Review

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Recommendations for the Clinical Approach to Primary Immune Thrombocytopenia

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Review

Recommendations for the Clinical Approach to Primary Immune Thrombocytopenia

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Abstract: Primary immune thrombocytopenia (ITP) is a complex autoimmune disease whose hallmark is a deregulation of cellular and humoral immunity leading to an increased destruction and a reduced production of platelets. The heterogeneity of presentation and clinical course hampers personalized approaches for diagnosis and management. In 2021, the Spanish ITP Group (GEPTI) of the Spanish Society of Hematology and Hemotherapy (SEHH) updated a consensus document which had been launched in 2011. The updated guidelines have been the reference for diagnosis and management of primary ITP in Spain ever since. Nevertheless, the emergence of new tools and strategies makes it advisable to review them again. For this reason, we have properly updated the main recommendations. Our aim is to provide a practical tool to enable the integral management of all the aspects concerning primary ITP management.

Keywords: primary immune thrombocytopenia; glucocorticoids; intravenous immunoglobulins; fostamatinib; rituximab; recommendations

1. Introduction

Primary ITP is defined as a platelet count <100×10^9/L whose cause has not been identified. The concept "secondary ITP" arises from scenarios where the low platelet counts are subsequent to diagnosed diseases known to cause immune destruction of platelets. The incidence of primary ITP is 2-4 cases per 100,000 individuals per year, in both adults and children. The prevalence is higher in adults (10 per 100,000 *vs.* 5 per 100,000 individuals in children) because the rate of chronicity is greater in this population [1].

There are many pathophysiological mechanisms playing a causal role in primary ITP, which explains the heterogeneity of the disease. Nevertheless, the consequences are basically of two types. On the one hand, there is an increase in platelet destruction, which is mainly, but not solely, caused by the onset of autoantibodies able to opsonize the cell surface for the subsequent complement- or phagocyte-mediated cell killing. The increased rate of platelet desialylation, which accelerates liver clearance, and a greater apoptosis rate also contribute to the low counts. On the other hand, platelet turnover decreases because of a lower rate of cell production. This is due to autoantibodies targeting thrombopoietin (TPO) receptor and preventing TPO from stimulating proliferation and differentiation of megakaryocytes, as well as to an apoptotic imbalance concerning these cells [2].

The autoantibodies identified in patients with primary ITP can bind a large variety of targets, which are frequently located at the platelet surface, for instance glycoproteins (GP) GPIIb/IIIa or GPIb/IX. Bleeding manifestations are not the only symptoms of primary ITP. Asthenia is also frequently found, and some patients are predisposed to experience thromboembolic events, infection or other autoimmune diseases. Primary ITP shows a self-limiting course in the majority of children and in one third of adults. According to the standardized terminology [3], the disease can be defined according to the time elapsed since diagnosis: i) "newly diagnosed primary ITP" encompasses all cases at diagnosis; ii) "persistent primary ITP" refers to the period lasting between 3 and 12 months from diagnosis; iii) "chronic primary ITP" is the term reserved for patients with primary ITP lasting for more than 12 months.

In contrast to the relevant advances achieved in the therapeutic field in the last decade, there has been little progress in the diagnosis of the disease, and reliable markers or solid confirmatory tests are lacking. Diagnosis continues to be essentially clinical and based on excluding other causes of thrombocytopenia. When a patient is suspected to have primary ITP, once the clinical history, physical examination, peripheral blood smear, immunoglobulin level and viral serology have

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allowed us to rule out other processes, the general rule consists of limiting tests to a minimum, since most of them will not be very informative. The paradigmatic laboratory finding is isolated thrombocytopenia, and careful examination of the peripheral blood smear is mandatory. In primary ITP patients, platelets are usually large and granular, with elevated mean platelet volumes and immature fractions. The systematic analysis of bone marrow is not recommended, except in the event that treatment response is inadequate, or when other abnormalities in the peripheral blood smear or in the clinical presentation lead to the suspicion of other disorders. These limitations may result in an incorrect diagnosis in one out of 7 patients identified as having primary ITP [4]. Further attempts to overcome this challenge are required.

Quality of life (QoL) of primary ITP patients is reduced to a similar extent to that seen in patients with other chronic diseases such as cancer, arthritis or diabetes mellitus [5]. The proper treatment of primary ITP not only has to pursue the recovery of platelet counts and cessation of bleeding. Minimizing the impact of the disease on the patient's QoL is highly advisable. Table 1 summarizes the most relevant topics regarding pathophysiology and diagnosis of primary ITP, and Table 2 compiles a list of definitions and concepts that have reached consensus and should be well known [3,6].

Table 1. Primary ITP: general aspects, pathophysiology and diagnosis .

General aspects
Primary ITP is defined as a platelet count <100×10⁹/L which is not justified by any known reason. The term secondary ITP is limited to those
situations where platelet count drop to values <100×10⁹/L is caused by diagnosed diseases able to induce immune destruction of platelets
Incidence of primary ITP is 2-4 cases per 100,000 individuals per year in adults and children
Bleeding manifestations are the main symptoms associated with primary ITP. Higher thrombotic risk, asthenia (occasionally unrelated to platelet
counts) and higher predisposition to infection can also be observed. Adverse events subsequent to administration of primary ITP therapies are often
seen
The development of new treatments has probably improved prognosis of primary ITP patients. However, the exact influence of these therapies on
causes of either mortality or mortality rate has not been established
Pathophysiology
Causal mechanisms underlying primary ITP lead to an increase in platelet destruction or a decrease in platelet generation
Platelet destruction is caused by autoantibodies, phagocytes, complement, apoptosis and clearence through Ashwell-Morel receptors of hepatocytes
The lower rate of platelet production is caused by autoantibodies able to block TPO function and by increased apoptosis of megakaryocytes
Diagnosis
Diagnosis of primary ITP is performed by excluding systematically other causes of thrombocytopenia, and is based essentially on clinical history,
physical examination, CBC and peripheral blood smear
Peripheral blood smear examination is paramount for diagnosis
Additional studies may be required and should be requested according to presentation and clinical course of the disease
Assessment of antiplatelet autoantibodies is not routinely indicated, although it may be useful in complex cases
The systematic analysis of bone marrow is not recommended except in the event of refractoriness to treatments or when another disease is
suspected. In these cases, bone marrow examination should include aspiration and biopsy, immunophenotyping by flow cytometry, cytogenetics and
molecular biology

CBC, complete blood count; ITP, immune thrombocytopenia; TPO, thrombopoietin.

Table 2. Consensual definitions and concepts in the context of primary ITP.

Primary ITP categories according to the phase of the disease [3]
Newly diagnosed ITP: within 3 months from diagnosis
Persistent ITP: between 3 and 12 months from diagnosis

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Chronic ITP: lasting for more than 12 months from diagnosis

Severe ITP: there are bleeding symptoms sufficient to mandate treatment, or new bleeding symptoms requiring additional therapeutic intervention with either an

increased dose or a different platelet-enhancing agent

Refractory ITP [3]

Two criteria must be met:

failure of splenectomy or subsequent relapse, and

severe ITP or bleeding risk that in the opinion of the attending physician requires therapy

Type of response [3]

Complete response: platelet count ≥100x10^9/L and absence of bleeding

Response: platelet count ≥30x10^9/L and at least doubling of the baseline count, and absence of bleeding

No response: platelet count <30x10^9/L or less than doubling of the baseline count, or bleeding

Corticosteroid dependence: the ongoing need for corticosteroid administration at least for 2 months to maintain a platelet count ≥30x10^9/L and/or to avoid bleeding

Type of response [6]

Durable response: platelet count ≥30x10^9/L and at least doubling baseline at 6 months

Early response: platelet count ≥30x10^9/L and at least doubling baseline at 1 week

Initial response: platelet count ≥30x10^9/L and at least doubling baseline at 1 month

Maintained response in the absence of treatment: response after 6 months without treatment

Texts excerpted from Rodhegiero et, Blood 2009;113:2386-2393 [3] and Neunert et al, Blood Adv 2019;3:3829-3866 [6]. ITP, immune thrombocytopenia.

