# HOW WE TREAT PRIMARY IMMUNE THROMBOCYTOPENIA IN ADULTS

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# Introduction

- Primary immune thrombocytopenia (ITP) is an acquired autoimmune bleeding disorder characterized by isolated thrombocytopenia (platelet count<$100 * 10^9/L$) in the absence of other etiologies.

- The incidence of the disease is approximately 2–10 per 100,000 adults each year, with a prevalence of 9–20 per 100,000 adults.

- It is more common in females of childbearing age compared with males of the same age-group, and the incidence often reaches a peak in adults after 60 years of age with equal sex distribution.

- Many patients are asymptomatic or only present with mild mucocutaneous hemorrhage ; however, severe bleeding occurs in 5–6% of patients.

- A population-based study revealed a 1.3–2.2-fold increase in the mortality rate for adult ITP patients compared with the general population due to bleeding episodes, infection, and cardiovascular events .

- Although the reported incidence of thrombosis was inconsistent, most studies demonstrated a slightly increased risk of thromboembolism in ITP patients.

**The international working group (IWG) on ITP and the American Society of Hematology (ASH) both updated their guidelines for the diagnosis and management of ITP in 2019 .**

# Pathogenesis of ITP

- The decrease in peripheral blood platelet count of ITP patients results from accelerated platelet clearance and impaired platelet production. The loss of immune tolerance to platelet autoantigens is the critical upstream step in ITP pathophysiology, which leads to the abnormal recognition of platelet autoantigens and subsequent activation of T and B cells.

- Autoantibody-mediated platelet destruction is the canonical mechanism of platelet destruction in ITP. Platelets coated by anti-glycoprotein (GP) autoantibodies are prematurely destroyed by macrophages via Fcγ receptors (FcγRs) in the reticuloendothelial system.

- Autoantibodies also accelerate platelet destruction through the induction of complement-dependent cytotoxicity (CDC) and platelet apoptosis.

- Platelet autoantibody production involves complex interactions between macrophages/dendritic cells (DCs), T cells, and B cells.

- Follicular T (TFH) cell numbers are also increased in the periphery, spleen, and bone marrow of ITP patients, suggesting that their B cell help activity is upregulated. By contrast, circulating and splenic Tregs in ITP are found to be numerically decreased and functionally impaired, contributing greatly to the perpetuation of ITP.

- Approximately 20–40% of ITP patients do not have detectable anti-GP autoantibodies, suggesting alternative mechanisms of platelet destruction.

- Many studies have demonstrated that CD8+ cytotoxic T lymphocytes (CTLs) from peripheral blood or spleen of ITP patients can directly lyse platelets or induce platelet apoptosis.

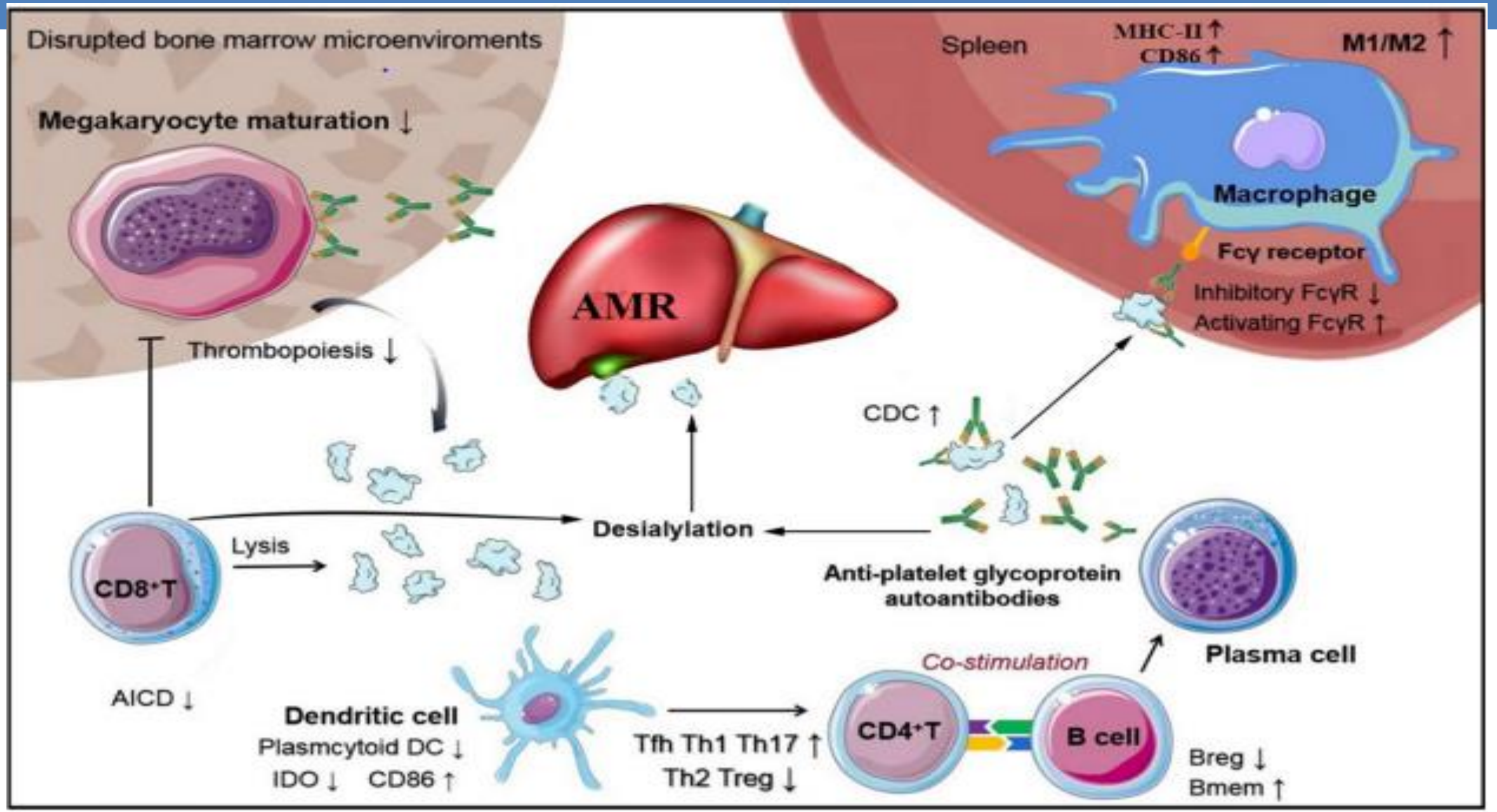
- platelet phagocytosis through hepatocyte in the liver is another mechanism of platelet eradication in ITP.

