

Approaches in Hematology

Hematology Made Easy

Causes & DD of Thrombocytopenia

❖ Increased destruction of platelets (normal BM):

- Destruction occurs either in
 - o Spleen (hypersplenism){sequestration}
Or
 - o Auto-antibody mediated.
 - ITP (anti-platelet Ab)
 - SLE
 - Anti-phospholipid syndrome
 - Evans syndrome (AIHA + low Platelets)
 - Or
 - o Consumptive coagulopathy Such as:
 - TTP
 - HUS
 - DIC
- Drug induced.
 - Heparin induced thrombocytopenia.
 - Vaccine induced thrombocytopenia and thrombosis (VITT related to Oxford/AstraZeneca vaccine for COVID19)
 - Others: thiazide & linezolid
- Miscellaneous
 - Post- transfusion purpura
 - Pregnancy (Gestational Thrombocytopenia)
 - Pseudo thrombocytopenia

❖ Decreased production. (BM disease)

- The patient often has low platelets that is associated with leukocytosis/leukopenia and anemia. For example:
 - Acute leukemias
 - Chronic leukemias (CLL mainly)
 - Myeloma
 - Lymphoma with BM infiltration
 - Solid malignancy with BM infiltration
 - BM aplasia (Aplastic anemia)
 - Myelodysplasia
 - Myelofibrosis
 - Inherited rare syndromes:
 - Bernard Soulier syndrome: rare inherited blood clotting disorder that is characterized by unusually giant platelet cells, thrombocytopenia, and prolonged bleeding time due to platelet dysfunction (thrombasthenia)

- Congenital amegakaryocytic Thrombocytopenia: rare, inherited disorder characterized by a severely low number of megakaryocytes resulting in low platelets.
- Wiskott Aldrich Syndrome: rare inherited disorder characterized by thrombocytopenia, Eczema, and recurrent pyogenic infection.

Focused history & Focused examination in patient with THROMBOCYTOPENIA

- ❖ Ask about bleeding tendency:
 - Mucocutaneous type
 - Bleeding gums
 - Epistaxis
 - Cutaneous bleeding [purpura] which might be either:
 - Small dots of bleeding under the skin [PETECHIAE]
 - Or
 - Large dots of bleeding under the skin (Bruise like) [ECCHYMOSIS]
 - Orificial bleeding
 - GIT bleeding [hematemesis ± melena]
 - Hematochezia
 - Hemoptysis (not common)
 - Hematuria
 - Vaginal bleeding & heavy menses in females
 - Deep internal bleeding
 - occurs only in severe Thrombocytopenia It can occur if platelets < 20,000, and more likely to occur if platelets < 10,000.
 - CNS bleeding: intracerebral hemorrhage
 - Intra-peritoneal hemorrhage
- ❖ Ask about history of collagen disease especially in females like SLE, APS
 - ↳ If negative history: you should explore its features:
 - Joint pain/painful swelling with morning stiffness
 - Facial rashes & photosensitivity & any unexplained rashes
 - Scalp lesions & alopecia
 - Oral ulcers
 - Chest pain /dyspnea
 - Jaundice & previous or current anemia
 - Puffy eyes /frothy urine /oliguria /hematuria
 - Fits/confusion /personality change /depression /myelitis
 - Previous lab denoting collagen disease or SLE (positive ANA or Anti-dsDNA)
 - History of thromboembolic disease (DVT, etc.)
 - History of abortions in females

- ❖ Ask about history suggesting hematological disease/malignancy.
 - Weight loss
 - Lymphadenopathy (neck lump, axillary lumps & pain in LUQ: splenomegaly)
 - Fever
 - Night sweating
- ❖ Ask about the family history of Thrombocytopenia associated with a bleeding tendency.
- ❖ Ask about history of drugs & vaccines.

Clues for TTP: Ask about history of recent occurrence of confusion + fever + pallor/jaundice + oliguria or ↑creatinine.

