IN THE NAME OF GOD

UPDATE ON ITP

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SPOTLIGHT ON ITP

Immune Thrombocytopenia is the commonest cause of thrombocytopenia in young children.

A thorough history, examination and peripheral smear evaluation is central to diagnosis.

The recent American Society of Hematology **guidelines 2019**, has shed light on diagnosis and management based on latest available literature.

Immune thrombocytopenia (ITP) is an acquired autoimmune disease characterized by a low platelet count (<100,000/mm3) due to 'antibody mediated' destruction of platelets and impaired mega-karyopoiesis with peak incidence in 2-5 years old .

Despite being the commonest cause of thrombocytopenia in children, there have been more controversies than consensus in its diagnosis and management.

American Society of Hematology 2019 guidelines for immune thrombocytopenia

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We herein delineate the important aspects of these guidelines.

Table I Highlights of Updates From the Previous ASH, 2011 and Current ASH, 2019 ITP Guidelines

	ASH, 2011 guidelines	*ASH, 2019 guidelines*
Outpatient *vs* Inpatient management	No recommendation	A child with newly diagnosed ITP with no/mild bleeding may be managed at home irrespective of the platelet count.* However, if the diagnosis is uncertain or follow up is difficult, admission is preferable.
Treatment *vs* observation	A child with newly diagnosed ITP with no/mild bleeding may be managed with observation alone, irrespective of platelet count	In a child with newly diagnosed ITP with no/mild bleeding, observation is preferable to pharmacotherapy (steroids,* IVIG,# anti-D Ig#) irrespective of platelet count
First line pharmacotherapy	Single dose IVIG (0.8-1 g/kg) or a short course of corticosteroids can be used. IVIG can be used if a more rapid rise in platelets is required.	Short course of steroids (<7 d) is preferred over IVIG or anti D therapy*
Steroid type and duration as first line pharmacotherapy	No steroid type or dose is preferred over the other	A short prednisolone course (2-4 mg/kg/d; max. 120 mg/d) of 5-7 d is preferable to dexamethasone (0.6 mg/kg/d; max. 40 mg/d) for 4 d*
IVIG *vs* anti D as first line pharmacotherapy	Grade of recommendation for use of IVIG as first line (grade 1B) is stronger than Anti-D Ig (grade 2C)	Either IVIG or anti-D Ig may be used*
Newly diagnosed ITP who are treatment non-responders (*i.e.* non responsive to first line therapy)/Persistent ITP/ Chronic ITP	Rituximab or high dose dexamethasone may be used for treatment both of which are preferred over splenectomy.	In children with non-response to first line therapy, TPO receptor agonists are preferred over rituximab which is preferred over splenectomy.

IMMUNE THROMBOCYTOPENIC PURPURA

DEFINITIONS & TREATMENT PLANS

ITP is termed acute/newly diagnosed, if lasting less than 3 months; persistent, if lasting 3-12 months, and chronic, if persisting beyond 12 months.

Majority of children **(60-75%) have acute ITP** that resolves within 2-3 months of diagnosis, regardless of therapy.

As per the latest ASH 2019 guidelines, routine testing for bone marrow aspirate/bone marrow biopsy (Grade 1B), anti-nuclear antibody (grade 2C) and *H. pylori* (grade 2C) is not recommended unless there are clinical pointers.

The utility of screening all ITP patients for **CVID, hepatitis C, HIV and Hepatitis B** is still unclear.

Thrombocytopenic syndromes (like Wiskott–Aldrich syndrome) and CVID are important masqueraders of immune thrombocytopenia.

While a detailed family history and a meticulous examination may diagnose these mimickers at outset, at times these syndromes are recognized later in cases mislabelled as ITP, who fail to respond to all therapy

ITP

TREATMENT ROADMAP

Clinically, ITP is characterized by bleeding events that show no linear correlation with the severity of thrombocytopenia.

Most of children (62-74%) with ITP spontaneously remit within a year. Therefore, the decision regarding use of platelet enhancing therapy should be based on **multiple factors**

access to care, **patient and provider preferences**, risk of bleeding, duration of disease, co-morbidities and age at presentation.

In newly diagnosed ITP with no/mild bleeding, the ASH 2019 guidelines recommend observation over treatment irrespective of the platelet count. Moreover, they suggest observation at home is preferable to hospital admission. However, they add that if a decision to observe on outpatient basis is made, it is desirable for the patient to be seen by a pediatrician within 24-72 hours

ITP

TREATMENT ROADMAP

Moreover, they suggest observation at home is preferable to hospital admission. However, they add that if a decision to **observe** on outpatient basis is made, it is desirable for the patient to be seen by a pediatrician **within 24-72 hours .**

In those set-ups, where patient follow-up is uncertain due to social/financial concerns or residence is in remote areas which are far from hospitals, admission to the hospital and treatment is preferable.

