Associazione Italiana Ematologia Oncologia Pediatrica

Working Group "Coagulative Disorders"

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Consensus Conference
Recommendations for management of newly diagnosed and persistent Immune TrombocytoPenia (ITP) in children

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1. Abbreviations

AIEOP Associazione Italiana di Ematologia ed Oncologia Pediatrica
AIHA Auto-Immune Hemolytic Anemia
ALPS Autoimmune LymphoProliferative Syndrome
ANA Anti-nuclear antibody,
Anti-D anti-D Immunoglobulin
ASH American Society of Hematology
CFS chronic fatigue syndrome
CR Complete response
DAT direct antiglobulin test
i.v. intra-venous
Fab Fragment Antigen Binding
FDA Food and Drug Administration
HD DXM high dose desametason
Hp Helicobacter pylori
ICIS Intercontinental Cooperative ITP Study Group
ITP Immune ThrombocytoPenia
IVIg Intra-venous Immunoglobulins
IWG International Working Group
MMF mycophenolate mofetil
MMR measles mumps rubella
m-PDN methyl-prednisolone
mTOR mammalian target of rapamicin
MYH9 Myosin heavy chain 9
NTDT Non–transfusion-dependent thalassaemia
OPSI overwhelming post splenectomy infection
OR Odds Ratio
PCR Polymerase Chain Reaction
PR Partial response
QoL Quality of life
SLE systemic lupus erythematosus
TCR T-cell receptor
TPO thrombopoietin
T-reg regulatory T cells

2. Methodology

The Recommendations for newly diagnosed and persistent Immune Thrombocytopenia (ITP) in childhood have been prepared by the "Coagulation Defects" Working Group of AIEOP (Associazione Italiana di Ematologia ed Oncologia Pediatrica) to update the previous document (http://www.aieop.org/web//?q=lineeguida.html).
The document contains shared information, available on AIEOP website and are intended to help Physicians and Health workers to manage children with new and or persistent ITP.

Methods

Representatives from 13 AIEOP centers participated in the "Acute and persistent ITP Committee". Issues to be addressed in the Recommendations were identified by the whole Committee; each topic was developed by a subgroup in a single document, which included a brief description of the state-of-the-art knowledge, followed by specific recommendations.
In order to draw up the pre-guideline documents, the authors extracted evidence from the literature included in the Medline database (initially searched from January 1, 2008, to December 31, 2018, and then updated in February 2022 during the compilation of the final draft).
All the collected evidence was attributed a strength that was scored using the level of evidence criteria reported below (Ladogana et al, 2017; Barone et al, 2015; Colombatti et al, 2013; De Mattia et al, 2010):
I (strongest) Prospective randomized trial with high statistical value
II Prospective randomized trial with lower statistical value
III Non-randomized study with concurrent control group
IV Non-randomized study with historical control group
V (weakest) Case report(s) with no control group, Guidelines, Metanalysis
The draft has been discussed and modified by the Acute and persistent ITP Committee. A Consensus Conference was held in Turin on July 4, 2019, with the participation of 26 healthcare professional, including pediatric hemato-oncologist, pediatric surgeons, hematologists, nurses, pharmacists, psychologists. During the Conference, specific statements were prepared and then voted. Other 29 pediatric Hemato-oncologists voted the statements via on-line questionnaires.
The strength of consensus was quantified on a 1-9 scale where 1 represented no consensus and 9 represented full consensus regarding the appropriateness and necessity of the practice. For each statement a mean score was calculated. Mean scores from 1 to 3 indicated an inappropriate practice, mean scores from 3.1 to 6.9 indicated uncertain appropriateness and mean scores from 7 to 9 signified an appropriate/necessary practice. The level of agreement among participants, indicating the rate of consensus, was also graded by evaluating the distribution of the standard deviations (SD) within each statement and then dividing the level of agreement into 3 categories:
A: strong agreement, variance < average of the variances);
B: moderate agreement, variance within 2 SD of average variance
C: disagreement, variance > 2 SD of average variance
These consensus recommendations are not intended as standards or fixed rules, but as an instrument to support pediatricians in the diagnostic work-up and initial treatment of newly diagnosed and persistent pediatric patients with ITP. The final decision on management is a responsibility of the attending Physician based on the individual clinical situation.

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3. Definitions
Margherita Nardi

The term "Idiopathic thrombocytopenic Purpura" (ITP) has previously been used to define a disorder with a favorable prognosis, characterized by isolated thrombocytopenia and absence of any evident underlying cause. The estimated incidence of ITP in childhood is 5/100.000, with about one third of cases becoming chronic, particularly in adolescents.
Knowledge about the pathogenesis of ITP has grown, shifting from a traditional concept of platelets destruction mediated by autoantibodies to a more complex immune mechanism, involving platelet production and T-cell mediated effects (Johnsen et al, 2012; Perdomo et al, 2013; Marini et al, 2019).
Due to the relative rarity of this disease, comparison among different clinical studies would be fundamental to understand the epidemiology, the clinical course, and the response to different treatment, but, until recently, definitions and clinical criteria varied largely among studies, making results evaluation very difficult (Ruggeri et al, 2008).
In 2007 an attempt of standardization of terminology was made by an International Working Group (IWG) of experts, whose results were subsequently published (Rodeghiero et al, Blood 2009). Afterwards, new definitions established by IWG have been widely accepted, both for adult and for childhood ITP and they are currently used as standard tool in clinical studies (Rodeghiero et al, 2009; Provan et al, 2010; Grace et al, 2012). Therefore, we decide to adopt the IWG definitions.

Definition of ITP
The acronym ITP is preserved, due to the widespread and historical value. The term "idiopathic" is replaced with "**immune**", to indicate the underlying immune-mediated mechanism (Perdomo et al, 2013, Marini et al, 2019). Moreover, on a pathogenetic point of view, "idiopathic" should be replaced with "primary", to indicate the absence of any evident promoting cause of thrombocytopenia. In fact, the distinction between primary and secondary thrombocytopenia is relevant, being the diagnosis of primary thrombocytopenia an exclusion one. Secondary forms include thrombocytopenias due to an underlying disease (i.e., HIV, H. Pylori infection, autoimmune diseases) or a drug exposure (quinine, heparin). The name of associated disease is usually indicated, when known (i.e.: quinine-induced or HIV-associated thrombocytopenia). Fetal and neonatal alloimmune thrombocytopenia, as well as post-transfusional thrombocytopenia, should maintain their qualification.
"T" and "P" are maintained for **ThrombocytoPenia**, while the term "purpura" is no longer used, considering that in children with ITP bleeding signs may be absent or minimal (Neunert et al, 2013; Arnold 2015).
Thrombocytopenia is defined as a platelet count lower than 100 x 10^9/L. Previously, a threshold of 150x10^9/L was used, but a prospective study showed that in a group of otherwise healthy subjects with a platelet count between 100 and 150 x10^9/L, the 10-year probability of developing more severe thrombocytopenia (< 100x10^9/L) was only 6.9% (Stasi et al, 2006). Moreover, in some non-Western populations platelet counts between 100 and 150 x 10^9/L are frequently observed in healthy people (Bounid et al, 2018).

