Aggiornamenti diagnostico-terapeutici della ITP

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29 Gennaio 2020

IMMUNE THROMBOCYTOPENIA (ITP)

Background

- Immune thrombocytopenia is a disorder of increased platelet destruction and impaired platelet production
- Incidence: 2 to 5 per 100,000 persons[1]
- Remission differs by age[2-6]
  - 60-70% of children
  - 20-40% of adults
- Bleeding is heterogeneous and serious bleeding is a rare event
  - ICH 1.4% in adults and 0.4% of children[7]
- Significant impact on health-related quality of life and associated with fatigue

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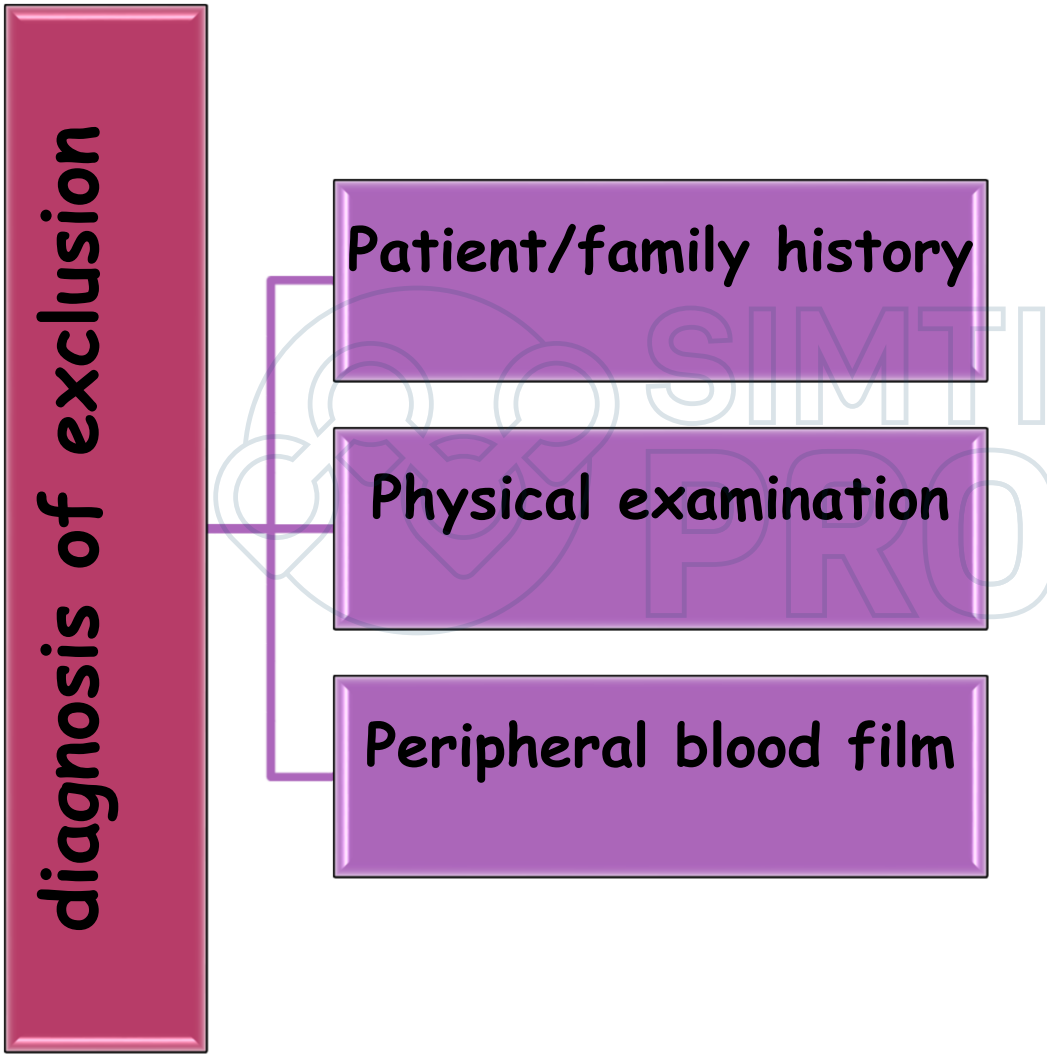
ALTERNATIVE CAUSES OF ISOLATED THROMBOCYTOPENIA (~50% OF CASES)