Similar recommendations have been stated by the Joint working group (JWG) of several European hematology societies (Germany, Austria, and Switzerland) published in 2018, wherein special emphasis has been placed on the **patient's choice of therapy**

ITP

- In children with newly diagnosed ITP who have no or minor bleeding, the ASH guideline panel suggests observation rather than corticosteroids (conditional recommendation based on very low certainty in the evidence of effect)

- In children with newly diagnosed ITP who have no or minor bleeding, the ASH guideline panel recom- mends observation rather than IV immunoglobulin (IVIG) (strong recommendation based on moderate certainty in the evidence of effect

PRIORITIES FOR RESEARCH

Comparative effectiveness trials of first-line agents that account not only for efficacy but also for cost, side effects, and patient- reported outcomes;

- Assessment of impact of treatments on patient-reported out- comes such as fatigue, HRQoL, and bleeding;
- Cost analysis of second-line therapies;
  Determination of patient and parent preferences that influence

treatment selection;

- Biologic studies to predict treatment response and investigate the effect of agents on immunomodulation;
- Randomized trials or observational trials to assess long-term outcomes;
- Additional studies of novel second-line agents in children.

ITP

DEBATES AND DILEMMAS

Minimizing the risk of hemorrhage and decreasing the long-term side effects of treatment are the goals of therapy.

Treatment is guided by the severity of bleeding rather than on the platelet count.

The ASH 2019 guidelines have defined major bleeding as any one of the following

(*i*) WHO grade 3 or 4 bleeding

(*ii*) Buchanan severe grade

(*iii*) Bolton-Maggs and Moon major bleeding,

(*iv*) IBLS grade 2 or higher,

(*v*) life-threatening bleeding or intracerebral hemorrhage.

Minor bleeding is any bleeding not meeting the criteria for major bleeding. Adolescents with ITP are treated as per pediatric guidelines

SEVERE BLEEDING EVENTS IN ADULTS AND CHILDREN WITH PRIMARY ITP
MMUNE THROMBOCYTOPENIA: A SYSTEMATIC REVIEW

adults and children with immune thrombocytopenia (ITP)

The frequency of bleeding events across a broad range of adults and children with ITP has not been established.

Furthermore, the measurement of bleeding poses significant challenges:

- First, patients commonly experience bruising, purpura and petechiae, which are difficult to quantify;
- second, the criteria used to define ‘severe’ bleeding have not been standardized
- third, life threatening bleeding such as intracerebral hemorrhage (ICH) is relatively uncommon.

Neunert C, Noroozi N, Norman G, Buchanan GR, Goy J, Nazi I, Kelton JG, Arnold DM. Severe bleeding events in adults and children with primary immune thrombocytopenia: a systematic review. J Thromb Haemost 2015; 13: 457–64.

Table 3 ITP-specific bleeding measurement tools used in prospective studies (n = 10)

Bleeding tool	Experience (Studies (patients, n))	Population	Description	Measurement properties*
Buchanan [13]	11 (480)	Pediatric	Grades (none, minor, mild, moderate, severe) for three anatomical sites, and overall	Good reliability and validity
Mazzucconi [37]	4 (201)	Adult	Severity grades 0–4, blood loss with or without sequelae	Not reported
Page [24]	4 (187)	Pediatric and adult	Ordinal scale from 0 (no bleeding) to 2 (more marked bleeding) at 11 anatomical sites, no overall score	Good reliability and validity
Buchanan [35]	2 (143)	Pediatric	Ordinal bleeding score 0 (definitely no new bleeding) to 4 (bleeding with a drop in hemoglobin> 1 g dL^{-1})	Not reported
Godeau [36]	1 (122)	Adult	Severity scores at seven anatomical sites plus age and overall	Not reported
Khellaf [23]	2 (120)	Adult	Severity scores for six anatomical sites and age, and overall	Not reported
Zhou [38]	1 (86)	Pediatric and adult	Ordinal scale from 1 to 4	Not reported
Dutch national pediatric ITP protocol [39]	1 (60)	Pediatric	Ordinal bleeding score 0 (none) to 4 (life threatening bleeding)	Not reported
Blanchette [34]	1 (53)	Pediatric	Bleeding grade: moderate or severe	Not reported
SMOG score [10]	1 (50)	Adult	Each of three anatomical sites (skin, mucosa, body organ) are graded from 0 to 4 based on explicit descriptions	Not reported