2. Methods

The AGREE methodology was followed for the compilation of these recommendations. The PICO (Population, Intervention, Comparison, and Outcome) framework was used to select the questions to be addressed regarding ITP management. These were as follows: first-line, second-line and multirefractory ITP treatment; follow-up of patients with primary ITP; primary ITP in selected patient populations; secondary ITP; primary ITP and thrombosis; ITP and COVID-19.

Each author was assigned one topic to perform a comprehensive literature search, especially focusing on the last 5 years and guided by relevant MeSH terms. In order to establish the recommendations, the reliability of the compiled information was evaluated, according to strengths and limitations. Finally, peer reviews of each topic were performed until a general consensus was reached.

3. First-Line, Second-Line and Multirefractory ITP Treatment

Table 3 summarizes the main issues to consider regarding first and second-line treatment, as well as those scenarios of recurrent refractoriness, and sets out the response rates expected for each therapeutic strategy [1,6–9].

Table 3. First-line and second-line treatment of primary ITP, and management of refractory patients.

First-line treatment
Decision relies basically on bleeding symptoms and platelet counts (<20×10^9/L)
First-line treatment are glucocorticoids (prednisone 0.5-1 mg/kg or dexamethasone 40 mg/day for 4 days)

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Treatment should not last more than 8 weeks in the case of prednisone or more than 3 cycles in the case of dexamethasone

ERR prednisona: 60-80%; SRR prednisone: 30-50%

IVIg are reserved for patients with severe hemorrhage or when steroids are contraindicated

ERR IVIg: 75-92%; SRR IVIg: 30-55%

In severe hemorrhage scenarios, combined treatment is suitable (IVIg, high dose methylprednisolone, platelet transfusion; consider whether antifibrinolytics and/or

TPO-RA are required)

Hospitalization for at least 48-72 hours is recommended for newly diagnosed patients with platelet counts $<20\times10^9$/L

Second-line treatment

The first choice should be TPO-RA (eltrombopag, romiplostim, avatrombopag) or fostamatinib

TPO-RA exhibits a good safety profile, although its cost is high. The choice of one TPO-RA or another should be based on administration route, patient preference

and potential future complications

ERR eltrombopag: 70-80%; SRR eltrombopag: 10-30%; ERR romiplostim: 70-80%; SRR romiplostim: 10-30%; ERR avatrombopag: 65%; SRR avatrombopag: not

known

Fostamatinib is a SYK inhibitor able to reduce the anti-platelet activity of phagocytes

ERR fostamatinib: 18-43%

Responses to fostamatinib are observed early, and good results in multirefractory patients have been described

Fostamatinib is particularly suitable as first option of second line treatment in patients with high thromboembolic risk

Rituximab should be the secondary scenario in second-line options. The more used regimen consists of 4 doses of 375 mg/m^2 each, administered on a weekly basis.

Nevertheless, the same temporal pattern reducing each dose from 375 to 100 mg/m^2 has been shown to have the same efficacy, while being possibly safer

ERR rituximab: 60-80%; SRR rituximab: 20-30%

Splenectomy can be considered in chronic phases after at least one second-line treatment has failed

ERR splenectomy: 80-90%; SRR splenectomy: 60-70%

The laparoscopic procedure is preferred if splenectomy is finally decided

Refractory patients

There is no clear recommendation about how those refractory patient treatments should be managed

Combined therapies are usually more effective than monotherapy in refractory patients. Ideally, agents with different mechanisms of action should be combined.

Rescues have been described using steroids concomitantly with rituximab or TPO-RA

In the event of no response to one treatment, adding a new therapy concomitantly may be better than suspending the former and starting with the new one only

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Other diagnoses, such as drug-induced thrombocytopenia, myelodysplastic syndrome or hereditary thrombocytopenia, should be considered in multirefractory

patients

The use of immunosuppressants, immunomodulators or cytostatic agents can be considered. Nevertheless, their side effects make it advisable to balance carefully the

benefit:risk ratio

ERR, expected response rate; ITP, immune thrombocytopenia; IVIg, intravenous immunoglobulins; SRR, sustained response rate; TPO-RA, agonist of thrombopoietin receptor; SYK, spleen tyrosine kinase.

First-Line Treatment

The aim of the treatment is to achieve hemorrhage cessation and prevent future bleeding events. Treatment must be started in newly diagnosed adult patients with active bleeding or when they present with platelet counts <20×10⁹/L (<30×10⁹/L when they are >65 years or present with hemorrhage risk factors). These criteria are not necessarily to be applied for a second treatment, since the patient´s opinion is particularly important in such a situation. First-line treatment has not evolved dramatically. Table 4 shows the main therapeutic options with their expected response rates. Glucocorticoids remain the cornerstone, although treatment duration has been reduced to minimize side effects. The initial dose of prednisone (0.5-1 mg/kg/day, not exceeding 80 mg daily) should not be kept beyond 3 weeks (two weeks in the event of no response). The dose must be progressively reduced and treatment must be terminated no later than 8 weeks from the start. Dexamethasone, at no more than 3-4 cycles consisting of 40 mg/day for 4 days each 2-4 weeks, is a validated alternative. Although the recovery of platelet counts is faster with the latter, long-term response rates are not different for the two therapies [10]. Intravenous (i.v.) immunoglobulins (IVIg) are recommended for patients with active bleeding or when steroids are contraindicated. The more widely used regimens are 1 g/kg administered 1 or 2 days, or 0.4 g/kg administered 3-5 days in patients >65 years. Nevertheless, alternative patterns have been suggested, such as a single dose of 0.2-0.4/kg, which could be repeated again 3 days afterwards in the event of no response. This last strategy has been shown to be effective and, furthermore, more sustainable [11].

Table 4. Guidelines for the follow-up of non-hospitalized primary ITP patients .

Newly diagnosed patients

The frequency of CBC should be established according to individual features in order to guarantee stable platelet counts

The patient has to be educated to recognize alarm signs early (hemorrhage; asthenia; pregnancy; start of anticoagulant or antiplatelet treatment; planned invasive

procedures)

Disorders that may lead to erroneous primary ITP diagnosis have to be ruled out: autoimmune diseases, thyroid disease, hematologic disorders, immunodeficiencies

Patients with persistent or chronic ITP who are not being treated

CBC on a 3-6 monthly basis

The patient has to be educated to recognize alarm signs

If still pending, continue proceeding with the differential diagnosis to rule out other autoimmune diseases

Attention should be paid to complications associated with the use of previous therapies

Patients currently on treatment (in all cases, the aforementioned actions to be taken in risk situations are applicable)

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With corticoids

Patients have to be informed about the more important side effects: hyperglucemia; hypertension; sleep disorder; state of mind disorder; osteoporosis; muscle

atrophy; weight gain; infection; acne; skin stretch

Prophylaxis of osteoporosis with calcium and vitamin D is recommended if steroids are used for >4 weeks

Infection prophylaxis as described is recommended

With IVIg

CBC has to be performed on a weekly basis to assess efficacy and, accordingly, duration of therapy

Patients have to be informed about the possibility of headache symptoms in the days following treatment administration

With TPO-RA

CBC has to be performed on a weekly basis until maintenance dose is reached. Thereafter, CBC will be performed on a 4-8 weekly basis provided that platelet counts

remain >50x10^9/L

Those patients with previous history of thrombembolism or with thrombembolic risk factors have to be informed about thromboembolic risk

Peripheral blood smear has to be carefully studied in the event that CVC results suggest the onset of fibrosis

Patients have to be informed about side effects they may experience, such as asthenia, headache, muscle and joint pain, or cutaneous symptoms, explaining that they

will not be severe

Liver function has to be monitored if eltrombopag is the chosen TPO-RA

With fostamatinib

CBC has to be performed on a monthly basis until maintenance dose is reached. Thereafter, frequency has to be adapted to each individual requirement

Blood pressure has to be controlled to monitor hypertension risk

Liver enzymes have to be monitored each 4-8 weeks

Patients have to be informed about possible side effects they may experience such as diarrhea or abdominal discomfort

