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REVIEW

# Older Adults and Immune Thrombocytopenia: Considerations for the Clinician

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**Abstract:** Many epidemiological studies have shown that the incidence of immune thrombocytopenia (ITP) increases after age 60 years and peaks in patients over age 80 years. Therefore, ITP is a concern for physicians taking care of older patients, especially regarding its diagnosis and management. The diagnostic work-up should exclude other causes of thrombocytopenia and secondary ITP, including myelodysplastic syndrome and drug-induced ITP. The treatment decision is influenced by an increased risk of bleeding, infectious diseases and thrombosis in this population and should take into account comorbidities and concomitant medications such as anticoagulant drugs. First-line treatment is based on short corticosteroids courses and intravenous immunoglobulin, which should be reserved for patients with more severe bleeding complications, with their higher risk of toxic effects as compared with younger patients. Second-line treatment should be tailored to the patient's history, comorbidities and preferences. Preferred second-line treatments are thrombopoietin receptor agonists for most groups and guidelines given their good efficacy/tolerance ratio, but the thrombotic risk is increased in older people. Other second-line options that can be good alternatives depending on the clinical context include rituximab, dapsone, fostamatinib or immunosuppressive drugs. Splenectomy is less often performed but remains an option for fit patients with chronic refractory disease. Emerging treatments such as Syk or Bruton tyrosine kinase inhibitors and FcRn antagonists are becoming available for ITP and may modify the treatment algorithm in the near future. The aim of this review is to describe the particularities of the diagnosis and treatment of ITP in older people, including the response and tolerance to the currently available drugs. We also discuss some situations related to co-morbidities that can frequently lead to adapt the management strategy in older patients.

**Keywords:** immune thrombocytopenia, ITP, elderly, intravenous immunoglobulin, IVIg, thrombopoietin receptor agonists, splenectomy, rituximab

## Introduction

Immune thrombocytopenia (ITP) is an autoimmune disease characterized by antibody-mediated platelet destruction and impaired platelet production resulting in bleeding symptoms.[1] Although it can affect individuals of all age categories, the disease incidence peaks in older patients.[2,3] Hence, combined with the worldwide trend in the ageing of the population, ITP is of particular interest for physicians taking care of older patients. ITP management is challenging in older versus younger patients given the frequent comorbidities and increased risk of bleeding, infections and thrombosis of the former group.[4,5]

A growing number of studies focusing on older patients with ITP are now available, as are new treatments for ITP. In this review, we provide an update on the diagnosis, prognosis and treatment of older patients with ITP in light of these recent data. We also discuss some situations related to co-morbidities that can frequently lead to adapt the management strategy in older patients. To date, no prospective study focusing on this population has been conducted and therefore most recommendations presented here are not evidence-based but rather extrapolated from observational and retrospective studies as well as our own experience.

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# ITP Diagnosis and Epidemiology

## Epidemiology

Several large epidemiological studies have shown that the ITP epidemiology is influenced by sex and age,[2,3,6] with peaks in young women and old men. ITP is also a geriatric disease, with incidence rates reaching 23.9/100 000 in men >80 years old in the United Kingdom[3] and 9/100 000 person-years in men >75 years old in France,[2] that is, an approximately 10-fold increase as compared with men aged 30 to 39 years in both studies. In a recent French study including 541 adults with incident ITP included in a prospective national registry, 251 (46%) were ≥65 years and among them, 47% were ≥80 years. In this later group of very old patients, 37.9% were exposed to antiplatelet drugs and 18.4% to anticoagulants.[7]

## Diagnosis

According to international guidelines, primary ITP is defined by isolated thrombocytopenia <100 x $10^9$/L of an autoimmune origin in the absence of any underlying cause or disorder.[8] ITP usually presents as isolated thrombocytopenia, and the diagnostic work-up mainly focuses on eliminating other etiologies because of no gold-standard diagnostic test. Secondary ITP refers to immune thrombocytopenia associated with other conditions (eg, hematological malignancies, systemic lupus, primary immunodeficiencies) at diagnosis. The main differential diagnoses of thrombocytopenia and causes of secondary ITP are shown in Table 1.

Patient history, physical examination, complete blood count and peripheral blood smear examination are the cornerstone of ITP diagnosis. In addition, some exams of interest to identify particular situations or secondary ITP include serologies for HIV, hepatitis C and B virus, antinuclear antibodies and protein serum electrophoresis. Other blood tests should be oriented to the clinical context. Because of lack of sensitivity and specificity, the search for antibodies against platelet antigens is not recommended in routine practice.[8,9]

However, the diagnostic approach proposed in the international guidelines is a global approach that addresses adults without taking into account age. In older patients, some points deserve consideration in the ITP diagnostic work-up. First,