- CTLs and anti-GP autoantibodies can induce the desialylation of platelet surface glycans, leading to premature platelet clearance.

- Platelet turnover studies have revealed that thrombopoiesis is decreased or normal in most ITP patients, and the absolute reticulated platelet counts are reduced , suggesting relatively insufficient platelet production in the bone marrow.

- After binding to megakaryocytes, anti-GP autoantibodies can interfere with the differentiation, maturation, and apoptosis of megakaryocytes.

- Platelet autoreactive CTLs in bone marrow can also impair megakaryocyte apoptosis through the downregulation of Fas and upregulation of Bcl-xl.


Disrupted bone marrow microenviroments
Megakaryocyte maturation ↓
Thrombopoiesis ↓
AMR
Spleen
MHC-II ↑
CD86 ↑
M1/M2 ↑
Macrophage
Fcγ receptor
Inhibitory FcγR ↓
Activating FcγR ↑
CDC ↑
Desialylation
Lysis
CD8⁺T
AICD ↓
Anti-platelet glycoprotein autoantibodies
Plasma cell
Co-stimulation
Dendritic cell
Plasmcytoid DC ↓
IDO ↓ CD86 ↑
Tfh Th1 Th17 ↑
Th2 Treg ↓
CD4⁺T
B cell
Breg ↓
Bmem ↑

- the above-mentioned pathological mechanisms may play varying roles in different patients due to the heterogeneity of the disease. Identifying which mechanism is dominant in each case is critical for the implementation of pathogenesis-oriented individualized treatment.

# Diagnosis and prognosis of ITP

- ITP remains a diagnosis of exclusion due to the lack of a “gold standard” diagnostic test.
- History taking, physical examination, complete blood count, and peripheral blood film assessment are the basic workups for suspected patients.
- Splenomegaly and constitutional symptoms (e.g., fever, weight loss, or lymphadenopathy) are unusual and, if present, should be investigated further to exclude the presence of other underlying diseases.

- **additional tests:** **reticulocyte counts, quantitative immunoglobulin (Ig) levels, blood groups, and serologic screening for HCV/HBV/HIV**

- **Therefore**, the diagnosis of ITP can be established with careful history taking and physical examination, as well as a review of peripheral blood smears and minimal further testing in most patients.

- However, the application of this diagnostic criterion will lead to misdiagnosis in a small proportion of patients with suspected ITP. According to several population-based studies, myelodysplastic syndrome (MDS) and secondary ITP, such as thrombocytopenia's due to systemic autoimmune diseases, malignancies, primary immune deficiency, or drug exposure, accounted for approximately 20% of the misdiagnosis

- To minimize the misdiagnosis rate, the Chinese ITP guidelines also recommend bone marrow examination and tests for antinuclear antibodies (ANAs), anti-phospholipid antibodies (APLAs), anti-thyroid antibodies, thyroid function, and coagulation parameters (prothrombin time, activated partial thromboplastin time, fibrinogen level, and D-dimer) as the basic evaluation.

- Bone marrow examination includes aspiration smear, biopsy, flow cytometry, and cytogenetic analysis. These differences may reflect a higher percentage of alternative diagnoses in China, as the incidence of aplastic anemia (AA) is higher and the average age of onset of MDS is lower than that in Western countries.

- Therefore, bone marrow examination can help reduce the misdiagnosis rate and shorten the time to diagnosis.

- These assays do not need to be routinely performed for ITP diagnosis; however, targeted testing may be useful in certain cases with special symptoms, signs, and laboratory findings.

- Anti-GP autoantibody detection is highly specific for ITP diagnosis, while the sensitivity is relatively low.

- The presence of anti-GP autoantibodies is helpful to confirm the diagnosis of immune thrombocytopenia, while it cannot distinguish the primary from the secondary ITP.

- Serum TPO levels are normal or slightly increased in ITP patients, while remarkably elevated in patients with AA or hypoproliferative MDS , thus being potentially valuable for the differential diagnosis of ITP.

- Detection of Helicobacter pylori infection using the urea breath test or stool antigen test can be performed in patients with dyspeptic symptoms, especially in areas with a high prevalence of Helicobacter pylori infection.

- It should be emphasized that the response to treatments, especially intravenous immunoglobulin (IVIg), is of great value for the confirmation of ITP diagnosis.

- As an immune-mediated disorder, a large proportion of patients with ITP will undergo repeated outbreaks and tend to run a protracted course, or are eventually diagnosed with thrombocytopenia secondary to connective tissue diseases such as systemic lupus erythematous (SLE).

- Therefore, it is critical to re-evaluate the diagnosis during the course of the disease, especially in patients who respond poorly to treatment and cases with new symptoms, signs, and new laboratory findings.

- According to the disease duration, ITP can be divided into newly diagnosed (12 months) phases. Adult patients are more likely to develop chronic disease than children.

- Moreover, higher platelet counts at diagnosis and the presence of ANAs and anti-thyroid antibodies may serve as predictors of disease chronicity.

- Severe ITP refers to patients with clinically relevant bleeding of sufficient magnitude to mandate disease-directed treatments, or cases showing new bleeding symptoms requiring additional interventions or an increase in drug dose.

- the description of “refractory ITP” is often reserved for patients who have failed multiple lines of therapy, especially thrombopoietic agents and rituximab, or splenectomy such as hematuria and visceral hemorrhage, and usually have a history of head trauma.