Phases of ITP
The previous definition of "acute" ITP, which was used to define a self-limited illness lasting for a short period, should be replaced by the term "**newly diagnosed**", according with IWG indications (Rodeghiero et al, 2009). New diagnosed ITP indicates an ITP lasting up to 3 months.
ITP lasting between 3 and 12 months is called "persistent ITP". This definition identifies a group of ITP patients who have not achieved a remission or who have experienced a relapse, within 1 year

from diagnosis. The term "persistent" better underlines that chances of spontaneous remissions are still significant during the first year (Stasi et al, 1995; Imbach et al, 2006).
The term "**chronic**" is used for ITP lasting for more than 12 months.

ITP severity

Severity is defined, according IWG criteria, on the basis of clinical features, regardless of the platelet count (previously, a platelet count below $20x10^9$/L). A severe ITP is characterized by the presence of relevant bleeding at presentation, defined as epistaxis (5 to 15 minutes duration), gastrointestinal bleeding, other mucosal bleeding requiring hospital admission and/or blood transfusions (Neunert et al, 2008, Rosthøj et al, 2003). Severe ITP makes treatment mandatory, or in case of the appearance of new hemorrhages subsequently, requires a re-treatment with different drugs or different doses. A retrospective study reclassified according IWG criteria ITP patients seen at a single pediatric centre over 7 years. The number of severe ITP resulted 77.4% using historical definition, and 33.7% according IWG definition (Grace et al, 2012).

Response to treatment

The response to treatment is defined on a quantitative platelet basis together with a bleeding outcome. IWG defines: "**Complete response**" in case of **resolution of bleeding symptoms, and a platelet count at least 100 x 10^9/**L; **"Response" in case of no clinically relevant bleeding and platelet count between 30 and 100 x10^9/L, at least doubling of the baseline count**; "**No response" when platelet count is lower than 30 x10^9/L or less than doubling baseline count or continued clinically relevant bleeding** (Rodeghiero et al, 2009; Buchanan et al, 2002).
The definition of "Refractory" ITP is quite controversial in childhood.
IWG defines as "Refractory" ITP patients who fulfill the following criteria: 1) have failed to achieve at least a remission after splenectomy (or have relapsed post- splenectomy); 2) have severe ITP, such as to require treatment to minimize bleeding risk; 3) have ITP diagnosis further confirmed (Rodeghiero 2009). These criteria do not fit children properly - as also underlined by IWG, who did not reach a consensus about it - due to the limited use of splenectomy in childhood (Chaturvedi et al, 2018; Provan et al, 2010). Moreover, splenectomy is almost exclusively performed in chronic ITP, making the definition of "refractory" inapplicable to newly diagnosed or persistent ITP.
Some Authors propose to define as "refractory" children with severe ITP who have failed first line treatment (steroid and IVIg), and, if performed, splenectomy (Grace et al, 2012).
Considering also the results obtained with new ITP treatment (TPO mimetics), it seems correct to **define refractoriness in childhood ITP specifying the failed therapy** (refractory to…).

Recommendations

1. For childhood ITP the consensus panel recommends to adopt the IWG definition for ITP preserving the acronym ITP, replacing I (idiopathic) by **Immune**, T and P (purpura) by **ThromboCytoPenia**, and thrombocytopenia defined as a **platelet count below 100 x 10^9/L (EO- Very low quality 8.2-A**)
2. For childhood ITP the consensus panel recommends to adopt the IWG definition for phases of ITP : "**newly diagnosed**" ITP indicating acute ITP within 3 months from onset, "**persistent"** ITP indicating an ITP **lasting between 3 and 12 months** and "**chronic"** ITP indicating ITP **lasting more than 12 months (EO- Very low quality 8.6-A).**
3. For childhood ITP the consensus panel recommends adopting the IWG definition for severity of ITP defining a **severe ITP on the basis of clinical features regardless of platelet counts**, as:

the presence of relevant bleeding at presentation, such to make treatment mandatory, or the appearance of new hemorrhages subsequently, requiring a re-treatment with different drugs or different doses **(EO- Very low quality 8.0-A)**

4. For childhood ITP the consensus panel recommends adopting the IWG definition for response to treatment, based on a quantitative platelet count together with a bleeding outcome, defining:

   Complete response as resolution of bleeding symptoms, and a platelet count at least 100 x 10^9/L.

   Response as no clinically relevant bleeding and platelet count between 30 and 100 x10^9/L, at least doubling of the baseline count.

   No response as platelet count lower than 30 x10^9/L or less than doubling baseline count or continued clinically relevant bleeding **(EO- Very low quality 7.9-B)**

5. The consensus panel underlines that IWIG criteria for defining refractory ITP cannot be adopted for newly diagnosed and persistent ITP in childhood and suggests at this time to define "**refractory**" ITP as a child with severe IT who has **failed first line treatment** (steroid and IVIg), and, if performed, (splenectomy **or other** immunosuppressant agents), by **specifying the failed therapy (refractory to….)** **(EO- Very low quality 7.8-A)**

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4. Etiology and pathogenesis
Giovanni Carlo Del Vecchio, Giuseppe Lassandro e Paola Giordano

Thrombocytopenia in pediatric newly diagnosed ITP has a heterogeneous etiology for different changes in the immune system pathway. These homeostatic anomalies give different repercussions on the duration of illness and on the response to therapies. These elements are not immediately and completely evident at the time of diagnosis. The history of pediatric ITP is, therefore, different of adult ITP (Cines et al, 2009; Johnsen 2012; Kistangari et al, 2013; Swinkels et al, 2018).
In ITP the normal life cycle of platelets is altered by immune factors that can interfere with multiple aspects of this process, including the production and the clearance phase, with a consequent reduction in the circulating number of platelets (Swinkels et al, 2018).