With rituximab

Serological control of HBV (anti-HBc, HBsAg) has to be performed

Patients have to be warned about infection risk, especially when they are being administered rituximab concomitantly with corticoids

Attention must be paid to neurologic signs consistent with progressive multifocal leukoencephalopathy, in order to allow its early detection, since this disorder has

been associated with this therapy, still not frequently

In the event of imminent vaccination (including SARS-CoV-2 vaccine), it is advisable to be aware that rituximab may influence efficacy. The vaccination calendar

had to be adapted accordingly

Before/after splenectomy

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Before surgery, patient has to be vaccinated against encapsulated bacteria (*Neisseria meningitidis*, *Streptococcus pneumoniae*, *Haemophilus influenzae*). Patients

must also be vaccinated against influenza each year, and serogroup B meningococcal vaccine has to be considered for those younger than 25 years. In the event

that splenectomy is performed as an emergency procedure, vaccination should be performed a posteriori

After surgery, proper thromboembolic prophylaxis should be initiated according to the patient's characteristics. Close monitoring is recommended to anticipate

thromboembolic complications

Re-vaccination against the aforementioned pathogens should be performed according to established guidelines

Patients have to be warned about the risk of infection after the procedure, and have to be educated for them to early detect symptoms coherent with this complication.

They have to be explicitly told to go to the doctor if they are experiencing febrile episodes lasting more than 48 hours

Anti-HBc, antibody to HBV core antigen; CBC, complete blood count; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; ITP, immune thrombocytopenia; IVIg, intravenous immunoglobulins; TPO-RA, agonist of thrombopoietin receptor.

In the event of severe hemorrhage, high dose methylprednisolone and platelet transfusion are recommended in addition to IVIg, and the use of TPO receptor agonists (TPO-RAs) can be considered. Among these, romiplostim at 5-10 µg/kg is the most frequently reported option [12], although there is no reason to think that eltrombopag at a daily dose of 75 mg will not be effective. The efficacy of treatments to stop severe hemorrhage has to be assessed according to blood cessation rather than platelet count recovery [13]. Finally, the combination of steroids with either rituximab, TPO-RAs or immunosuppressants is not recommended outside of clinical trials [14–17].

Prophylaxis with trimetropin-sulfametoxazol at 80 mg/400 mg twice a day 2 to 3 times a week to prevent infection by *Pneumocistiis carinii* must be administered in the following cases: patients on steroid treatment lasting >4 weeks at daily doses >30 mg; patients on prednisone >8 weeks at 15-30/mg/day; patients combining 15-30/mg/day prednisone with cyclosporine; patients with prednisone at >10 mg/day and meeting ≥2 of the following criteria: age >65 years, pulmonary disease, concomitant use of another immunosuppressant. Prophylaxis against herpes virus with acyclovir at 400 mg/day is advisable for either patients >60 years, patients on prednisone at daily doses >7.5 mg, or patients with history of infection with this pathogen.

Prophylaxis with entecavir at 0.5 mg/day is recommended for those patients with antibodies against VHBc and a positive test for hepatitis B virus (HBV) antigen, who are on treatment with prednisone either at >10 mg/day during ≥8 weeks, or at >20 mg/day during >4 weeks. In the event that the test for antibodies against VHBc was positive but that for HBV antigen was negative, the patient should be periodically monitored [18].

Prophylaxis to prevent osteoporosis with calcium and vitamin D (colecalciferol at weekly dose of 2,800 IU) is recommended for postmenopausal women, >50 years old (y.o.) male patients being on steroid treatment for >3 months, and in those patients who, having a T-score of bone mineral density (BMD) <-1.5, were being treated or were to be treated with steroids at doses >2.5 mg/day for >3 months. This prophylaxis should be applied to premenopausal women and <50 y.o. male patients only in the event of history of previous fractures or when the T-score was <-1.5 and treatment with steroids at doses >5 mg/day for >3 months was being administered or planned [19].

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Second-Line Treatment

Although initial response rates to glucocorticoids are high, many adult patients will relapse (Table 3). In these cases, re-exposing patients to these treatments is not suitable unless it is justified by an emergency situation. Personalizing therapy becomes paramount when choosing a second-line treatment option. Thus, each patient's comorbidities will notably influence the therapeutic decision. The findings observed in studies with TPO-RAs, fostamatinib and rituximab suggest that the first two are the more effective and less toxic therapeutic options to be used as second-line treatment of primary ITP [6,7]. Randomized studies to compare them directly have not been reported so far.

TPO-RAs induce platelet production and have an excellent efficacy/safety profile. We recommend using any of the commercially available TPO-RAs as the first option of second-line treatment, although the experience with eltrombopag and romiplostin is longer than that reported with avatrombopag so far. Patients will actively participate in decision-making, and the choice will also be influenced by their priorities and lifestyle. Responses have been reported in >80% cases with these agents [20,21], and cross-resistance has not been observed [22]. Furthermore, many patients will be able to suspend other treatments, even TPO-RAs themselves, without leading to a new drop in platelet counts. In the absence of response to a TPO-RA, switching to another one or to fostamatinib is recommended. If TPO-RA refractoriness is definitely confirmed, the use of other immunosuppressants such as mycophenolate mofetil, azathioprine or low-dose steroids can be considered [23].

Fostamatinib is another option of second line treatment in ITP. Fostamatinib is a spleen tyrosine kinase (SYK) inhibitor able to reduce the anti-platelet activity of phagocytes. This agent achieves rapid, long-lasting platelet count increases in 40-45% of those patients refractory to previous treatments [24]. Although the response rate is lower when considering heavily pre-treated patients, the efficacy of fostamatinib goes up to 75% when chosen as the first option of second-line treatment [25]. Furthermore, some studies have shown encouraging results regarding long-term efficacy [26,27]. We recommend fostamatinib as second line treatment even before TPO-RA in patients with high thromboembolic risk. The remarkably low incidence of thromboembolic events together with the absence of platelet peaks associated with fostamatinib, make it particularly suitable to be used by primary ITP patients presenting with either arterial or venous thrombosis or history of previous thromboembolic events, regardless of their severity [27].

Rituximab is a monoclonal antibody targeting the B-cell surface receptor CD20. The interaction induces B-cell depletion and the subsequent decrease in antibody generation. This agent is the second option of the second-line treatment. The experience with rituximab in primary ITP patients is extensive even though it has no specific approval to treat this disease [28]. Overall responses have been reported in 60-80% of patients, although the proportion of those achieving long-lasting responses after >3-5 years drops to 20-30% [29,30]. The standard and more widely used regimen consists of 4 doses of 375 mg/m^2 administered over 4 consecutive weeks. Nevertheless, the low-dose regimen, which uses 4 doses of 100 mg/m^2 instead of 375 mg/m^2, makes it possible to save costs and is associated with fewer adverse events, while showing a similar efficacy [31]. There is a third regimen consisting of 1 g/day doses administered at days 1 and 15, whose efficacy is similar to the previous ones [32]. In any case, vaccination against encapsulated bacteria is required before starting rituxumab. Active or latent HBV infection has also to be discarded, and, when applicable, treated. Finally, it must be beared in mind that progressive multifocal leukoencephalopathy has been classified as a complication of rituximab treatment, although it occurs very rarely [28].

Another second-line option is splenectomy. Its main advantage is its high efficacy associated with a low cost (Table 3) [33]. Nevertheless, there are also major limitations, such as the increased risk of thromboembolism or severe infection, and so the benefit:risk ratio must be carefully assessed. Since the current scenario offers several second-line safe and effective pharmacologic options (with others in the pipeline), GEPTI recommends limiting splenectomy to highly selected patients according to their comorbidities, lifestyle and priorities, as well as delaying the procedure in the hope that the patient may achieve a suboptimal response at least to one of the second-line therapies. In any case, splenectomy must not be performed within the first 12 months after diagnosis. In the event that

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splenectomy is finally the chosen option, the laparoscopic procedure is preferred, and a proper preoperative vaccine pattern and postoperative thromboembolic prophylaxis must be observed [1].