- HIV, HCV, H. pylori or other infections
- Other autoimmune disorders (including SLE)
- Malignancy
- Liver disease
- Exposure to environmental toxins
- Recent transfusions and recent immunisations

- Bone marrow diseases (aplastic anemia, MDS, etc)
- Inherited thrombocytopenia
- Drugs (prescription or non-prescription)
- Alcohol abuse, consumption of tonic water (quinine)

DIAGNOSIS


diagnosis of exclusion
Patient/family history
Physical examination
Peripheral blood film

CLINICAL GUIDELINES

blood advances

American Society of Hematology 2019 guidelines for immune thrombocytopenia

Cindy Neunert,[1] Deirdra R. Terrell,[2] Donald M. Arnold,[3,4] George Buchanan,[5] Douglas B. Cines,[6] Nichola Cooper,[7] Adam Cuker,[8] Jenny M. Despotovic,[9] James N. George,[2] Rachael F. Grace,[10] Thomas Kühne,[11] David J. Kuter,[12] Wendy Lim,[13] Keith R. McCrae,[14] Barbara Pruitt,[15] Hayley Shimanek,[16] and Sara K. Vesely[2]

REVIEW ARTICLE

blood advances

Updated international consensus report on the investigation and management of primary immune thrombocytopenia

Drew Provan,[1] Donald M. Arnold,[2] James B. Bussel,[3] Beng H. Chong,[4] Nichola Cooper,[5] Terry Gernsheimer,[6] Waleed Ghanima,[7,8] Bertrand Godeau,[9] Tomás José González-López,[10] John Grainger,[11] Ming Hou,[12] Caroline Kruse,[13] Vickie McDonald,[14] Marc Michel,[9] Adrian C. Newland,[1] Sue Pavord,[15] Francesco Rodeghiero,[16] Marie Scully,[17] Yoshiaki Tomiyama,[18] Raymond S. Wong,[19] Francesco Zaja,[20] and David J. Kuter[21]

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DIAGNOSIS

The diagnosis of ITP is based principally on the exclusion of other causes of isolated thrombocytopenia

Based on the evidence currently available, when there is isolated thrombocytopenia and no abnormal features present on physical examination or examination of the blood smear, a bone marrow examination is not required in the initial diagnosis (Grade B recommendation), whether or not treatment is recommended.

The detection of Helicobacter pylori infection, with the urea breath test or the stool antigen test, should be included in the initial work-up in appropriate geographical areas (evidence level IIa; Grade B recommendation).

The majority of authors routinely test for hepatitis B virus (HBV), HIV, and hepatitis C virus (HCV) in all adult patients (evidence level IIb).

Quantitative immunoglobulin (Ig) level testing is indicated to exclude an immune deficiency syndrome (evidence level IV; Grade C recommendation) or before treatment with IVIg. In children, Ig level testing may be considered at baseline and should be measured in those children with persistent or chronic ITP as part of a reassessment evaluation.

Bone marrow examination could be appropriate in those relapsing after remission, in patients not responding to initial treatment options, where splenectomy is considered, or if other abnormalities are detected in the blood count or morphology (evidence level III; Grade C recommendation). This examination should ideally include an aspirate, biopsy, flow cytometry, and cytogenetics (evidence level IV; Grade C recommendation).

ITP may be classified as primary or secondary to other medical conditions present at diagnosis. Furthermore, it may be further classified as newly diagnosed (0-3 months), persistent (.3-12 months), or chronic (.12 months).

Provan D et al, Blood Advances 2019

Isolated thrombocytopenia: initial assessment

- Basic evaluation (mandatory/highly recommended)
  - Physical examination
  - Peripheral blood count
  - Evaluation of peripheral blood smear
  - Bone marrow examination
  - Blood group Rh (D) typing
  - H pylori testing
  - HIV, HCV testing
  - Quantitative Ig level testing
  - Direct anti-globulin test

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Tests of potential utility

- Glycoprotein-specific antibody testing
- Antiphospholipid antibodies
- Antinuclear and extractable nuclear antigen antibodies
- Anti-thyroid antibodies and thyroid function testing
- Testing for other acute and persistent infections
- Thrombopoietin level
- Reticulated platelets/ immature platelet fraction.
- Coagulation tests

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ITP IN ADULTS: WHO SHOULD BE TREATED?