Risk factors
Genetic: see chapter 7.
Environmental: the relationship between infections and ITP, especially in children, has been known (Cines et al, 2009 A). Some infections are the basis for secondary forms of ITP: Helicobacter pylori (Russo et al, 2011), hepatitis C (Zhang et al, 2009), HIV (Nardi et al, 2007) but even in the so-called primary forms it is not excluded that an infectious agent may trigger a real autoimmune response.
Among the favoring factors other disorders may be included such as autoimmune diseases, lymphoproliferative diseases, drugs, transfusions, etc. (Cines et al, 2009 B).

Etiology
Autoantibodies: in many, although not all, cases of ITP it is possible to find autoantibodies especially towards platelet glycoprotein (GP) IIb / IIIa (McMillan et al, 1987) which should not be confused with the IgG associated with platelets (PAIgGs) that can be found unspecifically in each thrombocytopenia without revealing an autoimmune condition (George 1990).
Although it is not completely clear how these antibodies are generated, their effects on clearance and platelet production are now well elucidated: autoantibodies can increase platelet clearance through splenic macrophages and dendritic cells, complement deposition and platelet apoptosis, but also reduce platelet production by megakaryocytes.
B lymphocytes and CD4 + T lymphocytes: the presence of B lymphocytes producing anti-platelet antibodies has been demonstrated in biological samples from different sources (peripheral blood, spleen, bone marrow) (4). Their action is made more efficient by the action of CD4 + T lymphocytes and many data today show that many populations of "helper" (Th) T lymphocytes such as follicular Th1 / Th17 / Th22 / Th contribute to the pathogenesis of ITP similarly to the profiles of polarization of other forms of autoimmune diseases (Swinkels et al, 2008). However, not all patients have platelet-reactive B lymphocytes, suggesting other mechanisms of autoimmunity such as that mediated by CD8 + T lymphocytes.
CD8 + T lymphocytes: association studies show that subjects with ITP have ratios in favor of CD8 + T lymphocyte subsets or present with cytokine polymorphisms related to CD8 + T lymphocytes. It has been shown that CD8 + T lymphocytes can directly lysate platelets, induce platelet apoptosis and inhibit megakaryocyte thrombopoiesis (Swinkels et al, 2008).
Regulatory T lymphocytes: the importance of regulatory T lymphocytes (Tregs) in the pathogenesis of ITP is due to their reduced number and function in affected subjects and indicates how the loss of tolerance is essential in ITP (Swinkels et al, 2008).
Other immune cells: several other immune cells (e.g. neutrophils, CD16 + monocytes, NK etc.) have been studied in various ways in ITP (Swinkels et al, 2008).

Mechanisms involved in platelet clearance

FcãR-mediated platelet destruction: Fcã receptors mediate various functions including phagocytosis, antibody dependent cellular cytotoxicity and cytokine release (Nagelkerke et al. 2004) and their involvement in the pathogenesis of ITP has long been known and is among other things demonstrated by the therapeutic efficacy of Ig i.v. (Swinkels et al, 2008). When the Ig i.v. they are not effective, this can be traced back to specific polymorphisms of FcãR (Heitink-Polle et al, 2016).
However, there are mechanisms independent of Fcã receptors**.**

FcãR-independent platelet destruction: recent studies in animals allowed us to hypothesize that antibodies to GPIb can induce platelet degranulation and consequent desialization of the glycans of the platelet membrane (Jansen et al, 2012) with consequent attachment of the platelets by the Ashwell-receptor. Morrel (AMR) of hepatocytes and therefore acceleration of platelet clearance (Li et al, 2015). Among other things, platelet desialization correlates with the lack of response to first-line treatments (Tao et al, 2017).

C reactive protein (PCR) and reactive oxygen species (ROX): the role of PCR in the pathogenesis of ITP has recently been highlighted (Kapur et al, 2015): in subjects affected by ITP with high PCR, a increase in platelet phagocytosis in vitro and in vivo in the presence of anti-platelet antibodies and this could explain the aggravation of thrombocytopenia during infection.
The role of ROX was predicted in an HIV-related ITP model (4). In this model, the ROX induced by anti-platelet antibodies can directly lysate the platelets with a mechanism independent of the complement and involving the platelet NADPH system. It should be noted that dexamethasone could act precisely through the inhibition of NADPH oxidase (4).

In conclusion, from this brief examination of the etiopathogenesis of ITP, a less clear-cut limit emerges between primary and secondary forms as even in the so-called primary forms there must be an initial event that stimulates the immune response through antigenic mimicry or stimulation of the exposure of platelet antigens.
Fortunately, many pediatric subjects develop only a transient form of platelet-penia which probably resolves with the clearance of viral antigens without the development of sufficient CD4 + T lymphocytes which determine a perpetuation of the autoimmune response typical of the chronic forms more frequent in the adult (Swinkels et al, 2008).
In the future, it is hoped that new studies will provide further data on the mechanisms underlying the development of ITP, providing further therapeutic opportunities, especially for so-called “refractory” cases.

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5. Classification of bleeding symptoms and evaluation of bleeding risk
Emilia Parodi

Introduction

Bleeding signs and symptoms in children with ITP can range from none or minimal (eg, several small groups of petechiae or small bruises) to severe and life-threatening (eg, intracranial hemorrhage, ICH, or severe gastrointestinal, GI, or genitourinary bleeding) which are fortunately very infrequent. At presentation, more than half of affected children have only **cutaneous bleeding** (also referred to as **"dry" purpura**). **Mucosal bleeding** (also referred to as "**wet" bleeding**) may be present in as many as 40 percent of children with ITP and typically involves the nasal passages, buccal and gingival mucosa. Less often, mucosal bleeding may arise from the GI, genitourinary, or vaginal tracts. Conjunctival or retinal hemorrhages are infrequently seen. In a large registry study of children with newly diagnosed ITP, the following bleeding manifestations were reported: cutaneous (petechiae, purpura, or bruising) 86 %, oral 19%, nasal 20 %, no bleeding 9%, menstrual, gastrointestinal, or urinary bleeding <3 %. (Zeller et al, 2005, Kühne et al, 2011).

Serious bleeding (defined as epistaxis 5 to 15 minutes duration, gastro-intestinal bleeding, other severe mucosal bleeding requiring hospital admission and/or blood transfusions) develops in approximately 3 percent of children with ITP (Neunert et al, 2015, Neunert et al, 2008, Rosthøj et al, 2003).