Vaccination Prior to Splenectomy

After the procedure, those patients who have not been properly immunized are at a risk of severe bacterial infection which is 50-fold higher than that of non-splenectomized patients. The causal agents are *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Neisseria meningitidis* in 50-90%, 5-15% and 5-15% of cases, respectively [34]. Vaccination reduces the risk, but this does not disappear completely. Vaccines must be administered at least 2 weeks before the procedure. In the event that the severity of the situation prompts immediate surgical intervention, vaccination will be initiated as soon as possible, within the first 2 weeks after the procedure.

Finally, these patients must also be vaccinated against influenza each year, and serogroup B meningococcal vaccine has to be considered for those younger than 25 years [35].

Treatment of Multirefractory Patients

Multirefractory primary ITP is a severe condition that can be experienced by up to 20% of patients. The term "refractoriness" has been controversial. It has been recently defined as the total loss of response to one or more treatments, including rituximab and TPO-RA [36]. In these cases, reconsidering primary ITP diagnosis is advisable, and bone marrow examination is indicated. As far as the therapeutic attitude is concerned, eradication of *Helicobacter pylori*, a gram-negative bacterium which can be detected in the digestive tract of more than half of the total population, can be proposed, since it has been associated with primary ITP in several studies [37]. On the other hand, treatments consisting of combinations of agents able to induce platelet generation and prevent platelet destruction must be applied. Patient rescues subsequent to administration of steroids concomitantly with rituximab or TPO-RA have been described [38–40]. The use of immunosuppressants such as azathioprine, cyclosporine or mycophenolate mofetil, immunomodulators such as danazol or dapsone, or cytostatic agents such as cyclophosphamide or vinca alkaloids (vincristine, vinblastine) can also be envisaged [36,41–46]. Nevertheless, these agents may induce side effects that should prompt a careful examination of the benefit:risk ratio. Some patients may present without active bleeding and with no limitation in their QoL, thus not requiring pharmacologic support while their condition persists. Furthermore, there are no reliable studies either providing support for their use or comparing their efficacy. The Supplementary Table S1 provides details regarding dose, expected response and side effects associated with the treatments addressed in this section.

4. Follow-Up of Patients with Primary ITP. Scenarios and Recommendations

The fact that the diagnosis of primary ITP is performed by exclusion may lead to situations where the definitive diagnosis has not been made before the initiation of treatment. Patients should be closely followed-up by experienced practitioners, with the aim to rule out other diseases responsible for the symptoms attributed to primary ITP, and to control the subsequent onset of other disorders, especially when patients have persistent or chronic primary ITP, or are elderly. Furthermore, follow-up is required for the early identification of thrombocytopenia-derived complications and side effects of treatments. The scenarios that can be most frequently found throughout the follow-up period are described hereafter.

Hospitalization

The hospital admittance criteria for primary ITP patients are as follows [1]:

- Grade 2 hemorrhage according to the World Health Organization (WHO), and platelets $<30\times10^9$/L.
- Grade ≥3 hemorrhage (requires red blood cell transfusion), regardless of platelet counts.
- Adults who are newly diagnosed with primary ITP and present with platelet counts $<20\times10^9$/L, even if they are asymptomatic or present with minor mucocutaneous hemorrhage. This decision

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is supported by the following arguments: possible uncertainty regarding diagnosis; requirement to monitor platelet count evolution; possible bleeding complications; need to guarantee that treatment is administered correctly.

- The following patient profiles could also benefit from hospitalization:
    - those refractory to treatment.
    - those whose diagnosis is not solid enough.
    - those presenting with relevant comorbidities.
    - those using concomitant medication associated with high hemorrhagic risk.
    - those presenting with significant mucosal bleeding.
    - those either with low social support, living far away from hospital or whose follow-up cannot be guaranteed.

Those adult patients with newly diagnosed primary ITP with platelet counts >20x10^9/L who either are asymptomatic or present with minor mucocutaneous bleeding, are recommended to receive ambulatory treatment instead of hospitalization. Tabla 4 summarizes the guidelines to follow with the different profiles of primary ITP patients who are not hospitalized [1,6,8,9,47].

Follow-Up of Diseases Frequently Associated with Primary ITP

During follow-up, close monitoring for early detection of diseases classically overrepresented in primary ITP patients is advisable. The prevalence of diabetes, renal failure, hypertension, vascular disease and thyroid disease is 2-2.5-fold higher than that of the normal population, the prevalence of other autoimmune diseases is 5-fold higher, and that of hematological malignancies is up to 6-20 fold higher.

Surgery

The optimal platelet count-target to avoid surgery-associated risk is still controversial. As a general rule, it is accepted that presurgical treatment is required when platelet counts are <50x10^9/L, while it would not be needed with counts >100x10^9/L [48]. Nevertheless, these values not only are merely indicative, but they are non-directly applicable to primary ITP either, since bleeding manifestations are less frequent in patients with this condition than those observed in patients with other thrombocytopenias [49]. For minor procedures with a standard bleeding risk, platelet counts >50×10^9/L are recommended, which should increase to >70-100×10^9/L to undergo major surgery or procedures on the central nervous system.

In emergency situations, the approach must be the same as that followed in the scenario of severe bleeding, i.e., one or more of these actions should be taken: administration of IVIg; administration of corticosteroids, preferably dexamethasone to take advantage of its rapid-acting profile; platelet transfusion, ideally after the aforementioned measures have been applied. TPO-RAs are not the best option when surgery is to be performed shortly, since they induce platelet generation at long-term. However, their use could be considered to maintain suitable platelet counts after surgery, especially after complex procedures.

Finally, when surgery is going to be planned, the time spent for an agent to achieve a sufficient platelet count increase must be considered when setting the date of the procedure. There is currently no agent to be definitely chosen ahead of others for presurgical preparation. The same therapies that are suitable for first- and second-line treatment can be used for presurgical preparation with the same hierarchy [50]. Table 5 summarizes the recommended platelet counts according to surgical risk as well as the guidelines to proceed with urgent or planned surgical procedures.

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Table 5. Topics of interest regarding surgery in patients with primary ITP.

Recommended preoperatory platelet count			
Associated risk	Description	Procedures	Platelet count
Minor	Non-vital and exposed organs Easy identification and hemostasis in the event of bleeding Limited dissection	Tooth cleaning Simple tooth extractions Local dental anesthesia Broncho-alveolar lavage	≥20-30x10^9/L
Moderate	Vital organs Difficult identification and hemostasis in the event of bleeding Profound and/or extensive dissection	Complex tooth extractions Bronchoscopy with transbronchial biopsy Digestive endoscopy/biopsy Minor surgery Cesarean delivery Lumbar puncture	≥50x10^9/L
Major	Above described scenarios when furthermore bleeding can be life-threatening or compromise surgery Surgeries associated with frequent bleeding	Epidural anesthesia Major surgery CNS and eye surgery (except cataract)	≥70x10^9/L ≥80x10^9/L ≥100x10^9/L
Management of emergency surgeries			
Time to surgery	Therapeutic options (one or more)	Remarks	
<12-24 hours	Dexamethasone, 40 mg/day x 4 days IVIg, 1 g/kg/day x 2 days Peri/intra-surgical platelet transfusion	Contact blood bank to arrange strategy and required resources	
1-7 days	Dexamethasone, 40 mg/day x 4 days IVIg, 1 g/kg/day x 2 days	Platelet transfusion is a valid option for those cases where no response to previous measures is observed	
Management of scheduled surgeries			
Time to surgery	Therapeutic options		
<2 weeks	Dexamethasone, 40 mg/day x 4 days IVIg, 1 g/kg/day x 2 days TPO-RA Eltrombopag, 50 mg/day		

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	Romiplostim, 3 µg/kg/week	
	Avatrombopag, 20 mg/day	
4 weeks	Dexamethasone, 40 mg/day x 4 days	
	Prednisone, 0.5-1 mg/kg/day	
	TPO-RA	
	Eltrombopag, 50 mg/day	
	Romiplostim, 3 µg/kg/week	
	Avatrombopag, 20 mg/day	

CNS, central nervous system; ITP, immune thrombocytopenia; IVIg, intravenous immunoglobulins; TPO-RA, agonist of thrombopoietin receptor.

