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Polish recommendations for the management of ITP in adults developed by the Hemostasis Group of the Polish Society of Hematologists and Transfusiologists — update 2024

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Abbreviations used: ANA — antinuclear antibodies; DAT — direct antiglobulin test; DIC — disseminated intravascular coagulation; GCs — corticosteroids; HBV — hepatitis B virus; HCV — hepatitis C virus; HELLP — Haemolysis, Elevated Liver enzymes and Low Platelets syndrome; ITP — primary immune thrombocytopenia; IVIG — intravenous immunoglobulin; PC — platelet concentrate; bw — body weight; MDS — myelodysplastic syndrome; MMF — mycophenolate mofetil; NFZ — National Health Fund; PLT — platelets; RCT — randomized controlled trial; RDTL — rapid/emergency access to drug therapies; TPO — thrombopoietin; TPO-RA — thrombopoietin receptor agonist; VTE — venous thromboembolism

Summary

Primary immune thrombocytopenia (ITP) is a rare disease diagnosed by exclusion of other causes of thrombocytopenia. Nearly 14 years [1] have passed since the publication of the first edition of the Guidelines, during which time significant progress has been made in the treatment of ITP. The main aim of the present work is to update the principles of management in ITP. These recommendations are limited to the treatment of adult patients with ITP. The management of children with this disease will be published separately. Secondary immune thrombocytopenia has also been omitted from these guidelines. Although a platelet response can be achieved in secondary ITP by using the same drugs as in the primary form, the cornerstone of treatment for secondary forms is the removal of the immunization cause. The recommendations were based on research results and guidelines prepared by experts from other countries [2, 3]. The final shape of the document was prepared during consensus conferences involving members of the Haemostasis Group of the Polish Society of Hematology and Transfusion Medicine, which took place in 2023 and 2024. The primary recipients of the recommendations are physicians providing care for patients with ITP, as well as primary care physicians.

Summary for non-specialists

- Primary immune thrombocytopenia (ITP) is an acquired bleeding disorder with a complex pathogenesis and heterogeneous clinical presentation. It may lead to life-threatening bleeding episodes.
- The annual incidence in adults is 2–4 new cases per 100,000 individuals with an estimated prevalence of 9–26 cases per 100,000.
- Diagnosis relies on excluding other causes of thrombocytopenia through medical history, physical examination, and laboratory tests. There is no specific diagnostic test for ITP.
- The goal of treatment is to prevent dangerous bleeding. For some patients, observation alone may be sufficient.
- Eligible for treatment are patients with thrombocytopenia < 20–30 G/L or with higher platelet counts (PLT) if they experience spontaneous bleeding or are at other risk factors for dangerous bleeding such as comorbidities, intake of anticoagulants, surgery, or lifestyle with risk of injury.
- Treatment should be individually tailored to the patient and the phase of the disease. The phases include newly diagnosed ITP (within < 3 months of diagnosis), persistent (3–12 months), and chronic (> 12 months).
- First-line medications include glucocorticoids (GCs) such as prednisone or dexamethasone. For bleeding patients resistant to GCs, intravenous immunoglobulins (IVIG) can be administered. In individuals with Rh-positive blood type, anti-D, IVIG can be used (this medication is not available in Poland).
- Second-line treatment is for patients with persistent or chronic ITP. Among the medications with proven efficacy are thrombopoietin receptor agonists (TPO-RA: eltrombopag, romiplostim, avatrombopag; they activate the same signalling pathways as thrombopoietin and accelerate platelet production) and rituximab (a humanized antibody targeting the CD20 antigen on B lymphocytes). These drugs are available in Poland under the National Health Fund drug program.
- Among the potential second-line medications with proven efficacy are azathioprine, cyclophosphamide, mycophenolate mofetil, danazol, dapsone, and vinca alkaloids (vincristine, vinblastine). They are used when TPO-RAs and rituximab are unavailable or prove ineffective.

- Splenectomy still offers the greatest curative option for patients with ITP. It is considered for patients refractory to second-line pharmacological treatment. It should be performed not earlier than 12 months from the diagnosis of the disease.
- Asymptomatic pregnant women with ITP and platelet count > 20 G/L do not require treatment, just observation. Platelet count should be ≥ 50 G/L at delivery. Prednisone or IVIG are recommended for initial treatment, depending on the clinical situation. The method of delivery depends on obstetric indications.
- In emergency (life-threatening bleeding, urgent surgery), treatment methods that lead to a rapid increase in platelet count are used: IVIG, methylprednisolone, platelet transfusion.
- For patients unresponsive to multiple lines of treatment, the first step is to review the diagnosis. If "refractory" ITP is confirmed, the greatest chance of achieving a platelet response lies in combining medications with different mechanisms of action.
- Treatment for ITP is becoming increasingly effective, but due to the need for individualization and monitoring (especially for TPO-RAs), it should be conducted in specialized centers.

Introduction

Primary immune thrombocytopenia (ITP) is an acquired immune disorder, characterized by isolated thrombocytopenia. It is defined as a disease presenting with a decrease in platelet count (PLT) in peripheral blood < 100 GL in the absence of known causes of thrombocytopenia and/or disorders associated with thrombocytopenia. It was formerly referred to as idiopathic thrombocytopenic purpura (ITP).

Currently, the acronym (ITP) refers to both primary and secondary immune thrombocytopenia. For historical reasons and for the sake of simplifying terminology, in these guidelines we will use the abbreviation ITP in reference to primary immune thrombocytopenia.

The course of ITP is often variable, and the response to treatment is unpredictable, stemming from the complex pathogenesis of the disease. The treatment of ITP can therefore be a challenging task for physicians and should be managed by a haematologist or under hematologic supervision.

Epidemiology

The annual incidence in adults is 2–4 new cases per 100.000 individuals, while the prevalence is estimated at 9–26/100,000. Incidence in individuals < 18 years is higher, from 2–7/100.000/year, but since ITP rarely has a chronic course in children and adolescents, the prevalence in this group is only 4–5/100.000 [4]. The disease may occur at any age, with the average age at diagnosis being around 55 years. The frequency increases in older individuals (twofold in those > 60 years), ITP occurs more frequently in young women (2–3:1), but there is no gender partiality in the > 60 age group.

Clinical symptoms

Bleedings

The initial symptoms of ITP are highly variable, ranging from asymptomatic cases identified during routine blood morphology examination to life-threatening bleeding disorders. Bleeding usually correlates with the degree of thrombocytopenia. In patients with severe thrombocytopenia (< 10–20 G/L, skin and mucosal bleeding may occur, including bruising and petechiae and oral mucosa, as well as nosebleeds. Excessive menstrual bleeding in women is typical. Unlike bleeding disorders due to deficiency in clotting factors, there are no bleedings within the musculoskeletal system in ITP. Massive gastrointestinal bleeding is very dangerous but rare and may be associated with treatment (anticoagulants, glucocorticoids [GCs]). Individuals with severe thrombocytopenia are at increased risk of intracranial hemorrhage. Bleeding can occur spontaneously, due to injury, as a result of treatment, or in association with a concurrent disease.

Other symptoms

A common symptom reported by patients with ITP is a feeling of fatigue, which can be very bothersome. In a study by Kühne et al., fatigue was reported by 58% of individuals with ITP [5]. Compared to the general population, patients with ITP are significantly more likely to experience infections and thrombotic complications, with a 1.5-fold higher mortality risk [6].

Diagnosis

There is no characteristic biomarker for ITP or a single test that allows for the diagnosis of this disease. Therefore, the diagnosis is made via exclu-

ding other causes of thrombocytopenia as based on medical history, physical examination, and laboratory tests. Differential diagnosis should consider: secondary immune thrombocytopenia, thrombocytopenia associated with infection, drug-induced thrombocytopenia, as well as thrombocytopenia related to alcohol abuse, liver cirrhosis, portal hypertension, splenomegaly, increased platelet consumption in thrombotic microangiopathies, disseminated intravascular coagulation (DIC), primary and secondary bone marrow disorders, as well as congenital thrombocytopenia. In the era of SARS-CoV-2, the diagnosis should rule out COVID-19 and vaccination against this disease as possible causes of thrombocytopenia.

Medical history

The diagnostic process should be focused on excluding other causes of thrombocytopenia and determination of the severity of the bleeding disorder. To this aim, it is important to collect information regarding the duration of the disease (since when the bleeding episodes occur, when the lower platelet count was first observed in peripheral blood, and what was the lowest platelet count), the presence of thrombocytopenia in close family members, the type of spontaneous bleeding and its severity (bruising, nosebleeds [frequency, duration of individual episodes, need for additional intervention, spontaneous resolution], menstrual bleeding [duration with assessment of blood loss volume], gastrointestinal bleeding [fresh blood in stool, tarry stools, coffee ground vomitus], hematuria, and others), traumatic bleeding (especially after surgical procedures, dental extractions included), the presence of anemia and the need for iron supplementation, concurrent diseases, alcohol abuse, medications taken (including anticoagulants), history of vaccinations and infections, recent travel history.

Physical examination

In patients with ITP, the physical examination should not deviate from the norm, except for signs of bleeding disorders (bruising, petechiae, subconjunctival hemorrhages). Patients with severe bleeding disorders may present symptoms of anemia. The presence of hepatomegaly, especially splenomegaly and lymphadenopathy, indicate another cause of thrombocytopenia.

Laboratory tests

In cases of isolated thrombocytopenia with no symptoms of bleeding disorder, pseudo hrombocytopenia should be ruled out. To this aim, platelet count should be determined in the blood sample with anticoagulant, other than ethylenediaminetetraacetic acid (EDTA). The most reliable results are obtained using a reagent containing magnesium sulfate (e.g., ThromboEXact) [7].