Intracranial haemorrhage (ICH) the most serious consequence of ITP in children, is fortunately a rare complication, with reported rates ranging from 0.1 to 0.8 percent (Lilleyman 1994). This was illustrated in reports of the Intercontinental Childhood ITP Study Group (ICIS) registry, which reported 10 cases of ICH among 1784 patients (0.6 percent) (Kühne et al, 2011), and from the Nordic registry, which reported no case of ICH among 501 patients during the first six months after diagnosis (Rosthøj et al, 2003). A systematic review of 51 prospective clinical trials including 1965 children with ITP found that ICH occurred in 0.4 percent (95% CI 0.1-0.9)(Neunert et al, 2015). More than 90 percent of ICHs in children with ITP are supratentorial (Psaila et al, 2009). Children presenting with signs and symptoms concerning for ICH (eg, headache, persistent vomiting, altered mental status, seizures, focal neurologic findings, recent head trauma) require urgent evaluation (including neuroimaging), and treatment.

Bleeding assessment tool (BAT)

There are several bleeding severity instruments for ITP but no consensus regarding their use.
Published AIEOP guidelines classify the clinical symptoms at presentation of each patient into one of three categories:

- Type A: asymptomatic-paucisymptomatic ITP: clinical symptoms ranging from no bleeding to few petechiae and some bruises without mucosal haemorrhages.
- Type B: intermediate ITP: a clinical picture with several petechiae, bruises and mucosal haemorrhages. Essentially, the absence or presence of mucosal bleeding was the determining factor in classifying the patient as type A or type B.
- Type C: severe ITP: a clinical picture with severe cutaneous and mucosal bleeding symptoms with at least one of the following: retinal haemorrhage, intracranial haemorrhage, other internal haemorrhages, haemorrhagic shock, or life-threatening bleeding. In general, type C has a clinical picture characterized by severe bleeding with organ impairment or life-threatening symptoms. (De Mattia et al, 2000; Del Vecchio et al, 2008)

The Buchanan and Adix bleeding scale score provides an overall grade from 0 to 5 which incorporates skin, oral, and mucosal bleeding. Grade 0–2 includes bleeding of the skin only, grade 3 includes mucosal bleeding, and grade 4–5 is any bleeding that requires immediate medical attention or is life threatening. (Buchanan & Adix 2002)

Overall bleeding severity

0 – **None** – definitely 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); no mucosal bleeding
3 – **Moderate** – overt mucosal bleeding (epistaxis, gum bleeding, oropharyngeal blood blisters, menorrhagia, gastrointestinal bleeding, etc.) that does not require immediate medical attention or intervention
4 – **Severe** – mucosal bleeding or suspected internal hemorrhage (in the brain, lung, muscle, joint, etc.) that requires immediate medical attention or intervention
5 – **Life-threatening or fatal** – documented intracranial hemorrhage or life-threatening or fatal hemorrhage in any site

The International Working Group proposes the ITP Bleeding Assessment Tool based on a more precise definition of bleeding manifestations and on the grading of their severity (Rodeghiero et al, 2013). **Bleeding symptoms are grouped into three major domains: skin (S), visible mucosae (M), and organ (and internal mucosae) (O). The tool also defines the grades of severity of the various types of bleeding in each domain.** The tool does not allow for a total score, since it considers the three domains separately. There is an on-line version, that can be found at http://www.siematologia.it/LG/SMOG/SMOG.htm

Table 2. Grading of bleeding symptoms at presentation and at each subsequent evaluation

	Grade based on the worst incident episode since last visit*				
Type of bleeding	**0**	**1**	**2**	**3**	**4**
Skin					
Petechiae (does not include steroid-induced or senile purpura)	[ ] No	[ ] Less than or equal to 10 in a patient's palm-sized area† in the most affected body area‡ [ ] Any number if reported by the patient	[ ] More than 10 in a patient's palm-sized area or more than 5 in at least 2 patient's palm-sized areas located in at least 2 different body areas,‡ one above and one below the belt (in the most affected body areas)	[ ] More than 50, if scattered both above and below the belt	
Ecchymoses	[ ] None or up to 2 in the same body area,‡ but smaller than a patient's palm-sized area, if (a) spontaneous or (b) disproportionate to trauma/constriction§	[ ] 3 or more in the same body area,‡ but all smaller than a patient's palm-sized area, if (a) spontaneous or (b) disproportionate to trauma/constriction§ [ ] At least 2 in two different body areas,‡ smaller than a patient's palm-sized area, if (a) spontaneous or (b) disproportionate to trauma/constriction§ [ ] Any number and size if reported by the patient	[ ] From 1 to 5 larger than a patient's palm-sized area, if (a) spontaneous or (b) disproportionate to trauma/constriction§ with or without smaller ones	[ ] More than 5 larger than a patient's palm-sized area, if (a) spontaneous or (b) disproportionate to trauma/constriction§	
Subcutaneous hematomas	[ ] No	[ ] 1 smaller than a patient's palm-sized area [ ] Any number and size if reported by the patient	[ ] 2 smaller than a patient's palm-sized area, spontaneous [ ] 2 smaller than a patient's palm-sized area, disproportionate to trauma§	[ ] More than 2 smaller or at least 1 larger than a patient's palm-sized area, spontaneous [ ] More than 2 smaller or at least 1 larger than a patient's palm-sized area, disproportionate to trauma§	

Identification of patients at risk for severe bleeding

Reported risk factors for severe bleeding in general include (Neunert et al, 2015):

- Wet purpura in the mouth, hematuria, prolonged epistaxis, GI bleeding, or other pronounced mucosal bleeding
- Trauma (especially to the head)

- Exposure to antiplatelet medications (eg aspirin, ibuprofen, other nonsteroidal anti-inflammatory drugs [NSAIDs]) and anticoagulants (eg, heparin, warfarin)
- Very low platelet count (defined as platelet count < 10 x 10^9/L , or < 20 x 10^9/L, depending on the study). In most studies, the majority of severe bleeding events occurred in children with very low platelet counts; in one large cohort study, mucosal bleeding was more common with platelet counts < 10 x 10^9/L compared with ≥ 15 x 10^9/L (51 versus 19 percent) (Zeller et al, 2005).

However, most patients with platelet counts in this range do not experience severe bleeding events and a major dilemma for the treating physician is that ITP patients differ in their tendency to bleed despite similarly low platelet counts; furthermore, biomarkers that predict bleeding severity are lacking.

There are scant data addressing the question of whether tests of platelet function can predict bleeding in patient with ITP (Panzer et al, 2007, van Bladel et al, 2014) because most tests of platelet function are affected by thrombocytopenia. It has been recently reported that whole blood flow cytometry tests of platelet function in children with ITP, independent of platelet count, differ between individuals, but are consistent with individuals overtime. These platelet function tests (i.e. platelet surface activated GPIIb–IIIa, P-selectin and GPIbα) are associated with concurrent bleeding severity in children with ITP and may also be useful indicators of future bleeding (Frelinger et al, 2018).

