American Society of Hematology

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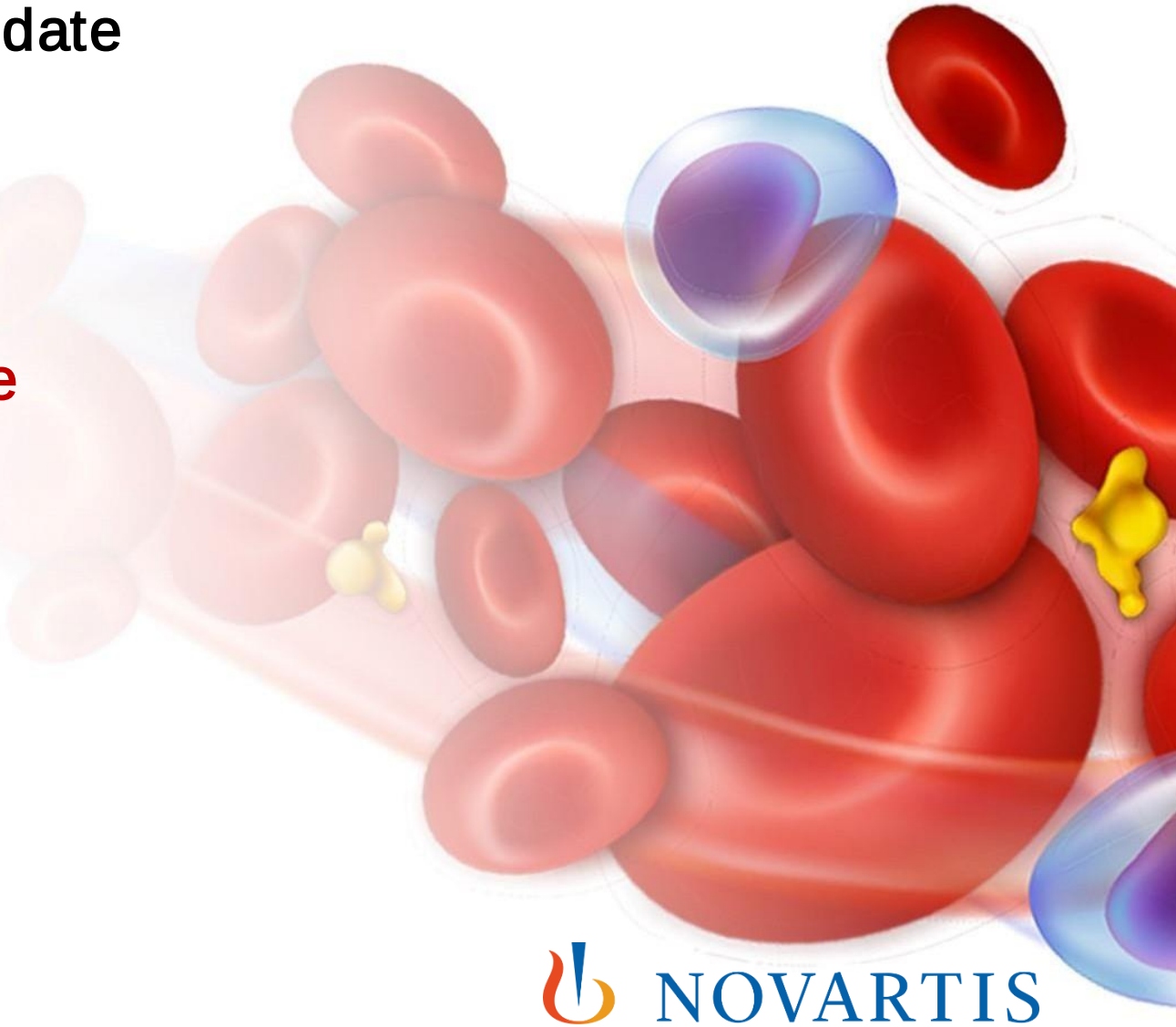
ASH 2019ITP Guidelines Update



