103]
Protocol for tapering eltrombopag
Patients who maintained platelet counts >50 × 10^9/l for at least 4 months were eligible for dose-tapering. Eltrombopag dose was reduced by 10–20% every 4 weeks as long as platelet count remained >50 × 10^9/l [104]

TRAs. Reviews cite persistent remission numbers between 13 and 30% [101, 102]. Therefore, if platelet counts are in the target range (> 50,000/μl) for a longer period, a TRA taper can be tried. It is important that TRAs are not halted abruptly but slowly tapered over many months (table 14).

TRA-Drug Interactions

Eltrombopag shows interactions with 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, usually cholesterol-lowering statins (for details and dose adjustment, see the prescribing information). Drug interactions for romiplostim are not listed in the prescribing information. Further relevant drug and disease interactions can be reviewed in online databases, e.g., *www.drugs.com*.

TPIAO

TPIAO is a recombinant thrombopoietin molecule that has been approved in China since 2005 for the treatment of chemotherapy-induced thrombocytopenia and since 2010 for the second-line treatment of ITP (*www.3sbio.com/en/products/oncology/tpiao*). While romiplostim and eltrombopag are not recommended or even contraindicated in pregnant women, TPIAO seems to be effective and safe in these patients [105].

Splenectomy

Degree of recommendation: EC
Level of evidence: 3

Splenectomy is indicated in all patients with persistent or chronic thrombocytopenia and severe bleeding (WHO III, IV) who have no or only an insufficient response to all other treatment modalities.

There is no compelling indication for splenectomy in patients with chronic, therapy-resistant ITP who have no, mild, or only moderate bleeding (WHO 0, I, II).

Splenectomy should not be performed before the 12th month.

The patient should not feel urged to undergo splenectomy for economic reasons.

Splenectomy has the highest rate of permanent remissions from all ITP therapies in the sense that no further treatment is necessary (two-thirds partial or complete remissions). TRAs achieve higher remission rates if only the platelet count response is considered, but if they are discontinued, the counts drop again, so that a permanent therapy is usually necessary.

There is a clear indication for splenectomy for all patients with persistent or chronic thrombocytopenia and severe bleeding (WHO III, IV) who do not respond sufficiently to all other treatment modalities. In emergencies (e.g., life-threatening bleeding that does not respond to steroids and IVIGs), splenectomy is even the therapy of choice because treatment with TRAs or rituximab is not immediately effective but needs some time to increase the platelet counts and stop the bleeding (often > 1 week).

There is no compelling indication for splenectomy for patients with chronic, therapy-resistant ITP who have no, mild, or moderate bleeding (WHO 0, I, II), even if their platelet counts are <30 × 10^9/l. In these patients, the decision for splenectomy must be individualized.

Before splenectomy, a bone marrow biopsy is recommended to achieve additional diagnostic certainty (see the section 'Bone Marrow Biopsy'). This is particularly true in atypical cases (e.g., lack of response to corticosteroids and immunoglobulins) and/or in patients > 60 years. All patients should preoperatively receive pneumococcal, *Haemophilus influenzae* b, and meningococcal vaccinations [106]. Meningococcal conjugate vaccine can only be given intramuscularly (i.m.), which might be a problem in severe thrombocytopenia. Then, the older meningococcal polysaccharide vaccines would be preferable, which can also be given subcutaneously (s.c.) (see the prescribing information); see also the Onkopedia guideline 'Prevention of Infections and Thromboses after Splenectomy or in Functional Asplenia' (*www.dgho-onkopedia.de*) and the recommendations of Asplenie-Net (*https://asplenie-net.org/*). Asplenie-Net is an initiative of the German Society for Infectiology (DGI) in cooperation with several other medical societies. Asplenie-Net is managed by the University Hospital Freiburg, Center for Chronic Immunodeficiency (CCI) and Center for Infectiology & Travel Medicine. Current recommendations on vaccinations, antibiotic prophylaxis, and emergency therapy for asplenia/splenectomy and order forms for an emergency card can be downloaded from the Asplenie-Net website.

Today, splenectomy is rarely performed in ITP. This is only partly due to concerns about the risks and side effects associated with splenectomy (table 15). Other important reasons are:

Only ~60% of patients achieve a permanent remission [107–109], the rest will experience a relapse of the thrombocytopenia sooner or later after splenectomy [110, 111]. These numbers derive from times before the introduction of TRAs. It is therefore not clear whether today's ITP patients who plan splenectomy because they have failed TRAs might have a more resistant type of ITP with lower response rates to splenectomy than the traditional 60%.

It is not yet possible to predict which patient will respond to splenectomy and who will not. A failure rate of 40% or more is

Table 15. Splenectomy risks and contraindications

Splenectomy risks and contraindications [for review see 109]
Postoperative morbidity approximately 10% (local wound infections, pneumonias)
Postoperative mortality <1% (might be higher for older patients)
Generally increased risk of infections
Overwhelming post splenectomy infection (OPSI, 3× higher risk)
Postoperative rise in platelet count (when >1,000 × 10^9/l consider acetylsalicylic acid or low-molecular-weight heparin)
Venous thromboembolism
Pulmonary hypertension
Contraindicated in patients with active infection (especially TBC)
Increased risk of infection with malaria or babesiosis

unacceptable for many patients. The 'International Consensus Report' recommends splenectomy when the platelet scintigraphy with radioactively labeled thrombocytes shows a predominantly splenic platelet destruction pattern [64]. This is only a weak recommendation because in patients where scintigraphy indicates that thrombocytes are not predominantly degraded in the spleen, splenectomy still has a success rate of 35–40% [112, 113]. To the knowledge of the authors, there are only a handful of nuclear medicine departments in Germany that offer platelet scanning.

It makes no difference whether splenectomy is performed laparoscopically or with laparotomy. This decision should depend primarily on the expertise of the surgeon. To raise the platelet count prior to splenectomy, give IVIGs, steroids and, in some cases, also platelet concentrates.