- occult cerebral microbleeds (CMBs) occur in almost 50% of ITP patients with platelet counts≤30× $10^9$/L , and the occurrence is associated with lower nadir platelet counts, longer disease duration, and higher organ bleeding scores .

- Platelet function and platelet microparticles also influence bleeding severity in ITP , but their exact roles remain to be evaluated.

**Table 1** Differential diagnosis of ITP and suggested tests to exclude the alternative causes of thrombocytopenia

| Alternative diagnosis | Clinical characteristics | Laboratory tests |
|---|---|---|
| Pseudothrombocytopenia | No thrombocytopenia-related symptoms (in vitro phenomena) | Platelet clumping on blood smear due to EDTA-dependent agglutinins |
| Acute or chronic Infections (HBV/HCV/HIV/EBV/CMV/B19/Zika/*H. pylori*) | High-risk populations<br>History, suggestive symptoms or signs | Serologic and PCR tests for viral infection<br>Urea breath test for *H. pylori* |
| Drug-induced (heparin, quinine, antibiotic, NSAIDs, etc.) | History of drug exposure | Drug-dependent antibody tests |
| Vaccine-associated | Recent history of vaccination (< 6 weeks) | – |
| Connective tissue diseases (SLE, rheumatoid arthritis, anti-phospholipid syndrome, etc.) | Fever, rash, arthralgias, mouth ulcers, hair loss, abortions, and thromboembolism | Targeted serologic tests (ANAs, anti-dsDNA antibodies, anti-CCP antibodies, APLAs, etc.) |
| Lymphoproliferative disorders (CLL, Hodgkin's lymphoma, etc.) | Fever, weight loss, night sweats, lymphadenopathy, splenomegaly | Lymph node biopsy, bone marrow examination, imaging examination |
| Immunodeficiency syndrome (common variable immunodeficiency) | Young age, recurrent infections, colitis, lymphadenopathy | Ig levels, lymphocyte ph, genetic testing |
| Evans syndrome | Hemolysis and thrombocytopenia | Coombs test |
| Bone marrow malignancy (MDS, leukemia, etc.) | Suggestive symptoms or signs (fever, splenomegaly, bleeding, etc.) | Blood smear, bone marrow examination |
| AA | Pancytopenia | Blood smear, bone marrow examination |
| Thrombotic microangiopathy (thrombotic thrombocytopenic purpura, hemolytic uremic syndrome) | Hemolysis, neurologic symptom, fever, renal damage | Blood smear (schistocytes), haptoglobin, LDH, ADAMTS13 level |
| DIC | Precipitating events,<br>severe patients, multiple organ damages | Coagulation tests, blood smear |
| Inherited or congenital diseases (Wiskott–Aldrich syndrome, Bernard–Soulier syndrome, MYH9-related disease, type IIb vWD, etc.) | Young-onset thrombocytopenia, family history, congenital abnormalities (deafness, cataract, development delay) | Blood smear, genetic testing |

*EDTA* ethylenediaminetetraacetic acid, *NSAID* nonsteroidal anti-inflammatory drug, *SLE* systemic lupus erythematosus, *ANA* antinuclear antibody, *APLA* anti-phospholipid antibody, *CLL* chronic lymphocytic leukemia, *MDS* myelodysplastic syndrome, *AA* aplastic anemia, *LDH* lactate dehydrogenase, *DIC* disseminated intravascular coagulopathy *ph* phenotype

# Treatment of ITP

- The main goals of ITP treatment are to prevent bleeding and maintain the platelet count above a safe level to minimize the bleeding tendency.

- the safe lower limits for platelet counts vary among patients and are related to individualized bleeding risks.

- The updated ASH guidelines recommend the initiation of disease-specific treatments if the platelet counts are $< 10 * 10^9/L$ .

- The association between platelet count and bleeding events is poor in ITP patients with platelet $count > 10 * 10^9/L$ .

- this is exactly the case even in very elderly patients, and the bleeding severity of whom was found to be strongly associated with anticoagulant exposure.

- Bleeding episodes are more influential than platelet counts in the clinical decision-making process of treatment initiation.

- Patient expectations and preferences, costs and availability of treatments, and factors that influence bleeding risks, such as age, comorbidities, concurrent therapies, lifestyle, and profession, should also be considered.

- In addition, HRQoL is an important factor that needs to be taken into account when making treatment plans.

- It is noteworthy that medications used in ITP, such as corticosteroids and immunosuppressants, may sometimes have detrimental effects on patient health status, resulting in a poor overall quality of life perhaps worse than the disease itself.

- Therefore, an optimized treatment strategy should improve platelet recovery with minimum toxicity and elevated HRQoL, and should always be tailored to the patients and disease phases.

- ITP treatment can be broadly divided into initial/emergency treatment, subsequent treatment, and regimens for patients who fail multiple treatments .

- New therapeutic agents and emerging evidence have facilitated a gradual shift in ITP therapeutic models away from immune suppression, especially for persistent and chronic patients.

# Initial treatment

- Corticosteroids remain the initial cornerstone therapy for ITP patients without relative contraindications.

1. Pulsed high-dose dexamethasone (HD-DXM, 40 mg/ day for 4 days, a maximum of 3 cycles)
2. predniso(lo)ne (1mg/kg/day for 2 weeks, not exceeding 80 mg/day, with a gradual taper and final stop by 6–8 weeks)

- response rate of 60–80%
- Approximately 20–40% of the patients could maintain the response after corticosteroid discontinuation.

- Prolonged corticosteroid courses are not recommended due to the adverse effects.

- Although sporadic studies have reported that HD-DXM could induce higher sustained response rates (SRR) than prednisone , most randomized clinical trials (RCTs) and a well-conducted meta-analysis did not find any difference in SRR between HD-DXM and prednisone at 6 months or longer.

- HD-DXM could induce a more rapid response and seems to have a better safety profile (lower incidence of steroid-related comorbidities) than prednisone.

- HD-DXM might lead to the occurrence of neuropsychiatric complications in very elderly patients and those with a history of psychiatric disease and should be avoided.

- Under such situations, a shorter duration (e.g., 4 weeks) of prednisone and faster tapering are more favored.