Recommendations

6. The consensus panel recommends to use **a uniform bleeding assessment tool** (BAT) at **each follow-up visit both for grading severity of bleeding and for evaluating response to** therapy **(EO- Very low quality 8.3-A)**
7. The consensus panel recommends to use the **Buchanan and Adix bleeding scale score** as it is **quick, easy to apply**, and has high interrater reliability for non-cutaneous bleeding **(EO- Very low quality 6.9-C)**
8. The consensus panel recommends to use the **Rodeghiero (SMOG) score** as it is **thorough and precise (EO- Very low quality 4.3-C)**
9. Risk factors for severe bleeding include: **wet** purpura (in the mouth, hematuria, prolonged epistaxis, GI bleeding, or other pronounced mucosal bleeding), **trauma**, exposure to **antiplatelet medications** (eg, aspirin, ibuprofen, other nonsteroidal anti-inflammatory drugs) and **anticoagulants** (eg, heparin, warfarin), very low platelet count (defined as **platelet count<10,000/microL**) **(V-Low quality 8.1-A)**

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6. Diagnosis and differential diagnosis
Chiara Gorio, Giovanni Del Borrello, Maurizio Miano

Primary immune thrombocytopenia (ITP) remains a diagnosis of exclusion and the differential diagnosis is often not easy. A retrospective chart review over a 10-year period showed that 17% of 492 children initially considered ITP were diagnosed with another disorder (Bryant et al, 2011). Specifically, familial thrombocytopenia, systemic lupus erythematosus, hypersplenism, neonatal alloimmune thrombocytopenia, Wiskott-Aldrich syndrome or systemic infection were the most common alternative diagnoses. In most cases, a comprehensive history alongside with a thorough physical examination and a few targeted laboratory tests can suggest these alternative diagnoses.

Clinical presentation

A negative family and past medical history and a presentation with a sudden onset of cutaneous bleeding manifestations, most often petechiae, are typical of ITP.

A family history of bleeding or thrombocytopenia is important, although its absence cannot exclude secondary congenital forms. There are also sporadic forms of congenital thrombocytopenia; Noris and Pecci highlighted how about 40% of MYH9 related diseases are due to de novo mutations (Noris et al, 2017, Pecci et al, 2014). **If available, a previous complete blood count (CBC) should be evaluated to verify a preexisting normal platelet count** .

A recent infection is often described in ITP, usually about 2 weeks before the onset (Labarque et al, 2014). A history of recent vaccinations, especially measles, mumps and rubella, can also be found.

Recent drugs administration could suggest a drug-related thrombocytopenia (Kam et al, 2014).

Children with ITP are usually well appearing, with no constitutional symptoms. The only signs often found are cutaneous or mucosal bleeding manifestations.

The International Consensus Report published by Provan et al, in 2010 stated that a mild splenomegaly might be found in primary ITP (Provan et al. Blood 2010). This sign was found in 17 of 1784 children with primary ITP by Khune et al, (Haematologica 2011).

The Canadian Paediatric Society (Friedman et al. https://www.cps.ca/en/documents/position/immune-thrombocytopenia 2018) has identified some red flags that can induce the physician **to suspect other causes of thrombocytopenia:** constitutional symptoms (fever, weight loss, night sweat), bone pain, recurrent thrombocytopenia, poor treatment response, lymphadenopathy, hepatosplenomegaly, ill-appearing child and sign of chronic disease (tables I and II).

Table I. Clinical data and their correlation with a diagnosis of ITP

Pros	Cons
Abrupt onset of symptoms	Fever, recurrent infections, weight loss, fatigue, bone and/or joint pain, skin rash
Recent viral infection	Ongoing medications
Recent vaccination, particularly with live vaccine	Family history for thrombocytopenia, cataract, deafness, renal failure, myelodysplasia, dismorphic features
Isolated thrombocytopenia, with normal red and white cell counts, except for bleeding-related anemia	Signs related to immune deficiency
Previous normal platelet count	Abnormal red and/or white cells

Table II. Clinical data suggesting congenital/hereditary thrombocytopenia

- Family history of thrombocytopenia
- Family history of acute myeloid leukemia
- No response to steroid and/or IVI therapy
- Thrombocytopenia onset at birth or during the first months of life
- Lack of previous normal platelet count
- Casual finding of mild thrombocytopenia (> 20 x 10^9/l)
- Long term persistence of mild thrombocytopenia
- Other non-hematological findings, i.e., short stature, arm/hand malformations, eczema, skin spots, deafness, cataract, kidney impairment)

Laboratory

Peripheral blood count.

ITP patients are characterized by **isolated thrombocytopenia**, defined as **platelet count <100 x 10^9/L**, previously considered <150 x 10^9/L. The international working group redefined this cut-off, considering that non-caucasian population may have lower platelet levels, without any bleeding risk. (Rodeghiero et al. 2009). In 2006 Stasi et al. published the results of a prospective study, in which it was evaluated the long-term follow-up of 260 apparently healthy individuals with a platelet count between 100 x 10^9/L and 150 x 10^9/L, incidentally identified during routine blood tests. The 10-y probability of a platelet count persistently below 100 x 10^9/L was only 6.9% (Stasi et al. 2006). Therefore, more recently Schiappi et al, a conducted a 5-y retrospective review of 113 pediatric patients referred to pediatric hematology-oncology for isolated thrombocytopenia. Patients with isolated mild thrombocytopenia (between 100 and 150 x 10^9/L) with a normal bleeding history and physical examination findings frequently normalize their platelet counts within 1 month (Schiappi et al, 2018).

Children often present at the onset with severe thrombocytopenia, without other alterations of blood cells. A comparative prospective observations registry of the Cooperative Immune Thrombocytopenia Study Group evaluated 1784 children with a newly diagnosed ITP and found that the mean platelet levels at presentation was 18.1 x 10^9/L. (Kuhne et al. 2011). Thrombocytopenia is the only laboratory finding, even if other abnormalities are possible, such as low Hb (due to severe bleeding) or mild eosinophilia. EDTA-mediated pseudo-thrombocytopenia may be suspected when there are no bleeding symptoms; it can be confirmed testing blood count with other anticoagulants (Labarque et al, 2014)

Peripheral blood smear

Evaluation of peripheral blood smear can guide the diagnosis. Some large platelets are typically found, but an excessive number of giant platelet, as well as small platelets, should point to other diagnoses. A retrospective study considered 87 children with isolated thrombocytopenia, 10,3% were diagnosed with secondary thrombocytopenia (Lee et al. 2018). This study showed the importance of a peripheral blood smear in the diagnosis, because it can rule out or suggest secondary causes of thrombocytopenia (such as the identification of atypical lymphocytosis due to perinatal CMV infection, the finding of giant platelets in MHY9-RD, the presence of blasts in patients with Down syndrome with transient abnormal myelopoiesis). Fiore et al. (Platelets 2016) conducted a comparative observational study of thrombocytopenic patients to discriminate ITP from inherited thrombocytopenia and they found that a mean platelet volume >11 fl and an excess of giant platelets on peripheral smear had a predictive positive value respectively=93.3% and 100%. Even if this study included adult patients with chronic thrombocytopenia, it is useful to understand the importance of these parameters.