Splenectomy-Sparing Therapies

Many patients want to avoid splenectomy and request so-called splenectomy-sparing or splenectomy-replacing medical therapies. This is because they see that in other countries alternative, non-surgical therapies (e.g., rituximab) are available before splenectomy. Postponing surgery also makes sense from the medical perspective and it is even recommended by guidelines because spontaneous remissions are not uncommon until the end of the first year [3, 58, 64].

The patient should be informed about the possibility of non-surgical treatments before splenectomy, e.g., with rituximab. The lack of regulatory approval does not relieve the physicians from their obligation to discuss these therapeutic alternatives with the patient. Patients should be told about the off-label status of rituximab. Risks and side effects need to be discussed in more detail. As a rule (in Germany), patients cannot claim financial reimbursement for off-label therapies.

Third-Line Therapy with Rituximab

Degree of recommendation: EC
Level of evidence: 2
Rituximab can be used in ITP as third-line therapy after failure of corticosteroids and TRAs.

Rituximab causes a selective depletion of CD20-positive B lymphocytes. In 1999, rituximab was for the first time successfully used in a patient with chronic, therapy-refractory ITP [114]. Since then, numerous case reports and studies have been published [115–119] (for a review, see [120]). On average, rituximab achieves a short-term increase in platelet counts in 60% of patients, but relapses are not uncommon. The long-term remission rates are between 10 and 40%.

There seem to be 2 types of response: Some patients show an improvement after the first infusions (early responders); in others, the rise in platelet counts occurs weeks after the end of therapy (late responders) [121]. Therefore, if the patient does not respond within the first 4 weeks, one must not assume a rituximab failure. The response may still come later. An explanation for these different behaviors might be that, in early responders, B lymphocytes loaded with anti-CD20 antibodies saturate and block the reticulohistiocytic system, while in late responders the reduced production of platelet autoantibodies comes into play.

Rituximab is effective before and after splenectomy.

Children seem to respond a little better than adults. In children, recurrences occur only in the first years, in adults, also later.

Women and girls seem to respond better to rituximab than men and boys. This may be due to the different metabolism of rituximab.

ITP patients early in the course of disease seem to respond better than patients with long-standing ITP.

The standard dose of rituximab is 375 mg/m^2 once a week for 4 consecutive weeks [120]. Other publications also tried lower doses [118]. As yet, the two approaches have not been compared. There are also no data for rituximab being given s.c., or for rituximab biosimilars.

Rituximab side effects: Treatment with rituximab is usually well tolerated. Relevant side effects are:

- Infusion reactions with weakness, nausea, fever, chills, headaches are common (about 60%) and mild. They usually occur only during the first infusion (therefore, premedicate with a corticosteroid).
- Anaphylactic reactions are rare (must not be confused with cytokine release syndrome in lymphoma patients).
- The risk of infection is increased (if the patient has a fever, he should see a doctor immediately, including on weekends).
- Up to 6 months after rituximab, vaccinations are little or not at all effective [122].

Some uncommon and serious side effects have also been reported, particularly severe infections and rare cases of progressive multifocal leukoencephalopathy. It is not clear to what extent they

were due to rituximab or to other immunosuppressive therapies (before or concomitant with rituximab). Before administering rituximab, viral hepatitis should be ruled out.

Off-label use of rituximab: Rituximab has no regulatory approval for the treatment of ITP in any country in the world and, given the expiration of patent protection, this is not to be expected in the future either. However, the absence of approval does not mean an absence of efficacy. There is no medical evidence for giving rituximab only after splenectomy.

Rituximab in secondary ITP in chronic lymphocytic leukemia (CLL) or in autoimmune diseases: Rituximab is effective against both CLL and autoimmune dysregulation and should be offered as a primary therapy (usually together with cytostatic drugs) in this particular situation. Rituximab has successfully been used in autoimmune diseases with secondary ITP (variable immunodeficiency syndrome (CVID), systemic lupus erythematosus (SLE)).

Rituximab in relapsed/refractory ITP with clinically relevant bleeding: In these patients, rituximab is often used as a rescue therapy when corticosteroids and IVIGs are not sufficiently effective. There are no randomized data to support this indication, but numerous case reports have shown its efficacy and rituximab should be offered to patients in this situation (see the section 'Combination Therapies for Multi-Refractory ITP').

Rituximab as splenectomy-sparing therapy for recurrent/refractory ITP without clinically relevant bleeding: Another option is the administration of rituximab as third-line therapy (after corticosteroids and TRAs) prior to splenectomy in patients without severe bleeding. There is no medical evidence why rituximab should not be used before splenectomy if the patient wishes to do so with a chance to avoid surgery. However, the off-label situation and the possibility that health insurance does not cover the costs should be addressed (see also the section on 'Splenectomy-Postponing Therapies').

Other Third-Line Treatments

For reviews, see [123, 124].

Degree of recommendation: EC
Level of evidence: 3

Traditional ITP treatments with 'historic' medical approvals (azathioprine, cyclophosphamide, *Vinca*) or treatments without medical approval should only be used after failure of steroids, TRAs, and rituximab.

Comment: 'Historic' means that these agents were licensed in the 1970s or 1980s before current standards of Good Clinical Practice and Evidence-Based Medicine were implemented.

Azathioprine

The standard dose is 1–3 mg/kg/day orally (p.o.).

Azathioprine is initially often combined with steroids and, after a few weeks, the steroid dose is slowly tapered (azathioprine as a 'steroid-sparing' agent).

Neutropenia is common (~30%); the leukocyte count should be checked regularly (initially every 2–4 weeks).

The response is slow and treatment should be given for at least 3–4 months before assessing its effectiveness.

Azathioprine has an 'historic' medical approval for ITP.

Azathioprine may be used during pregnancy after careful consideration of the benefits and risks.