Treatment should always be tailored to the patient, because many factors contribute to treatment decisions

Recommendations for treatment goals

- Treatment goals should be individualized to the patient and the phase of the disease.
- Treatment should prevent severe bleeding episodes.
- Treatment should maintain a target platelet level 20-30 x 10^9/L at least for symptomatic patients (because risk for major bleeding increases below this level).
- Treatment should be with minimal toxicity.
- Treatment should optimize health-related quality of life (HRQoL).

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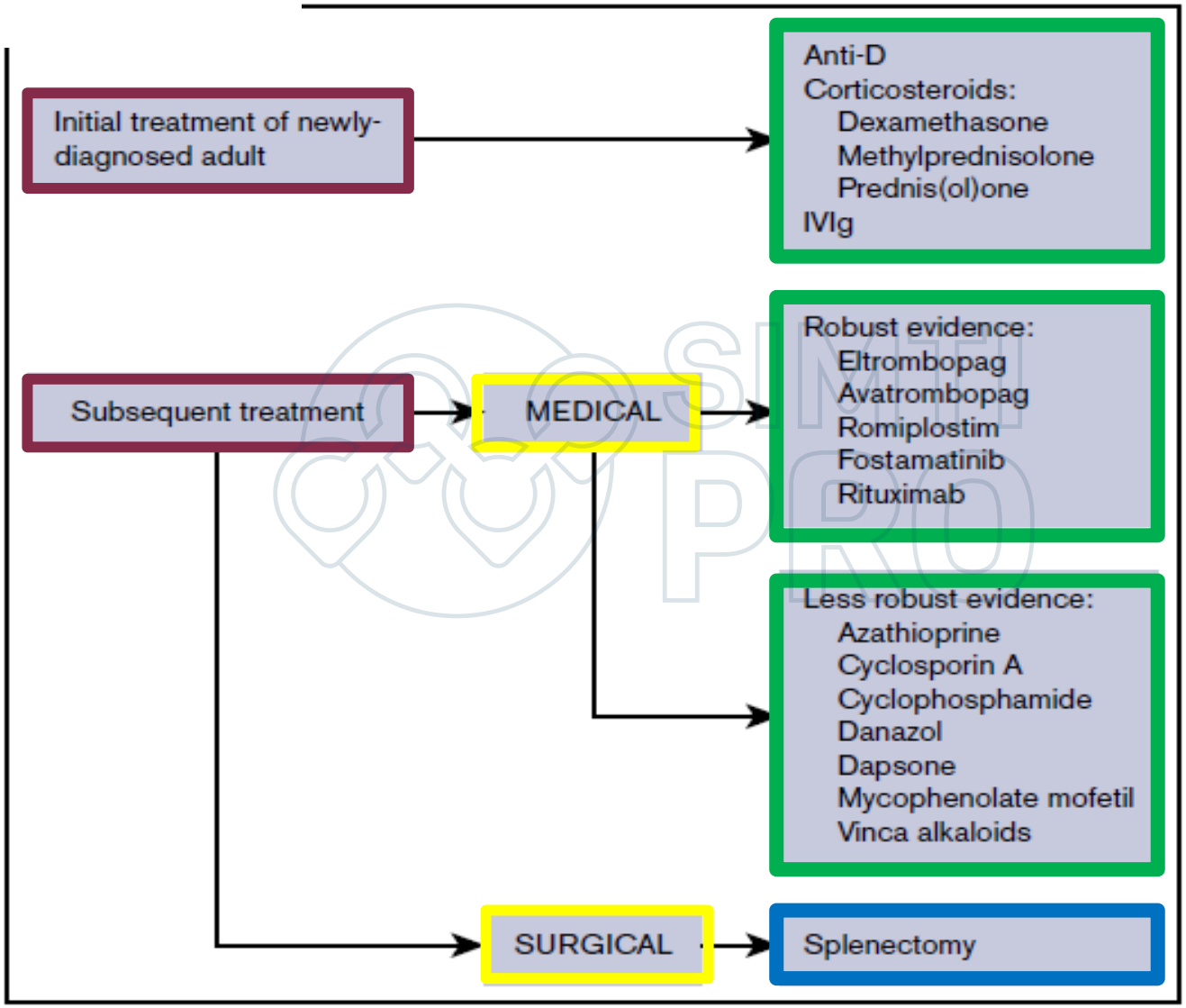
ITP IN ADULTS

Figure 1. Overview of therapies for the treatment of adult ITP. The evidence available for medical therapies is indicated.