Anti platelet antibodies

Although platelet autoantibodies (PAA) are thought to be the major underlying cause of ITP (Cines, et al, 2014), testing for PAA is not currently recommended for the diagnosis of ITP due to the perceived poor accuracy of the current tests (Neunert et al, 2011). On the other hand, a recent meta-analysis conducted on adult patients (Vrbensky et al, 2019) pointed out that direct testing for anti-glycoprotein autoantibodies (namely anti-GPIIbIIIa and anti-GBIbIX), especially when performed by **MAIPA** (**Monoclonal Antibody-specific Immobilization of Platelet Antigen**), shows low sensitivity (53%) but **high specificity (93%),** performing better than its indirect counterpart. As such, the authors concluded that direct PAA testing could be used to rule in a diagnosis of ITP, but not to rule it out.

In fact, a recent study (included in the aforementioned review) (Porcelijn et al, 2018), which tested for antibodies against three platelet glycoproteins (GPIIbIIIa, GBIbIX and GPV), applying a more stringent case definition (i.e. platelet counts persistently between 10 and 50 x 10^9/L without other explanation after thorough testing) and using thrombocytopenic patients affected mainly by hematological malignancies as controls, found that direct MAIPA testing had a sensitivity of 81% and a specificity of 98%, leading to a positive predictive value of 98%.

Many benefits in phenotyping ITP patients by the presence or absence of PAA (and their specific targets) are hypothesized, based on current pathophysiology models: reduced AMR-dependent platelet production has been found in the presence of anti-GPIbIX PAA (Xu et al, 2018), which could then benefit from early TPO-agonist administration; the complete absence of PAA has been shown to predict rituximab non-responsiveness (Porcelijn et al, 2017); the disappearance of PAA has been proposed as a marker for ITP permanent resolution, which could then guide therapy de-escalation (Porcelijn et al, 2018).

Other PAA testing technique (e.g. flow-cytometry based platelet immunoglobulin testing, human platelet antigen-specific antibody testing) **should be abandoned**, either because less accurate than direct anti-GP testing (flow-cytometry based platelet immunoglobulins testing) or because inappropriate (human platelet antigen-specific antibodies testing). The latter is useful only in the context of alloimmune neonatal thrombocytopenia).

No data are currently available for direct PAA testing in pediatric cases of ITP, more research is thus needed before any definitive conclusion can be drawn this subject.

Bone marrow aspiration

The AIEOP consensus guidelines published in 2000 did not recommend bone marrow aspiration (BMA) in typical cases. **It was however considered appropriate before starting therapy with steroids**.

The American Society of Hematology in 2011 dedicated a specific section of the evidence-based practice guidelines for pediatric patients. They concluded that **it is not recommended in children with typical onset** (grade 1B), even if corticosteroid therapy is considered (grade 2C) (Neunert C et al, 2011)

This recommendation agrees with other studies with pediatric and adult cohorts. **Some of these studies suggest avoiding BMA also if corticosteroid therapy is needed** (Mahabir et al. 2012, Mak et al, 2000, Calpin et al, 1998, Purhoit et al. 2016, Klaassen et al, 2001).

Immature platelet fraction (IPF%)

Some recent evidence shows that the inexpensive test for rapid assessment of immature platelet fraction (IPF) by automated hematology analyzers, may be useful to evaluate patients with thrombocytopenia. IPF% in ITP patients appears higher than in healthy controls (Naz et al, 2016). Retrospective studies pointed out that IPF% is high also in patients with thrombocytopenia due to bone marrow failure (BMF), but lower than in hereditary macrothrombocytopenia (Ferreira et al, 2017.) This result has not been confirmed (Cybulska et al, 2017). There is also some evidence in the pediatric population, in which a difference between ITP

and BMF patients has been identified (McDonnell et al, 2017). Moreover, one of these studies shows a decrease of IPF% in ITP patients in remission compared with the onset of the disease, indicating IPF% as a potential prognostic marker for the development of chronic ITP. (Aldy et al, 2015).

Helicobacter pylori testing

Several studies show the utility of testing Helicobacter pylori (H. pylori) in adult patients with newly diagnosed ITP (Provan et al. 2010) and this was also confirmed by the American Society of Hematology in 2011. The evidence of the utility in the pediatric population is not yet confirmed. The pediatric populations analyzed in literature are often affected by chronic ITP and conflicting results have been found. A multi-center prospective randomized study showed no beneficial effect of H. pylori eradication on platelet recovery in childhood chronic ITP (Treepongkaruna et al, 2009). However, the prospective controlled multi center Italian study led by the AIEOP-ITP Study Group and other studies have shown a benefit in term of platelet count after the eradication of H. pylori in affected patients (Russo et al, 2011; Brito et al, 2015; Ferrara et al, 2009).

Screening for autoimmune diseases

Thrombocytopenia can be associated with many autoimmune diseases (AID) such as systemic lupus erythematosus (SLE), celiac disease, Sjogren's syndrome (SS) or thyroiditis. Nevertheless, **The ASH guidelines do not recommend screening for these diseases in all newly diagnosed patients**.

ANA positivity is present with varying frequency in the healthy population, depending on geographical location and ethnic background. Seimi et al. (Automimmunity review 2016) described that ANA positivity is present in 18.1% of the general population, with a prevalence that increases with age.

A retrospective study analyzed children newly diagnosed with primary ITP (pITP) and those with ITP associated with SLE or SS. There were some differences in the clinical manifestations between the two groups. The AID cohort often presented symptoms such as arthritis, dry mouth, dry eye, and skin rash, rarely seen in pITP. Patients with SLE had significantly lower levels of total white blood cells and lymphocytes. Moreover, ANA positivity was found in 51.2% of pITP (Liu et al, 2016). Other studies evaluated the risk of SLE in patient with ITP and they found that the majority of patient with ANA positivity at the ITP onset did not develop SLE (Hazzan et al, 2006, Altinas et al, 2007). Liu et al, found no statistically significant difference between ANA positive and negative group, in term of risk of chronicity. However, patients with ENA positivity had a major risk of developing chronic disease. Clinical symptoms at the onset were not described in this study. (Liu et al, 2017).