**Table 1** Other Main Causes of Thrombocytopenia

| Secondary ITP | Non-Immune Thrombocytopenia |
|---|---|
| **Associated auto-immune disorder** | **Splenic sequestration** |
| Evans syndrome | Portal hypertension |
| Systemic lupus erythematosus | Splenomegaly |
| Antiphospholipid syndrome | Splenic infiltrative diseases |
| Other auto-immune disorders | |
| | **Decreased production** |
| **Drug-induced ITP and vaccine-induced ITP** | Inherited thrombocytopenia |
| | Primary and secondary bone-marrow failures |
| **Infectious diseases** | Hematological drug toxicity, alcohol toxicity |
| HIV | Folate and/or B12 deficiency |
| HCV | Viral infections: HIV, HBV, HCV EBV, CMV, parvovirus B19 |
| Helicobacter pylori | |
| | **Peripheral platelet consumption** |
| **Lymphoproliferative disorders** | Disseminated intravascular coagulation |
| Chronic lymphocytic leukemia | Thrombotic microangiopathy |
| Indolent B-cell lymphoma | Sepsis |
| Angioimmunoblastic T-cell lymphoma | |
| | **Alloimmune thrombocytopenia** |
| **Primary immune deficiencies/inborn error of immunity** | |
| Common variable immune deficiency | |
| Autoimmune lymphoproliferative syndrome | |

**Abbreviations**: ITP, immune thrombocytopenia; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

drug-induced ITP should be considered because exposure to treatments increases with age. Several mechanisms can be responsible for drug-induced ITP, but most commonly, platelet destruction is mediated by a drug-dependent antibody.[10] Patients usually present profound thrombocytopenia and bleeding symptoms soon (in a few hours to a few days) after drug introduction. Because in vitro confirmation of drug-induced ITP is usually unavailable, the diagnosis relies on a complete history of drug intake, the relative chronology with thrombocytopenia, and spontaneous recovery upon drug discontinuation. Many drugs but also vaccines have been implicated in drug-induced ITP and updated reviews have been published recently.[10–12]

### Interest of Bone-Marrow Evaluation (BME) in Older Patients

Another differential diagnosis of thrombocytopenia in older patients is myelodysplastic syndrome (MDS) affecting megakaryocyte lineage. Although most MDS cases exhibit associated thrombocytopenia (65%),[13] isolated thrombocytopenia is less frequent (12% of cases).[14] Therefore, the presence of other cytopenia or macrocytosis on complete blood count and signs of dyserythropoiesis and/or dysgranulopoiesis on peripheral blood smear examination should prompt a BME to rule out a myelodysplastic syndrome. Notably, patients with early ITP can present some abnormalities in megakaryocyte morphology as well as some reticulin fiber deposits on bone-marrow biopsy.[15,16] The coexistence of MDS and ITP has been described.[17]

We suggest to use a pragmatic approach and to propose a short course of corticosteroids or intravenous immunoglobulin (IVIg) when suspecting ITP. Although not validated in prospective studies, a response to these treatments suggests an immunological contribution to thrombocytopenia but does not rule out MDS.[5]

Performing systematic BME in patients >60 years presenting isolated thrombocytopenia has been debated in the past years. However, growing evidence suggests that the rate of abnormality on bone-marrow smear in this context is very low. In the prospective French registry, only one in 197 (0.8%) patients with ITP and older than 60 years had an abnormal bone-marrow smear result.[18] In a recent retrospective study of 324 patients with relapsed/refractory ITP, 56% had a BME, which resulted in eight other diagnoses (8% of tested patients). Of note, age was not associated with abnormal findings on BME in this study.[19]

Current international guidelines recommend BME only in patients with systemic symptoms, abnormal signs, or a suspected different diagnosis independent of age. BME can also be performed before splenectomy or in case of treatment failure.[8,20] If performed in older patients to rule out MDS, a cytogenetic study and next-generation sequencing should be performed at the same time; flow cytometry analysis and bone-marrow biopsy should be performed in case of suspected lymphoma.[8]

## ITP Prognosis: What Particularities in Older Patients?

Given the increased frequency of ITP in older patients, interest has been growing in determining whether the disease course, severity and complications are similar to those of younger patients. Infectious and thrombotic risk are also relevant when considering therapeutic options, especially in older patients.

### Disease Course

ITP can be classified according to disease duration as newly diagnosed (0–3 months), persistent (3–12 months), or chronic (>12 months).[8] In adults, newly diagnosed ITP evolves toward chronic disease in about 70% of cases. Chronic ITP has a very low probability of spontaneous recovery.[21] Whether older patients diagnosed with ITP are at increased risk of chronic disease is unknown.