For all patients suspected of ITP, the following should be performed [2]:

1. complete blood count with platelet count and platelet parametres and peripheral blood smear;
2. reticulocytes;
3. tests for HCV, HBV, and HIV;
4. tests for *Helicobacter pylori* (breath test or stool antigen);
5. immunoglobulin levels (IgG IgA, and IgM);
6. direct antiglobulin test (DAT (formerly Coombs' test);
7. ABO blood group and Rh type.

Blood morphology should be normal, except for a lower platelet count and a higher mean platelet volume (MPV). Thrombocytopenia may be accompanied by anemia due to bleeding. The evaluation of the peripheral blood smear is of crucial importance and should be performed by an experienced diagnostician. In ITP, the blood smear should be normal, except for a lower platelet count and the presence of large platelets. Abnormalities in blood cell morphology help differentiate ITP from other causes of thrombocytopenia. In ITP, red blood cells are usually normal (microcytosis may be present due to chronic bleeding and iron deficiency). The presence of schistocytes is characteristic of thrombotic microangiopathies, macrocytosis is associated with myelodysplastic syndromes and megaloblastic anemias often accompanied by thrombocytopenia. Tear-shaped red blood cells (lacrimocytes) and erythroblasts are diagnosed in myelofibrosis. Detection of Döhle bodies in neutrophils definitely suggests congenital thrombocytopenia associated with *MYH9* gene mutation. The presence of toxic granules in leukocyte cytoplasm indicates infection, atypical lymphocytes may indicate infectious mononucleosis, blast cells are characteristic of acute leukemias and leukocyte immaturity to myeloblasts may be associated with chronic myeloid leukemia or myelofibrosis. Platelet aggregates in individuals with reduced platelet counts suggest pseudothrombocytopenia. Small platelets may indicate Wiskott-Aldrich syndrome or X-linked thrombocytopenia, while large platelets may indicate *MYH9* gene mutation-associated thrombocytopenia, gray platelet syndrome, or platelet-type

von Willebrand disease. Giant platelets are characteristic of Bernard-Soulier syndrome.

Reticulocyte count helps to differentiate ITP from Evans syndrome and thrombotic microangiopathies.

HTV, HBV and HIV diagnostic tests should be performed at the onset of ITP, before the patient receives blood components (immunoglobulins, platelet concentrates [PCs], red blood cells). Thrombocytopenia associated with these infections may clinically resemble ITP and precede other symptoms by many years.

Helicobacter pylori test is recommended in countries where this infection is common, including Poland. Initial immunoglobulin levels are useful in detecting common variable immunodeficiency (CVID), often associated with thrombocytopenia.

A positive direct antiglobulin test result is obtained in about 20% of patients with ITP and overt hemolysis. it is not always determined. Patients with a positive direct antiglobulin test and concurrent anemia and/or reticulocytosis require further diagnosis for Evans syndrome.

ABO blood group and Rh type is significant when the patient is qualified for treatment with intravenous anti-D immunoglobulin (although anti-D immunoglobulin is not available in Poland). Additionally, anyone with a bleeding disorder should always carry information about their blood group.

Bone marrow examination

Bone marrow evaluation is not routinely performed, especially if the diagnosis of ITP is beyond doubt. However, it is recommended in the presence of general symptoms, lack of response to corticosteroids and/or intravenous immunoglobulins (IVIG), before splenectomy, in relapse after splenectomy, and abnormalities in other cell lines. Bone marrow examination should include cytological and histological evaluation, flow cytometry, and cytogenetics. Cytological examination of the bone marrow smear typically reveals numerous megakaryocytes that do not release platelets [2].

Tests with potential utility in diagnosis and treatment of ITP (recommended in some groups of patients and in specific clinical situations)

Testing for the presence of antiplatelet antibodies

Testing for the presence of antiplatelet antibodies is not routinely performed. Characteristic for the tests is high sensitivity and low specificity. Antibodies against epitopes on platelet glyco proteins Ib/IX and IIb/IIIa are detected in 60–80% of patients. Only platelet-bound antibodies (not free) are of diagnostic significance. Their determination may be helpful in distinguishing ITP from other causes of thrombocytopenia, but it does not allow differentiation between primary and secondary ITP [8].

Antiphospholipid antibodies

Antiphospholipid antibodies are detected in approximately 25–30% of adult patients with ITP. Their presence may increase the risk of thrombosis; however, they do not affect the response to treatment [9, 10]. They are not routinely determined but only in cases of suspected antiphospholipid syndrome (previous or current venous or arterial thrombosis, history of pregnancy loss).

Antithyroid antibodies, TSH, FT3, and FT4

Clinical symptoms of hyperthyroidism are observed in 8–14% of individuals with ITP during long-term follow-up [11]. Additionally, mild thrombocytopenia may occur in both hyperthyroidism (due to shortened platelet lifespan) and hypothyroidism (due to decreased platelet production).

Antinuclear antibodies (ANA)

A positive result of the ANA test is found in up to 33% of ITP patients, especially those with a chronic form of the disease [12]. Young women with ITP and elevated ANA titers respond well to treatment with hydroxychloroquine [13]. ANA tests may be considered before splenectomy due to increased thrombotic risk.

Pregnancy test in women at childbearing age

Pregnancy can both trigger and exacerbate ITP. It also affects the type of treatment for ITP because many medications are not allowed. During pregnancy, specific platelet disorders such as gestational thrombocytopenia and HELLP syndrome (hemolysis, elevated liver enzymes, low platelet count) may occur, as well as disseminated intravascular coagulation (DIC) and thrombotic microangiopathies.

PCR tests for Epstein-Barr virus, cytomegalovirus, and parvovirus B19

Acute or persistent infections with these viruses may cause or exacerbate thrombocytopenia.

Table 1. Indications for treatment of patients with ITP

1) Platelet count < 20–30 G/L
2) Platelet count < 20–30 G/L and:
– spontaneous bleeding
– necessity of using anticoagulant or antiplatelet drugs
– coexistant diseases that increase bleeding risk
– surgery or invasive diagnostic procedures
– patient's lifestyle with exposure to injuries

PLT — platelet count

Table 2. Recommended platelet count for surgical procedures and antithrombotic therapy in patients with ITP

Procedure/Drug	Platelet count (G/L)
Conservative dental treatment	≥ 20–30
Tooth extraction	≥ 30
Complex tooth extraction	≥ 50
Regional anesthesia	≥ 30
Minor surgical procedure	≥ 50
Splenectomy	≥ 50
Major surgical procedure	≥ 80
Major neurosurgical procedure	≥ 100
Antiplatelet or anticoagulant medication	≥ 30–50
Dual antiplatelet therapy or antiplatelet medication + anticoagulant medication	≥ 50–70

The concentration of endogenous thrombopoietin

In persons with ITP, the concentration of endogenous thrombopoietin (TPO) is typically normal, whereas in patients with central thrombocytopenia (bone marrow failure), it is significantly higher. Further research is needed to determine the utility of this parameter for predicting the response to treatment with thrombopoietin receptor agonists (TPO-RAs) [14, 15].

Therapeutic management in ITP

Qualification for treatment and general treatment principles

ITP is a heterogeneous disease in terms of pathogenesis and clinical course, as well as response to treatment [16]. Therefore, therapeutic management of ITP is often a challenging task for physicians. The primary goal of ITP management is to protect the patient from severe bleeding. To this aim, it is crucial to increase the platelet count to levels that ensure effective hemostasis. Most authors consider the platelet count of ≥ 30 G/L as the minimum for hemostasis. Portielje et al. demonstrated no difference between mortality risk in patients with ITP and a platelet count > 30 G/L and the general population, the risk however increased when the platelet count of < 30 G/L was maintained [17]. It should be kept in mind however that the platelet count does not always correlate with bleeding severity. The risk of bleeding also depends on the patient's age, lifestyle, concomitant diseases, and medications. The principles of qualifying ITP patients for treatment (indications for treatment) are presented in Table 1. A significantly higher platelet count is required to ensure hemostasis during invasive procedures and surgical interventions (Table 2). Considering that the risk of bleeding depends on many different factors, the approach should be individually tailored to the patient and the phase of the disease. Due to the duration of ITP, it is classified as newly diagnosed (< 3 months from diagnosis), persistent (3–12 months from diagnosis), or chronic (> 12 months) [18]. This classification has prognostic significance and is taken into account when making therapeutic decisions. Spontaneous remissions are common in individuals with newly diagnosed ITP, but rare in the chronic phase of the disease. On the other hand, life-threatening

Table 3. General principles of treatment for patients with ITP

1. Treatment individually tailored to the patient and phase of the disease
2. Treatment to prevent severe bleeding episodes
3. Sustain platelet count above 20–30 G/L
4. Prioritize minimal toxicity
5. Optimize health-related quality of life

intracranial hemorrhages are more likely to occur in the early stages of the disease than in the chronic phase [19, 20].

During the last 5 years, new management guidelines for immune thrombocytopenia (ITP) have been developed by the German-Swiss Joint Working Group of the German, Austrian, and Swiss Societies of Hematology and Medical Oncology (DGHO, ÖGHO, SGH, GPOH, and DGTI) — JWG, along with two updates from the American Society of Hematology (ASH) and the International Consensus Report (ICR) [2–4]. The development of new guidelines was necessary because about 10 years have passed since the last update [21, 22]. During this time experience with new drugs was accumulated. Contrary to earlier opinions, 1/3–2/3 of patients in the chronic phase of ITP may have spontaneous, partial, or even complete remission. Therefore, especially in the chronic phase of the disease, the priority was to improve the quality of patient's life and avoid adverse effects of medications. Provan et al. outlined five main principles of treatment, as presented in Table 3 [2].