Clues for HUS: pallor/jaundice/anemia + Oliguria/↑creatinine after recent diarrhea

Clues for Post- transfusion purpura: history of previous blood transfusion 7- 10 days ago + purpura

Clues for DIC: History of critical illness & sepsis

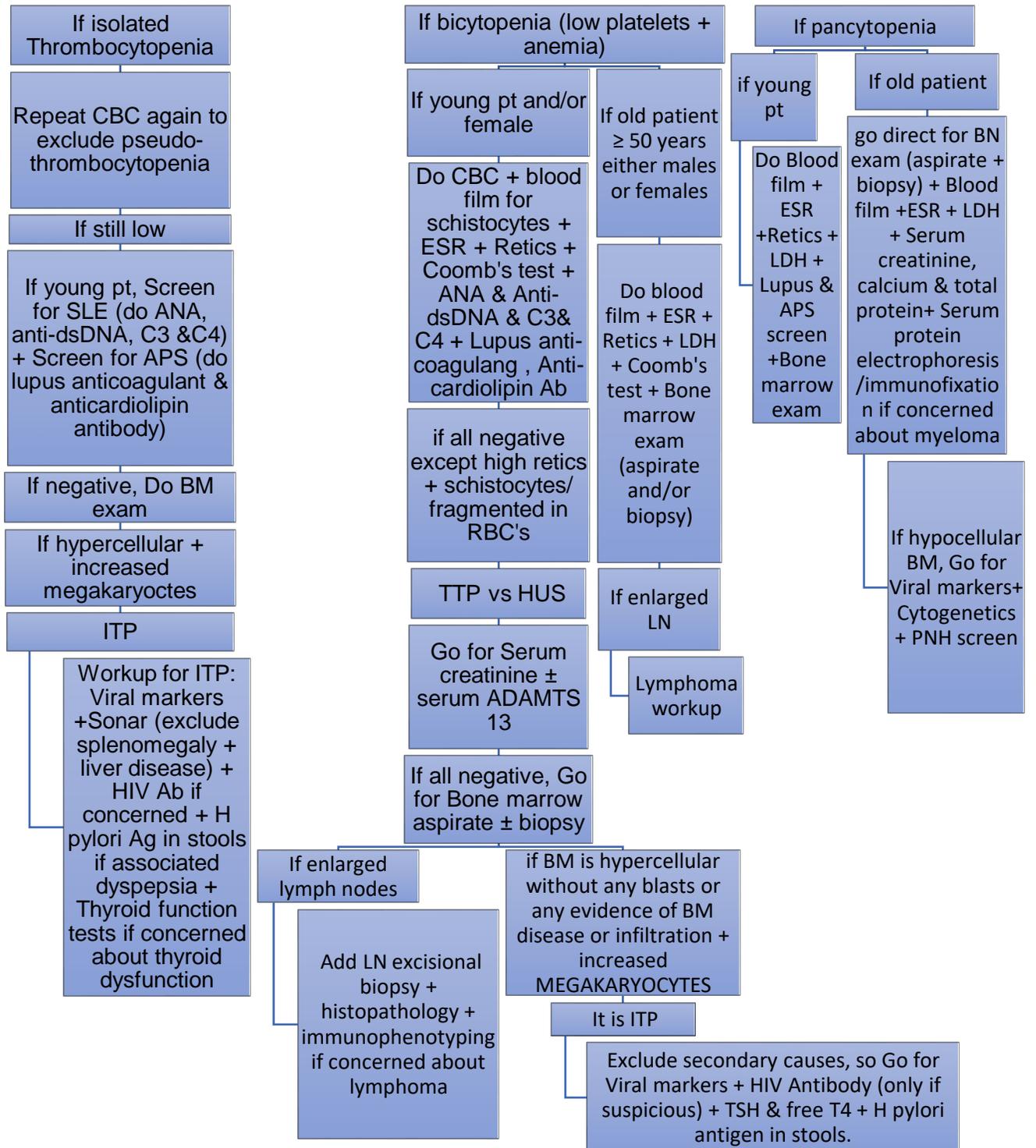
Clues for HELLP syndrome: History of pregnancy (gestational)

Clues for Heparin-induced thrombocytopenia (HIT): Heparin is very important. If the Thrombocytopenia occurs after 5 - 10 days of heparin use ± thromboembolism

Focused examination in patient with THROMBOCYTOPENIA

- General: examine for
 - Pallor (associated anemia)
 - Face for butterfly rash & discoid rash /any skin rash / scalp for alopecia
 - Jaundice
 - Lymph nodes
 - Gum hyperplasia & bleeding
 - Joints (UL >LL)
- Local: examine for
 - Enlarged liver.
 - Enlarged spleen.
 - Chest for effusion & auscultation for pleural/pericardial rub if concerned about SLE.