ITP can be also found in patients with anti-thyroid antibodies (aTA), but the clinical significance is still not well understood (Giordano et al, 2018). A prospective case-control study recently evaluated the ATA positivity in ITP pediatric patients with normal thyroid function (Mousa et al. 2017): aTA were more frequently positive in children with ITP than the control group and aTA positive children had more relapses than the aTA negative group. Also Ali Bay et al. (Pediatric Hematology and Oncology 2013) demonstrated that the thyroid-autoimmune-diseases-related autoantibodies are frequently found in childhood ITP, with a platelet count significantly lower than that in the seronegative group. They conclude that screening ITP patients for such antibodies is recommended, because of the potential negative effect on treatment response. However, there are no data regarding the management and the impact of subclinical thyroiditis, because thyroid ultrasound was not performed and a long-term follow-up is not available.

Also the association between ITP and coeliac disease is well documented (Olén et al, 2008, Bibbò et al, 2018, Guarina et al, 2021), but the clinical impact of this association is not described, however, there are some case reports that documented a normalization of the platelet count with gluten-free diet (Sarbay et al, 2011)

Differential diagnosis: Evans syndrome, Primary Immune deficiency and ALPS

ITP can represent the first or an additional sign of underlying immunological disorders, especially in children. In these cases, the disease is often resistant to first-line treatments, can become chronic, and/or relapse later on. Immune-dysregulation syndromes involving B and/or T-cell homeostasis such as Autoimmune Lymphoproliferative Syndrome (**ALPS**), "ALPs-like" disorders (i.e defects of CTLA4, PI3KCD, LRBA, STAT3), and Common Variable Immune Deficiency (**CVID**) are frequent underlying causes of secondary ITP in children, being autoimmune cytopenias a common sign of such disorders which may also include chronic benign lymphoproliferation, rheumatologic issues, and wider autoimmunity involving any other organ (Seidel et al, 2014). Due to the known incomplete penetrance of genetic mutations causing immune-dysregulation syndromes and their heterogeneous and "dynamic" phenotype characterized by the onset/relapse of different symptoms over the years, the diagnosis of these forms is challenging and must be potentially taken into consideration in the presence of any autoimmune cytopenia (Rieux-Laucat 2017) .

Sometimes, immune-mediated mechanisms can involve red blood cells, as in Evans Syndrome (ES). In about half of the affected patients the association may develop metachronously after a median interval of 3 years (Aladjidi et al, 2011). For this reason, **the diagnosis of ES should also be potentially considered at the onset of a monolinear cytopenia such as ITP** (Evans et al, 1951, Savasan et al, 1997, Wang 1988). It is well known that about half of the patients with ES have an underlying diagnosis of ALPS (Teachey et al, 2005), which is due to mutations of genes involved in the FAS-mediated apoptosis (FAS, FAS-L, CASP10) and well known to be related to the onset of autoimmune cytopenias. Diagnosis of ALPS is made according to specific diagnostic criteria (Oliveira et al, 2010) including, in particular, a high count of TCRαβ+CD4-CD8-T-cells ("double negative T-cells", DNTs). Since DNTs can also be abnormal in other "ALPS-like" conditions, their count is important to identify an underlying immune-dysregulation. Moreover, since hypogammaglobulinemia represents a typical feature of CVID and other monogenic immune-dysregulation syndromes associated with autoimmune cytopenias, immunoglobulin serum levels can also be helpful to correctly orientate the diagnosis.

As long as the administration of steroids and/or IVIg can impair the diagnostic work-up of an underlying immunological disorder (Miano 2016), an early diagnosis in selected patients with acute ITP can be crucial for those patients not responding to first-line therapies or becoming steroid-dependent in order to give a more targeted second-line treatment.

Recommendations

10. Blood smear observation is indicated to exclude inherited and/or secondary thrombocytopenia **(EO- Low quality 7.8-B)**
11. The use of PAA testing technique other than direct anti-GP testing should be abandoned, in both the clinical and the research setting **(EO - Low quality 7.6-B)**
12. In the pediatric ITP population, there is no current evidence to support the use of any PAA testing technique, which shall be used only in the research setting **(EO – Low quality 7.7-A).**
13. Bone marrow aspiration has no indication at the onset of ITP in newly diagnosed children with typical presentation **(EO- Moderate quality 8.2-A)**
14. Bone marrow aspiration is indicated prior to the administration of steroids, but can be omitted in patients with a recent history of complete response to IVIg (EO-Very low quality) **(EO- Very low quality 7.4-B)**
15. **H. pylori stool antigen screening** is indicated in **newly diagnosed** ITP **(V- Very low quality 4.6-C)**

16. **H. pylori stool antigen screening** is indicated in **persistent** ITP **(V- Moderate quality 7.9-A)**
17. **Anti-ENA and ANA** screening are indicated in **newly diagnosed** ITP only in patients with **symptoms or sign of autoimmune disease (EO- Very low quality 6.8-C)**
18. **Anti-ENA and ANA** screening are indicated in **persistent** ITP **(EO- Low quality 8.0-A)**
19. Screening for **thyroid function** and/or **anti-thyroid antibodies** is useful in identifying patients with high risk of relapse; therefore, it is indicated in **newly diagnosed** ITP **(V- Low quality 5.3-C)**
20. Screening for **thyroid function** and/or **anti-thyroid antibodies** is useful in identifying patients with high risk of relapse; therefore, it is indicated in **persistent** ITP **(V- Low quality 7.6-A)**
21. Screening for **coeliac disease** is indicated in **newly diagnosed** ITP **(V- Moderate quality 5.1-C)**
22. Screening for **coeliac disease** is indicated in **persistent** ITP **(V- Moderate quality 7.6-B)**
23. **ALPS/ALPS-like syndromes** and **CVID** should be considered as underlying cause of acute ITP in patients with personal/family history of autoimmunity, lymphoproliferation, or other sign of immune-dysregulation **(EO- Low quality 7.9-A)**.
24. Diagnostic work-up of patients with acute ITP associated with **signs/history of immune-dysregulation** should include **lymphocyte subset** count (including **TCR alfa-beta+CD8-CD4-T-Cells-**), **immunoglobulin** serum level, **antibody titres** to prior vaccination, and screening for **autoimmunity** before administration of steroids/IVIg **(EO- Low quality 7.8-A)**.
25. Patients with newly diagnosed ITP and history of **Autoimmune Haemolytic Anemia** should be considered as having an **Evans Syndrome** and investigated for **ALPS/ALPS-like and CVID (EO- Low quality 8.0-A)**.