### Bleeding Risk

Data from the literature are conflicting about bleeding risk in older patients. Some studies did not find an association between age and bleeding,[22,23] and others found more bleeding in older patients with similar platelet counts.[2,24–31] In a recent series comparing 311 patients aged <65 years to 154 aged ≥65 years, Palandri et al found no differences in platelet count at diagnosis or in bleeding symptoms but more grade 3/4 bleeding and thrombosis in older patients, with a first-line therapy started for higher platelet counts.[32] Several other factors such as comorbidities and drug exposure could influence

the bleeding risk, particularly in older patients. Comorbidities such as cardiovascular diseases, kidney or liver failure, or gastrointestinal diseases increase in number with age.[4,7,29] In a French cross-sectional study, age was significantly associated with severe bleeding on univariate analysis but not after adjustment for other covariates, including anticoagulant drugs. In this study, platelet count, female sex and exposure to non-steroidal anti-inflammatory drugs were associated with risk of any bleeding, and exposure to anticoagulant drugs was a major risk factor for severe bleeding.[33]

The definition of "older" has also varied among studies and may explain some discrepancies. In a recent study from our group, the disease course of very old patients (aged ≥80 years) was compared to those of old patients (aged 65–79 years). Although platelet counts at ITP diagnosis were similar, severe bleeding and mortality were more frequent in very old patients although not significantly. Comorbidities were also more frequent, and exposure to anticoagulant drugs was strongly associated with severe bleeding.[7]

Overall, these data suggest that platelet count and bleeding symptoms at ITP onset are probably independent of age as well as disease course but that older patients probably are at increased risk of severe bleeding, especially when exposed to anticoagulant drugs. In other words, the care of a patient over age 65 years without co-morbidities and not exposed to anticoagulants can probably be modelled on that of younger patients. However, a more aggressive strategy and a higher platelet threshold to decide to treat should probably be considered in very old patients, especially in the presence of a co-morbidity and exposure to anticoagulants because of greater risk of bleeding complications.

### Thrombosis and Infection

Multiple factors can contribute to arterial and venous thrombosis observed during the ITP course.[34] Paradoxically, ITP could be a prothrombotic disease, and thrombosis can occur even with low platelet counts.[35,36] Thrombotic risk also increases with age,[37,38] and cardiovascular risk factors are more frequent in older patients. Some ITP treatments that could favor thrombosis include IVIg,[39] splenectomy[40] or thrombopoietin receptor agonists (TPO-RAs).[41–45] In this context, the addition of treatment-related prothrombotic factors to patient- and ITP-related prothrombotic factors should be weighed carefully.

Older patients may be more sensitive to infections than younger patients. Infectious risk is also increased in ITP probably because of immunosuppressive drug use and splenectomy,[50] and contribute to mortality.[51,52] This is important to consider for ITP management and treatment decisions in older patients with a possibly increased risk of infection observed with some treatments such as corticosteroids, immunosuppressive drugs and rituximab.

## ITP Treatments: What Tolerance and What Efficacy in Older Patients?

### Treatment Decision

The treatment decision is mainly based on bleeding symptoms and platelet count, although other factors important to consider include disease duration, other medications, comorbidities, expected tolerance, accessibility of care, quality of life and patient expectations. Age but more importantly frailty also influence the treatment choice, but in any case, treatment should always be tailored to the patient, and guidelines highlight that ITP treatment should be personalized. This is especially true for older people because for the same number of platelets, many individual factors can influence the decision. Also, patients' concerns and fears and disease burden are often misjudged by the physician.[53,54] Therefore, the decision to treat must always be shared with the patient, as it has been shown in other hematologic diseases.[55] If the patient has high functional impairment, a fair discussion with the caregivers outlining the benefits, limitations and side effects of treatment is essential.

International guidelines have long proposed a threshold of 30 x $10^9$/L platelets to indicate treatment, even in a patient without bleeding.[56] We now have considerable evidence to suggest that this threshold can be lowered to 20 x $10^9$/L.[33] Because bleeding risk clearly increases with platelet count <20 x $10^9$/L, particularly in older patients (see above), the recommendation is to treat older patients with platelet count below this threshold.[8] However, bleeding symptoms secondary to thrombocytopenia are unusual with platelet count >50 x $10^9$/L, and a watch-and-wait approach should be proposed in this case unless a higher platelet count is required for an intervention.[8]

When platelet counts are 20 to 50 x $10^9$/L, no evidence-based medicine is available and the treatment decision should be based on the presence of additional risk factors of bleeding such as a history of bleeding; co-morbidities (eg, severe hypertension, renal or liver failure, peptic ulcer); age >80 years and frailty, including risk of falls; and drug exposure. In this setting, a watch-and-wait approach is easier when a rapid response to corticosteroids or IVIg is known from previous treatment courses, allowing for safe management of the potential occurrence of a bleeding complication.

When the patient is taking drugs interfering with hemostasis, the referring physician should be contacted to assess the risk/benefit balance. These drugs should not eventually be discontinued when indicated (except transiently when platelet counts are very low [ie, <10 x $10^9$/L] or in case of bleeding) because a low platelet count does not preclude thrombotic risk.[35,36] ITP treatment should be considered to maintain a safe platelet count. Anticoagulant drugs have been associated with increased risk of severe bleeding, and some experts and epidemiological studies argue that maintaining the platelet count above 50 x $10^9$/L is safer.[7,33,57] Although anti-platelet drugs interfere with primary hemostasis, the bleeding risk seems lower with these agents,[7,33] perhaps because platelet turnover is increased in ITP. Therefore, maintaining a higher platelet count is probably safer when the patient takes anti-platelet drugs, although the optimal threshold is unknown, but a threshold of 30 x $10^9$/L could probably be tolerated.