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Therapies for the treatment of ITP

Clinical situation	Therapy option
Initial treatment of newly diagnosed ITP	Corticosteroids
	Dexamethasone
	Methylprednisolone
	Prednis(ol)one
	IVIg
	Anti-D (licensed and available for ITP in only a few countries)
Subsequent treatment	Medical therapies
	Medical therapies with robust evidence
	Rituximab
	TPO-RAs: eltrombopag, avatrombopag, romiplostim
	Fostamatinib
	Medical therapies with less robust evidence
	Azathioprine
	Cyclophosphamide
	Cyclosporine A
	Danazol
	Dapsone
	Mycophenolate mofetil
	TPO-RA switch
	Vinca alkaloids
	Surgical therapies
	Splenectomy
Treatment of patients failing multiple therapies	Accessory splenectomy
	Alemtuzumab
	Combination of initial and subsequent therapies
	Combination chemotherapy
	Clinical trials
	HSCT
	Splenectomy, if not already performed
	Supportive care

Recommendations for initial treatment of newly diagnosed patients

Corticosteroids are the standard initial treatment for adults with ITP who need treatment and do not have a relative contradiction. Prednisone 1mg/kg/day for 2-3 weeks or DXM 40 mg/day for 4 days for 3 courses. If a response is seen (eg, platelets .50 x 109 /L), the predniso(lo)ne should be tapered in 6 weeks
If there is no response to the initial dose within 2 weeks, the predniso(lo)ne should be tapered rapidly over 1 week and stopped

Longer courses of steroids should be avoided

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 mg/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 predniso(lo)ne

Certain patients may have relevant contraindications to high-dose corticosteroid therapy and may be managed with only IVIg or IV anti-D as initial therapy.

TPO receptor agonists (TPO-RAs) and rituximab are not considered initial therapies

ITP IN ADULTS

Consensus-based recommendation for target platelet counts for surgery or medical therapy in adults

Type of surgery	Target platelet count, × 10^9/L
Dental prophylaxis (descaling, deep cleaning)	≥20 to 30
Simple extractions	≥30
Complex extractions	≥50
Regional dental block	≥30
Minor surgery*	≥50
Major surgery	≥80
Major neurosurgery	≥100
Splenectomy	See "Subsequent therapy: surgical"
Obstetrics	See "Thrombocytopenia presenting during pregnancy"
Single antiplatelet agent or anticoagulant (ie, 1 antiplatelet agent, warfarin, or TSOAC)	≥30 to 50
Dual antiplatelet or anticoagulant (ie, 2 antiplatelet agents or 1 antiplatelet agent plus warfarin or TSOAC)	≥50 to 70

Evidence level IV. Adult patients with ITP considered to be at "typical" bleeding risk from surgery. Target platelet count depends on the clinical situation and urgency and need for procedure.

TSOAC, target-specific oral anticoagulants.

*Cataract surgery with laser technique has no bleeding risk.

Recommendations for life-threatening bleeding

1. A combination of initial treatments, including IV corticosteroids and, usually, IVIg, should be used in emergency situations in which there is an urgent need to increase the platelet count within 24 hours (Grade C recommendation). Platelet transfusions may be helpful and must not be postponed in cases of life-threatening bleeding, especially intracranial hemorrhage (ICH).

2. In the case of life-threatening bleeding and the absence of a significant response to IVIg and platelet transfusion in a patient on corticosteroids, the use of a TPO-RA should be considered.

3. Additional options may include IV anti-D, vincristine or vinblastine, antifibrinolytics in combination with other initial therapies (Grade C recommendation), and, rarely, emergency splenectomy.

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ITP IN ADULTS

Recommendations for subsequent therapy strategy

1. There are many medical therapy options with few AEs.
2. Not all therapies are available in all countries; thus, the recommendations should be modified based on available resources and patient preference.
3. Some medical options may require ongoing continued treatment.
4. Up to one third of patients may remit in 1 year,[113] and up to 80% may remit in 5 years.[114,115] If possible, splenectomy should be deferred for ≥1 year to allow for remission.[113,115]

The main goal of subsequent treatment is to attain a sustained increase in the platelet count that is considered hemostatic for the individual patient while minimizing AEs and allowing for the possibility of attaining a remission.