- **IVIg** is another commonly used initial therapy that can raise the platelet counts rapidly in more than 80% of newly diagnosed ITP patients; however, it is relatively expensive and the response is usually transient .

- A study suggested that bleeding severity, rather than platelet count, could serve as a relevant indicator for IVIg treatment .

- IVIg is usually administered at a dose of 1 g/kg/day for 1–2 days or 0.4 g/kg/ day for 5 days with similar efficacy .

- IVIg at a lower dosage of 0.2 or 0.3 g/kg/day had a comparable response rate and onset time to the conventional dosage of 0.4 g/kg/day , suggesting the possibility of treating ITP patients more cost-effectively by lowering the IVIg dosages.

- The decision on IVIg treatment initiation ought to depend mainly on the bleeding severity grade rather than the platelet count.

- In addition, IVIg should be used with caution in patients with impaired renal function and cases with increased thrombosis risks.

- Intravenous anti-RhD Ig has been proposed as an alternative to IVIg in Rh-positive patients with intact spleens.

- Anti-RhD-coated erythrocytes can saturate macrophage FcγRs and inhibit autoantibody-mediated platelet destruction.

- A single infusion of anti-RhD Ig at a dose of 50 μg/kg could lead to an overall response rate of 65% in newly diagnosed ITP patients, with a median response duration of 3–4 weeks .

- The major concern regarding anti-RhD Ig therapy is the occurrence of rare but life-threatening episodes of severe intravascular hemolysis with acute renal failure and disseminated intravascular coagulation (DIC).

- Neither corticosteroids, IVIg, nor anti-RhD Ig is able to modify the natural course of ITP by preventing its chronic evolution.

- Hence, improving the initial response and maintaining the sustained response remain a big challenge. Under such circumstances, early combination strategies to intensify the effect of initial therapy have been developed.

- Two large RCTs investigated the upfront use of HD-DXM plus rituximab in treatment-naïve ITP patients. The results showed that the addition of rituximab to HD-DXM did not elevate the early response rates, while significantly improved the SRR at 6 and 12 months. However, an extended follow-up revealed no overall response benefit of rituximab inclusion beyond 1 year.

- In contrast to the conventional treatments that function mainly by decreasing platelet destruction, thrombopoietic agents functioning by stimulating platelet production have significantly changed the management of ITP.

- Due to their non-immunosuppressive character, thrombopoietic agents are often used of-label for newly diagnosed ITP patients in real-world settings.

- Several studies reported that HD-DXM in combination with eltrombopag had favorable SRR at 6 months (56.5–75%) and good tolerability in newly diagnosed treatment-naïve ITP patients.

- In a large prospective RCT, we recently showed that HD-DXM plus a limited course of recombinant human thrombopoietin (rhTPO) elicited a higher response rate at day 14 and month 6, and a slightly higher treatment-free remission rate thereafter than HD-DXM monotherapy .

- Other combination regimens include mycophenolate mofetil (MMF) plus corticosteroids, all-trans retinoic acid (ATRA) plus HD-DXM, and oseltamivir plus HD-DXM.

- ATRA is an active derivative of vitamin A that has multiple immunomodulatory activities. ATRA (10 mg twice daily for 12 weeks) plus HD-DXM induced a significantly higher SRR at 6 months than HD-DXM monotherapy (68% vs. 41%) in newly diagnosed ITP patients, and this novel combination treatment did not increase the occurrence of severe adverse events .

- we conducted combination of oseltamivir (75  mg twice daily for 10 days) with HD-DXM versus HD-DXM alone as the initial treatment for ITP. It was encouraging that patients in the combination arm achieved a higher initial response rate (86% vs. 66%) and SRR at 6  months (53% vs. 30%) than those in the HD-DXM monotherapy arm; however, the superiority of response was gradually lost, and there was no statistical significance in SRR between the 2 arms after 1 year.

# Emergency treatment

- In patients with life-threatening bleeding or those requiring emergency surgery, combination treatments are often needed to increase the platelet count rapidly.

- The IWG recommends the concomitant use of IVIg, intravenous corticosteroids, and platelet transfusion with general supportive care.

- TPO-RAs can also be administered concurrently at relatively more aggressive dosages to increase the response rate and reduce early relapse , especially for patients with refractory ITP in an emergency bleeding situation .

- Vinca alkaloids may also be considered, but the risk of peripheral neuropathy should be noted.

- Other agents that do not target ITP pathogenesis, such as antiffbrinolytics, recombinant activated factor VII, and oral contraceptives (for female patients with menorrhagia), can be helpful in stopping the active bleeding under certain conditions.

# Subsequent treatment

- Although newly diagnosed ITP patients have relatively high response rates to initial treatments, the vast majority of them undergo disease relapse, and about 60–70% of the patients will progress to persistent or chronic ITP

- Subsequent treatments in patients who fail the initial therapy can be classified into medical and surgical treatments, and therapeutic choices are primarily based on resource availability, required onset time, side effects, and patient or physician preference.

- Subsequent medical options with robust evidence include thrombopoietic agents, rituximab, and fostamatinib.

# Thrombopoietic agents

- TPO-RAs have making the avoidance of immunosuppressive agents possible in disease management.

- FDA and European Medicines Agency have approved 3 TPO-RAs for the management of persistent or chronic ITP: eltrombopag, romiplostim, and avatrombopag.

- The overall response rates of these above-mentioned thrombopoietic agents range from 70 to 90% in RCTs for previously treated chronic patients, and 50–60% of them could maintain the response with prolonged treatment duration .

# Thrombopoietic agents

- A more recent meta-analysis including more RCTs also revealed that TPO-RAs had significantly lower treatment failure (RR=0.42) and all-cause mortality rates (RR=0.21) than the placebo, and TPO-RAs did not increase the occurrence of adverse events . Mei et al. recently showed in an RCT that rhTPO (300 U/kg/day for 2 weeks) could induce a more rapid response and higher initial response rate within 15 days in persistent ITP patients compared with eltrombopag (25 mg/day for 2 weeks); however, the observation period was too short to draw further conclusions .
- A network meta-analysis comparing eltrombopag, romiplostim, and rhTPO plus rituximab in persistent ITP showed the superiority of romiplostim and eltrombopag over rhTPO plus rituximab in platelet response and treatment safety .