If a watch-and-wait approach is favored, patients should have a close monitoring of platelet count and bleeding symptoms. Our current strategy for ITP treatment decisions in older patients is summarized in Figure 1.

## First-Line Treatments

### Corticosteroids

ITP first-line therapy relies on a short course of corticosteroids.[8] Long-term corticosteroids should be avoided in most cases because they are poorly effective in maintaining remission at a low dose and do not affect the ITP natural history while generating side effects.[58,59] Prednisone 1 mg/kg for 3 weeks or dexamethasone 40 mg/day for 4 days (repeated up to three times if necessary) can be used. A number of controlled studies have suggested a faster and greater platelet response with dexamethasone over prednisolone, but the rate of long-term response was similar in both groups.[60,61]

Age does not affect the response to corticosteroids, but this treatment generates more adverse events in older patients.[27,29] Tolerance remains acceptable with short courses of corticosteroids: in a retrospective study of 440 patients aged >60 years who received corticosteroids (prednisone or dexamethasone) as first-line ITP therapy, only 16 (3.7%)

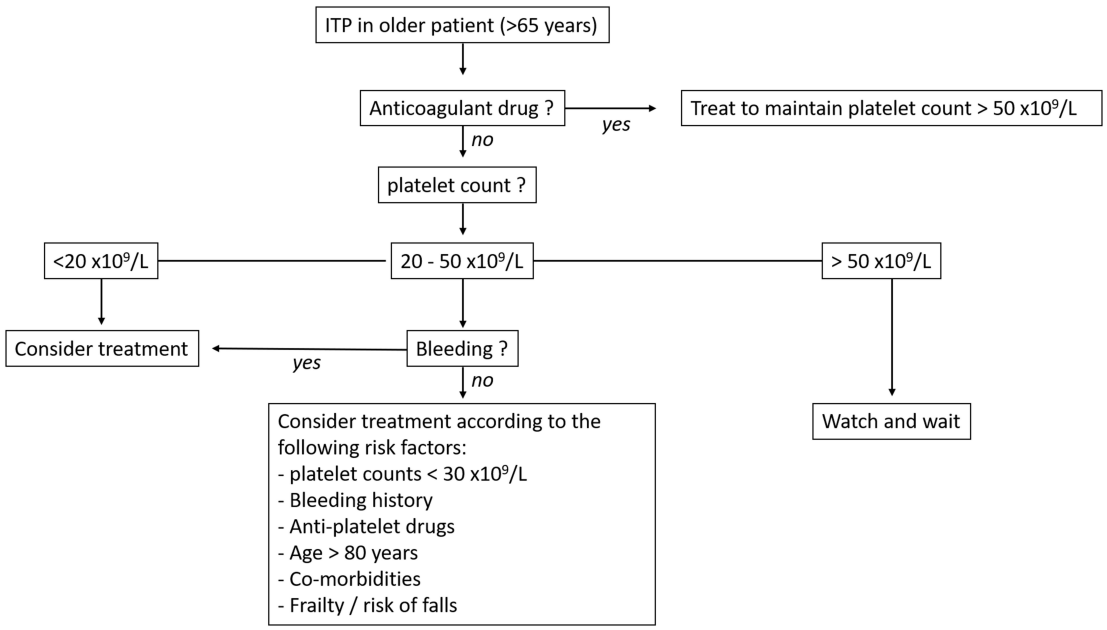


**Figure 1** Proposed algorithm for treatment decision. In patients with immune thrombocytopenia (ITP) without anticoagulant drugs and with platelet counts of 20 to 50 x$10^9$/L, treatment can be delayed if there are no bleeding risk factors but should be considered if there are more than 2 bleeding risk factors.

discontinued treatment because of toxic effects (mainly diabetes and psychiatric symptoms).[62] The risk of infection is also increased with corticosteroids but mainly with prolonged treatment, which should be strongly avoided in ITP.[63]

Several studies have suggested lower than standard corticosteroids dose regimens as an alternative strategy.[26,64] We frequently use a reduced dexamethasone dose of 20 mg/day (instead of 40 mg/day) in frail patients. Although particularly relevant in older patients to limit toxic effects, this dose remains to be validated in this particular population.