Table 1 Studies that reported bleeding in prospective studies of children and adults with primary ITP

	Number of studies (%) (N = 118; n = 10 908)
Population (n)	
Adults	5336
Children	5572
How bleeding was reported	
As an efficacy outcome	67 (56.8)
As a safety outcome	12 (10.2)
Other*	39 (33.1)
How bleeding was assessed	
Presence or absence of bleeding only	24 (20.3)
By anatomical site only	37 (31.4)
By severity only	7 (5.9)
By anatomical site and severity	49 (41.5)
Not reported	1 (0.8)
How bleeding information was obtained	
From history	1 (0.8)
From history and physical examination	14 (11.9)
Not specified	103 (87.3)
Bleeding measurement tools	
ITP-specific tool	29 (24.6)
WHO score	5 (4.2)
Adverse events tool (e.g. CTCAE)	3 (2.5)
Thrombosis bleeding assessment tool	1 (0.8)
No pre-existing tool used	80 (67.8)

*As a baseline variable or eligibility criterion. CTCAE, Common Terminology Criteria for Adverse Events.

SEVERE BLEEDING EVENTS PRIMARY ITP

Bleeding is the most clinically important outcome in ITP studies

It is what motivates physicians to institute treatment ; it provokes physician, patient and parental anxiety; and it is an important cause of morbidity and mortality

Our findings show that the rates of ICH were higher in adults than children (1.4% vs. 0.4%) and rates of (non-ICH) severe bleeding were higher in children than adults (20.2% vs. 9.6%)

Severe bleeds may be more common in children because children are more prone to trauma and less likely to have thrombocytopenia detected incidentally (as part of other investigations).

The rate of severe bleeding in children reported in the ICIS II Registry (n = 1106) was 3% however, severe bleeding was defined as requiring hospitalization, requiring a blood transfusion or interfering seriously with quality of life

SEVERE BLEEDING EVENTS IN PRIMARY ITP

The Nordic registry also reported a 3% rate of severe bleeding among children (n = 501) at diagnosis, defined as requiring a blood transfusion .

Our estimate of severe bleeding in children may be higher because of the more liberal definitions applied in primary studies, more frequent assessments in prospective studies and the inclusion of both incident and prevalent bleeds.

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Increasing Observation Rates in Low Risk Pediatric Immune Thrombocytopenia Using a Standardized Clinical Assessment and Management Plan (SCAMP®)

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An observational approach is recommended in newly diagnosed children with ITP at low risk of bleeding; however, there is no standard definition of risk. A SCAMP®, a modifiable practice guideline, was implemented and revised (SCAMP-1 and SCAMP-2) and applied to 71 newly diagnosed patients with ITP.

The Buchanan and Adix bleeding score guided treatment and was modified by stratifying by low and high risk grade 3 bleeding in SCAMP-2.

Observation rates increased from **40% to 74% from SCAMP-1 to SCAMP-2** ($p<0.05$) with no bleeding complications.

We propose a modified bleeding score that increased observation in low risk patients with ITP.

Recently, a group of experts designed

the 'SMOG' bleeding score

to quantify bleeding severity

from different sites:

skin (s), visible mucosa (m)

internal organs (o). A severity grade

from 0 (none) to 5 (fatal)

is assigned for each site and a

cumulative score is calculated

TABLE 1

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

Acute/newly diagnosed ITP

- In a child with newly diagnosed ITP with no/mild bleeding, ASH continues to recommend observation over pharmacotherapy irrespective of the platelet count.
- However, in a child with moderate to severe bleeding and/or a diminished health related quality of life, a **short course of corticosteroids (<7 days) is preferred over intravenous immunoglobulin (IVIG) or anti-D immunoglobulin (anti-D Ig) therapy**
- A short prednisolone course (2-4 mg/kg/day; maximum 120 mg/day) of **5-7 days is preferable to dexamethasone** (0.6 mg/kg/day; maximum 40 mg/day) for 4 days.

Acute/newly diagnosed ITP

- **The European joint working group** (JWG) has also endorsed a shorter course of steroids less **than 2 weeks**, without specifying the preferred type of steroid

- ASH 2019 states that as per limited available data IVIG and anti-D Ig have similar benefits, and both are associated with rare but potential black box warnings. Thus, either of them may be used.