Ciclosporin

Ciclosporin A (CSA; 2.5–8 mg/kg/day) is used as monotherapy or in combination with prednisone. Doses in the lower range (2.5–3 mg/kg/day) seem to be better tolerated and not less effective. The CSA plasma target level is 150–400 ng/ml.

Relevant side effects: fatigue, weakness, kidney failure, hypertension, neuropathy.

The response is slow and treatment should be given for at least 2–3 months before assessing its effectiveness.

CSA has no regulatory approval in Germany for the treatment of ITP.

Cyclophosphamide

The dose is 1–2 mg/kg/day p.o.; it should be adjusted to the leukocyte count.

In addition to the usual side effects of cytostatic agents (bone marrow suppression, etc.), rare cases of bladder cancer and secondary leukemia have been described. Fertility can be affected.

In Germany, cyclophosphamide has a 'historic' approval for 'serious immune diseases', which excludes mild cases of ITP.

Danazol

The dose is 400–800 mg/day.

Danazol is a modified androgen and liver function should be checked regularly during long-term therapy. It should not be given to women with ITP (virilization).

Other side effects are weight gain, myalgia, hair loss.

This treatment also responds slowly and should be given for at least 2–3 months before assessing its effectiveness.

Danazol has no drug approval and is not marketed in Germany. It can be obtained from pharmacies with a licensure to import foreign medications (Danol™, 200-mg capsules).

Dapsone

The dose is 75–100 mg/day p.o.

In patients from Mediterranean countries, especially Africans and African Americans, one must exclude a deficiency or defect of glucose-6-phosphate dehydrogenase before giving dapsone.

The therapeutic response may be slow and an effect is usually to be expected after 4–6 weeks. Then try to reduce the dose.

Dapsone (DAPSON-Fatol® 50-mg tablets) has no drug approval in Germany for treatment of ITP (but for other diseases).

Hydroxychloroquine

Hydroxychloroquine has multiple effects on the immune system. It was used in studies on ITP in patients with a positive test for ANA or confirmed SLE.

The dose is 200 mg p.o., 2 times daily.

The therapeutic response is slow and it should be given for at least 2–3 months before assessing its effectiveness. Hydroxychloroquine is initially often combined with steroids to slowly reduce the steroid dose after a few weeks ('steroid-sparing agent').

Hydroxychloroquine (Quensyl® 200-mg tablets) has no drug approval for ITP in Germany.

Mycophenolate Mofetil

Starting with a low dose and then increasing slowly improves tolerability: 250 mg twice daily for the first 2 weeks, 500 mg twice daily for the 3rd and 4th week, 1,000 mg/day twice daily after 4 weeks.

Gastrointestinal side effects (nausea, loss of appetite, diarrhea, vomiting) are common.

Mycophenolate Mofetil has no drug approval for ITP in Germany.

Vinca Alkaloids

Dose: vincristine 1–2 mg or vinblastine 5–10 mg once a week for a maximum of 4–6 weeks.

Typical side effects are thrombocytopenia, neuropathy, constipation.

The effect on the platelet counts usually does not last long, which is why this form of therapy has hardly been used since the introduction of immunoglobulins.

Vincristine has a 'historic' approval for ITP; vinblastine has no approval at all. It is the authors' opinion that *Vinca* alkaloids should no longer be used in ITP.

The order of the above-listed therapies does not imply any rank or preference. Treatment decisions have to be individualized (for dosage and approval status, see tables 10 and 11). One must not forget that azathioprine, cyclophosphamide, and *Vinca* alkaloids only have 'historic' approvals for ITP. This means that they have not been tested according to the current standards of Good Clinical Practice and Evidence-Based Medicine and that their approval is based more on tradition than evidence. Therefore, they should only be offered if more modern and better studied medications such as TRAs and rituximab have failed. The chance for a permanent remission is not very high, but side effects may be severe.

Combination Therapies for Multi-Refractory ITP

ITP with recurrent clinically relevant bleedings that does not respond to multiple therapies is a serious disease with high morbidity and mortality [125, 126]. In this situation, patients are usually offered a combination of ITP agents, e.g., rituximab plus steroids plus TRAs. As an example, 3 current protocols are listed below (further protocols available from the authors).

Choi et al., 2014 [127], 'TT4 protocol': rituximab (100 mg abs. dose i.v., days 7, 14, 21, 28), dexamethasone (40 mg/day p.o., days 1–4), ciclosporin (2.5–3 mg/kg/day p.o., days 1–28).

Veneri et al., 2015 [128]: rituximab (375 mg/m^2 i.v., days 1, 8, 15, 22), romiplostim (starting dose 1 µg/kg s.c., once a week).

Rashidi and Blinder, 2016 [129]: eltrombopag (50–75 mg/day p.o.), azathioprine (1 mg/kg/day p.o.), mycophenolate (1,000 mg/day p.o.), ciclosporin (1 mg/kg/day p.o.).

Antifibrinolytics

For mild oral mucosal hemorrhages, menorrhagia, and dental procedures, one can give the antifibrinolytic tranexamic acid to achieve sufficient hemostasis [130].

Dose

Oral: Cyklokapron® 500-mg film tablets, 20–25 mg/kg every 8 h.

Tranexamic acid 5%, mouthwash: Cyklokapron injection solution has a concentration of ~10%, → dilute with the same volume of normal saline for a 5% solution, mouth rinse 4 times daily.

Parenteral: injection solution with 0.5–1 g (Cyklokapron vials with 5 or 10 ml each) every 8–12 h slowly i.v. (CAVE: parenteral treatment with tranexamic acid can induce thromboses).

Antifibrinolytics are not sufficiently effective for bleedings in the eye, the central nervous system (CNS), or for visceral hemorrhages.

Treatment for Chronic ITP in Children and Adolescents

Degree of recommendation: EC
Evidence level: 5

As yet, there is no standard treatment for chronic ITP in children and adolescents. Patients should be referred to centers with expertise in pediatric hematology.