### Intravenous Immunoglobulin (IVIg)

A combined course of IVIg and corticosteroids has been found more effective than corticosteroids alone for time to response, platelet count and response duration.[65] Therefore, IVIg is a treatment of choice for patients with a high bleeding score,[66] although its cost, availability, transient response (less than 1 month) and potential adverse events limits its more general use.[8] The recommended dose is 1 g/kg/day, which can be repeated on day 2 in case of severe bleeding with a life-threatening situation or on day 3 with less severe bleeding and in case of lack of response after the first infusion.[67] Side effects include anaphylaxis, hemolytic reactions, and minor symptoms such as headache, nausea, or fever. Other adverse events such as renal failure, fluid overload and thrombosis seem more frequent in older patients and justify a lower daily dosage (0.5 g/kg days 1–4 or 0.4 g/kg days 1–5), with careful monitoring of hydration and renal function.[39,68–70]

### Anti-Rho(D) Drugs

Intravenous anti-Rho(D) drugs are not licensed in Europe but have been proposed to treat Rho(D)-positive patients who have not undergone splenectomy, with high response rates at the cost of rare but life-threatening side effects.[71] Fatal disseminated intravascular coagulation associated with acute hemoglobinemia or hemoglobinuria after Rho(D) intravenous administration has been reported, particularly in older people in whom this treatment should be avoided.[72]

### Management of Life-Threatening Bleeding and Refractory Disease

In case of life-threatening bleeding situations such as visceral hemorrhage with decreased hemoglobin level or intracranial bleeding, the addition of platelet transfusions to IVIg and dexamethasone should be administered with a proven beneficial hemostatic effect.[73,74] Drugs interfering with hemostasis should be stopped immediately. In patients with active bleeding and with disease refractory to first-line therapy, vinca alkaloids such as vinblastin (weekly injection of 5 mg/m² with a maximum of 10 mg) rather than vincristine due to better digestive tolerance can provide rapid response but should not be used for long-term treatment because of neurological toxic effects, particularly in older people.[8] TPO-RAs can also be used as an off-label salvage therapy in our experience but with a risk of thrombosis.[75] Until these encouraging results are confirmed by other groups, the use of high-dose TPO-RAs should be reserved for patients with very severe bleeding resistant to total therapy (IVIg + high-dose corticosteroids + multiple and repeated platelet transfusions).

## Second-Line Treatments

Most adults with ITP have a chronic disease course. When disease is refractory to or relapses after first-line treatment, an increasing number of therapeutic options are available for second-line treatment. Each has an expected pattern of response, but to date, there are no accurate predictors to help select the ITP treatment. The treatment choice also relies on caveats specific to each molecule that are described below and in Table 2. Co-morbidities and patient preference are also important in therapeutic decisions. According to the context, treatment should aim to avoid bleeding by maintaining a safe platelet count while limiting short- and long-term toxic effects. An overview of our current treatment strategy is proposed in Figure 2.

### Thrombopoietin Receptor Agonists (TPO-RAs)

TPO-RAs are drugs increasing platelet production without immunosuppression that have a demonstrated good efficacy/safety profile, which explains why they have become the preferred second-line treatment in older patients with ITP by most groups and guidelines (Figure 2).[4,5,46] Two TPO-RAs, namely eltrombopag and romiplostim, are currently licensed for chronic ITP in Europe, and a third one, avatrombopag, is also available in some countries. Although no head-to-head comparison is available, response rates seem similar between both drugs[76] and close to 80% within 2 weeks.[41,42] The molecule choice mostly relies on the administration route preference: romiplostim requires a weekly subcutaneous

**Table 2** Factors influencing second-line treatment choices for ITP

| | Avoid if Increased Thrombotic Risk | Avoid if Increased Infectious Risk | Avoid if Rapid Response Needed | Avoid if ITP is Secondary to Lymphoproliferative Disorder | Avoid if Severe Co-Morbidities | Avoid in Non-Chronic Patients |
|---|---|---|---|---|---|---|
| TPO-RA | x | | | | | |
| Rituximab | | x | | | | |
| Immunosuppressive drugs | | x | x | x | x | |
| Dapsone | | | x | | | |
| Danazole | x | | x | | | |
| Splenectomy | x | x | | x | x | x |
| Fostamatinib | | | | ? | | |

**Abbreviations**: ITP, immune thrombocytopenia; TPO-RA, thrombopoietin receptor agonist.

injection, whereas eltrombopag is administered orally but at the cost of food or drug interactions and potential poor compliance in patients with cognitive disorders. In case of non-response or intolerance to a TPO-RA, a switch to the other drug can provide a better clinical result.[77] In case of failure to eltrombopag and romiplostim, response can be obtained with a switch to avatrombopag.[78] Because they increase platelet production, TPO-RAs have long been considered to very rarely lead to sustained remission off-treatment in ITP, but we now have evidence for sustained remission after their discontinuation in 10% to 30% of patients.[79,80] Therefore, after a response is obtained, the treatment should be tapered in order to use the lowest dose to maintain platelet counts.[8]

Several studies have suggested that TPO-RA efficacy is similar in older and younger patients.[47,48,81] Although the overall tolerance of TPO-RA is good, there are some concerns about long- and short-term adverse events. The risk of