- Eltrombopag, avatrombopag, and hetrombopag are small-molecule non-peptide TPO-RAs with similar efficacies of approximately 70–80% in persistent or chronic patients.

- **Eltrombopag** is generally initiated orally at a dose of 50 mg/day (25 mg/day in patients of East Asian descent), to keep the goal platelet count of 50–200× 109 /L.

- **hetrombopag** is typically started at a dose of 2.5 mg/d, which is adjusted between 2.5 and 7.5 mg/day to maintain the goal platelet counts.

- **Avatrombopag** is administered at an initial dose of 20 mg/day and can be titrated to a maximum dose of 40 mg/day in treating ITP .

- Both eltrombopag and hetrombopag interact with food because of their metal ion-chelating ability. By contrast, avatrombopag has no food–drug interactions and is better absorbed with food.

- **Romiplostim** is a peptide with 4 TPO receptor binding sites linked to an IgG1-Fc component. It is injected subcutaneously at a starting dose of 1 µg/kg/week, which can be increased to a maximum of 10 µg/kg/week to reach the goal platelet counts. An aggressive starting dose of 3 µg/kg/week is also acceptable, as the majority of the patients require doses≥3 µg/kg/week to respond.

- The selection of these thrombopoietic agents mainly depends on drug availability, patient-preferred administration form.

- failing one thrombopoietic agent does not preclude the use of another, as there is accumulating evidence supporting TPO-RA agent switching due to treatment failure, which could induce a platelet response in up to 50–75% of patients.

- Thrombopoietic agents are generally well tolerated.

- Thrombotic risk remains a major concern, though its elevation has not been reported in numerous RCTs.

- Fewer than 10% of patients with prolonged TPO-RA exposure might show a moderate increase in bone marrow reticulin deposition, which was reversible upon medication withdrawal.

# Rituximab

- Rituximab is a chimeric monoclonal antibody targeting CD20-expressing B cells. It has been commonly used as an of-label treatment for ITP for nearly 2 decades.

The short-term response rates range from 60 to 70% in patients treated with the standard 4 weekly doses of 375 mg/m2 rituximab, and the response is usually achieved within 4–8 weeks .

Alternative dosing schedules of rituximab, such as 100 mg/week for 4 weeks, 1000 mg on day 1 and day 15, or a single dose of 375 mg/m2 , have been explored in ITP patients showing similar short-term efficacy.

With the clearance of rituximab from the body and the gradual recovery of B cells, most patients will relapse after 6 months.

- In spite of the high relapse rate, most relapsed patients still responded to retreatment with rituximab.

- young female patients with a relatively short disease duration often respond better than patients of other demographics

- Acute infusion reactions are common and can be handled easily, whereas the major concerns regarding rituximab include an increased risk of infection due to chronic B cell depletion, hypogammaglobulinemia, lateonset neutropenia.

- rituximab is associated with an **increased risk of HBV reactivation** and is thus unsuitable for patients with evidence of active HBV infection.

- However, in certain chronic HBV-infected cases who do not have other effective therapeutic options for ITP, rituximab could be given with concomitant antiviral treatments and close monitoring of HBV DNA load and disease fare.

- In addition, rituximab can blunt the immune responses to different vaccines, including COVID-19 vaccines; therefore, special attention should be paid to rituximab use during the COVID19 pandemic.

# Fostamatinib

- Fostamatinib is an oral spleen tyrosine kinase (Syk) inhibitor approved for ITP patients who have failed at least one previous regimen.
- The starting dose of fostamatinib is 100 mg twice daily, which can be up titrated to 150  mg twice daily in patients with an inadequate response.
- A study demonstrated a durable response rate of 44% in patients on fostamatinib maintenance therapy for a median of≥28 months.
- The most commonly observed adverse events include diarrhea, hypertension, nausea, and transaminase elevation, which are generally mild to moderate and can be observed in up to 30% of patients.

# Splenectomy

- Splenectomy remains the most effective therapy for corticosteroid-resistant or relapsed ITP patients by removing the major site of platelet phagocytosis and autoantibody production.

- Although splenectomy is becoming less preferred nowadays due to the availability of emerging non-surgical medications, it still offers the best chance for long-lasting remission, with an estimated durable response rate of 60–70% , even in TPO-RA and/ or rituximab-resistant or relapsed patients.

- There is also evidence that even though CR was not achieved after splenectomy, most patients displayed a milder course of the disease and responded better to medical treatment. Most guidelines recommend deferring splenectomy for 12–24 months after diagnosis as some patients have a chance of spontaneous remission or stabilization of platelet count at a hemostatic level.

- Reconfirmation of the disease diagnosis is necessary before splenectomy, and under such circumstances, tests such as bone marrow evaluation, assays of anti-GP autoantibodies, and serum TPO levels are helpful.

- **Laparoscopic splenectomy** is as effective as open splenectomy for alleviating patient's thrombocytopenia, but it has lowered perioperative risks, shortened hospitalization, and decreased blood loss, thus becoming the standard procedure in most centers.

- Splenectomy is associated with a persistent 3–fourfold increase in the risk of venous thromboembolism (VTE) among ITP patients , and the risk remains elevated both early (<90 days) and late (≥90 days) after splenectomy ; therefore, postoperative thromboprophylaxis is appropriate in high-risk cases.

- There is also an increased risk of infection in splenectomized ITP patients, among whom the reported incidence of **sepsis** ranges from 2.1 to 6.0% . The necessity for **antibiotic prophylaxis** in splenectomized adult patients is still undetermined, and we suggest antibiotic prophylaxis in high-risk patients, such as immunocompromised cases, or those with a poor response to vaccination.