Chronic childhood ITP usually does not require treatment, unless the patient has frequent and clinically relevant bleedings. There is no standard of care. TRAs are effective in chronic ITP in children and adolescents [49, 52, 84, 131–133]. Eltrombopag has been approved for this indication since 2016. Approval for romiplostim

Table 16. Target platelet counts for surgeries and other invasive procedures [134, 135]*

Surgery or other invasive procedure	Target platelet count
Dental cleaning, dental calculus removal	>20–30 × 10^9/l
Tooth extraction (simple)	>30 × 10^9/l
Tooth extraction (complex, surgical, molar teeth)	>50 × 10^9/l
Regional anesthetic nerve block for tooth extraction	>30 × 10^9/l
Lumbar puncture (elective)	>50 × 10^9/l
Lumbar puncture (emergency)	>20 × 10^9/l
Spinal anesthesia	>50 × 10^9/l
Epidural anesthesia	>80 × 10^9/l
Central line placement	>20 × 10^9/l
Gastrointestinal endoscopy without biopsy even with very low platelet counts possible.	
Gastrointestinal endoscopy with biopsy	>20 × 10^9/l
Bronchoscopy, bronchial lavage	>20 × 10^9/l
Bronchoscopy with transbronchial biopsy	>50 × 10^9/l
Puncture of a joint	>20 × 10^9/l
Liver biopsy, transjugular (preferred for thrombocytopenic patients)	>10 × 10^9/l
Liver biopsy, transcutaneous	>50 × 10^9/l
Bone marrow biopsy from iliac crest even with very low platelet counts possible.	
Other organ biopsies/punctures	>50 × 10^9/l
Minor surgery[1]	>50 × 10^9/l
Minor surgery at a location where compression can be applied to stop bleeding	>20 × 10^9/l
Major surgery[2]	>80 × 10^9/l
Neurosurgery	>70–100 × 10^9/l
Surgery at posterior segment of eyeball	>70–100 × 10^9/l

[1]Minor surgeries are operations with a low risk of bleeding, including the majority of extremity operations.

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

*These target values were developed from experience with patients with platelet production disorders (e.g. MDS). There is no corresponding data for ITP patients. The individual bleeding history should also be considered, e.g. whether a patient has already bled with the indicated platelet counts in the past or not

is expected in 2018. Common side effects are headaches and upper-airway symptoms (as in adults). No serious side effects such as neutralizing antibodies or myelodysplasia have been reported, so far (but this could also be due to the low number of bone marrow examinations in children). Few children showed a slight increase of reticulin fibers (degrees 1–2).

Splenectomy should be avoided in children. It can be offered as a last option in therapy-resistant ITP with frequent bleedings.

In pediatric ITP patients, antifibrinolytic therapy with tranexamic acid is commonly used, especially for mucosal hemorrhages.

Preparation for Surgery and Dental Procedures

If a patient with ITP plans to go for surgery or an invasive diagnostic procedure, then the question usually arises which platelet count would be safe and should be achieved preoperatively (table 16) [134, 135]. For emergency surgery, steroids are often combined with IVIGs and sometimes also with platelet concentrates. In all other situations, especially for elective surgery, give corticosteroids, TRAs, or other treatments that have previously effectively raised the platelet counts in this individual patient.

ITP and Vaccinations

Degree of recommendation: EC
Level of evidence: 3

ITP patients should receive all recommended vaccinations except for live attenuated vaccines during immunosuppressive therapy.

Patients with frequent severe bleedings and resistance to standard therapies, where splenectomy is an obvious therapeutic option, should receive pneumococcal, meningococcal and *Haemophilus influenzae* type b vaccination as early as possible.

ITP patients should receive all standard vaccinations recommended by national health authorities. Only live attenuated vaccines are contraindicated for ITP patients with immunosuppressive treatments (e.g., cortisone, rituximab, etc., but not with TRA therapy). IVIGs can also affect the efficacy of live vaccines. Manufacturers usually recommend an interval of at least 3 months after IVIGs (for details, see the prescribing information of each live vaccine preparation).

To avoid muscle bleeding in ITP patients with low platelet counts, most vaccinations can be given s.c. instead of i.m. (analogously to vaccinations in patients with therapeutic anticoagulation, consult the manufacturer if necessary).

Vaccination does not induce a relapse or worsening of the thrombocytopenia in patients with a history of ITP who are now in remission or in patients currently suffering from chronic ITP. If the patient foregoes the vaccination and then gets the infection, they may have an even higher risk of thrombocytopenia [136]. MMR vaccination (measles, mumps, rubella), which has a definitive but low risk of thrombocytopenia, should also be offered to all children with ITP who have not yet been vaccinated.

ITP patients are at risk for a more severe course of hepatitis B when they get infected during immunosuppressive therapy. Also, when they travel to countries with medical services that do not meet European standards, there is always a certain risk of infection when they need emergency blood products. Therefore, hepatitis B vaccination is recommended to all patients with ITP.

ITP after Vaccinations

Vaccination-associated ITP has been described and is usually short-lived. Studies find an ITP incidence of 0.15 per 1 million vaccinations (various vaccines), 20 per 1 million MMR vaccinations, 0.16 per 1 million measles vaccinations.

Under the assumption that the natural background ITP incidence (not vaccine associated) is 0.2–0.4/10,000/year (see the section 'Epidemiology'), then 1.6–3.0 cases of ITP per 1 million children or adults would develop during the 4 weeks after a vaccination merely by coincidence. After an MMR vaccination, the ITP incidence is 1:40,000, but studies do not find an increase of chronic ITP [136]. In the rare patient where a causal relationship between a previous vaccination and the subsequent occurrence of ITP cannot be ruled out, the benefit of any further vaccination with this or other vaccines containing similar components should be weighed against the risks.