Stepwise lab approach & diagnostic workup



Immune thrombocytopenia

- ✓ ITP: It is called Immune Thrombocytopenic Purpura or Idiopathic Thrombocytopenic purpura. Recently" Immune thrombocytopenia"
- ✓ It is an immune-mediated {autoantibody mediated} disease resulting in destruction of platelets with low numbers below <150,000, severe ITP leads to bleeding tendency with numbers below 20,000 to 10,000 or less with a risk of life-threatening bleeding!!
- ✓ ITP might be:
 - Acute ITP: Progressive decline in platelets' number often after viral infection, it occurs mainly in children.
 - Chronic ITP: Gradual decline in platelets count in adults due to an autoimmune mechanism that affects the platelets in peripheral blood and megakaryocytes in the bone marrow as well. Chronic ITP might be:
 - ❖ Primary ITP, in which the antibody-mediated destruction of the platelets is not associated with other underlying diseases.
 - ❖ Secondary ITP: in which the antibody-mediated destruction is caused by or related to underlying diseases such as:
 - SLE
 - Infections: HIV & HCV & H pylori infection
 - Thyroid dysfunction
 - Chronic lymphocytic leukemia [CLL]

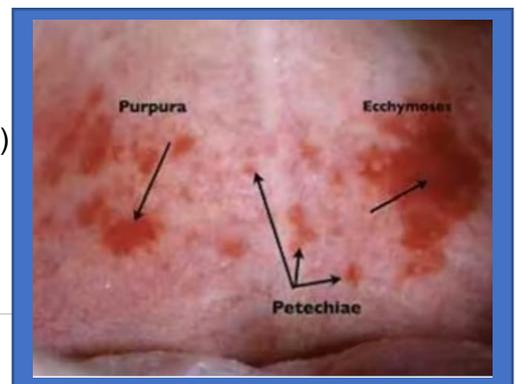
Classification of ITP:

- Newly diagnosed ITP: up to 3 months since diagnosis
- Persistent ITP: 3 - 12 months since diagnosis
- Chronic ITP: more than 12 months since diagnosis

Clinical picture

- A. It might be asymptomatic (often with platelets number $\geq 50,000$)
- B. Symptomatic if the platelet count is below 30,000 - 50,000. It presents with [Platelet type of bleeding], which is often Mucocutaneous bleeding.

- ✚ Mucocutaneous bleeding:
 - gum bleeding
 - Epistaxis
 - PURPURIC eruption: bleeding under the skin
 - ↪ It might be ECCHYMOSIS (bruise-like)
Or
 - ↪ Petechiae (small dots under the skin)
 - Sites: LL (mostly), UL, trunk



- Purpura is not raised, non-blanching on pressure, and not palpable (to differentiate it from Vasculitic purpura)
- N.B: purpuric rash is often seen on the skin, and it is called DRY PURPURA.
- It might occur in the mucus membranes in the form of hemorrhagic blisters (gums & inner cheeks) it is called " WET PURPURA " It indicates more risk of severe bleeding.

✚ Orificial bleeding:

- Hematemesis, Melena, Hematochezia
- Hematuria
- Vaginal bleeding & heavy menses in females

C. Severe ITP: often occurs when the platelet count < 20,000 to 10,000 or less. That results in potentially life-threatening bleeding:

- intracerebral hemorrhage
- Severe GIT bleeding
- spontaneous intra-peritoneal bleeding