Review of the American Society of Hematology 2019guidelines for immune thrombocytopenia

Neunert C, et al. Blood Advances. 2019;.3:3829-66

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Objectives of the 2019 ASH guidelines for ITP

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Goal

- The ITP guidelines are intended to support children and adults with ITP and their health care professionals when making clinical decisions about the management of the disease

Focus of the panel of experts

- Avoiding medication side effects
- Shared decision-making (especially regarding second-line treatment*(*
- Future research should include
  - Standard corticosteroid dosing regimens
  - Patient-reported outcomes
  - Cost analysis evaluations

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Neunert C, et al. Blood Advances. 2019;.3:3829-66

Strength of recommendations and quality of evidence

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Grading of Recommendations Assessment, Development, and Evaluation (GRADE(

Recommendation	For patients	For clinicians
Strong recommendation	Most individuals would want the intervention	Most individuals should receive the intervention
Conditional recommendation	A majority of individuals would want the intervention, but many would not	Different choices will be appropriate for different patients, depending on their values and preferences. Use shared decision-making

Certainty of the evidence	Very low	Low	Moderate	Strong

Guyatt GH, et al., GRADE Working Group. BMJ. 2008;336:924-6.
Neunert C, et al. Blood Advances. 2019;.3:3829-66

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Table 3. Definition of terms in 2019 ASH guideline on ITP

Terms and definitions
Corticosteroid-dependent: Ongoing need for continuous prednisone >5 mg/d (or corticosteroid equivalent) or frequent courses of corticosteroids to maintain a platelet count ≥30 × 10^9/L and/or to avoid bleeding
Durable response: Platelet count ≥30 × 10^9/L and at least doubling of the baseline count at 6 mo
Early response: Platelet count ≥30 × 10^9/L and at least doubling baseline at 1 wk
Initial response: Platelet count ≥30 × 10^9/L and at least doubling baseline at 1 mo
Major bleeding: (1) WHO grade 3 or 4 bleeding, (2) Buchanan severe grade, (3) Bolton-Maggs and Moon "major bleeding," (4) IBLS grade 2 or higher, or (5) life-threatening or intracerebral hemorrhage bleeding
Minor bleeding: Any bleeding not meeting the criteria for "major bleeding"
Newly diagnosed ITP: ITP duration of <3 mo
Persistent ITP: ITP duration of 3-12 mo
Chronic ITP: ITP duration of >12 mo
Remission: Platelet count >100 × 10^9/L at 12 mo

IBLS, ITP Bleeding Scale; WHO, World Health Organization.

Modified Buchanan and Adix bleeding score, overall bleeding severity

Grade		
0	None	No new hemorrhage of any kind
1	Minor	Few petechiae (≤100 total) and/or ≤ 5 small bruises (≤ 3 cm diameter), no mucosal bleeding
2	Mild	Many petechiae (>100 total) and/or > 5 large bruises (>3 cm diameter)
3	***Low Risk* Moderate***	***Blood crusting in nares, painless oral purpura, oral/palatal petechiae, buccal purpura along molars only, mild epistaxis ≤ 5 minutes***
	High Risk* Moderate	***Epistaxis > 5 minutes, hematuria, hematochezia, painful oral purpura, significant menorrhagia***
4	Severe	Mucosal bleeding or suspected internal hemorrhage (brain, lung, muscle, joint, etc) that requires immediate medical attention or intervention
5	Life threatening/ Fatal	Documented intracranial hemorrhage or life threatening or fatal hemorrhage at any site

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Bolton-Maggs and Moon grading (UK)

- no symptoms;
- mild symptoms
  - (bruising and petechiae, occasional minor epistaxis, very little or no interference with daily living)
- moderate symptoms
  - (more severe skin manifestations with some mucosal lesions, and more troublesome epistaxis and menorrhagia)
- severe symptoms
  - (bleeding episodes [epistaxis, melena, and/or menorrhagia] requiring hospital admission and/or blood transfusion— symptoms interfering seriously with quality of life).