Available treatment modalities have different mechanisms of action and can be broadly categorized into those that are given only once (or for only 1 course) and are intended to induce a long-term response (rituximab, splenectomy) and those that need continued or chronic administration (low-dose corticosteroids, immunosuppressive agents, TPO-RAs). Patients on agents in the latter category may improve at any time, but who will improve and when is unpredictable (supplemental Table 3).

Subsequent therapy: medical

Medical therapies with robust evidence

- ❑ TPO-Ras, romiplostim, eltrombopag,
- ❑ Avatrombopag
- ❑ Rituximab

Medical therapies with less robust evidence

- ◉ Azathioprine
- ◉ Cyclosporine
- ◉ Cyclophosphamide
- ◉ Danazol
- ◉ MMF
- ◉ Vinka Alkaloids

ITP IN ADULTS

Recommendations for surgical therapy for persistent and chronic ITP in adults

Splenectomy is associated with long-term treatment-free remissions. It is recommended **to wait 12 to 24 months** from diagnosis before performing splenectomy because of the chance of remission or stabilization of a platelet count at a hemostatic level. (Grade C recommendation).

Laparoscopic splenectomy is as effective as open splenectomy in terms of response and is more comfortable for the patien. (Grade B recommendation).

Postoperative thromboprophylaxis should be considered in patients undergoing splenectomy as long as the platelet count is .30 to 50 3 109 /L. (Grade C recommendation).

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 (increased rates of thrombosis, infection, and cancer) and educated to follow advice aimed at mitigating these complications (Grade C recommendation).

Antibiotic prophylaxis should be given as per national guidelines (Grade C recommendation).

Recommendations for adults failing multiple therapies

Recommendations for adults failing multiple therapies

1. For patients failing multiple prior therapies, it is important to:
   a. Reconsider the diagnosis
   b. Perform bone marrow examination if not already done
   c. Reassess the need for treatment (consider platelet count/bleeding risk)
   d. Consider referral to an ITP treatment center
   e. 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?)
   f. Assess the risks and benefits of further treatment
   g. Reassess the possibility of splenectomy if not already performed
   h. Consider other medical therapies if not already attempted (eg, MMF, fostamatinib, rituximab, azathioprine, dapsone, danazol)
   i. Consider enrollment in a clinical trial
2. In patients who relapse >1 year after responding to splenectomy, a search for accessory spleen should be conducted and, if found, resected (Grade C recommendation).
3. Switching from 1 TPO-RA to another and sequential therapy have been shown to have a positive effect on response and AEs.
4. 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 (Grade B recommendation; evidence level III).

CLINICAL GUIDELINES

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ITP IN ADULTS: FIRST LINE THERAPY

Corticosteroids Versus Observation

- ***Should corticosteroids or observation be used for adults with newly diagnosed ITP and a platelet count of <30 x 10^9/l who are asymptomatic or have minor mucocutaneous bleeding?***
- **Recommendation 1a.** In adults with newly diagnosed ITP and a platelet count of <30 x 10^9/l who are asymptomatic or have minor mucocutaneous bleeding, the ASH guideline panel suggests corticosteroids

- Conditional recommendation based on moderate certainty in the evidence

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ITP IN ADULTS: FIRST LINE THERAPY

Corticosteroids Versus Observation

- ***Should corticosteroids or observation be used for adults with newly diagnosed ITP and a platelet count of ≥30 x 10^9/l who are asymptomatic or have minor mucocutaneous bleeding?***
- **Recommendation 1b.** In adults with newly diagnosed ITP and a platelet count of ≥30 x 10^9/l who are asymptomatic or have minor mucocutaneous bleeding, the ASH panel recommends against corticosteroids

- Strong recommendation based on very low certainty in the evidence

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ITP IN ADULTS: FIRST LINE THERAPY

Corticosteroids Versus Observation

- Recommendation 1a:
  - Observation may be appropriate for a subset of patients
  - Consideration should be give to the severity of thrombocytopenia, additional comorbidities, use of antiplatelet or anticoagulation medications, need for upcoming procedures, and age of the patient
- Recommendation 1b:
  - Treatment with corticosteroids may be appropriate for patients at the lower end of this threshold and elderly patients (> 60 years old)
  - Consideration should also be given to additional comorbidities, use of antiplatelet or anticoagulation medications, need for upcoming procedures