Vaccinations before Splenectomy or Rituximab

ITP patients for whom splenectomy is a realistic option because of resistant disease and frequent severe bleedings should receive pneumococcal, meningococcal and *Haemophilus influenzae* b vaccination as early as possible (see the section 'Splenectomy'). The same applies to patients who are to receive rituximab, because when this treatment fails and when they need to go for splenectomy, vaccination is not possible for the next 6 months.

Secondary ITP

One distinguishes a primary type of ITP, in which no causative factor can be identified, from secondary types, in which ITP is triggered by drugs or other diseases (table 1). About 20% of all ITPs are secondary [7, 137]. The most common causative factors are:

- Autoimmune diseases (Sjögren's syndrome, SLE, rheumatoid arthritis, autoimmune thyroiditis, and others)
- Inflammatory bowel diseases (ulcerative colitis, Crohn's disease)
- Immunodeficiency syndromes (e.g., CVID)
- Hematologic malignancies: MDS and lymphomas (2–5% of CLL patients have secondary ITP)
- After allogeneic stem cell transplantation
- Solid tumors
- Viral infections (Epstein-Barr virus (EBV), cytomegalovirus (CMV), hepatitis B and C virus (HBV, HCV), human immunodeficiency virus (HIV), and others)
- Medications (see the section 'Drug-Induced Thrombocytopenia')

Especially in older patients one should always look for secondary ITP. Splenectomy has lower long-term remission rates in secondary ITP than in primary ITP. The removal of the spleen might also worsen any preexisting immunosuppression and increase the risk of infections. It should be avoided in secondary ITP. As a rule, treatment should primarily be directed towards the underlying disease.

ITP and Pregnancy

Degree of recommendation: EC
Level of evidence: 3

Pregnant ITP patients who require treatment should receive corticosteroids or IVIGs.

The mode of delivery (C-section vs. vaginal) should not be determined by the ITP, but only by the obstetric situation of the mother.

Epidemiology

Of all pregnancies, 6–12% develop thrombocytopenia [63, 64, 138]. The most common causes are gestational thrombocytopenia, pre-eclampsia, eclampsia, and HELLP syndrome. The next most common thrombocytopenia in pregnancy accounting for 1–4% of all patients is ITP. The absolute frequency in pregnancy is 1 ITP per 1,000–10,000 [138]. Only one-third of cases have been diagnosed beforehand, two-thirds are detected during pregnancy.

Bleeding and Other Risks during Pregnancy

The risk of bleeding for pregnant women with ITP is estimated at 16–22% and is therefore lower than for non-pregnant women with ITP. It is possible that procoagulatory changes of the hemostatic system during pregnancy play a role in the reduced bleeding tendency.

The unborn child is also affected by the mother's ITP because the placental transmission of platelet antibodies can trigger thrombocytopenia in the newborn. The risk is about 5–10%. Intracerebral bleeding occurs at <1.5% and neonatal mortality is <1%.

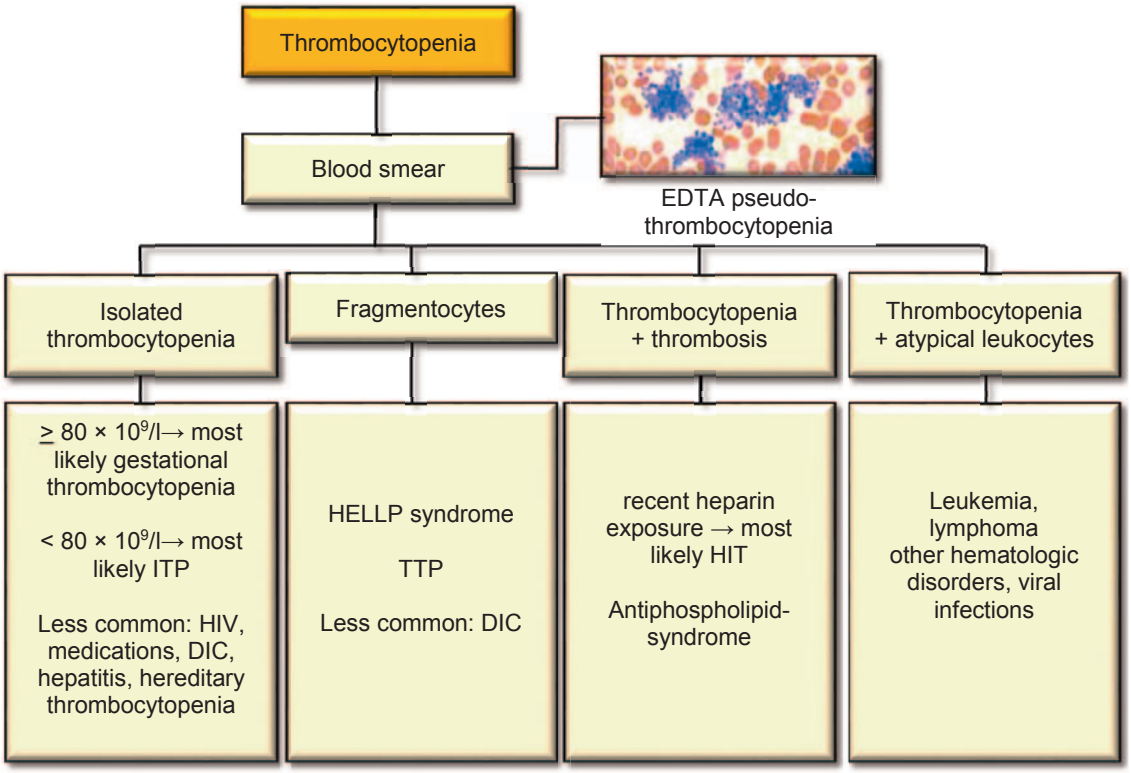

Fig. 2. Differential diagnosis of thrombocytopenia in pregnancy.

Bleeding usually does not affect the fetus in utero as with neonatal alloimmune thrombocytopenia, but during delivery and up to 1 week thereafter [139, 140].