- **In practice, the choice between the three available treatments is usually guided by cost, availability and adverse effects**

Persistent ITP

- If treatment with steroids, IVIG or anti-D Ig has been successful, these options may be used to prevent bleeding as needed, especially in the first **12 months of diagnosis** when the possibility of spontaneous remission is high
- In children with ITP who have non–life-threatening mucosal bleeding and/or diminished HRQoL and do not respond to first-line treatment, the ASH guideline panel suggests the **use of TPO-RAs** rather than rituximab.
- There were reported episodes of infection with the TPO-RAs (4.8%); however, these may be unrelated to the drug, compared with 1.4% seen with rituximab, which are more likely directly attributed to drug use.

CONSIDERATIONS

- Guideline panel determined that there is low-certainty evidence for TPO- RAs rather than rituximab in children with ITP who are unresponsive to first-line treatment.
- Based on the body of evidence, the risks associated with TPO-RAs were thought to be low and the potential benefits high.
- The panel also placed high value on avoiding immunosuppression in the pediatric population, especially given that many children are likely to undergo spontaneous remission.
- A single course of rituximab is similar in cost to 1 month of low-dose TPO-RA use; however, given the need for ongoing TPO-RAs over time rituximab, will cost less. TPO-RAs were thought to be acceptable to stakeholders; however, there may be high patient variability in terms of goals and feasibility

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Type: E-Poster Presentation
Session title: Platelet disorders

Background

Immune Thrombocytopenic Purpura (ITP) is an immune mediated disorder characterized by an isolated decrease of the platelet count. Symptoms are usually mild, with cutaneous and/or mucosal bleeding, rarely serious symptoms occur, such as intracranial hemorrhage. ITP is classified into 3 groups: newly diagnosed (within 3 months from the onset), persistent (3 to 12 months from the onset), chronic (after 12 months from the onset). Infusion of immunoglobulin or steroid therapy are the first line of treatment. Current guidelines suggest the use of thrombopoietin receptor agonists (TPO-RAs), such as Eltrombopag (EPAG), in patients with persistent thrombocytopenia. They stimulate thrombopoiesis through the activation of the thrombopoietin receptors, furthermore TPO-RAs can influence platelet antibody production and T regulatory cell count. EPAG is an effective and safe therapy, although its use is currently approved in patients with ITP after at least 6 months from the diagnosis. Some studies, in the adult setting, have already described the safety and efficacy of EPAG in patients before the 6th month from the onset (off label use).Currently there are no studies on the use of EPAG in the same setting in a cohort of pediatric patients with ITP.

Aims

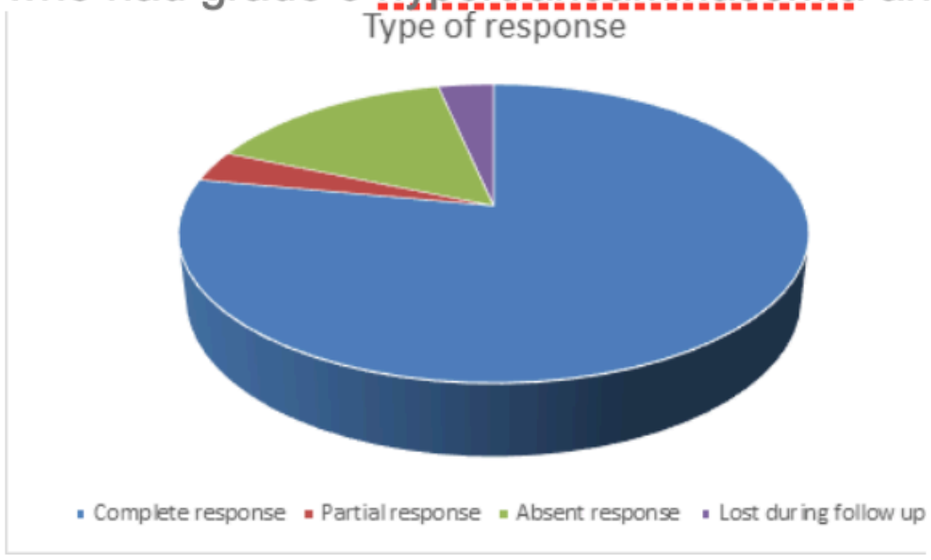
Evaluate the safety and efficacy of the use of EPAG within 6 months from the onset on a cohort of pediatric patients with ITP.