To evaluate the effectiveness of treatment, the criteria of the International Working Group should be used [18]. The platelet response is defined as an increase in the platelet count to ≥ 30 G/L with at least a 2-fold increase from baseline in the absence of bleeding (measured twice with an interval of > 7 days): early response — after 7 days, initial response — after one month, sustained response — after 6 months of treatment. Complete response, on the other hand, is defined as an increase in the platelet count to ≥ 100 G/L (measured twice with an interval of > 7 days).

First line treatment in adults with ITP

First-line treatment for ITP has not been significantly changed for several decades. The same drugs are still in use: corticosteroids, IVIG, and intravenous anti-D immunoglobulin (Table 4). These drugs act quickly, but for most patients, they do not lead to a lasting platelet response. The choice of medication depends on the clinical situation. When the bleeding disorder is stable with no life-threatening hemorrhages, the treatment usually begins with corticosteroids. This is effective in over 70% of patients, but most of them experience a relapse of thrombocytopenia when the dose is reduced or corticosteroids are discontinued. In the recent guidelines from international experts, there is a trend toward shortening corticosteroid treatment and/or using smaller doses to minimize the risk of adverse effects [2]. The initial dose of prednisone is typically 1 mg/kg body weight, not exceeding 80 mg/day, and the duration of treatment, which depends on the platelet response, should not exceed 2, exceptionally 3, weeks. Although treatment with prednisone remains the gold standard, according to some researchers, both the dose and the duration of administration should be re-evaluated in light of the potential side effects. The percentage of initial responses as well as durable remissions can be achieved by using oral dexamethasone at a dose of 40 mg/day for 4 days with the possibility of repeating the cycle every 2–4 weeks. The results of recent studies do not confirm greater efficacy of dexamethasone; however, they indicate a shortened time to platelet response [23]. Therefore, according to ASH guidelines, dexamethasone should be the preferred treatment option if rapid increase in platelet count is desired [3]. An additional advantage of dexamethasone pulses is the less frequent occurrence of Cushing's syndrome symptoms [24].

IVIG should be additionally administered to individuals with severe bleeding episodes or at high risk of life-threatening bleeds and those on therapy. Typically, they are administered at a dose of 1 g/kg body weight per day for 1–2 days or 0.4 g/kg body weight per day for 5 days. Platelet response is usually achieved within 1–4 days, and the increase in platelet count is maintained for 1–4 weeks. Anti-D immunoglobulin can be used instead of IVIG in Rh-positive individuals. As mentioned earlier, this medication is not available in Poland.

In most adults with ITP discontinuation of corticosteroids leads to relapse of thrombocytopenia (platelet count < 30 G/L). In a small percentage of cases, the disease can be controlled with low

Table 4. Initial treatment of newly diagnosed ITP

1. Stable condition, low risk of severe bleeding:
1) Prednisone at 1 mg/kg per day (maximum dose 80 mg/day) for no longer than 2–3 weeks. Once platelet count is above 50 G/L, gradually reduce the dose and discontinue within 6–8 weeks from the start of treatment. If there is no platelet response during the first 2 weeks of prednisone therapy, discontinue the medication within 7 days.
or
2) Dexamethasone at 40 mg/day for 4 days, repeated for 1–3 courses (shorter time till platelet response) — preferred if a rapid platelet response is desired. Prolonged use of corticosteroids should be avoided due to adverse effects. The only exception are patients in whom chronic low-dose prednisone (≤ 5 mg/day) allows to maintain platelet count at a hemostatic level.
2. High risk of serious bleeding or unresponsive to corticosteroids:
Additional IVIG at 0.4 g/kg per day for 5 days or 1.0 g/kg per day for 1–2 days. In cases of contraindications to corticosteroids, IVIG is the only initial treatment option. Subsequent doses of IVIG should be administered every 2–3 weeks to maintain platelet count above 30 G/L, not longer than the end of the newly diagnosed ITP phase.

Anti-D immunoglobulin is not included in the recommendations because it is unavailable in Poland.
GCs — glucocorticosteroid(s); IVIG — intravenous immunoglobulins; PLT — platelets

doses of corticosteroids (prednisone 2.5–5 mg/day), which do not cause significant adverse reactions [2]. Even nowadays, a common mistake is a long term use of high corticosteroid doses to maintain a platelet response. Such practice exposes patients to severe corticosteroid-related complications, which may prove more dangerous than the disease itself.

Second-line treatment (persistent/chronic ITP)

When initial treatment is ineffective in terms of sustained increase in platelet count, sufficient hemostasis and risk of severe bleeding patients qualify for a change in therapeutic approach (Table 5). If there is no platelet response after treatment with glucocorticoids (GCs) and intravenous immunoglobulin (IVIG), the diagnosis requires revision. This also applies to patients who experience a significant increase in platelet count after administration of IVIG. In the first scenario, the differential diagnosis should include both secondary immune thrombocytopenia and non-immune-related thrombocytopenias.

Patients with confirmed ITP qualify for a change of treatment. Until the early 21st century, splenectomy was the gold standard for second-line treatment. With the introduction of modern, effective medications for ITP, splenectomy is performed less frequently. It is recommended to postpone the procedure by ≥ 12–24 months of diagnosis because spontaneous remission may occur [2].

At this stage, TPO-RA and rituximab are the preferred groups of drugs [2, 3].

Agonists of the thrombopoietin receptor

The efficacy and safety of TPO-RA have been demonstrated in large randomized controlled trials (RCTs). The therapy is costly and available only in affluent countries where it is reimbursed by the government. The use of TPO-RA in second-line treatment (before splenectomy) in Poland became available only in 2023 with the introduction of the drug reimbursement program.

Unlike other drugs used in ITP therapy, TPO-RA stimulates platelet production. Three drugs from this group are in use: romiplostim, eltrombopag, and avatrombopag. TPO-RA drugs bind to the thrombopoietin receptor (TPO-R), also known as the MPL receptor. This leads to phosphorylation and activation of JAK2 — STAT5 signalling pathways, as well as differentiation of hematopoietic cells into megakaryocyte precursors. This process facilitates cell maturation into megakaryocytes that release platelets.

TPO-RA differ in many aspects: chemical structure, receptor binding site as compared to endogenous TPO, form, route of administration, dosage, and side effects (Table 5a). Their common feature is high effectiveness in treating ITP. Over 60% of patients with chronic ITP, both splenectomized and with preserved spleen, achieve platelet response. In some cases resistant to TPO-RA, a suboptimal platelet response can be achieved by adding small doses of prednisone [15]. Platelet count increase is maintained during treatment for ≥ 6–8 years, as demonstrated in clinical studies [25]. The efficacy and safety of TPO-RA in the second-line treatment of ITP have been confirmed in randomized controlled trials (RCTs) as well as in single-arm studies with long-term use [25–27].

Table 5. Second choice pharmacological treatment for ITP

1. Preferred group of drugs are TPO-RAs as part of the drug program: romiplostim or eltrombopag or avatrombopag[a]
2. Medication doses should be adjusted to maintain 50–150 G/L platelet count

1) Romiplostim — initial dose of 1 μg/kg body weight once weekly, with an increase of 1 μg/kg body weight per week (maximum 10 μg/kg body weight) until platelet response (platelet count > 50 G/L); treatment with romiplostim at a dose of 3 μg/kg body weight is suggested when a rapid response is desired due to the risk of severe bleeding.

2) Eltrombopag — initial dose of 50 mg orally once daily, maximum dose of 75 mg daily.

3) Avatrombopag — initial dose of 20 mg orally once daily, maximum dose of 40 mg once daily.

[a]Avatrombopag registered solely for the treatment of chronic ITP
PLT — platelets; TPO-RA — thrombopoietin receptor agonists

Table 5a. Second choice pharmacological treatment for ITP

Assessed Parameter	Romiplostim	Eltrombopag	Avatrombopag
Chemical Structure	Fusion protein	Non-peptide small molecule	
Binding Site on TPO-R relative to endogenous TPO	Same site	Within the transmembrane domain of the receptor	
Dosage Form	Vial	Tablet	Tablet
Route of Administration	Subcutaneous (s.c.)	Oral (p.o.)	Oral (p.o.)
Food Interactions	None	Some interactions	None
Dosage	1–10 μg/kg mc./week	25–75 mg/day	5–40 mg/day
Efficacy	High (++)	High (++)	High (++)
Immunogenicity	+ (positive)	None	None
Thromboembolic complications	+	+	+
Hepatotoxicity	None	+	None
Cataracts	None	Unconfirmed	None
Bone marrow fibrosis	+	+	+
Clinically Significant bone marrow fibrosis	Not observed	Not observed	Not observed

[a]with some see text
p.o. — orally; s.c. — subcutaneously; TPO — thrombopoietin; TPO-R — thrombopoietin receptor

A drawback of TPO-RA is the need for prolonged use. After discontinuation, the platelet count returns to baseline values within 2 weeks.

Chronic stimulation of the MPL receptor may increase the risk of thromboembolic complications and bone marrow fibrosis. Thrombotic complications may occur after a sudden increase in platelet count above the normal range following TPO-RA therapy. Therefore, during treatment, platelet count should be monitored and the dose adjusted accordingly. Bone marrow fibrosis may be associated with megakaryopoiesis stimulation and increased production of transforming growth factor β_1 (TGF-β_1). However, long-term observations indicate that bone marrow fibrosis affects only a small percentage of patients, is usually clinically insignificant, and resolves after discontinuation of TPO-RA [28]. For safety reasons, periodic examination of peripheral blood smears is recommended, and in justified cases, histological examination of the bone marrow with staining for the presence of reticulin and collagen fibers.