Suspension of Treatment with TPO-RA

The long-term use of TPO-RA has allowed specialists to report long-lasting responses. This finding, together with the good safety profile associated with these drugs [51,52], has prompted their continuous use. Another argument to support this measure is the drop in platelet counts to pre-treatment values as early as 2 weeks after treatment suspension, which has been occasionally described [53]. Nevertheless, cases of long-term remission after treatment withdrawal [so called sustained remission off-treatment (SROT)] have also been reported [54–57], which may be due to immunomodulatory actions performed by this therapeutic group [57]. This last observation encouraged some practitioners to reduce progressively the TPO-RA dose, and, finally, suspend treatment, provided that a drop in the platelet count was not detected. This procedure not only saves costs but also reduces the risk of TPO-RA-associated adverse events [56]. Normally, candidates to achieve SROT after progressive dose reduction followed by suspension would be those who had presented with stable platelet counts (50-100x10^9/L) during a 4-6 months period on TPO-RA treatment, regardless of disease stage [55–57]. Patients must be properly informed about this therapeutic option, for them to decide after balancing risks and benefits. Several protocols to reduce dosage and suspend treatment have been proposed [58–61]. Ours is detailed in the Supplementary Table 2, where the profiles of SROT candidate and non-candidate patients are also described [59,62,63].

5. Primary ITP in Selected Patient Populations

Pediatric Patients

Primary ITP is usually self-limited in children. The highest incidence is reported in 2-8 y.o. patients, and history of a triggering infectious episode is not an infrequent occurrence. The trend to spontaneous remission is observed even after 2 years' evolution. The diagnostic approach is similar to that of adults. Although most pediatric patients with newly diagnosed primary ITP do not present with relevant bleeding symptoms and do not require treatment, it is mandatory that parents and children be aware of the risks associated with a severe or potentially fatal hemorrhage.

Hospitalization is recommended for those pediatric patients with active hemorrhage, bleeding risk factors or platelet counts ≤20x10^9/L. In order to make therapeutic decisions, platelet counts should not be the only factor for guidance. Other variables such as the nature of mucocutaneous symptoms, the type of active hemorrhage and the bleeding risk factors should also be considered on

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a case-by-case basis. The aim of the treatment should focus on the control of clinically relevant hemorrhages rather than the platelet count recovery. First-line treatments are either corticosteroids such as prednisone (oral) or methylprednisolone (i.v.), or high dose IVIg. In the event of no response to the firstly chosen agent, the alternative one can be tried [64,65]. TPO-RA can be used as second-line option [66,67]. Failure of first and second treatment lines should prompt not only bone marrow examination but also the consideration of other drugs such as mycophenolate mofetil or rituximab, even although the experience with these agents is limited in children. Splenectomy may be an option in scenarios of life-threatening hemorrhage. Table 6 provides details about these therapeutic guidelines.

Table 6. Management of primary ITP in pediatric patients, elderly patients and pregnant women .

Pediatric patients
Therapeutic decisions should not rely on platelet counts only. The type of bleeding manifestations and hemorrhagic risk factors have also to be considered
The aim of the treatment should prioritize the control of clinically relevant hemorrhages rather than platelet count recovery
First-line options
Oral prednisone or i.v. methylprednisolone, 4 mg/kg/day (maximum dose 180 mg/day in 3 daily doses) during 4 days, 2 mg/kg during 3 days, then suspend
High dose IVIg, one single dose of 0.8-1 g/kg
Second-line options
In persistent ITP
(if Rh+) i.v. anti-D Ig , one dose of 50-75 µg/kg, one-hour perfusion
Methylprednisolone, i.v., 30 mg/kg/day during 3 days, 2-hour perfusion
Dexamethasone, oral, 0.6 mg/kg/day (one daily dose, 40 mg/day maximum dose) during 4 days each month
In chronic ITP
TPO-RA (long-term treatment)
Romiplostim, s.c., one weekly dose, initial dose 1 µg/kg, weekly increases of 1 µg (10 µg maximum dose) until platelet counts ≥50x10^9/L are reached
Eltrombopag, oral daily dose of 25 mg (<6 years) or 50 mg (≥6 years). If platelet counts remain <50x10^9/L after 2 weeks, increase daily dose in 12.5 mg (<6
years) or 25 mg (≥6 years). This pattern is repeated until platelet counts >50x10^9/L are reached, never using daily doses >75 mg
Third-line options
Mycophenolate mofetil, 20-40 mg/kg/day orally, in 2 daily doses (response in 4-6 weeks)
Rituximab, currently under surveillance for suspicion of risk of progressive multifocal leukoencephalopathy; furthermore, risk of infection due to prolonged B-cell
depletion. Infusion has to be closely monitored to anticipate acute immunoallergic reactions
Splenectomy:
- in ITP of new or persistent diagnosis if there is bleeding emergency which is life-threatening and does not respond to previous treatment

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- in chronic ITP if there is life-threatening bleeding emergency

- can be considered in patients >5 y.o. and >2 years evolution who are symptomatic and refractory to previous treatments, provided that ITP interferes the normal life development

Elderly patients

Differential diagnosis is particularly important to reliably discard other entities and avoid wrong therapeutic approaches

The aim of the treatment is to maintain platelet counts ≥30x10^9/L in patients >75 y.o. (or in those >60 y.o. if there are concomitant bleeding risk factors), and improve QoL

When there is severe bleeding

Hospitalization and immediate instauration of treatment

First-line options

(general measures: local hemostasis, platelet and/or RBC transfusion, TXA, suspension of hemostatic medication)

IVIg, 0.4-0.5 g/kg/day during no more than 5 days (controlling hydration and renal function). Administer concomitantly with corticosteroids

Corticosteroids

Prednisone, but change to second-line in the event that doses >5 mg/day were required during >3 months to maintain the desired platelet count

Do not prolong treatment beyond 6-8 weeks

Dexamethasone (avoid if possible; if chosen, avoid administering more than 2-3 cycles; these should not exceed 20 mg/day or 4 days)

Additional options when rapid increases in platelet counts are required

TPO-RA: romiplostim, eltrombopag, avatrombopag

Vinca alcaloids: vinblastine, vincristine

When there is no bleeding

First-line options

Corticosteroids

Prednisone, but change to second-line in the event that doses >5 mg/day were required during >3 months to maintain the desired platelet count

Do not prolong treatment beyond 6-8 weeks

Dexamethasone (avoid if possible; if chosen, avoid administering more than 2-3 cycles; these should not exceed 20 mg/day or 4 days)

IVIg (only with severe thrombocytopenia [<10x10^9/L] or when bleeding risk is unacceptable), 0.4-0.5 g/kg/day during no more than 5 days, controlling hydration and renal function, and being administered concomitantly with corticosteroids

Second-line options

TPO-RA (first choice, ahead of the other second-line drugs)

Eltrombopag, oral daily dose of 25-75 mg

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Romiplostim, s.c., weekly dose of 1 µg/kg,; if needed, increase dose progressively, never exceeding 10 µg/kg, until the target of platelet count is reached. We

suggest starting with 3 µg/kg/week to optimize time to response.