Methods

Study population: 59 patients aged between 1 and 18 years were enrolled from February 2013 and December 2020.

Response evaluation: We evaluated the type of response based on the platelet count: complete if the platelet count was at least > 100.000 in one determination, partial if the platelet count was at least once between 30.000 and 100.000, absent if the platelet count never overcame 30.000.

persistent ITP. 14 patients (23,7%) had at least one adverse event. 3 patients presented with significant thrombocytosis (over 1.000.000) that promptly resolved after a temporary, brief suspension of the treatment. Other adverse events were hypertransaminasemia, nausea, hypoferritinemia with or without anemia. In one patient who had grade 3 hypertransaminasemia and acydosis EPAG was suspended.



Conclusion

This study is, to the best of our knowledge, the first reporting on the use of EPAG in a pediatric population with newly diagnosed or persistent (3-6 months) ITP. Our data highlight the efficacy of this therapy and its safety, with only a small proportion of patients reporting reversible adverse events. Therefore, given the difficulties to treat patients who do not respond to the first line therapy or who have an early relapse, EPAG could be an option.

We believe further studies are needed to explore the use of EPAG in these contexts.

Second-Line Therapies for Children

- In children with ITP who have non–life-threatening mucosal bleeding and/or diminished HRQoL and do not respond to first- line treatment, the ASH guideline panel suggests rituximab rather than splenectomy

- Second-Line Therapies for Children

In children with ITP lasting ≥3 months who have non-life-threatening mucosal bleeding and/or diminished health-related quality of life and do not respond to first-line treatment, the ASH guideline panel **suggests** the following options for second-line therapies presented in the order they should be pursued :

Thrombopoietin receptor agonist (eltrombopag or romiplostim)[1]

Rituximab

Splenectomy[2]

[1] Individual patient preference may place a higher value on the use of a daily oral medication (eltrombopag) or one that requires weekly subcutaneous injections (romiplostim). For pediatric patients, eltrombopag dosing should avoid consumption of calcium containing foods such as dairy products by four hours. This may limit the ability of some children to take this medication.

[2] **If possible, splenectomy should be delayed as long as possible after diagnosis because of the potential for spontaneous remission in the first year.**

Table 1. 2019 ASH and ICR guideline recommendations for paediatric ITP (Cont...)

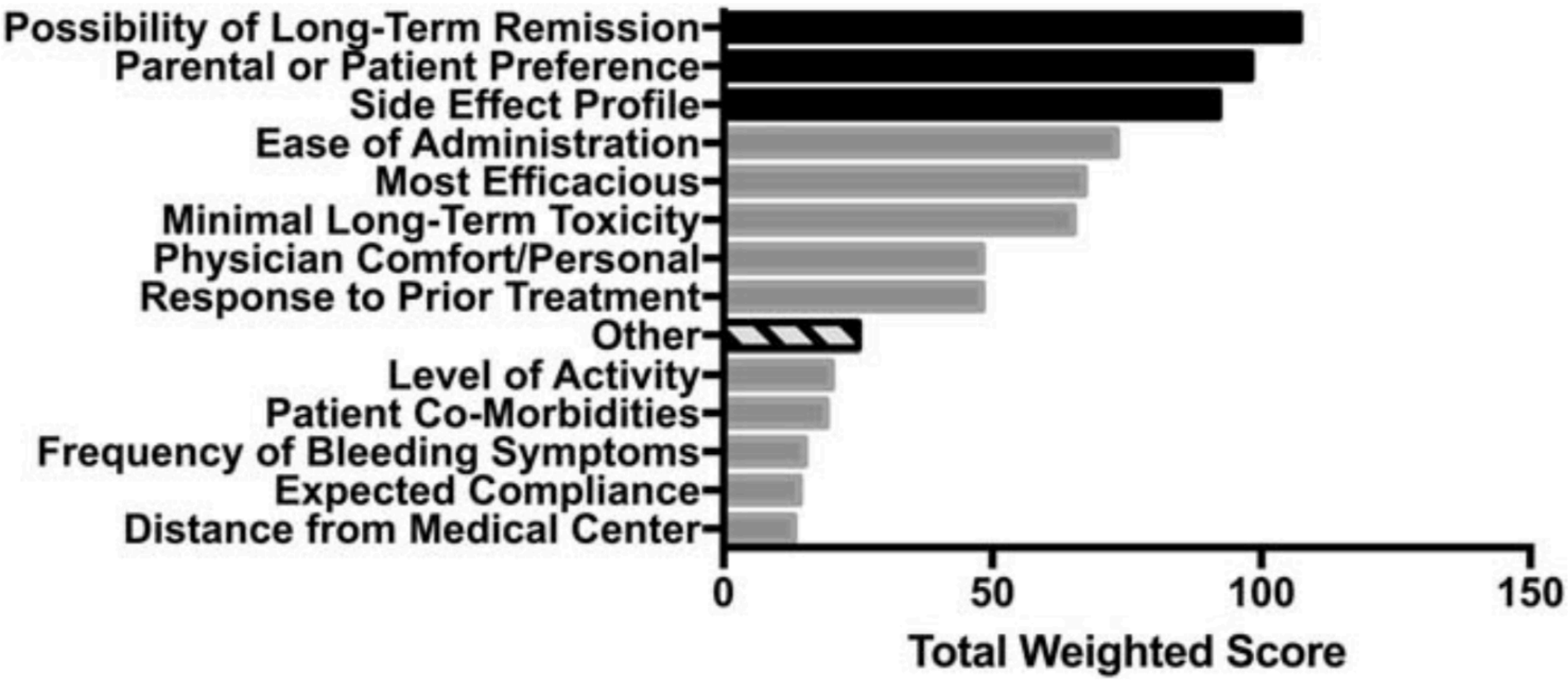
Emergency treatment in children at any stage of their ITP	ICR guidelines recommend:[2] • Combination therapy: platelet transfusions, IV corticosteroids, IVIg – IVIg or steroids can be used to attempt to ensure the most likely and fastest platelet increase – Antifibrinolytics may be given if bleeding continues despite therapy • ICH: consider emergency splenectomy and/or neurological control of bleeding in conjunction with emergency platelet-raising therapy – Medical treatment should never be delayed because of surgical or radiological intervention if possible • Consider TPO-RAs: they may aid acute response in patients and prevent a decrease in platelet count if initial response to emergency therapy is lost