A significant challenge in clinical practice, are considerable fluctuations in platelet counts observed in some patients, especially in the initial period of TPO-RA therapy. An increase in platelet count above reference values may bring about thrombotic complications, while a sudden decrease may lead to dangerous bleeding. Fluctuations in platelet count should be closely monitored and may warrant a change in TPO-RA [29].

Romiplostim is a fusion protein consisting of an Fc domain responsible for prolongation of half-life, coupled with two peptide chains containing

four sites that interact with the MPL receptor. Romiplostim binds to the receptor in the same location as endogenous TPO. It is administered once a week via subcutaneous injections. The initial dose is 1 μg/kg of body weight per week, adjusted thereafter based on platelet count. The maximum weekly dose is 10 μg/kg body weight. A small fraction of patients may develop antibodies against romiplostim, leading to loss of platelet response. These antibodies do not neutralize endogenous TPO.

Eltrombopag is a small-molecule organic compound for oral administration. It binds to the transmembrane portion of the MPL receptor, unlike endogenous TPO and romiplostim. Eltrombopag is taken orally at a dose of 25–75 mg/day (starting dose of 50 mg/day, reduced to 25 mg/day for individuals of Asian descent), adjusted based on platelet count. Eltrombopag should be taken at least 2 hours before or 4 hours after consuming products such as antacids, dairy, or mineral supplements containing multivalent cations to avoid significant reductions in eltrombopag absorption caused by chelation. Eltrombopag may exhibit hepatotoxic effects; liver function (aminotransferase activity and bilirubin levels) should therefore be monitored. Studies on rodents suggested an increased risk of cataracts associated with eltrombopag, but this has not been confirmed in humans.

Avatrombopag was the last to be registered for ITP treatment, but only for the chronic phase of the disease in adults resistant to other treatment methods (e.g., corticosteroids, immunoglobulins). It is a small- molecule non-peptide compound for oral use. Like eltrombopag, it binds to the transmembrane portion of the receptor. The initial dose of the drug is 20 mg/day, which is then adjusted according to the platelet count, up to a maximum of 40 mg/day. Unlike eltrombopag, avatrombopag does not interact with food and does not exhibit hepatotoxic effects.

The choice of thrombopoietin receptor agonist (TPO-RA)

Up to date, there have been no studies on direct comparison of the efficacy and safety of romiplostim, eltrombopag, and avatrombopag. Indirect analyses suggest comparable efficacy of these drugs in ITP therapy [30, 31]. The choice of TPO-RA depends on registration indications, availability, comorbidities, side effects, physician's experience, the patient's preferences (Table 6). Avatrombopag is registered for treatment of chronic ITP, so it is to be administered only a year after the diagnosis (as of January 2024). Romiplostim, administered subcutaneously, will be the first choice drug for individuals with absorption disorders. Like avatrombopag, it will also be safer than eltrombopag for patients with liver diseases. On the other hand, patients may prefer eltrombopag and avatrombopag due to the oral route of administration. The longest period of experience is with romiplostim and eltrombopag, which were approved for ITP treatment in 2009 and 2010, respectively.

Table 6. Factors effecting the choice of TPO-RA

1) Drug availability
2) Coexisting diseases
3) Coexisting diseases
4) Coexisting diseases
5) Coexisting diseases
6) Toxicity/adverse effects

Due to the differences in the chemical structure and receptor interaction sites of these drugs, when one of them fails or the patient proves unresponsive, switching to another TPO-RA drug allows to achieve or restore a platelet response in most cases [29, 32]. Therefore, all three drugs from this group should be available for the treatment of patients with ITP.

Attempts at discontinuation of thrombopoietin receptor agonist

Until recently, it was believed that to maintain a platelet response to TPO-RA, chronic use of these drugs was required. Data from phase II and III of randomized controlled trials (RCTs) confirmed this. Within 2 weeks of drug discontinuation, the platelet count returned to baseline or even fell below the threshold. Later observations however — especially those from studies on long-term use of TPO-RA — indicate that in some patients, the platelet response persists after discontinuation of the drug. Based on a published meta-analysis, it can be expected that approximately 18% of patients will not require further treatment after discontinuing TPO-RA [33]. As of now, it has not been established which ITP patients can achieve long-term remission. Based on expert panel consensus, gradual dose reduction until discontinuation of TPO-RA may be considered after 6–12 months of treatment in individuals with a platelet count persisting > 50 G/L in ≥ 75% of measurements. However, an optimal approach calls for long-term prospective studies [34].

Other drugs used in the second-line treatment of ITP

Rituximab

It has been successfully used in the treatment of ITP for over 20 years, although it is not registered for this indication. Rituximab is a chimeric, humanized antibody targeting CD20 antigens on B lymphocytes. In the treatment of ITP, it is administered intravenously at a dose of 375 mg/m^2 repeated weekly for a total of 4 doses. Lower doses (100 mg/m^2 weekly for a total of 4 doses) may also be effective, but it takes longer to achieve a response. Literature data indicate that approximately 60% of patients with ITP respond to treatment, and 20% remain in remission after 5 years [35]. The increase in platelet count most commonly occurs 1–8 weeks after the first dose of the medication. The greatest efficacy of rituximab has been demonstrated in young women (< 40 years old) with ITP lasting ≤ 2 years [36]. Rituximab is contraindicated in patients with confirmed active hepatitis B, while individuals with present antibodies to HBc, should be administered prophylaxis against HBV reactivation. In Poland, rituximab can be used in the treatment of ITP as part of the National Health Fund (NFZ) drug program.

Fostamatinib

Fostamatinib (available in Poland under the Rapid/Emergency Access to Drug Technologies [RDTL] since January 2024) is a spleen tyrosine kinase (SYK) inhibitor, which has been registered for the treatment of adult patients with chronic ITP and inadequate response to other treatment methods as based on the results of Phase III trials [37]. This medication, at an initial dose of 100 mg twice daily or 150 mg twice daily if there is no response, increased the platelet count to ≥ 50 G/L in 43% of patients. The response rate reached 78% with fostamatinib used as second-line treatment. The median time to platelet response was 15 days. In over half of the patients, the platelet response was sustained during long-term treatment [38]. Fostamatinib is well-tolerated; most adverse events are mild and unrelated to the drug. The most common side effects are diarrhea and arterial hypertension. An additional advantage of fostamatinib is its beneficial effect on the course of COVID-19 [39]. Unlike TPO-RA, it does not increase the risk of thrombosis [40]. The drug is very expensive, but funding can be applied for under the RDTL.

Which drug to choose?

Effectiveness expressed by long-term platelet response favours the use of TPO-RA. Drugs from this group are also safer than immunosuppressive drugs increased risk of COVID-19. TPO-RA treatment however, is costly and long, whereas rituximab is administered only for 4 weeks.

The choice between TPO-RA and rituximab largely depends on the patient's preferences [3]. If quick results and short-lasting therapy are the priority, starting with rituximab may be the answer.

On the other hand, individuals seeking high treatment effectiveness and accepting long-term therapy are candidates for TPO-RA. When the patient is unresponsive to TPO-RA, an attempt to use the second or even the third drug from this group is indicated. If this approach proves ineffective, switching to rituximab is recommended (Table 7).

Fostamatinib should be reserved for patients resistant to both TPO-RA and rituximab.

Further treatment of ITP; drugs of lower efficacy and/or greater toxicity

This group of drugs includes "old immunosuppressive drugs", danazol, dapsone, and vinca alkaloids (Table 8). They are less effective than the drugs previously discussed and are more toxic. Their main advantage is low cost. For this reason, until recently, they were the primary drugs used in second-line treatment of ITP in Poland. With the access to TPO-RA and rituximab, they are not recommended anymore. Nevertheless, according to the experience of the authors' of these recommendations, there is still a group of Polish patients who benefit from the use of these drugs.

Immunosuppressive drugs (oral)

This group includes azathioprine, cyclosporine, mycophenolate mofetil (MMF), and cyclophosphamide, which inhibit the production of antiplatelet antibodies. Their efficacy has not been demonstrated in large RCTs. They increase the risk of infection. An additional drawback of immunosuppressive drugs is their delayed onset of action, which limits their usefulness in patients with severe bleeding symptoms. Platelet counts increase no earlier than 2 weeks after starting immunosuppressive therapy, and treatment failure can be inferred only after 3 months of treatment. In Poland, they were the primary drugs used in second-line ITP treatment until 2023, when the TPO-RA drug program was introduced. However, it is important to remember that a certain group of

Table 7. When TPO-RA treatment fails

Loss of platelet response or unresponsiveness to TPO-RA, calls for attempts with a second and, if unsuccessful, a third drug from this group. If treatment is still ineffective, it is recommended to:
1) administer rituximab i.v. 375 mg/m^2 every 7 days for 4 weeks (4 doses) — treatment under the National Health Fund's drug program
or
2) perform splenectomy (provided > 12 months have elapsed since diagnosis).

i.v. — intravenously

Table 8. Further treatment of ITP if TPO-RA and rituximab are unavailable

Options:
1) Azathioprine po at 1–2 mg/kg, response to treatment within 4 months
2) Cyclosporine po at 2.5–3 mg/kg, response within 3–4 weeks
3) Mycophenolate mofetil po at 0.5–1.0 g twice daily, response within 4–6 weeks
4) Cyclophosphamide po at 1–2 mg/kg or i.v. at 0.3–1 g/m^2, 1–3 doses every 2–4 weeks
5) Danazol po at 2–4 × 200 mg/day, response within 2 weeks to 3 months
6) Dapsone po at 50–100 mg/day, response within 4 weeks

i.v. — intravenously, *p.o.* — oral

ITP patients still receive these drugs if they have proven effective.