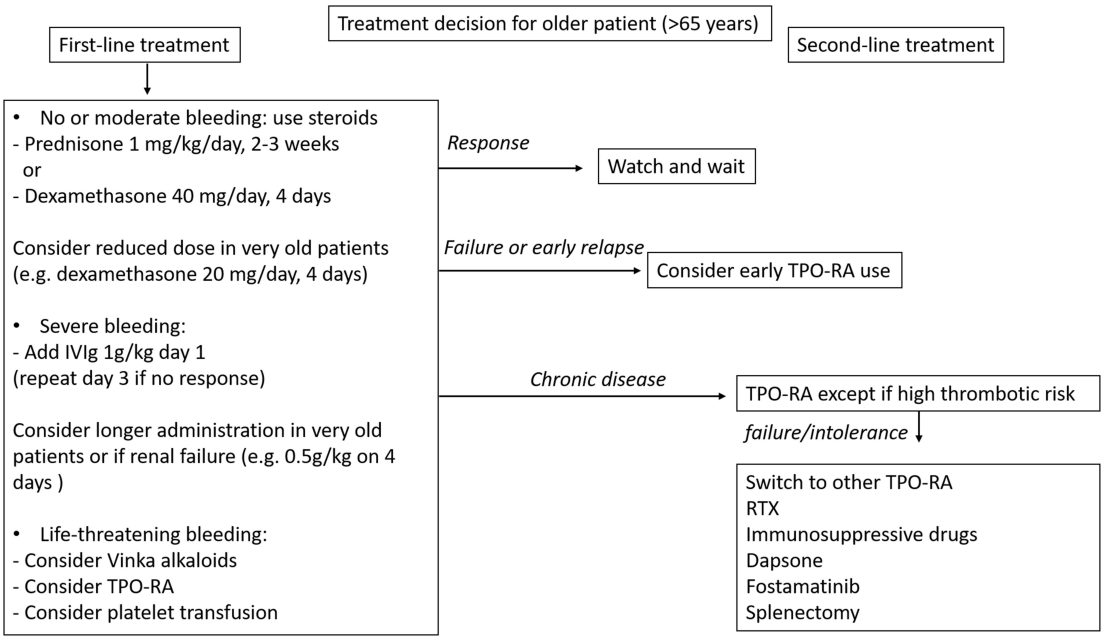


**Figure 2** Proposed therapeutic strategy for ITP in older patients.
**Abbreviations**: ITP, immune thrombocytopenia; IVIg, intravenous immunoglobulin; RTX, rituximab; TPO-RA, thrombopoietin receptor agonist.

reticulin deposits in bone marrow has been raised in patients with long-term use of TPO-RAs but does not lead to bone-marrow failure and is reversible after drug discontinuation.[82,83]

Although not evidenced in pivotal trials, some studies have suggested a two- to three-fold increase in thrombosis risk with TPO-RA use as compared with untreated ITP patients.[41–45] This risk is particularly relevant in older patients because age is an independent risk factor for thrombosis,[37,38] in addition to the risks with other ITP treatments such as IgIV[39] or splenectomy[40] and the disease itself.[35,36] Despite these multiple confounding factors, a higher rate of thrombotic events has been described in older patients particularly those exposed to TPO-RAs.[46–49]

## Anti-CD20 Monoclonal Antibodies

The efficacy of rituximab is well documented in ITP, with initial response rates of about 60%, decreasing to 40% at 2 years and to almost 30% after 5 years.[84–90] Although low, these long-term responses suggest that rituximab can be a curative treatment for ITP, and re-treatment was found effective in most relapsing patients.[88,89,91]

Rituximab is usually administered as four weekly infusions of 375 mg/m², but a more convenient dosage of 1000 mg on days 1 and 15 also used in other autoimmune diseases is considered equivalent.[88] Treatment with lower doses (100 mg weekly for 4 weeks) has comparable short-term response but with slower time to response and shorter response duration.[92] Several retrospective studies suggested a lower response rate in older patients[85,86] and in patients with longer disease duration.[88] However, a large prospective register including almost 250 patients with 5 years of follow-up did not show a difference in long-term response according to age.[89]

The tolerance profile of rituximab is good, but some points are important to consider when treating older patients. The infectious risk is only moderately increased,[93] although severe infections are predominantly observed in older patients, without excluding that concomitant prolonged corticosteroids and/or immunosuppressive drugs could have been the cause of these severe infectious events.[88] Hypogammaglobulinemia is uncommon after one course of rituximab, and the risk of severe hypogammaglobulinemia after repeated courses and/or the addition of immunosuppressive agents is unknown in ITP but seems rare when anti-CD20 antibodies are used to treat other autoimmune diseases such as rheumatoid arthritis.[94] Rituximab is associated with a risk of hepatitis B virus reactivation that is preventable.[95] Progressive multifocal leukoencephalopathy is exceptional.[96] Most importantly, an impaired vaccine response in the months following rituximab treatment has been well documented[97] and is particularly relevant for older patients requiring yearly influenza and/or SARS-CoV-2 vaccination. Anti-pneumococcal vaccination should also be performed before rituximab administration in older patients. During the COVID-19 pandemic, most groups avoided rituximab use in older patients because of the fear that rituximab would increase the risk of fatal infections, even if this risk has not been confirmed in the setting of ITP, for which rituximab is rarely associated with a strong immunosuppressive treatment.