Avatrombopag, oral daily dose of 20-40 mg (dose adjustment with respect to other adult populations is not required)

Fostamatinib, start with 2 oral daily doses of 100 mg, increase to 150 mg if required to reach the target. Recommended option when there is high

thromboembolic risk

Rituximab, 4 doses of 100 or 375 mg/m^2 during 4 consecutive weeks (long-term remissions are scarce, and toxicity is higher)

Other options

Immunosuppressants or immunomodulators (if moderate disease): mycophenolate mofetil, cyclosporin, azathioprine, danazol, dapsone (well-characterized

profiles of safety/efficacy)

Pregnant patients

Before making therapeutic decisions, the differential diagnosis must be carefully assessed in order to rule out other causes of thrombocytopenia, especially those

which are pregnancy-related

Patients with platelet counts ≤20-30×10^9/L require treatment. To undergo delivery, the recommended target for platelet count is >50×10^9/L for vaginal one and

>70×10^9/L for cesarean or if epidural anesthesia is going to be used

First-line options

Prednisone, 10-20 mg/day, using the lowest possible dose which is enough to reach platelet counts in the range of 20-30x10^9/L

IVIg (daily dose of 1 g/kg during 2 days or daily dose of 0,4 g/kg during 5 days), in the event of prednisone-induced side effects, severe bleeding or requirement of

rapid recovery of platelets to prepare for delivery

Other options

Azathioprine, cyclosporin. If splenectomy is decided (data regarding safety/efficacy are limited, risk of neonatal thrombocytopenia), the procedure should be

performed in the second trimester

Management of neonates will depend on their platelet count values

If these are <100x10^9/L, repeat on a daily basis

If these are <50×10^9/L, perform cranial ultrasound. If hemorrhage was detected, administer IVIg and steroids, at minimal doses and during a short period of time,

pursuing a platelet count-target of >100×10^9/L

If these are <30×10^9/L or there are hemorrhagic symptoms, administer one single dose of IVIg (1g/kg) to achieve rapid response

Ig, immunoglobulins; ITP, immune thrombocytopenia; i.v., intravenous; IVIg, intravenous immunoglobulins; QoL, quality of life; s.c., subcutaneous; RBC, red blood cells; TPO-RA, agonist of thrombopoietin receptor; TXA, tranexamic acid; y.o., years old.

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Elderly Patients

The incidence of primary ITP goes up to 9 per 100,000 individuals per year in >75 y.o. patients [1]. Nevertheless, the fact that some comorbidities causing thrombocytopenia can lead to an inaccurate diagnosis due to "ITP imitation" must be kept in mind. Furthermore, the incidence of these entities, such as megaloblastic or iron deficiency anemias, myelodysplastic syndromes (MDS) or acute leukemias, increases with age. For this reason, differential diagnosis is particularly important. When reasonable doubts arise, bone marrow analysis, including cytogenetic and flow cytometry approaches, is recommended.

Elderly primary ITP patients are at higher risk of bleeding, thromboembolism and infection, and they require frequently antiplatelet and anticoagulant therapies. Platelet counts are the main determinants of bleeding risk, and should be maintained at values >30x10^9/L in >75 y.o. patients, as well as in those >60 years with concomitant bleeding risk factors [68,69]. TPO-RAs, IVIg and vinca alkaloids can be considered when rapid platelet count increase is required [68].

The therapeutic attitude with elderly ITP patients with no active bleeding consists of the use of corticosteroids for first-line treatment, still at lower doses (prednisone at 0.5mg/kg/day) and for shorter periods than those used with younger patients [1,68]. IVIg are indicated in the event of severe thrombocytopenia only (<10x10^9/L), or with high bleeding risk [69]. According to patient's comorbidities, dexamethasone at standard doses may be an option. The choice of the second-line treatment should be made on an individual basis, and the patient should participate actively [1]. The good safety/efficacy profile of TPO-RAs in elderly patients makes them the main second-line therapeutic option [1,70]. Furthermore, their sustained response rates seem to be comparable to those observed with TPO-RAs in other adult populations [55,71,72]. Nevertheless, it must be remarked that the risk of thromboembolism associated with these drugs is higher in the elderly, since the concomitant presence of several other thromboembolic risk factors is not uncommon [73]. An alternative option for patients at high thromboembolic risk can be fostamatinib [74,75]. Rituximab may also be considered, although long-term remissions are scarce and more associated toxicities have been reported [1,69]. Finally, immunosuppressants or immunomodulators such as mycophenolate mofetil, cyclosporine, azathioprine, danazol or dapsone may be a valid option for those elderly patients presenting with moderate symptoms, since the safety/efficacy profile of these agents is well known. Nevertheless, many of these drugs require several months to achieve the intended effect [1,68]. Splenectomy is not recommended in the elderly except in isolated cases of multirefractory patients, because the procedure is less effective and triggers more bleeding and infectious complications than in other populations. Table 6 provides details regarding the treatment of primary ITP in the elderly.

Pregnant Patients

When primary ITP is suspected in a pregnant woman, other pregnancy-related causes of thrombocytopenia should be ruled out. In fact, although thrombocytopenia is the second hematologic disorder more frequently found in pregnancy, around 80% of cases are of gestational origin. The hallmark of these is a progressive decrease of platelet counts, starting in the mid-second trimester and persisting in the third one [76]. The procedure to diagnose primary ITP in pregnancy requires assessment of blood pressure, urine proteins, hemostatic status, and antiphospholipid and antinuclear antibodies (ANA) [77].

Severe complications are not frequently found in pregnant women with primary ITP, and neonatal incidences of thrombocytopenia or bleeding events are low. Particularly risky scenarios would be those of patients unable to maintain stable platelet counts >30x10^9/L with standard treatments, or patients with history of previous pregnancies with severe neonatal thrombocytopenia. Recommended platelet counts to undergo vaginal delivery are >50×10^9/L. This value goes up to >70×10^9/L in the event that cesarean delivery is required or epidural anesthesia is going to be used. The choice of type of labor will be made according to obstetric criteria only [78].

Pregnant women with platelets >20-30×10^9/L do not require treatment systematically. With lower values, the first-line options are glucocorticoids and IVIg. Starting with prednisone is

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recommended. This should be used at doses of 10-20 mg/day, since these are the lowest ones enough to achieve platelet counts in the range of 20-30x10^9/L. In order to avoid fetal risk, dexamethasone should not be used. IVIg has to be administered only in the event of side effects associated with steroids, severe hemorrhage or requirement for particularly rapid platelet count recovery, especially when delivery is close in time [7]. The usefulness of TPO-RAs as second-line option has not been established yet, since enough clinical evidence is lacking (only isolated cases and one case series have been reported [79,80]). The data sheets of these drugs do not include this indication, and any decision concerning this medication should be made in accordance with the patient's wishes, once she has been properly informed. If TPO-RAs are finally chosen, it is advisable to avoid them in the first trimester. Rituximab does not seem to be teratogenic. However, it has been associated with prolonged B-cell lymphocytopenia and the requirement to delay vaccination in neonates exposed in utero. For this reason, this agent should not be used within at least 6 months of planned conception [81]. Fostamatinib has been associated with fetal mortality in animal models [82].

Azathioprine and cyclosporin can be used without teratogenic risk. Finally, data regarding safety/efficacy of splenectomy in pregnant patients are limited. If the procedure is finally chosen, it should be performed during the second trimester, keeping in mind that an associated risk of neonatal thrombocytopenia exists [1].

After labor, platelet counts must be assessed in the neonate. If these are <100×10^9/L, they should be monitored daily. With values <50×10^9/L, cranial ultrasound should be performed and, if hemorrhage was detected, IVIg and steroids should be administered, at minimal doses and for a short period of time, pursuing a platelet count-target of >100×10^9/L. In those neonates presenting with hemorrhagic symptoms or platelet counts <30×10^9/L, one unique dose of IVIg is recommended in order to achieve rapid response. Finally, those neonates with thrombocytopenia lasting beyond 3 weeks from birth should quit breastfeeding [1]. Table 6 summarizes the most relevant topics regarding management of primary ITP in pregnant women and neonates.

6. Secondary ITP

Secondary forms of ITP account for the 9-20% of all ITP cases in adults. This rate increases with age [83,84]. Those pathologies able to induce immune tolerance disorders leading to secondary ITP are varied. Systemic lupus erythematosus (SLE) is the most commonly found entity [85–98] (Table 7). Thrombocytopenias secondary to drug use are particular conditions [99,100]. Indeed, treatment with the causal agent must be immediately suspended. When this is heparin, another anticoagulant should be started, preferably i.v. administered thrombin direct inhibitors. After platelet count recovery, these can be substituted by coumarins, starting at low doses [101]. Direct oral anticoagulants might be another option, although there is not enough evidence to recommend them specifically yet.