Azathioprine is the only immunosuppressive drug registered for the treatment of ITP. It is administered at a dose of 50–200 mg/day (Table 8). Its full effect in ITP may only become apparent after several months. Long-term remission was achieved in 51.2%, 64.2%, and 38.1% of patients in three clinical studies [2, 41]. Half the patients responsive to the treatment required chronic use of the medication. Azathioprine can be used during pregnancy and lactation. Attempts have been made to combine this drug with danazol; data indicating the benefits of this approach is however insufficient. Azathioprine is a prodrug degraded into its active form by thiopurine S-methyltransferase (TPMT). TPMT deficiency occurs in 0.25% of the population, and the use of azathioprine in this group may result in severe cytopenia, and TPMT activity should be assessed through a blood test.

Cyclosporine treatment of ITP either as monotherapy or in combination with prednisone. The initial dose is 3–6 mg/kg body weight per day [3]. The dosage of the medication is then adjusted based on its concentration in the blood. In two studies, platelet response was achieved in 37.8–56.7% of patients after one month and a sustained response was observed in 23.3–44% [42, 43]. Frequently occurring adverse effects such as nephrotoxicity, gingival hyperplasia, arterial hypertension, and nausea limit the long-term use of cyclosporine.

Mykophenolate mofetil (MMF) is an ester of mycophenolic acid with cytostatic effects on T and B lymphocytes. Because it is better tolerated, it is now used more frequently than cyclosporine. MMF acts gradually. About 15% of patients show a platelet response on day 7, while around 50% respond after one month of treatment; a durable response can be achieved in 57–62% of patients [3, 44, 45]. During treatment, blood morphology should be monitored due to the risk of neutropenia, anemia (including selective red blood cell aplasia).

Cyklofosfamid is an organic chemical compound of the cyclic diamidophosphates group. It is rarely used for ITP therapy due to numerous side effects including bone marrow suppression, hair loss, hemorrhagic cystitis, and irreversible ovarian dysfunction. Since 2005, no studies regarding the efficacy of cyclophosphamide in ITP have been published. In two earlier studies, platelet response was achieved in 10% and 70% of patients after one month of treatment [3, 46]. On the other hand, in the case of long-term use of the drug, a sustained response occurred in 60% of patients [47].

Other drugs used for treatment of ITP

Danazol is a synthetic derivative of 17α-ethinyl testosterone. Its mechanism of action in ITP remains unclear. On one hand, danazol binds to steroid receptors, enhancing the action of glucocorticoids (GCs), on the other , it reduces the binding sites for Fc fragments on monocytes. It is administered orally at 200 to 800 mg/day for the treatment of ITP.

Clinical studies have shown platelet response rates in the first month of treatment ranging from 24% to 58% of patients [3]. In a large retrospective analysis involving 319 patients, danazol monotherapy was effective in 63% of cases, while in combination with GCs, it was effective in 48% of ITP patients [48]. Combined treatment resulted in fewer relapses of thrombocytopenia. The main adverse effects are virilization in women and hepatotoxicity.

Dapsone is a medication of the sulfa group, exhibiting bacteriostatic and bactericidal properties. Traditionally used in the treatment of leprosy, it also finds application in conditions like dermatitis herpetiformis and other dermatoses, as well as for prevention against malaria and pneumocystosis. Dapsone has been used in the treatment of ITP since the late 1980s. It is an inexpensive and well-tolerated drug; however, its broader use in ITP has been limited due to the lack of understanding of its mechanism of action and the absence of data regarding its efficacy and safety profile. It is speculated that dapsone-induced hemolysis may limit the phagocytosis of platelets by splenic macrophages [49]. In the treatment of ITP, dapsone is administered orally at a dose of 75–100 mg/day. Platelet response can be achieved in 40–62% of patients [50]. The increase in platelet count typically occurs after 4 weeks. Although dapsone is well-tolerated, it may induce hemolytic anemia and methemoglobinemia. Individuals with glucose-6-phosphate dehydrogenase deficiency are particularly prone to symptomatic hemolysis. Dapsone is not approved for sale in Poland and has not been registered for use in ITP. This medication can only be obtained in Poland through targeted import.

Alkaloids of Vinca rosea (Vinca rosea alkaloids) belong to antineoplastic drugs that inhibit mitosis. Their mechanism of action in ITP is probably related to the inhibition of platelet phagocytosis. Vincristine is administered intravenously at a dose of 1–2 mg per week (total dose of 6 mg), and vinblastine at a dose of 10 mg per week (total dose of 30 mg). An increase in platelet count usually occurs on days 7–10 and affects 10–75% of patients. The response is typically short-lived and lasts for 3–8 weeks. Due to the transient increase in platelet count and neurotoxicity, these drugs are rarely used in the treatment of ITP [2, 3].

Choice of drug: These drugs should be administered only if TPO-RA and rituximab are unavailable or have proved ineffective. The physician chooses the drug according to his experience, knowledge of the mechanisms of action, adverse effects, comorbidities, and drug availability. In Poland, azathioprine, danazol, cyclosporine, and MMF have been most commonly used. Awaiting the effect of these drugs, in the initial period of treatment of severe ITP, it is recommended to administer also corticosteroids and IVIG.

Splenectomy

The generally accepted indications for splenectomy for patients with chronic ITP include severe thrombocytopenia (platelet count < 10 G/L) or a high risk of bleeding with a platelet count < 30 G/L, along with the need for chronic corticosteroid therapy to maintain a "safe" platelet count [51]. According to an international group of experts, splenectomy should be deferred for ≥ 12–24 months of diagnosis of ITP, i.e., it should be performed in the chronic phase of the disease, because spontaneous remission may occur [2]. However, if bleeding persists despite multi-line pharmacotherapy, the decision of earlier splenectomy may be fully justified.

Efficacy of splenectomy in ITP

Amongst all the treatment methods for ITP, splenectomy offers the greatest chance of a lasting cure. The spleen is the main organ where platelet sequestration and destruction processes occur, and platelet-targeting antibodies are produced. An analysis involving 1223 laparoscopic splenectomies showed a 92% early response rate and a 72% sustained response rate 5 years after surgery [52]. In a study of 2623 adults with ITP who underwent splenectomy, Kojouri et al., observed complete remission without additional treatment throughout the entire follow-up period (1–153 months, median 29 months) in 66% of patients [53].

A high rate of sustained remissions, up to 80%, has also been observed in children with ITP [54]. The results of a retrospective analysis of long-term outcomes of splenectomy in 233 patients with ITP were presented by Vianelli et al. [55]. Early complete response (platelet count > 100 G/L) was achieved in 77%, and partial response (platelet count 30–100 G/L and at least double baseline) in 11% of patients. 68 (33%) individuals in this group experienced relapse of thrombocytopenia, most commonly (75%) within 4 years after splenectomy. 138 patients maintained a platelet response throughout the entire ≥ 10-year follow-up period with no need for any additional treatment. The results of the aforementioned analyses were from the pre-TPO-RA era, and rituximab was then also used only in a small number of patients. Mageau et al tried to determine whether splenectomy rema-

ined an effective treatment for ITP in individuals unresponsive to TPO-RA and rituximab [56]. They presented the results of splenectomy performed on 185 patients with ITP, the majority of whom had previously been unsuccessfully treated with TPO-RA (n = 100; 54.1%) and/or rituximab (n = 135; 73%). Early and sustained responses in the entire study group were observed in 77.8% and 65.4% of patients, respectively. A sustained response was noted in 61% of individuals previously treated with TPO-RA and/or rituximab. In 13 out of 21 participants (62%) previously unsuccessfully treated with TPO-RA, return to administration of these drugs after splenectomy failed had proved effective. Splenectomy remains an important treatment method for chronic ITP, especially in cases of resistance to TPO-RA and in patients who wish to avoid prolonged treatment.

Predicting response to splenectomy

A crucial issue for decision about TP therapy is the exclusion of patients who do not qualify for splenectomy due to a high likelihood of resistance to this treatment. The issue however is still unresolved. Among clinical data such as age, gender, disease duration, response to corticosteroids and/or IVIG and the number of ITP treatment lines, only younger age at the time of the procedure appears to be an independent predictive factor for remission [53]. According to some authors, a platelet count of $> 70–80 \times 10^9$/L before splenectomy or $> 140 \times 10^9$/L after the procedure is a favourable prognostic factor. However, this correlation has not been confirmed in other reports [57–60]. Currently, there is no reliable laboratory test to predict the effectiveness of splenectomy in patients with ITP. Preoperative location of the autologous platelet destruction site stained with indu 111 isotope (^{111}In) in scintigraphy may be helpful. With predominant spleen uptake the outcome of the procedure is approximately 90%. This test is unavailable in Poland.

Adverse effects of splenectomy

Splenectomy in ITP is most commonly performed with the laparoscopic method. It is safer than the classical one and equally effective. The most important adverse effects include: excessive bleeding, infection, thrombosis, and need for additional intervention or invasive procedures The incidence of complications and perioperative mortality with laparotomy is approximately 12.9% and 1.0%, respectively, while with the laparoscopic method, approximately 9.6% and 0.2% [53].