The maternal platelet counts do not correlate with those of the newborn. This is particularly important for splenectomized women. Then, the mother's platelet counts may be slightly decreased or even normal, while the antibody, which has not disappeared after splenectomy, causes a much stronger thrombocytopenia in the child. The only predictive marker is whether thrombocytopenia of the newborn had already occurred in a previous pregnancy [139]. If this is the case, then there is a high likelihood that this will happen again with a subsequent pregnancy.

Diagnostic Workup

No further diagnostic workup is necessary when thrombocytopenia is diagnosed during pregnancy for the first time and when it is mild, e.g., > 100 × 10^9/l. There is a high likelihood that this is gestational thrombocytopenia, which is harmless. For platelet counts < 100 × 10^9/l, a basic diagnostic panel like the one for non-pregnant ITP patients is recommended (see fig. 2 and chapter 'Diagnostic Workup').

When to Treat during Pregnancy

The treatment of ITP during pregnancy is more difficult because one has to consider side effects from medications on both the mother and the fetus. Fortunately, the platelet levels are usually not very low, so only about half of all pregnant women need treatment.

Treatment is usually indicated

- for clinically relevant bleeding,
- before any invasive procedures (e.g., C-section, spinal anesthesia),
- for platelet counts < 20 × 10^9–30 × 10^9/l in the first and second trimesters,
- for counts < 50 × 10^9/l in the last trimester. A platelet count above 50 × 10^9/l is considered sufficient for a C-section and values above 80 × 10^9/l for spinal anesthesia.

Treatment Options in Pregnancy

For a review, see [138].

Steroids (predniso(lo)ne): If this is not an emergency requiring higher doses, one will start with 20–30 mg/day and then try to reduce the dose quickly as long as the platelet counts stay above 20 × 10^9–30 × 10^9/l (usually 10–20 mg prednisone/day). There are no experiences with dexamethasone in pregnancy, but negative effects on fetal development cannot be ruled out.

In addition to the well-known side effects of steroids on the mother (high blood pressure, diabetes, osteoporosis, Cushing's syndrome, etc.), an increased incidence of cleft lip and cleft palate malformations in newborns have been noted recently. However, these malformations are so rare that foregoing steroids simply for fear of this risk does not seem justified.

IVIGs: IVIG treatment is an alternative therapy for pregnant women who might otherwise need higher doses of steroids or if

relevant steroid side effects occur (hypertension, diabetic metabolism, osteoporosis, strong weight increase, psychosis, etc.). Immunoglobulins can be given repeatedly and especially at the end of pregnancy in preparation for childbirth.

Splenectomy: Splenectomy is indicated for severe, otherwise uncontrollable thrombocytopenia and bleeding. If possible, splenectomy should be performed laparoscopically during the 2nd trimester.

Other Treatments

Platelet concentrates may be given for otherwise uncontrollable thrombocytopenia and clinically relevant bleeding (see the section 'Emergency Therapy').

TRAs are contraindicated during pregnancy.

Recently, the successful administration of TPIAO in pregnant women was reported (see the section 'TPIAO'). TPIAO is currently not available in Germany.

Peri- and Postpartum Management

In the past, C-section was recommended to women with ITP on the assumption that the birth trauma and risk of bleeding for the child were lower than with vaginal delivery. Today, the decision to proceed for surgical delivery should not be based on the thrombocytopenia, but solely on the obstetric situation of the mother [141].

Immediately after delivery, the child's platelet count can be measured, e.g. from the umbilical cord blood, and a transcranial ultrasound should be performed. If the newborn has $<20 \times 10^9$ platelets/l, or in case of bleeding signs, give IVIGs and steroids. Counts should be checked for up to 1 week postpartum because the platelet count may need some days to reach its nadir.

Postpartum the mother often has platelet counts $> 50 \times 10^9$/l or even in the normal range because of the treatment she has received before delivery. ITP is a 'prothrombotic' disorder and thromboprophylaxis (compression stockings, low-molecular-weight heparin) should be considered when counts are really high and particularly with reduced mobility (e.g., after C-section) (see the section 'ITP as a Risk Factor for Venous and Arterial Thromboembolism').

ITP in Older Patients and in Patients with Comorbidities and Comedications

Older Patients

For reviews, see [142, 143].

Between 20 and 40% of all ITP patients are >60 years old. In older patients, the ITP incidence is almost twice as high as in younger patients. The ITP of the elderly differs from that in younger patients:

- Bleeding is more common in older patients.
- Elderly patients take more medications and have an increased incidence of drug-induced thrombocytopenia.
- Elderly patients do not respond as well to ITP treatments as younger patients. Side effects are also more common.
- In older patients, other diseases that may present with isolated thrombocytopenia, e.g. MDS, are more easily misdiagnosed as ITP.
- Many older patients have comorbidities.

Comorbidities

Almost two-thirds of all ITP patients over 60 years have comorbidities that affect the course and treatment of ITP. The most common comorbidities are: hypertension, diabetes, cardiovascular disease, neuropsychiatric diseases, pneumonia, anemia, and cataracts.

ITP patients are 3 times more likely than non-ITP patients to develop malignancies and lymphomas [144, 145].

ITP and Anticoagulants

The median age of ITP patients is above 50 years. For this reason, many of them have concomitant cardiovascular disorders that require anticoagulation. At the same time anticoagulants are usually contraindicated with thrombocytopenia. There are only case reports that do not allow evidence-based recommendations for this difficult situation. The authors recommend an approach as outlined in figure 3 for patients with both thrombocytopenia and an urgent indication for therapeutic anticoagulation.

ITP as a Risk Factor for Venous and Arterial Thromboembolism

ITP does not protect against heart attacks, strokes, or thromboses [146, 147]. On the contrary, the risk for venous and arterial thromboembolic events appears to be about 2 times higher in ITP than in matched non-ITP patients. This means for clinical practice that, when an ITP patient presents with typical symptoms, the possibility of venous or arterial thromboembolism should not be ruled out simply because of the patient's thrombocytopenia.