Stepwise approach & diagnostic workup

- ✓ Most cases present with isolated thrombocytopenia ± mild degree of anemia (HB: 10-12 in Females & 10 -13 in Males) resulting from bleeding.
 - So, the first step is to exclude other causes of thrombocytopenia, most importantly TTP/HUS & Leukemia
 - Blood film is vital here to exclude the presence of Fragmented RBCs (schistocytes) and abnormal cells like blasts, etc.
 - Bedside U/S abdomen to exclude splenomegaly.
- ✓ In young patients < 50 years: Do the following:
 - Retics % (if associated anemia)
 - ESR
 - Coombs test if associated anemia (Evans syndrome)
 - SLE screen (ANA, anti-ds DNA, C3 & C4)
 - APS screen (Lupus anticoagulant & Anti-cardiolipin Antibody). If negative do Bone marrow aspiration
 - if the BM is normocellular or hypercellular + increased megakaryocytes ---> picture of ITP
- ✓ If ITP is diagnosed, you have to exclude secondary causes (If you are concerned about the history and exam, but it is not mandatory as a routine according to ASH& BCSH guide)
 - Viral makers (HCV & HIV antibodies)
 - TSH & free T4 (if history & exam is suggestive for underlying thyroid disease)
 - H pylori Ag in stool (If history of associated dyspepsia)

ITP diagnosis and management

According to American Society of Hematology Guidelines ASH (2019 last update) & International Consensus Report Guidelines:

✓ **Diagnosis**

- ASH recommends testing adult patients with ITP for hepatitis C virus and HIV.
- ASH suggests further investigations if the blood count or peripheral blood smear reveals abnormalities other than thrombocytopenia and perhaps findings of iron deficiency.
- ASH suggests that a bone marrow examination is not necessary irrespective of age in patients presenting with typical ITP (typical ITP = isolated thrombocytopenia with normal spleen after exclusion of other common causes such as splenomegaly and drugs)

في حالة وجود نقص في عدد الصفائح فقط بدون انيميا ،، وبعد استبعاد الاسباب الاخرى ،، فان احتماليه وجود سبب اخر غير ال ITP في نخاع العظم غير منطقي وبالتالي لا داعي لبزل النخاع ،، اما في حالة تواجد انيميا ايا كانت الدرجه مع نقص الصفائح ،، فبذل النخاع مهم جدا .

✓ **Treatment recommendations**

- The 2019 ASH guidelines recommend against treatment of patients with a platelet count $\geq 30 \times 10^9/L$ who are asymptomatic or have mild mucocutaneous bleeding.

في حالة ان الصفائح عددها اكثر من ٣٠ الف وفي غياب النزيف او وجود نزيف بسيط ،، لا ينبغي اعطاء المريض اي علاج وبنكتفي بمتابعة الصفائح فقط

- For newly diagnosed adult patients with a platelet count $< 30 \times 10^9/L$, the guidelines suggest treatment with corticosteroids.
- For adults with a platelet count $< 20 \times 10^9/L$ who are asymptomatic or have minor mucocutaneous bleeding, the guidelines suggest hospital admission for newly diagnosed patients but outpatient treatment for those with an established diagnosis of ITP.
- In addition, those patients who are not admitted to the hospital should receive education and expedited follow-up with a hematologist within 24 to 72 hours of the diagnosis or disease relapse.

℞ For first-line treatment, the guidelines recommend a short course (≤ 6 weeks) of steroids over a prolonged course (> 6 weeks, including treatment and taper).

- Additional first-line treatment suggestions include the following

℞ Either prednisone (0.5-2.0 mg/kg per day) or dexamethasone (40 mg per day for 4 days) as the type of corticosteroid

- Corticosteroids alone rather than rituximab and corticosteroids

غالبا بنعطي المريض/المريضه سوليوبريد ٦٠ مجم على مدار اليوم متقسمه باى طريقه كجرعة بداية

- The following 2011 ASH treatment suggestions remain unchanged.

℞ IVIG may be used with corticosteroids when a more rapid increase in platelet count is required.

℞ Either IVIG or anti-D (in appropriate patients) may be used if corticosteroids are contraindicated