The relation between splenectomy and post-splenectomy sepsis has long been recognized. The precise frequency of this complication in patients with ITP is difficult to estimate. In the studies by Ejstrud et al. [62] and Bisharat et al. [63], the frequency of bacteremia and severe infections was 2.3 per 100 person-years and 3.2%, respectively. Boyle et al., studied a database of patients discharged from California hospitals and identified a cohort of 9,976 patients with ITP, 1,762, of whom had splenectomy [64]. Sepsis was diagnosed in 1,016 patients, including 191 post- splenectomy cases. The cumulative incidence of early (< 90 days post-surgery) and late (≥ 90 days) sepsis was 2.6% and 8.8%, respectively. The median time from surgery to hospitalization for sepsis was 35.5 months. The risk of developing sepsis was higher in individuals aged ≥ 60 years, males, Black race, and increased with a number of comorbidities. Although Boyle et al. study is based on a large group of cases, its main limitations stem from the selected cohort of patients and lack of clinical and laboratory data. The most reliable data regarding post-splenectomy infections come from Danish studies based on a national registry of patients, encompassing 3,812 individuals who underwent this procedure [65]. The overall frequency of infections requiring hospitalization was 7.7 per 100 person-years in the group of patients who underwent splenectomy compared to 2.0 per 100 person-years of the general population. The relative risk of infection (adjusted odds ratio) compared to the general population was the highest during the first 90 post-procedure days, and was estimated at 18.1 The risk progressively decreased to 4.6 (3–12 months) and 2.5 (> 12 months). Analysis of infection related to the cause of splenectomy revealed that individuals with splenomegaly were at the highest risk, followed by patients with congenital hemolytic anemia. Patients with ITP were at the lowest risk. Compared to the group of ITP patients who were considered for splenectomy but did not undergo the procedure, the risk of infection remained slightly elevated during the first 90 post-splenectomy days (relative risk [RR] 2.6) and did not differ significantly in the later periods. Vianelli et al. demonstrated the frequency of infections to be higher in individuals unresponsive to splenectomy or who experienced a relapse of thrombocytopenia [66]. This is most likely due to the use of immunosuppressive drugs in this group.

Several large studies have demonstrated an increased risk of post-splenectomy thromboembolic complications [64, 67]. These typically

manifest with/as venous thromboembolism (VTE) and visceral vein thrombosis. The pathogenesis of post-splenectomy thromboses is complex and results from surgical trauma, complications of the procedure, a sudden post splenectomy increase in platelet count, lack of a spleen and the underlying disease. Patients with ITP (after splenectomy or preserved spleen) are at higher risk of thrombotic complications, especially venous thrombosis. This risk is associated with many factors, such as the prothrombotic effects of drugs used in ITP therapy (antifibrinolytic drugs, corticosteroids), significant fluctuations in platelet count induced by pharmacotherapy resulting in the presence of young, more active platelets, increased presence of procoagulant microparticles in the blood, and a higher incidence of antiphospholipid antibodies in the ITP patient group. On the other hand, the absence of the spleen can lead to hypercoagulability due to factors such as the increased presence in the blood of old, damaged erythrocytes and procoagulant microparticles [67].

Boyle et al., demonstrated that splenectomy increased the risk of VTE both in the early (< 90 days; hazard ratio [HR] 5.2) and late (≥ 90 days; HR 2.7) post-splenectomy periods [64]. This complication occurred in 4.3% of patients after splenectomy and in 1.7% of patients with ITP with preserved spleen. In a retrospective analysis involving 233 ITP patients who underwent splenectomy, the incidence of VTE was 8% over a 10-year observation period [55].

Splenectomy is a risk factor for pulmonary hypertension [67]. Post-splenectomy pulmonary hypertension is associated with pre-existing pulmonary embolism. However, in some cases local thrombotic changes within the pulmonary vessels cannot be ruled out.

Thrombosis of the portal vein or its tributaries is observed in 5–37% of individuals who undergo splenectomy. It is usually asymptomatic and does not require treatment. The frequency of symptomatic portal vein thrombosis is estimated at < 2% [65]. Thrombosis within the portal system typically develops within 2 weeks of procedure, and all reported cases occurred within the first 2 months post-splenectomy. Portal vein thrombosis arises from local vascular damage during surgery and is probably not directly related to the absence of the spleen. This complication occurs more frequently after laparoscopic procedures.

There is no significant correlation between post-splenectomy increase in platelet count and portal vein thrombosis. Post-splenectomy infectious and thromboembolic complications are closely associated with two factors: the underlying disease that justified spleen removal and the time elapse since the surgery. Complications most commonly manifest within the first 90 days post-splenectomy and occur less frequently in ITP patients than in patients with other hematologic disorders [68].

In preparation for splenectomy and perioperative management

Every patient undergoing elective splenectomy should be vaccinated against *Streptococcus pneumoniae, Neisseria meningitidis, and Haemophilus influenza* at least 2–4 weeks before the surgery [2, 3].

Before the procedure, comprehensive examinations (ultrasonography [USG] and/or computed tomography [CT] of the abdominal cavity) should be performed to assess the size and location of the spleen and any accessory splenic tissue. Accessory spleens is found in approximately 10–20% of cases. If accessory spleen is not removed it may lead to relapse of thrombocytopenia after initially successful splenectomy.

Splenectomy can be safely performed if the platelet count is ≥ 50 G/L (sometimes decisions about splenectomy are made with a lower platelet count). Intravenous immunoglobulin (IVIG) or dexamethasone pulse is most commonly used. If blood transfusion is necessary during splenectomy, the splenic artery should be clamped. Thromboprophylaxis should be applied according to generally accepted principles to reduce the risk of thromboembolic complications in the postoperative period.

Post-splenectomy care

Splenectomy results in lifelong impairment of immunity. Patient education is therefore of crucial importance. Individuals should be informed about the higher risk of severe infections. They should be provided with a broad-spectrum antibiotic for oral use to be taken as soon as infection symptoms appear. Whenever fever appears, the patient should immediately contact a physician. Some centers, provide patients with identification cards or bracelets informing of splenectomy. As protection against *Streptococcus pneumoniae* infection, the patient is administered a single dose of the 20-valent conjugate vaccine (PCV-20). If the patient is given a 15-valent vaccine (PCV-15), it is recommended to administer an additional polysaccharide 23-valent vaccine (PPSV-23) after ≥ 12 months. Every year, patients should be vaccinated against influenza [21].

Table 9. Recommendations for splenectomy in ITP

1. Splenectomy is still an effective treatment option for chronic ITP adults, including those previously unresponsive to TPO-RA and rituximab
2. Splenectomy should be performed no sooner than 12–24 months of diagnosis as spontaneous remission may occur
3. A patient eligible for splenectomy must be informed about other alternative methods of ITP therapy, the efficacy of the procedure, the risk of failure or relapse, and potential complications
4. Prior to splenectomy, imaging studies (ultrasonography, computed tomography) should be performed in search for accessory splenic tissue
5. Every patient undergoing elective splenectomy should be vaccinated against *Streptococcus pneumoniae, Neisseria meningitidis, and Haemophilus influenzae*
6. Splenectomy can be performed using either traditional or laparoscopic methods, with the latter being safer
7. Splenectomy should be performed by an experienced surgeon familiar in identifying splenic tissue.
8. The platelet count before splenectomy should be ≥ 50 G/L
9. It is recommended to provide patients with identification cards informing of splenectomy

Recommendations for splenectomy are presented in Table 9.

ITP resistant to treatment

Until the introduction of modern, effective treatments for ITP, resistance was defined as lack of response to splenectomy or recurrence of thrombocytopenia after initially successful splenectomy. Currently, this definition needs modification because only a small percentage of ITP patients are eligible for splenectomy. The authors of these guidelines favour the definition of refractory ITP proposed by Arnold et al.: 'Persistent severe thrombocytopenia (< 20 G/L) with accompanying bleeding despite treatment with rituximab, two different TPO-RAs, and ≥ 1 immunosuppressive agent in a patient unresponsive to high doses of corticosteroids or IVIG or achieves only a short-lived (< 7 day) response to them' [69].

Patients with refractory ITP are the greatest challenge. Since the introduction of more effective medications, the percentage of patients unresponsive to treatment is systematically decreasing. The first step in the management of these patients is to confirm the diagnosis. Miltiadous et al. demonstrated that in 50% of refractory ITP cases the true diagnoses were: secondary immune thrombocytopenia, myelodysplastic syndromes (including neoplasms), marrow hypoplasias and aplasias, congenital and drug-induced thrombocytopenias [70]. After confirming the diagnosis of ITP, indications for treatment should be assessed based on platelet count and bleeding symptoms. In refractory patients, with platelet counts between 10–20 G/L and with no significant bleeding, treatment can be discontinued. If further therapy is necessary, the choice of treatment method depends on the previous management. It is crucial to assess whether the patient was managed properly, the medication was administered at appropriate doses and for an adequate period. If a patient did not respond to romiplostim and eltrombopag, it may be worth considering avatrombopag. However, the greatest chance of achieving a platelet response is through drug combination therapy introducing medications with different mechanisms of action. A significant percentage of platelet responses has been reported with the combination of azathioprine with MMF and cyclosporine (73.7% response rate), dexamethasone with rituximab and cyclosporine (60% response rate), TPO-RAs with IVIG and cyclosporine or MMF (72.2% response rate), and eltrombopag with cyclosporine (75% response rate) [2, 71, 72].