- The risk of venous and arterial thromboembolism is not only increased after the diagnosis of ITP when thrombocytopenia is being treated and platelet counts rise, but also before treatment.
- ITP with a low platelet count ($<50 \times 10^9$/l) also has an increased risk.
- The risk is particularly high:
  - after splenectomy,
  - with rapid platelet rise, e.g., under treatment,
  - in older patients,
- for ITP with antiphospholipid antibodies or lupus anticoagulant [148].

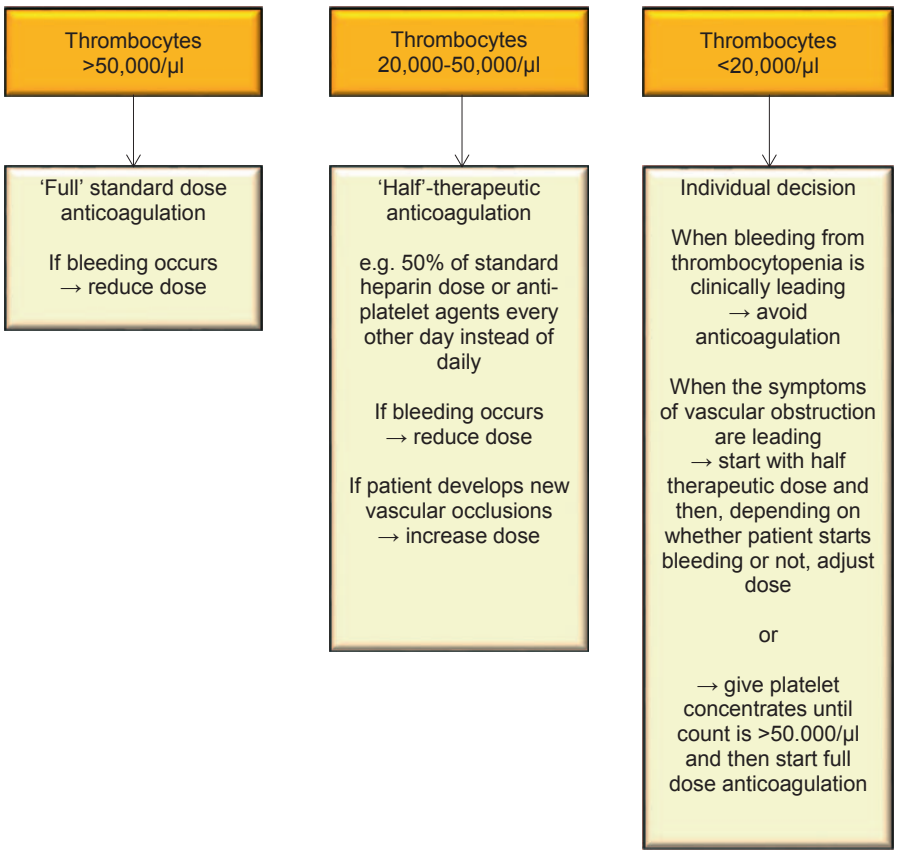

Fig. 3. Thrombocytopenia and anticoagulation.

The reason for this increased thromboembolic tendency in ITP is not clear. Changes in coagulation and fibrinolytic factors and the increased release of microparticles are being discussed.

Therefore, all ITP patients should be educated about the fact that their disease not only has a bleeding risk but also a risk of venous and arterial thromboembolism. They should be informed about the typical symptoms and should also know whom to contact and where to go when they develop symptoms outside the usual working hours and on weekends. Risk factors (e.g., smoking, high blood pressure, hyperlipidemia, etc.) should be addressed and, if necessary, the patient should be referred to a specialist.

Quality of Life

ITP patients have a quality of life close to that of cancer patients, in some cases even worse [149]. This is particularly true during the initial phase of the disease when bleeding symptoms are still frequent and when the patients and their relatives must first learn how to cope with thrombocytopenia [150]. In addition to the bleeding symptoms and low platelet counts, ITP patients experience numerous other limitations:

- ITP-associated non-bleeding symptoms: cognitive impairment, fatigue, weakness, depression,
- increased risk of infection (this is one of the most frequent causes of death in ITP besides bleeding),
- long, sometimes even lifelong therapy,
- side effects of ITP treatments (especially due to steroids) [151],
- gender-specific restrictions (risk of bleeding during pregnancy and delivery, risk of thrombocytopenia in the newborn),
- social stigmatization from visible hematomas (sports, beach, swimming pool),
- increased risks when treating other diseases (increased risk of bleeding from anticoagulation for arrhythmias or coronary heart disease),
- time spent on doctor and hospital visits,
- reduced productivity,
- co-payments and other costs of therapy ('financial toxicity'),
- limited experience of other medical disciplines in dealing with this rare disease and frequent referral and travels to centers with experience in ITP even for simple routine procedures,
- changes in lifestyle,
- restrictions at work and at home, limitations when traveling,
- restrictions or higher costs for health or other insurances.

It does not reflect the true life situation of ITP patients if therapeutic efficacy is defined solely by reducing bleeding symptoms and raising the platelet count. All the above aspects must be considered when deciding on a therapy.

ITP and Sports

ITP patients can participate in sports. This is especially true for children and young adults. At low platelet counts ($<50 \times 10^9$/l), combat and contact sports (e.g., rugby, football, ice hockey) should be avoided; swimming, cycling, athletics are unproblematic [152].

Degree of Disability, Social Rights (Applies only to the Federal Republic of Germany)

The definition of the degree of disability according to the 'Sozialgesetzbuch IX' (SGB IX – Rehabilitation and Participation of Disabled Persons) is based on the 'Versorgungsmedizinische Grundsätze' part B (VMG-B, Principles of Medical Care) [153]. They have no recommendations specific for patients with thrombocytopenia. ITP is subsumed under the group of 'other bleeding disorders'; the following degrees of disability are defined according to no. 16.10 of the VMG:

Bleeding tendency: degree of disability (German law)

- Minor bleeding, without or with only mild effect on daily activities 10%,
- with moderate effects 20–40%,
- with strong effects (heavy bleeding already with minor trauma) 50–70%,
- frequent and clinically relevant bleedings (spontaneous bleeding, risk of life-threatening bleeding) 80–100%.