- If used, IVIG should be administered in a single dose of 1 g/kg; the dose may be repeated if necessary.
 - For adults with ITP for ≥ 3 months who are corticosteroid dependent or unresponsive to corticosteroids, the 2019 second-line treatment suggestions include the following, depending on preference.
 - R A TPO-RA (either Eltrombopag or Romiplostim) {Eltrombopag--> Revolade}
 - R Rituximab, for those who value avoiding surgery and long-term medication {Mabthera}
 - R Splenectomy, for those who value avoiding long-term medication and gaining a durable response.
 - The ASH guidelines recommend delaying splenectomy for at least 1 year after diagnosis, if possible, because of the potential for spontaneous remission in the first year. The 2011 recommendation that for medically suitable patients, laparoscopic and open splenectomy offer similar efficacy, also remains unchanged.
- لا ينبغي التسرع في اخذ قرار استئصال الطحال كخطوه رقم (٢) في العلاج بعد فشل الخطوه الاولى (الكورتيزون) قبل سنه من بداية التشخيص لتجنب خطر رجوع المرض حتى بعد استئصال الطحال
- While no ASH recommendations were made regarding the association of Helicobacter pylori in adult ITP, every adult with gastrointestinal symptoms with ITP or with chronic unresponsive ITP may benefit from H pylori diagnostic testing, and triple therapy should be administered to all those who test positive for H pylori infection.
 - Remissions after treatment of H Pylori were observed more frequently in reports from Japan and Italy (28%-100%) than in the US and other European countries (< 13%).

International Consensus Report Guidelines for diagnosis and management of ITP in Adults

- + Diagnosis: Basic evaluation in all patients should consist of the following:
 - Patient history
 - Family history
 - Physical examination
 - CBC and reticulocyte count
 - Peripheral blood film
 - Quantitative Ig level measurement
 - Blood group (Rh)
 - HIV serology - Recommended by the majority of the panel for adult patients in the appropriate geographic setting.
 - Hepatitis C virus serology - Recommended by the majority of the panel for adult patients in the appropriate geographic setting Hepatitis B virus serology.
- + Tests of potential utility in patients with ITP include the following:

- Glycoprotein-specific antibody (can be used in difficult cases, but has poor sensitivity and is not a primary diagnostic test)
- Antiphospholipid antibodies (including anti-cardiolipin and lupus anticoagulant) if there are clinical features of antiphospholipid syndrome
- Anti-thyroid antibodies and thyroid function
- Pregnancy test in women of childbearing potential
- Antinuclear antibodies (ANA): A positive ANA may be a predictor of chronicity; hydroxychloroquine may be an effective treatment if ANAs are present, especially in young women; ANA testing can be considered before splenectomy because of the increased risk for thrombosis
- Polymerase chain reaction (PCR) testing for Epstein-Barr virus, cytomegalovirus, and parvovirus
- Bone marrow examination (may be informative in patients with systemic symptoms, abnormal signs, or with suspicion of a different diagnosis)
- Direct antiglobulin test Helicobacter pylori testing (should be considered in adults with typical ITP, in those with digestive symptoms, and those from areas of high prevalence)

✚ The following tests have no proven role in the differential diagnosis of ITP from other thrombocytopenias and do not guide patient management:

- Thrombopoietin level
- Reticulated platelets/immature platelet fraction
- Bleeding time
- Serum complement.

✚ Therapy: Recommendations for initial treatment of newly diagnosed patients are as follows:

℞ Prednisone or Prednisolone at 1 mg/kg (maximum dose 80 mg, even in patients weighing >80 kg) for 2 weeks, to a maximum of 3 weeks; or dexamethasone 40 mg/d for 4 days, repeated up to 3 times.

- Corticosteroids are the standard initial treatment for adults with ITP who need treatment and do not have a relative contraindication:
- If a response is seen (eg, platelets > 50 × 10⁹/L), taper the prednisone.
- prednisolone, aiming for discontinuation by 6 weeks (maximum 8 weeks), even if the platelet count drops during the taper.