A drug with a unique mechanism of action is the spleen tyrosine kinase inhibitor — fostamatinib (as mentioned above). It may be effective in individuals unresponsive to TPO-RAs, rituximab, and splenectomy. Splenectomy is also worth considering. Mageau et al. demonstrated that splenectomy remains an effective treatment option for ITP in adults previously unresponsive to TPO-RAs and rituximab [56]. Furthermore, patients unresponsive to splenectomy or experienced relapse may benefit from reintroduction of TPO-RAs. When thrombocytopenia reoccurs ≥ 12 months from initially successful splenectomy, accessory splenic tissue should be sought. Its removal may restore remission. Lack of Howell-Jolly bodies in erythrocytes may indicate the presence of accessory spleen. Single cases of remission have beern reported following both autologous and allogeneic bone marrow transplantation [21]. Due to life-threatening complications, such management should be limited to cases of severe chronic ITP with dangerous bleeding unresponsive to other treatment methods. In women with "refractory"

Table 10. Management of patients when multiple lines of treatment fail

1. Review of diagnosis and treatment indications
2. Analysis of previously used treatment methods
3. Switch to a different thrombopoietin receptor agonist not previously used
4. Fostamatinib
5. Splenectomy (if not previously performed)
6. In individuals experiencing recurrence of thrombocytopenia after successful splenectomy, searching for additional splenic tissue and its removal
7. Combination therapy with drugs used in initial and subsequent treatment
8. Combination chemotherapy
9. Treatment within clinical trials
10. Autologous or allogeneic hematopoietic stem cell transplantation (in exceptional cases of severe progression, after exhausting all available treatment methods)
11. Symptomatic treatment: tranexamic acid, estrogen with progestogen, or levonorgestrel-releasing intrauterine devices

Table 11. Emergency management (life-threatening bleeding) in patients with ITP

It is recommended to use methods that rapidly increase the platelet count:
1) IVIG at a dose of 1 g/kg for 1–3 days + high-dose glucocorticosteroids, e.g., methylprednisolone 1 g/d IV for 1–3 days + PC transfusion (PC transfusion after IVIG may lead to a prolonged increase in platelet count)
2) Consider TPO-RA in case of inadequate platelet response after IVIG, PC transfusion
3) Other treatment options when the above is ineffective: anti-D immunoglobulin (unavailable in Poland), vincristine 1–2 mg IV, vinblastine 10 mg IV, and urgent splenectomy
4) Additionally: antifibrinolytic drugs
5) Transfusion of RBCs as needed

i.v. — intravenously; IVIG — intravenous immunoglobulins; PC — platelet concentrate

ITP and severe menstrual bleeding improvement may be achieved with toral contraceptives or intrauterine progesterone containing devices. Antifibrinolytic drugs may be effective in mucosal bleeding (see below).

Advancement in research on the pathogenesis of ITP have led to the development of new drugs which act through different mechanisms. These drugs are currently in clinical trials. It is fully justified to include in these trials patients who are unresponsive to conventional treatment.

Recommendations for management after failure of multiple lines of treatment are presented in Table 10.

Management in life-threatening bleeds (Table 11)

General principles

In life-threatening bleeding, it is recommended to immediately discontinue platelet-inhibiting medications, minimize trauma risk , stop menstruation, and monitor vital signs. In patients requiring anticoagulant or antiplatelet therapy (e.g., due to artificial heart valves or coronary stents) a higher platelet count should be sustained (Table 5). In renal failure, hemostasis can be improved with desmopressin or estrogen, along with maintaining hemoglobin levels > 10 g/dL. To control bleeding prompt increase of platelet count is essential (with methods that rapidly elevate platelet levels).

Transfusion of platelet concentrates (PC) and intravenous immunoglobulin IVIG)

Although transfused platelets are rapidly destroyed by antibodies, some patients experience a transient increase in platelet count after PC transfusion, and this may stop bleeding. In studies from the 1980s, an increase in platelet count > 20 G/L following PC transfusion was observed in 42% of bleeding patients with ITP [73]. Salama et al. described successful treatment (bleeding cessation) in 10 refractory ITP patients with transfusion of apheresis PCs (3–7 PCs per patient, 1 PC every 30 minutes; each PC contained an average of 2.7×10^{11} platelets) [74]. The effect is enhanced when IVIG is administered before or during transfusion [75].

Transfusion of IVIG at a dose of 1 g/kg/day typically increases the platelet count within 24 hours.

However, in life-threatening bleeding waiting for the effect of IVIG is too risky and PC transfusion becomes necessary.

Methylprednisolone

Intravenous high-dose methylprednisolone may increase platelet count in a shorter time than oral corticosteroids. It is administered at a dose of 30 mg/kg/day (maximum 1 g/day) for 2–3 consecutive days.

Vinca alkaloids

Vincristine at a dose of 1–2 mg once weekly for 2–4 weeks, or vinblastine at a dose of 10 mg once weekly for 1–3 weeks, leads to a platelet response in approximately 70% of patients by day 7 following administration. Sustained responses are much less common (approximately 28%), so these drugs are not currently recommended in chronic ITP. Additionally, they are associated with frequent neurotoxicity.

Splenectomy

Splenectomy may be considered in urgent cases when the patient is unresponsive to other treatment methods.

Antifibrinolytic and topical hemostatic agents

Tranexamic acid (1 g 3 × day) i.v. or p.o. is used to reduce bleeding from mucous membranes. The second of this group of drugs, ε-aminocaproic acid is currently unavailable in Poland because the production of the domestic agent has been discontinued. The addition of an antifibrinolytic drug to therapy targeting an increase in platelet count in life-threatening bleeding may be considered, although such an approach has not been evaluated in randomized trials.

In certain clinical situations, the use of topical hemostatic agents may be justified.

Management of ITP in pregnant women

The incidence of ITP in pregnancy is estimated at 0.83 per 10.000 pregnancies [76]. ITP is the most common cause of severe thrombocytopenia (platelet count < 50 G/L) in pregnancies [77]. Its course can vary greatly, but typically worsens with the progression of pregnancy [78]. However, in a recently published prospective study, no increased risk of severe bleeding was observed in pregnant women with ITP [79]. It should also be noted that the hypercoagulability accompanying pregnancy may alleviate symptoms of bleeding disorders.

Diagnostic procedures for ITP in pregnant women do not differ from ITP unrelated to pregnancy, except for the necessity of differentiation from pregnancy-specific thrombocytopenias such as gestational thrombocytopenia, preeclampsia, or HELLP syndrome. These complications occur in the third trimester of pregnancy, whereas ITP is the most common cause of thrombocytopenia in the first half of pregnancy. Platelet count decreases by about 10% in the second half of pregnancy compared to baseline values, reaching a nadir during delivery. This is associated with blood dilution, platelet activation and accelerated clearance, as well as platelet sequestration in the placenta. On the day of delivery, approximately 10% of women with uncomplicated pregnancies have mild thrombocytopenia < 150 G/L (gestational thrombocytopenia). The diagnosis of ITP in pregnancy is based on excluding other causes of thrombocytopenia. Peripheral blood smear evaluation is particularly important, as thrombocytopenias associated with thrombotic microangiopathies exhibit schistocytes. Increased aminotransferase activity is characteristic of HELLP syndrome, while disseminated intravascular coagulation complicating pregnancy is characterized by prolonged coagulation times (coagulopathy).

Treatment (Table 12)

More than a third of pregnant women with ITP require treatment, most commonly in the late stages of pregnancy to prepare for childbirth. Recommendations for managing ITP in pregnant women stem from clinical experience and expert consensus, as large RCT results are still lacking. A woman with a stable platelet count of 20–30 G/L, without significant bleeding and with no planned invasive procedures, can remain under observation. Towards the end of pregnancy, in preparation for delivery, the platelet count should be increased to > 50 G/L.

The care of a pregnant woman with ITP requires collaboration among a hematologist, obstetrician-gynecologist, anesthesiologist, and neonatologist.

Initial treatment

In the first-line treatment, low-dose glucocorticosteroids are used [2]. The recommended initial dose of prednisone is 20 mg/day, which is then adjusted to the lowest dose that provides a minimum hemostatic effect while simultaneously

Table 12. Treatment of ITP (ITP) during pregnancy — recommendations

1. Women with ITP planning pregnancy should receive comprehensive information from a hematologist and gynecologist about the risks to both themselves and the baby
2. Women of reproductive age with ITP treated with TPO-RA are advised to use effective contraception to prevent pregnancy (a criterion for exclusion from the drug program, TPO-RA according to the Summary of Product Characteristics (SPC) is not recommended during **pregnancy**)
3. Make the decision to continue TPO-RA (available under the National Health Fund program) in a pregnant woman after a thorough analysis and discussion with the patient of the benefits to the pregnant woman and the risks to the fetus. If discontinuation of TPO-RA entails a high risk of severe thrombocytopenia and uncontrollable bleeding, the decision to continue TPO-RA is fully justified.
4. Pregnant women with no symptoms of bleeding with a platelet count > 20 G/L do not require treatment, only observation. Platelet count should be ≥ 50 G/L before childbirth
5. Prednisone or IVIG is recommended for initial treatment depending on the clinical situation
6. IVIG is used in emergency (to control bleeding) or to increase the platelet count before childbirth
7. Combination therapy (IVIG + glucocorticosteroids) may achieve a platelet response in patients resistant to these drugs when used in monotherapy
8. High-dose intravenous methylprednisolone in combination with IVIG and/or azathioprine may be effective in women unresponsive to IVIG or oral glucocorticosteroids
9. Rituximab may be considered **in pregnant women in selected severe cases**, refractory to other treatment methods, considering the consequences of immunosuppression during the peripartum period and in the newborn
10. Consider the use of thrombopoietin receptor agonists **in late pregnancy when previous treatment methods fail**. Of the 3 available agonists, romiplostim is recommended — the drug is most commonly used in pregnancy (access to TPO-RA under the National Health Fund drug program)
11. If splenectomy is absolutely necessary, it is recommended in the second trimester
12. Vinca alkaloids, danazol, and immunosuppressive drugs other than those mentioned above should not be used during pregnancy

SPC — Summary of Product Characteristics, GCs — glucocorticosteroids, i.v. — intravenously, IVIG — intravenous immunoglobulins, NHF — National Health Fund, PLT — platelets, TPO-RA — thrombopoietin receptor agonist

not significantly increasing the risk of glucocorticosteroid-related adverse events (hypertension, hyperglycemia, osteoporosis, weight gain, psychosis). After childbirth, the prednisone dose should be gradually reduced under platelet count monitoring.