First-line treatment is similar in most cases of primary and secondary ITP, namely glucocorticoids and/or IVIg. However, the second-line option has to consider seriously the underlying disease when managing secondary ITP. For instance, the benefit:risk ratio regarding TPO-RA use or splenectomy should be balanced in cases of ITP secondary to SLE or antiphospholipid syndrome. Rituximab may be considered in the context of common variable immunodeficiency (CVID). The guidelines to treat secondary ITP are summarized in Table 7.

Table 7. Secondary ITP, causes and management.

Disruption of immune tolerance/Underlying etiology	(%)*	Management
Central		
ALPS	1	Treat in case of lymphoproliferation or immune cytopenia (needes in 50% of cases due to onset of autoimmunity) Immunosuppressants or, in very selected cases, splenectomy, can be considered [85]
SLE	5	Treat when platelet counts are <20-30x10^9/L. Corticoids are recommended for the first-line, although early relapses are not infrequent

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		Recent recommendations suggest rituximab as second-line option In refractory cases immunosuppressants (azathioprine, cyclosporine, cyclophosphamide, mycophenolate mofetil), splenectomy, TPO-RA and belimumab, alone or concomitantly with rituximab, have also been used [86,87]
Evans syndrome	2	The first-line treatment choice are corticosteroids. IVIg, rituximab, splenectomy and immunosuppressants have also been used In cases associated to genetic abnormalities, therapies against the corresponding genetic target have been suggested [88]
PAPS	2	It must be reminded that, in clinical practice, patients with thrombocytopenia and antiphospholipid antibodies but not meeting criteria for APS are frequently found. ITP associated with APS is treated similarly to SLE-associated ITP [89]
Differentiation		
CVID	1	Prednisone, 1 mg/kg during at least 3 weeks with subsequent dose decrease and final suspension, can be used as first-line choice In case of unsatisfactory response, IVIg, 1 g/kg, can be used Both therapies could be concomitantly administered when rapid response was required In refractory patients, rituximab, 375 mg/m^2/week for 4 weeks, can be used Splenectomy is recommended only when the first- and second-line treatments have failed. The risk of infection associated to splenectomy and immunosuppresants should always be in mind [90]
Lymphoproliferative syndromes/CLL	2	Response to corticoids and IVIg is worse than in primary ITP. However, good responses to rituximab have been reported In refractory cases, TPO-RA may be used, and splenectomy could be considered In severe and multirefractory cases, treatment specific for CLL should be administered in the absence of other criteria of treatment to control thrombocytopenia [85]
ITP post-transplantation	1	The most frequently found profile corresponds to patients <3 months who have undergone umbilical cord cell transplantation The therapeutic regimen is well defined: first-line, IVIg 1 g/kg/day during 3 days, and monitor weekly In the event of inadequate response, methylprednisolone can be used at 2 mg/kg/day during 14 days with subsequent dose decrease and suspension not beyond 8 weeks from the start TPO-RAs are valid options in the second-line treatment [98] As third-line choice, rituximab at 375 mg/m^2/dose up to 4 doses (controlling IgG) can be used; bortezomib, mycophenolate mofetil or sirolimus may be options for multirefractory patients [91]
Peripheral immune response		
Viral infection	6-7	Frequent in pediatric viral infection Described in association with CMV, EBV, VZV, ZIKV, HIV, HCV, SARS-CoV-2, as well as in post-vaccination periods Usually, specific treatment is not required. If needed, IVIg should be used ahead of corticoids, as the latter could facilitate viral replication. The efficacy of antiviral therapy to accelerate cytopenia resolution has not been demonstrated [92] TPO-RAs, especially avatrombopag, are indicated to manage HCV-induced thrombocytopenias [93] The use of eltrombopag and romiplostim in patients with HIV-induced thrombocytopenia has been described as safe [94] In the presence of SARS-CoV-2 (see Table 8), management is similar to that described for primary ITP, although the use of TPO-RAs has to be carefully balanced due to the risk of thromboembolism and liver toxicity [95]

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	Helicobacter pylori	1	Although its association with thrombocytopenia has not been demonstrated beyond doubt, there are studies showing that the options to achieve platelet count recovery increase 14-15-fold after the eradication therapy has been administered [96]. Thus, in these cases, the treatment to eradicate *Helicobacter pylori* (which, furthermore, is well defined) could be also useful to overcome thrombocytopenia [97]
	Drugs	n.c.	The web link "*Platelets on the Web*" is useful to review the drugs that have been associated with ITP [99]. Since these are numerous, the associated pathophysiological mechanisms are manifold. The incidence is 1 case/100,000 inhabitants/year, although this value is probably underestimated The treatment with the drug causing ITP should be immediately suspended. If the drug is heparin, another anticoagulant should be started, preferably i.v. administered thrombin direct inhibitors [101]. Since symptoms are usually resolved in the 2 days following drug suspension, there is no need for specific therapy In severe cases with associated bleeding, corticoids, IVIg or platelet transfusion have been used [100]

Modified from Cines et al [85]. *Percentage with respect to the total amount of ITP (primary and secondary). ALPS, autoimmune lymphoproliferative syndrome; APS, anti-phospholipid syndrome; CLL, chronic lymphocytic leukemia; CMV, cytomegalovirus; CVID, common variable immune deficiency; EBV, Epstein-Barr virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IgG, immunoglobulin G; ITP, immune thrombocytopenia; i.v., intravenous; IVIg, intravenous immunoglobulins; n.c., non-calculated; PAPS, primary anti-phospholipid syndrome; SLE, systemic lupus erythematosus; TPO-RA, agonist of thrombopoietin receptor; VZV, varicella zoster virus; ZIKV, Zika virus.

Table 8. Primary ITP in special scenarios: thrombosis, COVID-19.

Primary ITP and thrombosis
The risk of thrombosis, either venous or arterial, is 2-fold higher in patients with primary ITP The origin is multifactorial, and there are many actors of primary hemostasis, coagulation and fibrinolysis playing a role. Some therapies for primary ITP also contribute to the increase in thromboembolic risk Thrombocytopenia is associated with a poorer prognosis in patients with acute coronary syndromes. Thus, platelet count recovery must be a priority target Treatment must be individualized according to hemorrhagic history and thromboembolic risk. In an acute arterial episode with platelet counts >10×10^9/L aspirin could be used, while double antiplatelet treatment may be considered with platelet counts >30×10^9/L Anticoagulants can be used at full doses with platelet counts >50×10^9/L. With lower counts, the options are either dose reduction or suspension. In those situations where anticoagulation is contraindicated while immediate measures are required, a vena cava filter can be placed or, with platelet counts <10×10^9/L, prophylactic platelet transfusion could be performed In patients with thromboembolic history, the preferred choices for first- and second-line treatment are glucocorticoids and fostamatinib, respectively. Only in the event of no response to the latter, if maintenance of the platelet count was required in order to continue administering antiplatelet or anticoagulant treatment safely, the use of TPO-RAs could be considered
Primary ITP and COVID-19

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The diagnosis of ITP in the context of COVID-19 is a diagnosis of exclusion

Patients with platelet counts <20×10⁹/L and/or active bleeding have to be treated with prednisone, 0.5-1 mg/kg/day for no more than 2 weeks, with progressive

reduction and suspension not beyond 8 weeks from the start

Those patients with severe COVID-19 who are already with corticoids and present with platelet counts <20×10⁹/L and/or active bleeding, could be additionally

treated with IVIg, 2 g/kg total dosis. If counts <20×10⁹/L and/or active bleeding persist, one TPO-RA could be administered, although at the lowest possible dose

Fostamatinib may be one alternative option to TPO-RA

Rituximab must be avoided, since the patient's ability to produce antibodies would be compromised. For the same reason, other immunosuppressants should also be

avoided whenever possible

When patients with chronic primary ITP who are being well controlled with treatment are infected by SARS-CoV-2, their therapeutic regimen should not be

modified. In the event that the infection induces a relapse, IVIg should be administered in case of severe thrombocytopenia and, if bleeding occurred, platelet

transfusion could be performed. Those patients who are already in treatment with TPO-RA could consider either a dose increase or the addition of another TPO-RA

or fostamatinib

If patients with primary ITP who are receiving anticoagulant/antiplatelet treatment are infected by SARS-CoV-2 and present with severe symptoms,

if they are on LMWH, the can continue treatment at full dose provided that platelet counts are >30×10⁹/L

if they are on other other anticoagulant or antiplatelet agents, treatment at full dose could be administered with platelet counts >50x10⁹/L

The risk of secondary ITP subsequent to SARS-CoV-2 vaccination is not higher than that induced by other antiviral vaccines; SARS-CoV-2 vaccine is not

contraindicated in pregnant women or patients with history of ITP

ITP, immune thrombocytopenia; IVIg, intravenous immunoglobulins; LMWH, low molecular weight heparin; TPO-RA, agonist of thrombopoietin receptor.