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Table I. The immune thrombocytopenic purpura bleeding score assessment.

	Bleeding grade		
Site	0	1	2
Skin [physical examination (PE)]	None	1–5 bruises and/or scattered petechiae	>5 bruises with size >2 cm and/or diffuse petechiae
Oral (PE)	None	1 blood blister or >5 petechiae or gum bleeding that clears easily with rinsing	Multiple blood blisters and/or gum bleeding
Skin (Hx)	None	1–5 bruises and/or scattered petechiae	>5 bruises with size >2 cm and/or diffuse petechiae
Oral (Hx)	None	1 blood blister or >5 petechiae and/or gum bleeding <5 min	Multiple blood blisters and/or gum bleeding >5 min
Epistaxis	None	Blood when blowing nose and/or epistaxis <5 min (per episode)	Bleeding >5 min (per episode)
Gastrointestinal (GI)	None	Occult blood	Gross blood
Urinary (U)	None	Microscopic (+ve dipstick)	Macroscopic
Gynecological (GYN)	None (normal period)	Spotting not at time of normal period	Bleeding >spotting not at time of period or very heavy period
Pulmonary	None	N/A	Yes
Intracranial haemorrhage	None	N/A	Yes
Subconjunctival haemorrhage	None	Yes	N/A

ITP in children

Newly diagnosed ITP in children

Diagnosis of ITP

1.1.A. We recommend:

- Bone marrow examination is unnecessary in children and adolescents with the typical features of ITP (grade 1B)
- Bone marrow examination is not necessary in children who fail IVIG therapy (grade 1B)

1.1.B. We suggest:

- Bone marrow examination is also not necessary in similar patients prior to initiation of treatment with corticosteroids or before splenectomy (grade 2C)
- Testing for antinuclear antibodies is not necessary in the evaluation of children and adolescents with suspected ITP (grade 2C)

Children who are treatment nonresponders

H pylori testing in children with persistent or chronic ITP

2.3.A. We recommend:

- Against routine testing for *H pylori* in children with chronic ITP (grade 1B)

Management of MMR-associated ITP

3.1.A. We recommend:

- Children with a history of ITP who are unimmunized receive their scheduled first MMR vaccine (grade 1B)
- In children with either nonvaccine or vaccine-related ITP who have already received their first dose of MMR vaccine, vaccine titers can be checked; if the child displays full immunity (90% to 95% of children), then no further MMR vaccine should be given; if the child does not have adequate immunity, then the child should be reimmunized with MMR vaccine at the recommended age (grade 1B)

Management strategies considered by the panel of experts

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- Observation
- Corticosteroids
- IVIG
- Anti-D immunoglobulins
- TPO-RAs
- Rituximab
- Splenectomy

The panel of experts highlight the lack of data from randomized trials to assist physicians with clinical decision-making about the management of ITP patients

Emerging ITP therapies introduced after 2017 were not considered

Neunert C, et al. Blood Advances. 2019;.3:3829-66

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IVIG, intravenous immunoglobulin; TPO-RA, thrombopoietin receptor agonist.

Individualized selection of second-line therapy in adults based on shared decision-making ((3/3