As mentioned earlier, IVIG increases platelet count in a shorter time compared to prednisone (approximately 2 ±1 days vs 16 ±19 days, respectively). Retrospective studies indicate comparable efficacy between IVIG and glucocorticosteroids [80]. Some pregnant women with ITP may require periodically repeated IVIG infusions throughout pregnancy to maintain a hemostatic platelet count. IVIG may also be indicated before childbirth to achieve a safe platelet count.

Treatment of pregnant women with ITP unresponsive to initial therapy

Patients resistant to prednisone and IVIG used in monotherapy may respond to the combination of these drugs. The combination of high-dose intravenous methylprednisolone with IVIG or azathioprine may also be effective. Cyclosporine and azathioprine can be safely used in pregnancy, as demonstrated in a group of pregnant women who received these drugs after organ transplantation. The onset of action of cyclosporine and azathioprine may range from several weeks to 4 months.

Thrombopoietin receptor agonists in pregnancy

Although thrombopoietin receptor agonists (TPO-RA) have demonstrated efficacy in ITP, they are not recommended during pregnancy because they may cross the placenta. However, there have been literature reports of TPO-RA used in the treatment of pregnant women when several lines of therapy have proven ineffective. Rottenstreich and Bussel conducted an analysis of 45 cases of TPO-RA in pregnancy (romiplostim — 23 cases, eltrombopag — 22 cases) [81]. The median of previous lines of treatment was 3. Platelet response was observed in 86.7% of patients and did not differ significantly between the romiplostim and eltrombopag groups. The safety profile was favourable. No thromboembolic complications occurred. Thrombocytopenia occurred in 1/3 of newborns. In another study, the course of pregnancy was analyzed in 186 women with ITP who received romiplostim from 20 days before pregnancy until the end of pregnancy [82]. In 70 cases, the drug was administered in the first trimester, and no increased risk

of miscarriage was observed. The results of the aforementioned analysis suggest that TPO-RAs are both effective and safe during pregnancy. The authors of these studies, however, believe that until more convincing safety data on drugs in this group are available, they should not be routinely used during pregnancy, especially in the first trimester. In the event of deciding to initiate TPO-RAs, romiplostim is the preferred drug due to greater experience with its use in pregnancy, subcutaneous administration, and its lack of hepatotoxic effects.

According to the provisions of the drug program in Poland, women with ITP treated with TPO-RAs are excluded from the program upon becoming pregnant. Moreover, according to the Product Characteristics, these drugs are not indicated during pregnancy. Therefore, for patients of childbearing age with ITP treated with TPO-RAs, effective contraception is recommended.

The decision to maintain TPO-RAs (available within the National Health Fund drug program) in a woman who becomes pregnant should be made after careful analysis and discussion with the patient regarding the balance of benefits for the pregnant woman and the risks to the fetus. If discontinuation of TPO-RAs is associated with a high risk of severe thrombocytopenia and dangerous bleeding that cannot be prevented (no other methods of ITP treatment have been effective), then the decision to continue TPO-RAs is fully justified.

Splenectomy

Splenectomy is performed in pregnant women very rarely. If necessary, it is best to perform splenectomy in the second trimester.

Childbirth/Delivery in a pregnant woman with ITP (Table 13)

The optimal management of childbirth in a pregnant woman with ITP is based on obstetric indications, avoiding procedures that may induce bleeding. The risk of intracranial hemorrhage in the fetus/newborn of a mother with ITP is very low, and it has not been shown to decrease with cesarean section delivery. The minimum platelet count for delivery is 50 G/L, applicable to both vaginal delivery and cesarean section. In clinical practice, efforts are often made to achieve a platelet count ≥70 G/L, allowing for the use of spinal or epidural anesthesia.

Management of newborns of mothers with ITP (Table 14)

The platelet count should be determined from cord blood sample. In the case of thrombocytopenia, the platelet count should be repeated on days 3–5 after birth when the newborn's spleen reaches maturity. The frequency of intracranial bleeding in newborns with a platelet count < 30 G/L is estimated at < 1%. Due to the serious consequences of this complication, prophylactic administration of IVIG is recommended. Significant fluctuations in the platelet count of newborns may be associated with pseudothrombocytopenia, as result of platelet clumps formed when there occur difficulties in obtaining unclotted blood for testing. The highest risk of thrombocytopenia in newborns concerns mothers with ITP who have undergone splenectomy, as well as those who have previously given birth to a child with thrombocytopenia. If severe thrombocytopenia persists for a week in a breastfed newborn, consideration should be given to discontinuing breastfeeding for a few days and monitoring the platelet count. Antiplatelet antibodies can penetrate into maternal milk and contribute to thrombocytopenia in the child.

Management of elderly patients with ITP (> 65 years old)

Although ITP may occur at any age, the incidence increases after 60, especially in men [83]. The population in Poland is aging, it can therefore be assumed that the number of elderly patients with ITP will increase. So far, no separate recommendations for the treatment of the elderly patients with ITP (above 65) have been published. Coexisting diseases, more common in older age, can complicate both the diagnosis and treatment of ITP.

During the differential diagnosis of ITP in the elderly patients, special attention should be paid to drug-induced thrombocytopenia and myelodysplastic syndrome (MDS). Although thrombocytopenia accompanies most cases of MDS (approximately 65%), isolated platelet count reduction at diagnosis is observed in only about 12% of patients [84]. To rule out MDS, some authors recommend bone marrow examination in anyone above 60 suspected of ITP [21]. The morphology of megakaryocytes in ITP may exhibit various abnormalities, which complicate differentiation from MDS, and furthermore, ITP may coexist with MDS. It is then worthwhile to perform a trial with intravenous immunoglobulin (IVIG) or glucocorticoids (GCs).

Table 13. Guidelines for managing labor in pregnant women with ITP

1. Prior to delivery, the platelet count should be ≥ 50 G/L
2. Regional anesthesia can be safely administered with a platelet count ≥ 70 G/L, provided there are no other hemostatic defects
3. The mode of delivery should be determined by obstetric indications rather than the anticipated thrombocytopenia in the newborn
4. During delivery, procedures that may increase the risk of bleeding in the infant should be avoided (such as placing electrodes on the fetal scalp, fetal blood sampling, vacuum extraction, or forceps delivery)

PLT — platelets

Table 14. Guidelines for management of newborns of mothers with ITP

1. During delivery, the platelet count in cord blood should be determined
2. The frequency of further determinations depends on the platelet count in cord blood and the results of subsequent tests, as well as the response to treatment. If the initial platelet count is <100 per liter, it should be monitored daily until stabilization or increase. Pseudothrombocytopenia should be ruled out
3. Transfontanelle ultrasound imaging should be performed if the platelet count during delivery is < 50 G/L
4. In the case of intracranial bleeding, IVIG and corticosteroids should be administered, and the platelet count should be maintained > 100 G/L in the 1st week and > 50 G/L in the 2nd week. It should be noted that transfusion of PCs in newborns carries the risk of complications. If platelet transfusion is necessary, a pathogen-inactivated or irradiated concentrate should be transfused
5. If symptomatic bleeding occurs or the platelet count is < 30 G/L, IVIG administration is recommended. If severe thrombocytopenia persists in a breastfed newborn for a week, consider discontinuing breastfeeding for a few days and monitor the platelet count
6. A newborn of a mother who underwent splenectomy for ITP may have thrombocytopenia even if the mother's platelet count is normal
7. The only reliable prognostic factor for thrombocytopenia in a newborn is the presence of this complication in an older sibling

GCS — glucocorticosteroids; i.v. — intravenously; IVIG — intravenous immunoglobulins; PC — platelet concentrate; PLT — platelets; USG — ultrasonography

In the literature, there are conflicting data regarding the risk of bleeding in elderly patients with ITP. Some authors have found no correlation between age and bleeding, while others have observed a higher bleeding risk in older patients with the same platelet count [83]. In two recently published studies, a higher occurrence of severe bleeding was reported in the older patient group [85, 86]. The risk of bleeding is particularly high in patients with ITP on both antiplatelet and anticoagulant medications.

Many factors contribute to thrombotic complications in ITP. The disease itself is a prothrombotic state, and the risk of thrombosis increases with age. Treatment methods used in ITP (splenectomy, TPO-RA, and IVIG) may also contribute to thrombus formation.

Elderly patients are more susceptible to infections. The risk of infection is also higher in ITP, primarily due to the applied treatment (immunosuppressive drugs, rituximab, glucocorticoids, splenectomy). Infections, along with bleeding, are the second most important cause of death associated with this disease.

When making therapeutic decisions about the optimal individual treatment for the elderly patients with ITP, it is essential to carefully analyse the risk of bleeding, severe infection and thrombotic complications.

Final remarks

These recommendations reflect the current state of knowledge for ITP management and are tailored to Polish conditions. Advancement in understanding the pathogenesis of ITP has shown it to be an autoimmune disorder that develops as result of various pathogenetic mechanisms. Unfortunately, there are no diagnostic tests to determine the pathogenesis of ITP in individual patients, so all ITP patients are subjected to similar therapies. Until recently, the treatment of chronic ITP was toxic, often ineffective, and associated with a health-dependent reduction in quality of life. For over 10 years, drugs of confirmed efficacy

and safety (in randomized trials) have been available for the treatment of ITP. In Poland, patients have gained access to TPO-RA since May 2023 under the new drug reimbursement program. It is still however, uncertain which patients should be treated with these drugs, which drug is the best choice for the patient and for how long it should be administered Unnecessary, intensive treatment may negatively impact the patients' quality of life. Undoubtedly, patients should be more effectively stratified so that a therapy is administered only to those who will benefit from it. Clinical trials are underway for new, promising therapies. Attempts are made to bring TPO-RA and other drugs into initial treatment. Rapid development of methods for ITP treatment calls for more frequent updates of guidelines.

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