- If there is no response to the initial dose within 2 weeks, taper the prednisone/prednisolone rapidly over 1 week and discontinue.
 - Longer courses of steroids should be avoided, although occasional patients may benefit from continuous low-dose corticosteroids (eg, ≤ 5 mg/d).
- \mathcal{R} Use of IVIG (1 g/kg on 1 or 2 consecutive days or 0.4 g/kg per day for 5 days), or IV anti-D (50-75 μ g/kg once) where available, may be appropriate in patients with bleeding, at high risk for bleeding, who require a surgical procedure, or who are unresponsive to prednisone/prednisolone.
- If using anti-D, exercise consideration over potential triggering of disseminated intravascular coagulation (DIC) or hemolysis and consider steroid premedication to minimize acute infusion reactions (e.g., headaches, fever-chills, and/or intravascular hemolysis).
 - Patients with contraindications to high-dose corticosteroid therapy (eg, insulin-dependent diabetes, uncontrolled diabetes, psychiatric disorders, active infection) may be managed with only IVIZG or IV anti-D as initial therapy.
- \mathcal{R} TPO receptor agonists (TPO-RAs) and rituximab are not considered initial therapies. For subsequent therapy, medications with robust evidence of efficacy are as follows:
- Rituximab
 - TPO-RAs: Eltrombopag, Avatrombopag, Romiplostim
 - Fostamatinib
- Medical therapies with less robust evidence are as follows:
- \mathcal{R} Azathioprine
 - \mathcal{R} Cyclophosphamide
 - \mathcal{R} Cyclosporine
 - \mathcal{R} Danazol
 - \mathcal{R} Dapsone
 - \mathcal{R} Mycophenolate mofetil (MMF)
 - \mathcal{R} Switching from one TPO-RA to another
 - \mathcal{R} Vinca alkaloids
- Consensus-based recommendations for target platelet counts ($\times 10^9/L$) for surgery in adults are as follows:
- Minor surgery: ≥ 50
 - Major surgery: ≥ 80
 - Major neurosurgery: ≥ 100
- Treatment of life-threatening bleeding:

- R* In emergency situations in which there is an urgent need to increase the platelet count within 24 hours, a combination of initial treatments, including IV corticosteroids and, usually, IVIG, should be used.
- R* Platelet transfusions may be helpful and must not be postponed in cases of life-threatening bleeding, especially intracranial hemorrhage (ICH).
- R* In the case of life-threatening bleeding and the absence of a significant response to IVIG and platelet transfusion in a patient on corticosteroids, consider use of a TPO-RA.
- R* Additional options may include IV anti-D; vincristine or vinblastine; antifibrinolytics in combination with other initial therapies; and, rarely, emergency splenectomy.

- Surgical therapy for persistent and chronic ITP:
 - R* Splenectomy is associated with long-term treatment-free remissions. However, deferring splenectomy for ≥ 12 to 24 months from diagnosis before performing splenectomy is recommended because of the chance of remission or stabilization of the platelet count at a hemostatic level; up to one third of patients may remit in 1 year, and up to 80% may remit in 5 years.

 - When available, indium-labeled autologous platelet scanning may be useful prior to splenectomy to confirm that the spleen is the main site of platelet sequestration.
 - Laparoscopic splenectomy is as effective as open splenectomy in terms of response and is more comfortable for the patient.
 - Postoperative thromboprophylaxis should be considered in patients undergoing splenectomy as long as the platelet count is > 30 to $50 \times 10^9/L$.
 - Splenectomy should be performed by a surgeon experienced in identifying accessory splenic tissue, which is common and should be removed.
 - Appropriate vaccination against *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* must be provided ≥ 2 weeks before splenectomy and maintained according to national guidelines; recent treatment (within 6 months) with rituximab may impair vaccination efficacy.

- Patients should be informed of the long-term risks of splenectomy (ie, increased rates of thrombosis, infection, and cancer) and educated to follow advice aimed at mitigating these complications.
 - Antibiotic prophylaxis should be given as per national guidelines.
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- Approach when multiple treatments have failed:
 1. Reconsider the diagnosis
 2. Perform bone marrow examination if not already done
 3. Reassess the need for treatment (consider platelet count/bleeding risk)
 4. Consider referral to an ITP treatment center
 5. Reassess the adequacy of prior therapies (eg, was the full dose of TPO-RA explored? Did the addition of a small dose of corticosteroid improve response?)
 6. Assess the risks and benefits of further treatment
 7. Reassess the possibility of splenectomy if not already performed
 8. Consider other medical therapies if not already attempted (eg, MMF, fostamatinib, rituximab, azathioprine, dapsone, danazol)
 9. Consider enrollment in a clinical trial
 10. In patients who relapse >1 year after responding to splenectomy, an accessory spleen should be searched for and, if found, resected.
 11. Switching from one TPO-RA to another and sequential therapy have been shown to have a positive effect on response and adverse effects.
 12. Other therapies that have been used as last resorts include combination chemotherapy, alemtuzumab, and hematopoietic stem cell transplantation (HSCT).

 - The side effects of these treatment options may be severe, and the data supporting their use are limited.