Summary of recommendations
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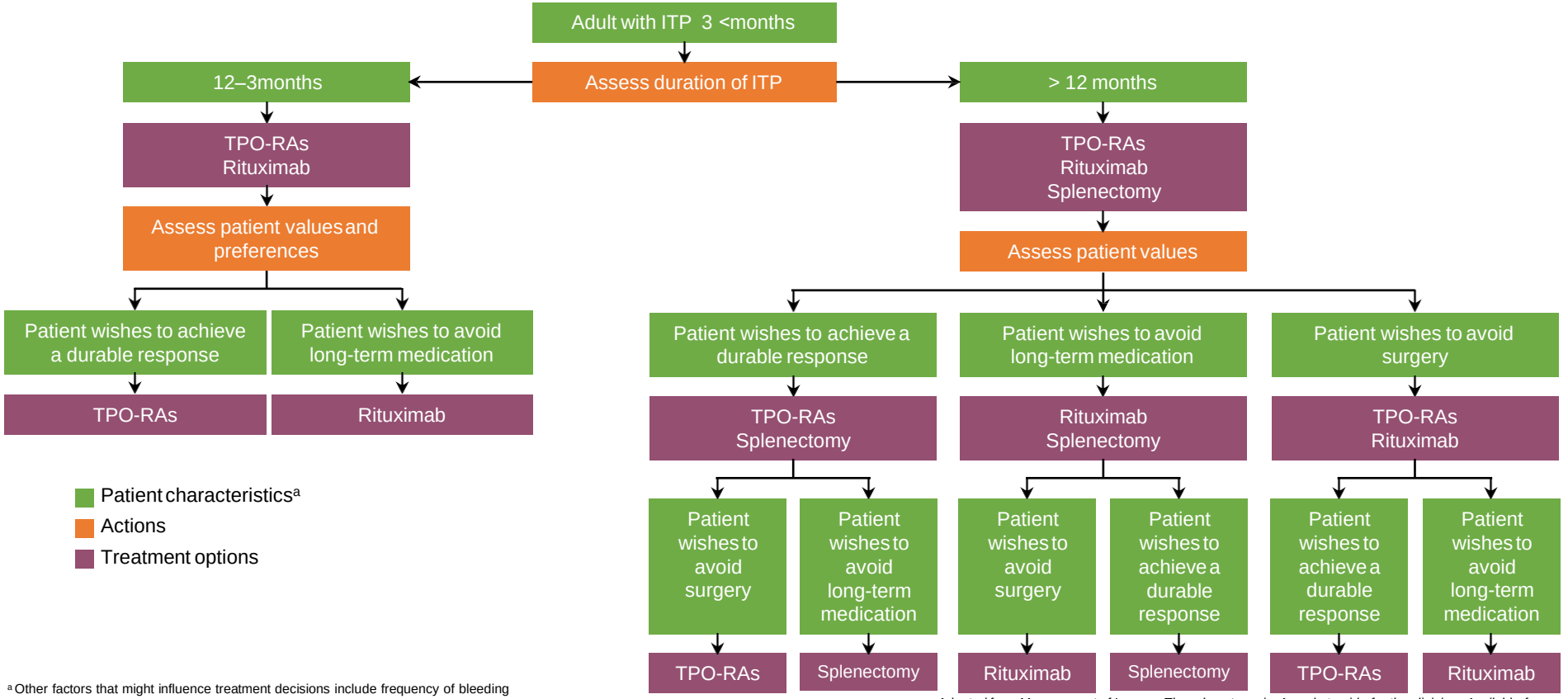

[a] Other factors that might influence treatment decisions include frequency of bleeding sufficient to require hospitalization or rescue medication, comorbidities, compliance, medical and social support networks, cost, and availability of treatments.

Adapted from Management of Immune Thrombocytopenia. A pocket guide for the clinician. Available from: www.hematology.org/Clinicians/Guidelines-Quality/Documents/10115.aspx. Accessed 9January .2020

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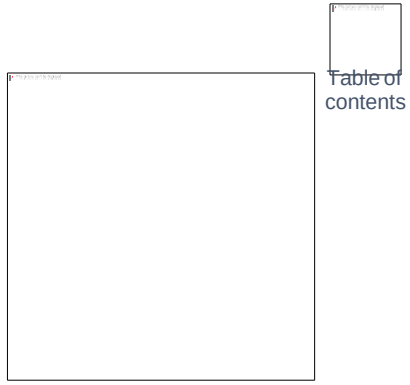

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Management of children with ITP

Newly diagnosed patients

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Outpatient vs inpatient management

Criterion	Management
Newly diagnosed children with platelet count < 20 x 10^9/L who have no or mild skin bleeding	Outpatient management[a] C E
Newly diagnosed children with platelet count ≥ 20 x 10^9/L who have no or mild skin bleeding	Outpatient management[a] C E

[a]For patients with uncertainty about the diagnosis, social concerns, living far from the hospital, and for whom follow-up cannot be guaranteed, hospital admission may be preferable.