- Moreover, patients should be treated empirically with antibiotics at the first sign of infection. Vaccinations against encapsulated organisms (Streptococcus pneumoniae, Neisseria meningitidis, and Haemophilus influenzae) should be given≥2 weeks before splenectomy and maintained. The incidence of surgical complications and mortality rates are relatively higher in patients >60 years of age. Therefore, splenectomy should be considered a last resort and only be performed after a comprehensive assessment of the disease in elderly patients.

# Other agents

- other agents, such as azathioprine, cyclosporine A, danazol, dapsone, hydroxychloroquine, MMF, and vinca alkaloids, are also used in treating ITP.
- Depending on the population and agents used, approximately 30–60% of the ITP patients respond.

- Considering the emergence of new medications with promising efficacy, these immunosuppressive agents are used less frequently and are usually prescribed as rescue therapies for patients who fail multiple treatment options.

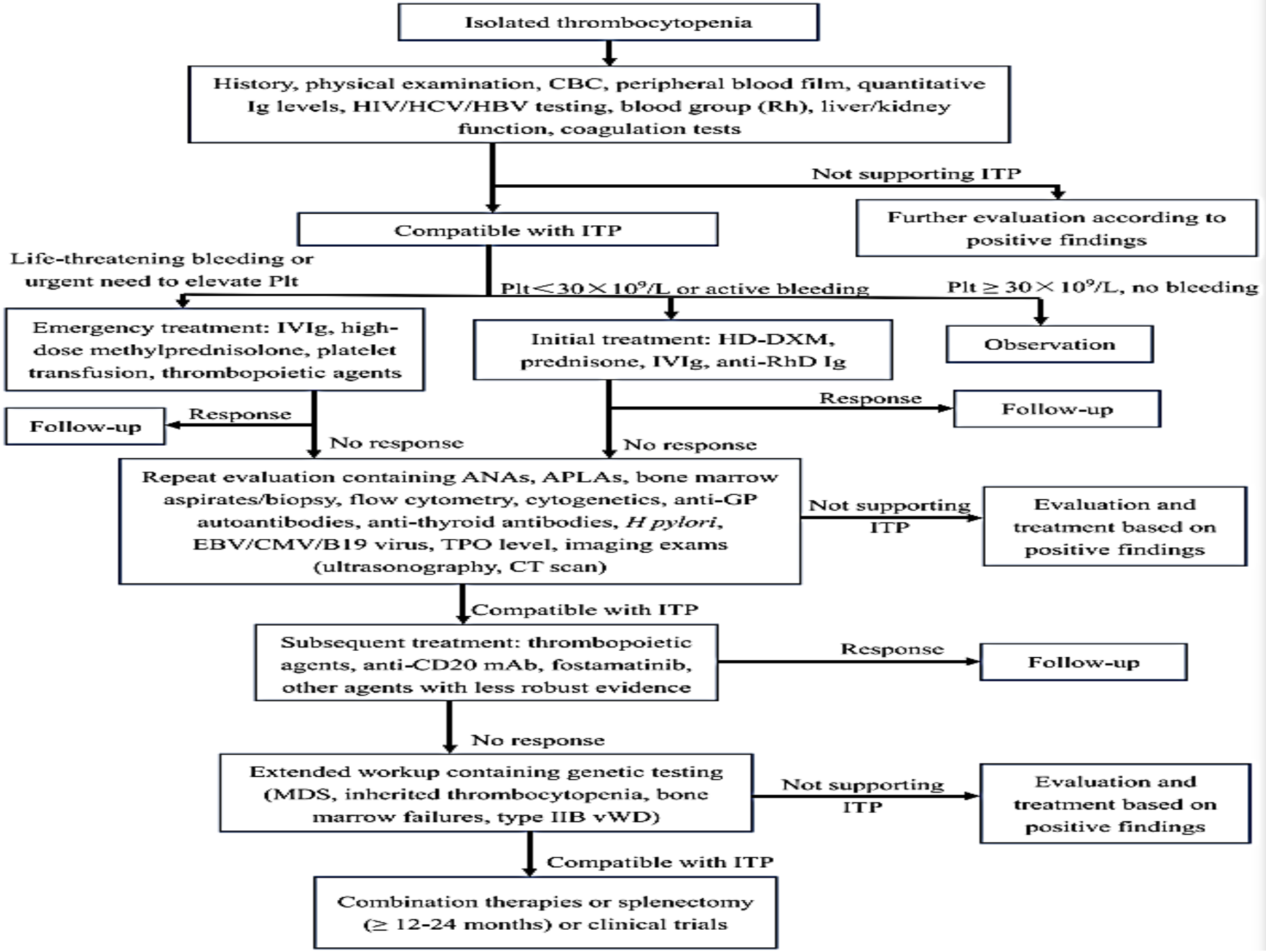

Isolated thrombocytopenia
History, physical examination, CBC, peripheral blood film, quantitative Ig levels, HIV/HCV/HBV testing, blood group (Rh), liver/kidney function, coagulation tests
Not supporting ITP
Further evaluation according to positive findings
Compatible with ITP
Life-threatening bleeding or urgent need to elevate Plt
Plt＜30×10⁹/L or active bleeding
Plt ≥ 30×10⁹/L, no bleeding
Emergency treatment: IVIg, high-dose methylprednisolone, platelet transfusion, thrombopoietic agents
Initial treatment: HD-DXM, prednisone, IVIg, anti-RhD Ig
Observation
Response
Follow-up
Response
Follow-up
No response
No response
Repeat evaluation containing ANAs, APLAs, bone marrow aspirates/biopsy, flow cytometry, cytogenetics, anti-GP autoantibodies, anti-thyroid antibodies, H pylori, EBV/CMV/B19 virus, TPO level, imaging exams (ultrasonography, CT scan)
Not supporting ITP
Evaluation and treatment based on positive findings
Compatible with ITP
Subsequent treatment: thrombopoietic agents, anti-CD20 mAb, fostamatinib, other agents with less robust evidence
Response
Follow-up
No response
Extended workup containing genetic testing (MDS, inherited thrombocytopenia, bone marrow failures, type IIB vWD)
Not supporting ITP
Evaluation and treatment based on positive findings
Compatible with ITP
Combination therapies or splenectomy (≥ 12-24 months) or clinical trials