7. Primary ITP and Thrombosis

Pathophysiology, Risk Associated with the Treatment of Primary ITP

Patients with primary ITP are at twice the risk of venous or arterial thrombosis compared to the normal population, even when platelet counts are markedly low [102]. The origin is multifactorial, with causal roles played by the classical thromboembolic risk factors and the therapies that are being administered to treat thrombocytopenia [103]. On the one hand, patients with primary ITP have higher circulating levels of neutrophil extracellular traps (NETs), E-selectin, plasminogen activator inhibitor-1 (PAI-1) and microparticles rich in phosphatidylserine and tissue factor (TF), as well as hyperreactive immature platelets, within a proinflammatory scenario that also promotes coagulation, occasionally boosted by lupus anticoagulant and/or anticardiolipin or anti-β2-glycoprotein-I antibodies [104–106]. On the other hand, most primary ITP treatments induce some extent of thrombotic risk. Corticosteroids could increase the expression of TF and factor VIII, reduce that of thrombomodulin, and promote cell adhesion via von Willebrand factor; occasionally, IVIg could

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trigger thromboembolic venous events in patients with concomitant risk factors and arterial events in patients of advanced age and/or with atherosclerosis; platelets of TPO-RA-treated patients tend to present apoptotic patterns leading to expression of phosphatidylserine on the cell surface, thus promoting the assembly of the prothrombinase complex; finally, splenectomy may also promote thrombosis, either portal or systemic [58,106].

Antiplatelet and Anticoagulant Treatments in the Context of Primary ITP

It must be recalled that thrombocytopenia is predictive of a poor prognosis in patients with acute coronary syndromes. In order to minimize the bleeding risk associated with the use of antiplatelet agents in patients with thrombocytopenia, non-steroidal anti-inflammatory drugs and inhibitors of GPIIb/IIIa should be avoided, proton pump inhibitors should be administered, aspirin should be given at low dose, the prolonged use of triple antithrombotic therapy should be avoided and, in those patients undergoing stent placement, double antiplatelet therapy should be limited to one month after the procedure. Treatment should be decided on an individual basis, and should be influenced by the thrombotic risk and the hemorrhagic history of each patient. Aspirin could be used in cases of acute arterial events provided that platelet counts are $>10\times10^9$/L, while the double antiplatelet treatment should be restricted to patients with counts $>30\times10^9$/L [107].

There are no studies designed to evaluate the safety and efficacy of anticoagulant treatment in primary ITP patients. Nevertheless, the administration of therapeutic doses of anticoagulants to patients with platelet counts $>50\times10^9$/L is generally accepted. Bleeding risk increases when counts are $<50\text{x}10^9$/L. In such cases, the options would be suspending anticoagulation or reducing anticoagulant drug dose. In the event of total contraindication for anticoagulation, a vena cava filter could be placed provided that the thrombus is below the placement area.

In those patients with history of thromboembolism, glucocorticoids and fostamatinib would be the first-line and second-line options, respectively. In the event that there is no response to fostamatinib and platelet counts must be maintained to avoid complications associated with anticoagulation or antiplatelet drugs, the use of TPO-RAs could be considered.

Table 8 summarizes the guidelines to follow in the management of patients with primary ITP and thromboembolism or thromboembolic risk.

8. ITP and COVID-19

SARS-CoV-2, like other viral agents, is able to induce ITP. In this case, the diagnosis of secondary ITP is also by exclusion.

The treatment of ITP in patients with COVID-19 and platelet counts $<20\times10^9$/L and/or active bleeding should consist of prednisone at 0.5-1 mg/kg/day for no more than 2 weeks, followed by progressive dose reduction and, finally, suspension no later than 8 weeks from the start. Those patients with severe COVID-19 who are already on corticoids and present with platelet counts $<20\times10^9$/L and/or active bleeding could be additionally administered IVIg, at a total dose of 2 g/kg. In the event that counts continue to be $<20\times10^9$/L and/or active bleeding persists, TPO-RA could be administered, although at the lowest possible dose. An alternative option may be fostamatinib, which could be beneficial not only for platelet count recovery but also to relieve COVID-19-triggered inflammatory processes [108]. Rituximab, and other immunosuppressants, should be avoided, since these agents reduce the ability to produce antibodies [109–111].

Those patients with primary ITP in its chronic phase who are being well controlled with their ITP treatment, should not change their therapeutic regimen if they are infected by SARS-CoV-2. If the infection leads to a relapse of the thrombocytopenia, patients should be administered IVIg if the drop of platelet counts is severe, and platelets should be transfused in the event of bleeding. In those patients who were already being treated with a TPO-RA, an increase of the dose or the addition of another TPO-RA or fostamatinib could be proposed [112,113].

When those patients with primary ITP and, furthermore, on anticoagulant treatment, are infected by SARS-CoV-2, even if COVID-19 symptoms are severe, they can continue using low

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molecular weight heparin (LMWH) at prophylactic dose provided that cell counts are >30×10^9/L. Anticoagulation or antiplatelet agents can be used at therapeutic doses with counts >50x10^9/L [112].

Finally, it must be remarked that the risk of secondary ITP associated with SARS-CoV-2 vaccination is very low, in the range of that induced by other commercially available vaccines against other viral agents [114,115]. There is no contraindication against using COVID-19 vaccines in pregnant women or patients with preexisting ITP [116,117].

The most important notions concerning treatment of ITP secondary to COVID-19 and managing SARS-CoV-2 infection in patients with primary ITP are summarized in Table 8.

9. Limitations

The field of primary ITP is a rapidly changing landscape. Many of the guidelines and recommendations are aimed to provide some guidance only. Large series and/or randomized prospective studies to compare therapeutic approaches or assess reliably the efficacy of treatments are lacking in the primary ITP scenario. This is a common problem to all guides and consensus documents addressing this disorder. Recommendations have thus not been graded because they are taken from expert opinions and non-comparative studies, and therefore have only a low level of evidence. On the other hand, the pathophysiology has not been addressed in depth, since the aim of this article was to provide physicians with an updated reference for their day-to-day practice. Finally, secondary ITP would deserve one updated review focusing exclusively on this complex condition.

10. Conclusions

Primary ITP management remains a challenge. Its diagnosis is performed by exclusion and requires the involvement of experienced practitioners. There is now a consensus on the disease categories, criteria used to define refractoriness and types of treatment response, and all these should be considered when managing patients with thrombocytopenia. Glucocorticoids and IVIg remain the cornerstones of first line of treatment. Regarding second line treatment, TPO-RAs are usually the first choice. Fostamatinib is also a valid option, and has been shown to be even better than the former for those patients with high thromboembolic risk. A variety of immunosuppressants, immunomodulators or cytostatic agents may be considered for multirefractory patients, after carefully weighing up their risks and benefits. The increasing choice of therapeutic options means that splenectomy is now only performed on a very limited set of patients. Treatments may be adjusted in specific subpopulations (pediatric, elderly, pregnant women) or in the presence of concomitant conditions (thrombosis, COVID-19). Primary ITP management is continuously evolving, and regular updates are necessary.

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