Good practice statement

- The referring physician should ensure that the patient has a follow-up with a hematologist within 24–72 hours of diagnosis or disease relapse

Neunert C, et al. Blood Advances. 2019;3:3829-66.

Observation vs treatment

Summary of recommendations
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Criteria	Management
No or minor bleeding	Observation ✓ E rather than treatment with corticosteroids, C E IVIG, or anti-D immunoglobulins ✓ E
Non-life-threatening mucosal bleeding and/or diminished HRQoL	Treatment with corticosteroids; ✓ E prednisone rather than dexamethasone ✓ E Corticosteroids should also be preferred over anti-D immunoglobulins and IVIG C E if recommended dose and duration are applied

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Neunert C, et al. Blood Advances. 2019;3:3829-66.

Corticosteroids: type, dosage, and duration

Summary of recommendations
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At the recommended doses, the panel of experts suggests prednisone rather than dexamethasone

C E

Prednisone	• A short course of ≤ 7 days ✓ E • Dosage of 2–4 mg/kg/day (maximum 120 mg/day) for 5–7 days
Dexamethasone	• Dosage of 0.6 mg/kg/day (maximum 40 mg/day) for 4 days C E

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Management of children with ITP

Patients who are refractory to corticosteroids

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Second-line therapeutic options compared one against the other

Children who have non-life-threatening mucosal bleeding and/or diminished HRQoL

- The panel of experts suggests
  - TPO-RAs rather than rituximab C E
  - TPO-RAs rather than splenectomy C E
  - Rituximab rather than splenectomy C E

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Eltrombopag vs romiplostim ((2/3

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Patients with ITP *duration* ≥ 3 months

- For treatment with TPO-RAs, the ASH guidelines suggest **eltrombopag or romiplostim** C E

→ **Shared decision-making – patients may prefer**

- A daily oral medication (eltrombopag)
- A weekly subcutaneous injection (romiplostim)

Cost considerations

Cost analysis studies have shown that **eltrombopag is less expensive than romiplostim**

- In a US analysis of primary trial results, it was estimated that the total costs of eltrombopag and romiplostim are USD 66,560 and USD 91,039, respectively, while eltrombopag was shown to be associated with fewer bleeding events
- In a UK analysis, eltrombopag was shown to be less expensive than romiplostim but the 2 drugs were equally effective

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Highlights of the 2019 ASH guidelines for ITP

1

The guidelines provide new recommendations for the use of corticosteroids, including guidance on when they should be used, for how long, who should take them, and how use should be monitored .

There is also guidance on keeping the course of treatment as short as possible, since long-term corticosteroid use can cause harm without additional *benefit*.

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Highlights of the 2019 ASH guidelines for ITP

2- The guidelines review other therapies that may be given if initial therapy is not effective, including rituximab, TPO-RAs, and splenectomy

- The guidelines recommend delaying splenectomy for at least 1 year due to the life-long side effects that can result from the procedure

- For treatment with TPO-RAs and rituximab, the guidelines recommend considering differences in the route of administration, duration of disease, short vs long-term treatment, and patient comorbidities to make the best choice for the individual patient. Shared decision-making is highly encouraged

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Highlights of the 2019 ASH guidelines for ITP

The guidelines emphasize the need to avoid unnecessary treatment in children with ITP.

Specifically, the guidelines can be used to help physicians to avoid giving interventions and treatments that have little evidence of success and may have side effects that outweigh the potential *benefits*.

This is important because bleeding is minimal in the majority of children with ITP and the disease often resolves without treatment.

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