**Table 2** Efficacy and safety of different treatments for ITP

| Medications | Dosage | Time to response | Overall response | Response durability | Side effects |
|---|---|---|---|---|---|
| *Initial treatment* | | | | | |
| Prednisone | 1 mg/kg/day for 1–2 weeks, then gradually tapper and stop by 6–8 weeks, rapid tapering in nonresponders | 1–2 weeks | 60–80% | 30–50% of patients maintain the response after discontinuation | Weight gain, Cushingoid appearance, mood disorders, gastrointestinal toxicities, hyperglycemia, insomnia, hypertension, increased risks of infection, neuropsychiatric symptoms |
| HD-DXM | 40 mg/day × 4 days, up to 2–4 cycles | 1–9 days | 60–80% | 30–50% of patients maintain the response after discontinuation | Weight gain, gastrointestinal toxicities, hyperglycaemia, insomnia, hypertension, increased risk of infection, neuropsychiatric symptoms |
| IMg | 0.4 g/kg/day × 5 days or 1 g/kg/day × 1–2 days | 1–4 days | Up to 80% | Transient | Headache, renal insufficiency, aseptic meningitis, anaphylactic reactions in IgA deficient patient |
| Anti-RhD | 50–75 μg/kg | 4–5 days | Up to 80% | Transient | Hemolysis, fever, chills, renal failure |
| *Subsequent treatment with robust evidence* | | | | | |
| Eltrombopag | 25–75 mg/day | 2–4 weeks | 60–80% | 40–60% with maintenance therapy, 10–30% keep the response after drug discontinuation | Headache, upper respiratory tract infection, diarrhea, hepatotoxicity, thromboembolic events, bone marrow fibrosis |
| Avatrombopag | 5–40 mg/day | 1–2 weeks | 65% by day 8, 85% by day 28 | 70–80% with maintenance therapy | Headache, arthralgia, increased risk of thrombosis and bone marrow fibrosis |
| Hetrombopag | 2.5–7.5 mg/day | 15–25 days | 58.9–64.3% | 40–50% with maintenance therapy | Headache, upper respiratory tract infection, diarrhea, hepatotoxicity, increased risk of thrombosis and bone marrow fibrosis |
| Romiplostim | 1–10 μg/kg once weekly | 1–2 weeks | 74–88% | 40–60% with maintenance therapy | Headache, muscle aches, thrombosis, bone marrow fibrosis or increased reticulin |
| rhTPO | 300 U/kg/day | 1–2 weeks | 60–75% | – | Drowsiness, dizziness, hypertension, fatigue, rash, urticaria, diarrhea |
| Rituximab | 375 mg/m$^2$ weekly × 4 weeks, 100 mg weekly × 4 weeks, 1000 mg on day 1 and day 15 | 1–8 weeks | 60–80% | 40–50% | Infusion-related reactions, hypogammaglobulinemia, increased risk of infections and HBV reactivation, progressive multifocal leukoencephalopathy |
| Fostamatinib | 50–150 mg twice daily | 1–2 weeks | 40–50% | 18–43% with maintenance therapy | Diarrhea, hypertension, nausea, dizziness, transaminitis |

**Table 2** (continued)

| Medications | Dosage | Time to response | Overall response | Response durability | Side effects |
|---|---|---|---|---|---|
| *Subsequent treatment with less robust evidence* | | | | | |
| Azathioprine | 1–2 mg/kg/day | 6–12 weeks | 30–60% | Up to a quarter of patients off therapy keep the response after long treatment duration | Fatigue, transaminitis, neutropenia, increased risk of malignancy |
| Cyclosporin A | 2.5–3 mg/kg/day, titration to blood levels of 100–200 ng/ml | 3–4 weeks | 50–80% | 50% keep the response on low-dose maintenance | Hypertension, renal dysfunction, hypertrichosis, gingival hyperplasia, tremor |
| Cyclophosphamide | 1–2 mg/kg/day orally for at least 16 weeks or IV 0.3–1 g/m$^2$ 1–3 doses every 2–4 weeks | 1–16 weeks | 24–85% | Approximate 50% | Nausea, vomiting, hematuria, neutropenia |
| Danazol | 200 mg, 2–4 times daily | 3–6 months | 30–60% | – | Acne, hirsutism, hypercholesterolemia, amenorrhea, transaminitis |
| Dapsone | 75–100 mg/day | 3–4 weeks | 30–60% | – | Nausea, rash, dyspepsia methemoglobinemia, hemolytic anemia in glucose-6-phosphate dehydrogenase |
| MMF | 1.5–2 g/day | 4–8 weeks | 30–60% | 40% | Headache, gastrointestinal symptoms, increased risks of infection and cancer, |
| Vinca alkaloids | Vincristine: 1–2 mg weekly for 2–3 weeks<br>Vinblastine: 10 mg weekly for 2–3 weeks | 5–7 days | Transient. response in 10–75% of patients | – | Neuropathy, neutropenia, constipation, hepatotoxicity |
| *Novel agents under investigation* | | | | | |
| Rilzabrutinib | 400 mg twice daily | 1–10 weeks (median 11.5 days) | 40% | – | Diarrhea, nausea, fatigue, infection |
| Rozanolixizumab | Starting at 4 mg/kg weekly, can be uptitrated to a maximum of 20 mg/kg weekly | 1–2 weeks | 35–45% | – | Headache, diarrhea, vomiting, pyrexia, infection |
| Efgartigimod | 5 mg/kg or 10 mg/kg weekly × 4 weeks | 8–43 days | 38.5% | – | Rash, hypertension, vomiting, cystitis |
| Decitabine | 3.5 mg/m$^2$/day × 3 days for 3 cycles with a 4-week interval between cycles | 2–10 weeks | 51% | SR rate at 6 months was 44% | Nausea, fever, diarrhea, constipation, transaminitis |
| *Surgical treatment* | | | | | |
| Splenectomy | Open or laparoscopic surgery | immediately | 75–90% | 50–70% | Bleeding, infection, thrombosis, increased risk of cancer |

***HD-DXM*** **high-dose dexamethasone,** ***IVIg*** **intravenous immunoglobulin,** ***rhTPO*** **recombinant human thrombopoietin,** ***MMF*** **mycophenolate mofetil**

# Combination therapies

- A multicenter retrospective cohort study indicated that patients who failed splenectomy, rituximab, romiplostim, and eltrombopag had significantly increased morbidity and mortality, and the **combination** of immunosuppressants with TPO-RAs might be an effective strategy for these multirefractory cases .