From the legal standpoint, the actual bleeding tendency only decides about the degree of disability and not on any abstract risk for future major bleedings derived from low platelet counts.

In everyday life, however, patients experience the exact opposite: They have to accept restrictions at work and in social contacts (e.g., refused admission of ITP children to daycare facilities and kindergarten, no participation in school or private sports activities, no access to public civil servant positions), not because of their actual bleeding tendency but because of the potential risk of bleeding and concerns about liability. This discrepancy between being judged as a low risk when the degree of disability and entitlement for financial support is determined and the assessment as a high risk in almost all other areas of life often leads to the feeling of being at the mercy of a social system that is not committed to the patient's well-being. This leads to dissatisfaction with conventional medicine therapies and many patients turn towards alternative forms of treatment.

Complementary and Alternative Methods of Treatment

More than half of all patients with chronic ITP try so-called complementary and alternative methods of treatments. These include vitamins, micronutrients, ginkgo, mistletoe, acupressure, acupuncture, traditional Chinese medicine, colostrum, reiki, magnet therapy, diet change, various diets, but also meditation, psychotherapy, prayers, and many more. The value of such unscientific methods may be debatable. However, many patients feel better and safer, and sometimes alternative treatments are more like an expression of dissatisfaction with conventional medical therapies and the desire to actively contribute to one's own recovery.

From a scientific point it is not possible to recommend or completely reject any of these alternative methods, but every physician who cares for ITP patients should actively ask about them. It cannot be excluded that some naturopathic preparations might interact with ITP treatments. Therefore, the platelet count should be controlled more frequently when patients start taking such alternative therapies.

Adherence/Compliance and Implementation of Guideline Recommendations

Studies show that only a very limited number of guideline recommendations are implemented in routine daily practice. The most frequent deviations by physicians taking care of ITP patients are [154]:

- Blood smear was not examined.
- Bone marrow biopsy was performed without a clear indication.
- Immunoglobulins were given even when the patient did not bleed at all.
- Splenectomy was performed too early (before the 6th month).
- Steroids were prescribed too often and for too long.

But on the side of the patient there are also numerous reasons why guidelines and therapy recommendations are not followed. These must be specifically looked at, especially when a therapy does not achieve the expected response:

- The patient perceives the recommended therapy as too difficult to follow.
- The therapy requires changes in lifestyle.
- Frequent appointments at the doctor's, waiting times and expenses for transport, co-payments are burdensome.
- Even mild side effects may become intolerable when they persist for longer periods.
- Socio-economic status, cultural background.
- Personal distance to conventional medicine, preference for alternative forms of treatment (see the section 'Alternative Treatment Methods').

The following measures are recommended to strengthen patient adherence:

- Provide an ITP passport (analogous to the maternal health passport for pregnant women) or an ITP patient folder (analogous to treatment folders for cancer patients), in which all relevant findings and therapies are recorded with time and therapy response.
- ITP centers with barrier-free access for doctors and (!) patients (table 2).
- Provide contact with self-support groups.
- Provide information material in lay language.

Final Statement

In this guideline, the authors describe the current state of knowledge in the treatment of ITP. All statements are intended exclusively as an aid to medical decision-making and are not suitable for defining a medicolegal standard.

The authors assume no liability for the correctness, completeness, up-to-dateness, quality and availability of the text contents and references. Liability claims against the authors relating to material or immaterial damage caused by the use or non-use of the

information provided or by the use of incorrect or incomplete information are excluded. As far as laws, norms, regulations, or similar contents are quoted, the authors do not guarantee the correctness and/or topicality. In cases of doubt, the original sources must be consulted. The authors accept no liability for information on procedures or applications, forms of application and dosages. Each user is encouraged to determine, e.g., by reading the instructions for use of medical-technical equipment, by studying the instruction leaflet for the preparations used and, if necessary, by additional consultation with a specialist or other literature, whether the recommendation for use or dosage given there or the observance of contraindications differs from the information in this guideline. Any use, application or dosage is at the user's own risk.

The information in this guideline is no substitute for individual professional advice or treatment by a licensed physician with expertise in hematology.

Self-Support Groups and Additional Resources

Self-Support Groups

Germany: ITP-Selbsthilfegruppe Gießen
www.itp-information.de
Contact: Fr. Arnold (via Homepage)

Germany: ITP-Selbsthilfegruppe Sömmerda
Contact: Fr. Riese (s-riese@t-online.de)

USA: Platelet Disorder Support Organization
www.pdsa.org

Great Britain: ITP Support Association
www.itpsupport.org.uk

Additional Resources

International ITP Alliance
www.globalitp.org/

ITP-Foundation, USA
www.itpfoundation.org/itpdefined.htm

European Society for Blood and Marrow Transplantation
www.ebmt.org
This website provides valuable additional information, e.g., an ITP manual in German and English for nurses and other health professionals.

Evidence Levels and Grades of Recommendation

The evidence levels follow the recommendations of the Oxford Centre of Evidence-Based Medicine, as of March 2009 (*www.cebm.net*).

The grades of recommendation, A, B, or 0, follow the recommendations of the 'Nationales Programm für Versorgungsleitilinien' (National Program for Medical Service Guidelines, Method Report of 2010, *www.leitlinien.de*).

Levels of recommendation
- A: Strong recommendation 'must'.
- B: Recommendation 'should'.
- 0: Recommendation open 'can'.
- Expert consensus (EC): There is insufficient scientific data. Notwithstanding, a recommendation should be made that, in the opinion of the majority of experts involved, comes closest to good clinical practice.

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