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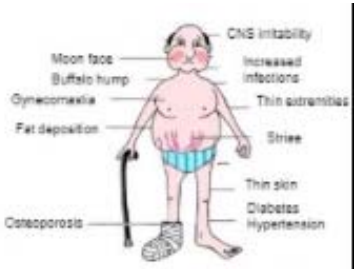
ITP IN ADULTS: FIRST LINE THERAPY

Good Practice



- The panel agreed that best practice is to ensure adequate follow-up for potential corticosteroid side effects.
- This includes close monitoring for hypertension, hyperglycemia, sleep and mood disturbances, gastric irritation or ulcer formation, glaucoma, and osteoporosis.
- Given the neurotoxicity and impact of corticosteroids on mental health, the panel also encouraged assessment of HRQoL (depression, fatigue, mental status etc.) while patients are receiving corticosteroids.

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ITP IN ADULTS: FIRST LINE THERAPY

Inpatient Versus Outpatient Management

- ***Should adults with newly diagnosed ITP and a platelet count of <20 x 10^9/l and who are asymptomatic or have mild mucocutaneous bleeding be treated as outpatients or be admitted to the hospital?***
- **Recommendation 2a.** In adults with newly diagnosed ITP and a platelet count of <20 x10^9/l and who are asymptomatic or have minor mucocutaneous bleeding, the ASH panel suggests admission to the hospital rather than treatment as an outpatient

- Conditional recommendation based on very low certainty in the evidence

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ITP IN ADULTS: FIRST LINE THERAPY

Inpatient Versus Outpatient Management

- In adults with an established diagnosis of ITP and a platelet count of <20 x10^9/l and who are asymptomatic or have minor mucocutaneous bleeding, the ASH panel suggests outpatient management rather than hospital admission

- Conditional recommendation based on very low certainty in the evidence

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ITP IN ADULTS: FIRST LINE THERAPY

Inpatient Versus Outpatient Management

- ***Should adults with newly diagnosed ITP and a platelet count of ≥20 x 10^9/l and who are asymptomatic or have minor mucocutaneous bleeding be treated as outpatients or admitted to the hospital?***
- **Recommendation 2b**. In adults with a platelet count of ≥20 x 10^9/l and who are asymptomatic or have minor mucocutaneous bleeding, the ASH guideline panel suggests outpatient management rather than than hospital admission
- Conditional recommendation based on very low certainty in the evidence

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ITP IN ADULTS: FIRST LINE THERAPY

Inpatient Versus Outpatient Management

- The need for admission is variable across the range of platelet counts in these recommendations (0-20 x 10^9/l and 20-150 x 10^9/l)
- Hospitalization should be considered for patients:
  - Who are refractory to treatment
  - There is uncertainty about the diagnosis
  - Those with significant comorbidities for bleeding risk
  - With more serious mucosal bleeding
  - With social concerns
- Patients not admitted to the hospital should receive education

Good Practice Statement: Ensure follow up with a hematologist within 24-72 hours of diagnosis

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ITP IN ADULTS: FIRST LINE THERAPY

Duration and Type of Corticosteroids

- ***Should a short course (≤ 6 weeks) or a prolonged course (including treatment and taper) of prednisone be used for adults with newly diagnosed ITP?***
- **Recommendation 3.** In adults with newly diagnosed ITP, the ASH guideline panel recommends against a prolonged course (>6 weeks) of prednisone

- Strong recommendation based on very low certainty in the evidence

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ITP IN ADULTS: FIRST LINE THERAPY

Duration and Type of Corticosteroids

- ***Should adults with newly diagnosed ITP be treated with prednisone (2 to 0.5 mg/kg/day) or dexamethasone (40 mg/day for 4 days) as the type of corticosteroids for initial therapy?***
- **Recommendation 4.** In adults with newly diagnosed ITP, the ASH guideline panel suggests either prednisone (0.5 to 2.0 mg/kg/day) or dexamethasone (40 mg/day for 4 days) as the type of corticosteroid for initial therapy

- Conditional recommendation based on very low certainty in the evidence

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ITP IN ADULTS: FIRST LINE THERAPY

Dexamethasone vs prednisolone

- **Remark:** If a high value is placed on rapidity of platelet count response, an initial course of dexamethasone over prednisone may be preferred, given that dexamethasone showed increased desirable effects with regards to remission and response at 7 days.