- another treatment modality using a combination of rituximab (100 mg weekly for 6 weeks) and ATRA (20 mg/m2 daily for 12 weeks) also yielded favorable outcomes in corticosteroid-resistant or relapsed patients, with a significantly higher overall response rate (80% vs. 59%) and SRR (61% vs. 41%) than rituximab alone .

- Other combination strategies, such as dexamethasone and low-dose rituximab combined with cyclosporine A, thrombopoietic agents plus immunosuppressants, or triple therapy with thrombopoietic agents, immunosuppressants, and IVIg, have also been tested for the management of refractory ITP in single-arm observational studies with overall response rates of 30–70%.

# Strategies for selecting subsequent treatment

- several studies have compared the efficacy of different subsequent treatments using network meta-analysis, caution should be taken when interpreting their results because of the heterogeneity in included patients, treatment duration, and definition of response.

- Selection of subsequent treatments is primarily based on individualized patient factors, including age, lifestyle, comorbidities, concomitant medications, response to previous treatment, and patient preference and adherence.

- Treatment factors such as cost-efectiveness and medication availability also occupy an important position in treatment selection.

- Among the treatment options with the most robust evidence, the updated ASH guidelines made conditional recommendations on the selection of TPO-RAs, rituximab, and splenectomy for patients under **post-relapse** conditions .

- TPO-RAs were suggested over rituximab and rituximab over splenectomy; by contrast, one was not suggested over the other between TPO-RAs and splenectomy.

- It is notable that the updated ASH guidelines put a high value on patient preference in treatment decision-making; thus, patient education and shared decision-making are critical.

# Strategies for selecting subsequent treatment

- Our experiences under several specific situations are listed as follows:

a) In ANA-positive young female patients (aged< 40 years), rituximab is the preferred treatment. Hydroxychloroquine, an inexpensive and widely available agent commonly prescribed to treat SLE, can also be used in ANA-positive ITP patients, with a reported overall response rate of 50%.

b) In postmenopausal female cases, we have a preference for danazol plus ATRA.

c) In elderly patients with clonal hematopoiesis, we often prescribe low-dose decitabine as the first subsequent treatment.

d) Thrombopoietic agents and splenectomy should be used with caution in cases at high risk of thromboembolism or with a history of thrombosis.

e) Rituximab, immunosuppressive agents, and splenectomy should be avoided in cases with a history of recurrent infection or neoplasia.

# ITP in pregnancy

- Diagnosis of ITP in pregnancy is also based on the exclusion of other thrombocytopenic disorders.

- The differential diagnoses include gestational thrombocytopenia, pregnancy-related hypertensive diseases such as preeclampsia and HELLP syndrome, and other non-pregnancy-specific thrombocytopenic disorders.

- The recommended screening tests include complete blood counts, blood smears, reticulocyte counts, liver function, coagulation, thyroid function, ANAs, and APLAs.

- Pregnant ITP patients with a platelet count **≥20–30× $10^9$** /L and **no bleeding** symptoms can be managed with close observation only till close to term.

- A platelet count **≥50× $10^9$** /L is needed for normal delivery and **≥80× $10^9$** /L for safe spinal or epidural anesthesia.

- There are fewer treatment options for pregnant ITP patients compared to non-pregnant patients. Prednisone at 20 mg/day can be given initially and then tapered to the minimum dose necessary. IVIg infusion (1–2 g/kg) is useful in pregnant patients with an urgent need to increase platelet count.

- Patients who fail a single initial treatment can receive a combination of **high-dose methylpredniso(lo)ne and IVIg**.

- Moreover, rhTPO cannot cross the placenta and is appropriate for refractory cases.
- Azathioprine and cyclosporine A can also be used as the subsequent treatments in pregnant patients with ITP.
- Other TPO-RAs and rituximab are not recommended in pregnant patients, although their of-label uses have been reported.
- Splenectomy is not considered an appropriate therapy for ITP in pregnancy. If necessary, splenectomy is best performed laparoscopically in the second trimester.
- Vinca alkaloids and MMF are forbidden during pregnancy.

# ITP and the COVID-19 pandemic

- COVID-19 infection not only increases the incidence of ITP but also leads to the exacerbation of thrombocytopenia in previously diagnosed ITP patients.

- However, the mechanisms of thrombocytopenia after COVID-19 infection are usually multifactorial and quite different from the conventional model of platelet consumption in ITP.

- ITP secondary to COVID-19 usually occurs 2–3 weeks after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and recovers within 1 week, suggesting a different pathophysiological process compared to classical ITP.

- High-quality evidence about the optimal treatment for ITP patients during the COVID-19 pandemic is scarce, and recommendations from recently issued guidelines are primarily based on available case series and expert opinions.

- **TPO-RAs** are preferred as the initial treatment in new/relapsed ITP patients who have not been infected with SARS-CoV-2, while **prednisone** at a low starting dose (usually 20 mg/day) and short duration is recommended for cases who are positive for COVID-19.

- **IVIg** (1 g/kg) is usually used in patients with an urgent need to elevate platelet counts, or as rescue therapy for patients who fail corticosteroids.

- If possible, rituximab and immunosuppressant agents should be avoided in new or relapsed patients. For patients with chronic stable ITP, their current medications should be maintained.

- Patients with a platelet count**≥30× $10^9$ /L and increased thrombotic** risk should receive proper **thromboprophylaxis**, whether hospitalized or not.

- With regard to COVID-19 vaccination, several studies have supported the safety of the currently available vaccines in ITP patients, although approximately 10% of them might undergo clinical exacerbation .