Professor Kühne summarised by reminding attendees "ITP is a diagnosis of exclusion and there is still an algorithm

Table 1. 2019 ASH and ICR guideline recommendations for paediatric ITP (Cont...)

Subsequent investigation of children with persistent or chronic ITP	ICR guidelines recommend:[2] 1. Reassess diagnosis – repeat history, physical examination, complete blood count and blood smear 2. No response to treatment at 3–6 months – if no spontaneous platelet increase perform bone marrow aspiration, biopsy and/or cytogenetics 3. No response to treatment before 3–6 months within expected timeframe – bone marrow aspiration, biopsy, cytogenetics 4. Bone marrow biopsy is not indicated prior to further therapy (e.g. with a TPO-RA) unless the diagnosis is uncertain 5. Additional evaluation – could it be lupus/other autoimmune disease, a chronic infection, complex immunodeficiency disease, inherited thrombocytopenia or bone marrow failure syndrome? 6. In the setting of increasingly difficult-to-treat persistent or chronic ITP consider including bone marrow examination in the re-evaluation of the diagnosis

- Rituximab (36%)
- Romiplostim (26%)
- Eltrombopag (17%)
- Oral Immunosuppressants (16%)
- Splenectomy (3%)
- Dapsone (3%)



Grace et al., AJH 2018

- **Clinical Characteristics and Quality of Life of Children with ITP Starting Second Line Treatments: Data from the ITP Consortium of North America ICON1 Study, ASH 2016**
  - Physician assessment of patient HRQoL was similar to the child and parent proxy report of HRQoL
  - Longer duration of ITP was associated with a better HRQoL

- **Health Related Quality of Life and Fatigue Improve on Second Line Treatments in Pediatric Immune Thrombocytopenia (ITP), ASH 2017**
  - All second line treatments appear to significantly improve HRQoL in ITP
  - Fatigue scores were less affected by second line treatment

What we really need to know:

- True severity of disease or risk of bleeding
- Negative impact of drug side effects
- Cost of medications
- Priorities of the patients and families

- **Impact of the disease and treatment on the patient**

ICON 2 CONCLUSIONS

- Evidence is lacking to guide management of pediatric ITP
- Physicians often rely on experience to determine treatment approaches
- Application of patient-related outcomes and understanding physician decision-making can help to merge evidence with experience

RESEARCH STRATEGIES

- Health- related quality of life assessment
- Cost analysis
- Comparative effectiveness
  - Direct comparison of strategies
  - Balances benefits and harms
- Qualitative methods
- Biology correlates

THANK YOU FOR YOUR TIME