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ITP IN ADULTS: FIRST LINE THERAPY

Up front rituximab?

- ***Should adults with newly diagnosed ITP be treated with rituximab and corticosteroids or corticosteroids alone for initial therapy?***
- **Recommendation 5.** In adults with newly diagnosed ITP , the ASH guideline panel suggests against rituximab and corticosteroids rather than corticosteroids alone for initial therapy
- Conditional recommendation based on very low certainty in the evidence
- **Remark**: If high value is placed on possibility for remission over concerns for potential side effects of rituximab, then an initial course of corticosteroids with rituximab may be preferred.

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ITP IN ADULTS: FIRST LINE THERAPY

Up front rituximab

- Moderate desirable effects were seen with concomitant use of rituximab and corticosteroids, particularly with regard to higher durable response (RR, 1.70; 95% CI, 1.34 to 2.16) and remission (RR, 1.58; 95% CI, 1.00 to 2.52)
- There was no difference with regard to impact on 1-month response, prevention of major bleeding or mortality and no data regarding HRQoL
- The panel thought there was very low certainty in the evidence for benefits, due to missing HRQoL data, unknown and non-standardized dose of corticosteroid for comparison, and a lack of longer-term follow-up

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ITP IN ADULTS: SECOND LINE THERAPY

In adults with ITP ≥3 months who are corticosteroid-dependent or unresponsive to steroids, should splenectomy, rituximab or TPO-RAs be used?

- Goal of treatment: to achieve a sustained increase in platelet count considered hemostatic for an individual patient, minimize adverse events and possibly achieve remission[1]
- In practice, decision usually considers all 3 options but evidence only available for dichotomous comparison with placebo/standard of care
- Preference to ***avoid splenectomy*** in patients with diagnosis <12 months, due to possibility of disease remittance
- Choice of therapy also influenced by factors not captured in clinical trials
  - Patient-specific: age, co-morbidities, bleeding risk
  - Disease-specific: ITP duration, response/side effects to previous treatments
  - **Patient preference and values**

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ITP IN ADULTS: SECOND LINE THERAPY

Advantages and limitations of second-line agents

	Splenectomy	Rituximab	TPO-RAs
Advantages	• High response rate/durable CR • Single treatment • Cost-efficient	• Short course of therapy • ~Easy to access and initiate treatment	• High response rate/durable CR • Option for subcutaneous or oral route
Limitations	• Morbidity/ mortality with surgical procedure • VTE risk (splenic vein thrombosis) • Sepsis	• Lower durable CR; possible need to retreat • Parenteral • Availability • Risk of infusion reactions, HBV reactivation, progressive multifocal leukoencephalopathy (PML)	• Need for continual treatment • Cost • Availability • Eltrombopag: dietary interactions, transaminitis • Romiplostim: weekly injections in clinic, risk of neutralizing antibodies, thrombosis
	Criteria for medical insurance / coverage		

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ITP IN ADULTS: SECOND LINE THERAPY

Remark

".. **Each of these second-line treatments may be effective therapy and therefore the choice of treatment should be individualized** based on duration of ITP, frequency of bleeding episodes requiring hospitalization or rescue medication, comorbidities, age of the patient, adherence, medical and social support networks, patient values and preferences, cost and availability. Patient education and shared decision-making are encouraged. If possible, **splenectomy should be delayed for a least one year after diagnosis** because of the potential for spontaneous remission in the first year. Patients who value avoidance of long-term medication may prefer splenectomy to rituximab. Patients who wish to avoid surgery may prefer a thrombopoeitin receptor agonist (TPO-RA) or rituximab. Patients who place a high value on achieving a durable response may prefer splenectomy or TPO-RAs"

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ITP IN ADULTS: SECOND LINE THERAPY

Summary

- Evaluated second-line therapy in adults including splenectomy, rituximab and TPO-RA
- Consider efficacy (durable response), safety and patient's values and preferences
  - Avoiding surgery – TPO-RA or rituximab
  - Avoiding long-term medication – splenectomy or rituximab
  - Achieving durable response – splenectomy or TPO-RA
- **There is no single second-line treatment that is optimal for all patients with ITP. Choice of treatment based on patient and disease related factors**

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Grazie per l'attenzione