Despite these limitations, rituximab remains a valid option for older patients and should be assessed on an individual basis. Anti-CD20 treatment is also a good option in the particular case of ITP associated with B-cell lymphoid malignancies or with associated systemic autoimmunity. Associating rituximab with other agents such as dexamethasone and/or ciclosporin has also been proposed, with higher response rates but at the cost of greater toxic effects, including infections and decreased gamma globulin levels.[98–101] Promising results were obtained by combining belimumab with rituximab in a pilot study.[102] The efficacy and tolerance of these combined strategies in older patients are unknown.

## Splenectomy

Splenectomy has been used to treat ITP for decades and provides a high rate of long-term response with an overall long-term remission rate of 60% to 70%.[103] It is now admitted that splenectomy should be deferred for at least 12 months to allow for spontaneous remission.[8] Given the availability of new ITP treatments, the rate of splenectomy is decreasing, particularly in older patients.[32,104] Response rates in older patients could be lower with increased surgical risk. Although laparoscopic surgery can reduce the risk of post-operative complications,[103,105] some studies reported a higher rate of immediate surgical complications such as severe bleeding[105,106] in older patients, which could be explained by the frequency of co-morbidities in this population.[107] Some studies have suggested a lower response rate[105] and higher relapse rate[104,105,108] in older patients. In a recent multicenter retrospective study after TPO-RA introduction in France, lack of sustained response after splenectomy was associated with older age on multivariable analysis (60–75 years: odds

ratio 0.39 [95% confidence interval 0.17–0.86], p =.02; >75 years: 0.28 [0.10–0.75], p =.013).[104] Splenectomy also exposes to increased risk of thrombosis, which should be prevented by prophylactic use of an anticoagulant immediately after the procedure, but given that this risk persists over time, it should be taken into account in the treatment decision.[40,109] Lastly, splenectomy also favors infection, particularly infection to encapsulated germs, and prior immunization against influenza and *Streptococcus pneumoniae* is recommended, as is patient education to take immediate antibiotics in case of fever.[40,109]

Nonetheless, our current opinion is that splenectomy can still be considered a third-line treatment in older patients, particularly for those with few comorbidities and low risk of thrombosis, and should not be contra-indicated solely on an age basis.[29] Some groups suggest that a platelet isotopic study could be useful to select the best patient candidates for splenectomy because in case of a predominant splenic sequestration pattern, most studies reported an excellent positive predictive value of response to splenectomy.[110] However, conflicting results were published in case of a hepatic or mixed sequestration pattern. A large UK study showed that most patients with mixed platelet destruction experienced clinical benefit after splenectomy despite being classified as non-responding.[111]

Partial splenic embolization was recently reported as a safe and effective treatment by Japanese colleagues.[112] If these good results are confirmed, this technique could be an interesting alternative in older patients with disease refractory to medical treatment and in whom splenectomy appears dangerous because of comorbidities.

### Immunosuppressive Agents

Immunosuppressive drugs have been used in ITP with various response rates. Mycophenolate mofetil[113–116] and azathioprine[117,118] are the most widely used, but data on ciclosporin,[119–121] rapamycin[122–124] or cyclophosphamide[125,126] efficacy have also been published. The treatment usually takes several months to obtain a response and requires long-term use with a high risk of relapse in case of stopping and with increased infectious risk that can be problematic in older patients. Despite these limitations, mycophenolate mofetil is widely prescribed as second-line therapy in the United Kingdom and has even been proposed as first-line therapy in a prospective controlled study.[116] This attitude is not widely adopted, and in France, our strategy is to reserve immunosuppressive drugs for patients with failure to respond to TPO-RAs and rituximab. We have also observed good responses in refractory patients when combining immunosuppressive drugs with TPO-RAs (unpublished observations).

## Dapsone

Dapsone is an effective treatment for ITP that can be used in older patients with moderate response rates (20–60%).[127–130] Previous splenectomy is associated with low efficacy, and it should not be used when a rapid response is needed given that the median time to response is close to 1 month. This treatment induces hemolysis, requiring a close monitoring of hemoglobin level especially in the first weeks of treatment, but in many patients, the decrease in hemoglobin level is transient (a few weeks) and limited (1 to 2 g/dL) and does not require discontinuation of the treatment. In contrast, the patient should be aware of the risk of dapsone-induced hypersensitivity syndrome that combines a generalized skin eruption with fever, with lymphadenopathy and hepatitis in the more severe forms. The syndrome always occurs in the first 4 weeks after the beginning of treatment. In our experience, skin eruption is observed in 7% of patients, and its severity is probably diminished when dapsone is associated with a short course of prednisone.[131]

## Danazol

Danazol has been used for years as second-line treatment for ITP and is considered efficient, with 40% to 70% response rates, even in older patients.[27,132,133] Its use is limited by its long time to response and its toxic effects (androgenic effects in women, risk of accelerated prostate cancer in men, liver cytotoxicity and increased thrombotic risk) but also by the concurrence of alternative second-line treatments for ITP.

## Fostamatinib and Emerging Agents

Fostamatinib, a Syk inhibitor, has been approved recently in the United States and the European Medicines Agency for treating chronic ITP. Both pivotal trials included older adults,[134] but to date there are no data regarding its specific use in

older people. Common adverse events reported in a pivotal study, such as diarrhea, hypertension, nausea, and increased transaminase levels, should be considered in the therapeutic decision. Other treatments such as anti-FcRn, rizalbrutinib (which inhibits Bruton tyrosine kinase) or daratumumab (an anti-CD38 monoclonal antibody) are currently under development for chronic ITP, but their respective efficacy/tolerance ratio in older patients remains to be determined.[135]

## Management of Particular Situations

### B-Cell Malignancies

The frequency of clonal B-cell disorders increases with age, and ITP is a well-known complication of B-cell lymphoid malignancies such as indolent lymphomas or chronic lymphoid leukemias. In this particular setting, lymphoma treatment should prevail over ITP treatment. With no indication for treating the B-cell disorder, rituximab[136–138] and TPO-RAs[139] can be used, and splenectomy should be avoided.

### Myelodysplastic Syndrome (MDS)

In older people, MDS can coexist with ITP or complicate the ITP course and is associated with increased bleeding risk.[17] The overall therapeutic strategy is unchanged, but the risk of acute myeloid leukemia transformation favored by TPO-RAs has been a concern. However, the risk seems limited and reassuring data have been produced recently.[17,140–143] In a randomized double-blind trial, the risk of leukemic progression in thrombocytopenic patients with low-risk MDS was similar between romiplostim and placebo,[143] although there are fewer data available for the use of TPO-RAs in high-risk MDS.

### Management of Thrombosis and TPO-RAs

Thrombotic events have been described in older patients receiving TPO-RAs.[46–49] In a real-life study of 384 patients >60 years and receiving TPO-RAs with a median follow-up of 2.7 years, Palandri et al observed 43 thromboses in 35 patients (including 22 arterial thromboses), corresponding to a cumulative incidence of 6.2% at 12 months.[48] The authors found a significant association between thrombosis history and thrombosis. Median platelet count was 127 x $10^9$/L at the time of thrombosis event, which confirms that thrombosis can occur even with low/moderate platelet counts. Of note, thrombosis recurrence was observed mostly in patients who continued TPO-RAs, particularly those not receiving long-term anti-thrombotic treatment, which suggests that it could be used as a secondary prophylaxis if TPO-RA continuation is needed. These data strongly suggest that TPO-RAs should be used with caution in older patients with a history of thrombosis, especially if they are no longer receiving anticoagulants. In this situation, we suggest considering another therapeutic strategy.

### Refractory Patients

Despite the increasing therapeutic options to treat ITP, some patients do not respond to or lose response after the initiation of second-line treatment.[144] In these cases, a differential diagnosis should be ruled out, if necessary, by performing BME. When the disease is refractory to several second-line treatments such as both TPO-RAs and rituximab, the treatment choice should be personalized according to the context and the expected benefit/risk ratio. A better knowledge of the pathophysiology of ITP suggested that a combination of treatments could be synergic.[135] According to this hypothesis, we propose that the combination of immunosuppressive drugs and TPO-RA could produce a significant response in multirefractory ITP with previous failure to respond to TPO-RAs and immunosuppressive drugs alone.[140] Splenectomy can also be discussed for patients with few comorbidities and low risk of thrombosis.

# Conclusion

ITP is increasingly frequent in older patients, and the diagnostic work-up is mainly the same as in younger patients, with special attention to ruling out a differential diagnosis. The underlying mechanisms responsible for disease may differ and are probably a hot topic for research because it could help tailor therapy in the future. One of the limits of this review is that evidence-based medicine is lacking in older patients, although there is a growing number of retrospective studies focusing on this particular population. Age is associated with the accumulation of chronic conditions but is probably not a prognostic factor in ITP after controlling for other variables. Thus, the therapeutic decision should be patient-tailored according to the patient's preferences, co-morbidities and fitness rather than age itself. The efficacy of second-line

treatments has relegated splenectomy to patients with refractory disease only, and the good efficacy/safety profile of TPO-RAs has changed the therapeutic landscape of ITP in older people at the cost of increased thrombosis risk. The availability of new treatments will likely modify our therapeutic strategy in the next years.

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