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7. Genetics
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In childhood ITP genetic factors may contribute not only to the susceptibility to the disease, but also to the clinical course and the response to different therapies.
Even though individual genotype profiling is expected to greatly improve both biological understanding of the disease and clinical practice in the field (Bergmann et al, 2010), the rarity of the condition and its biologic heterogeneity complicates patient selection and sample-sizing (Salanti et al, 2005).
In a study applying a family-based-linkage approach to ITP (Peng et al, 2017) a gain of function mutation in the gene encoding the B-cell receptor TACI (Transmembrane Activator and CAML Interactor, previously associated with Common Variable ImmuneDeficiency, CVID) was identified in a single pedigree and was subsequently found to be overexpressed in a cohort of unselected sporadic ITP patients.
Whole Exome Sequencing analysis has only been applied to a single cohort of chronic ITP pediatric patients so far (Despotovic et al, 2015).
A few association studies in pediatric ITP have been published, too (Table I).
Many of these reports suffer from several limits (i.e., allocation of both acute and chronic cases, pediatric and adult patients; difficulties in extrapolating results from one ethnic group to the other) and almost all the reported associations between a specific single-nucleotide polymorphism (SNP) or haplotype and ITP were not confirmed in further studies.
Only polymorphisms in Fc gamma receptors (FcγRs) have been repeatedly studied in relation to pediatric ITP with consistent results. Multiple studies suggested that function-enhancing SNPs in FCGR3A and FCGR2A predispose to ITP in childhood (Li et al, 2019).
Recently, an association between SNPs in FCGR2B (one of the principal therapeutic targets through which IVIg exert their immuno-modulatory action) and outcome in paediatric acute ITP (Laarhoven et al. 2015, Heitink-Polle´ et al. 2018) has been reported, too: patients carrying both the increased-expression 2B.4 promoter haplotype and the wild type I/I genotype at codon 232 showed a higher rate of spontaneous platelet recovery within 1 week (44% vs 12%, $p < 0,01$) and higher rate of immediate response to IVIg therapy (92% vs 66%, $p < 0,05$); patients carrying the function-diminishing T/T genotype at codon 232 showed 0% response to IVIg and those carrying the I/T genotype showed 0% spontaneous recovery at 1 week. FCGR2B profiling has therefore recently been introduced in clinical management algorithms for ITP in tertiary-level pediatric centers in the Netherlands (Heitink-Polle´, personal communication).
Regarding the role of SNPs in predicting disease evolution (chronic vs acute), in a single prospective study the presence of non-wild type FCGR2B at codon 232 predisposed to ITP duration over 6 months (Bruin et al, 2004), while a more recent study showed no difference in rates of disease resolution at 12 months (Heitink-Polle´ et al, 2018). No association between bleeding profile and FC gamma receptors polymorphisms has been found so far.
Genetic analysis may help management of ITP cases in situations where an actual monogenic disease is suspected, too.
ITP can represent the first or an additional sign of underlying immunological disorders as autoimmune hematologic manifestations are a relatively common feature of Primary ImmunoDeficiencies and immune Dysregulatory disorders (PIDD) arising in childhood (Notarangelo 2009).
A recent report (Hadjadj et al, 2019) showed that up to 65% of pediatric Evans syndrome cases (i.e. any combination of at least two auto-immune cytopenias, most commonly ITP and autoimmune hemolytic anemia) were the result of a definite or probable pathogenic genetic mutation, and for 36% of them specific mechanism-directed therapies were available (e.g. sirolimus in autoimmune

lymphoproliferative disease, abatacept for LRBA and CTLA4 deficiencies, tocilizumab for STAT3 deficiency, leniosilib in activated PI3K-syndrome…),
As most ITP cases in children are transient and self-limited, genetic analysis should not be routinely offered to the patient with an acute decrease in platelet count. However, a subtype of patients with high suspicion of a monogenic PIDD - identifiable by means of thorough history taking, rational clinical examination and basic laboratory testing - might benefit from early access to genetic testing (Richardson et al. Curr Allergy Asthma Rep 2018).

Recommendation

26. There is currently not enough evidence to suggest the use of any SNP as predictive of chronicity **7.6-B**

Table I. Reported DNA variations in pediatric ITP

Gene/gene product	SNP	Number and characteristics of pts	Study design	Main findings*	Proposed pathophysiologic role	Ethnicity	Reference
IL-4, IL-6, IL-10	IL-4: intron 3 VNTR, IL-6: −572 , Il-10: −627	50 pediatric aITP 30 pediatric cITP 100 controls	Retrospective case-control	IL-4 RP1/RP2 genotype and IL-10 A/C genotype were underrepresented in cITP.	Skewed Th1 vs Th2 immunologic response	Asian (Taiwan)	Wu et al. BJH 2005
FCGR2C	Stop vs ORF (in exon 3)	72 paediatric ITP 100 controls	Retrospective case-control	FCGR2C-ORF is associated with ITP	Increased phagocytes- and NK-mediated ADCC. See main text for further discussion	Caucasian (Netherlands)	Breunis et al. Blood 2008
CNR2/CB2	Q63R	86 paediatric aITP 104 paediatric cITP 600 controls	Retrospective case-control	RR homozygosity is associated with chronic course of ITP	Reduction in endocannabinoid-induced inhibition of proliferation of auto-reactive T-cell	Caucasian (South of Italy)	Rossi et al. Haematologica 2011
SDF-1	rs2839693, rs266085, rs2297630, rs1801157, rs1065297	45 paediatric aITP 55 paediatric cITP 126 controls	Retrospective case-control	AA homozygosity at rs2297630 is associated with chronic course of ITP	Reduced TPO-independent megakaryopoiesis	Asian (Taiwan)	Ku et al. EJH 2012
IL-10 promoter region	− 1082 (A/G) − 819 (C/T) −592 (C/A)	41 paediatric aITP 44 paediatric cITP 64 controls	Prospective/retrospective case-control	GCC haplotype is associated with acute course of ITP, compared to cITP	Increased IL-10 expression leading to faster immune clearance of autoreactive lymphocytes	Caucasian (South of Italy)	Tesse et al. Gene 2012

IL4 , IL10	IL4: intron 3 VNTR, IL10: -627	30 paediatric aITP 40 paediatric cITP 50 controls	Retrospective case-control	Overexpression of AA genotype at IL10 in aITP (lower cytokine expression). Over expression of RP2/RP2 genotype at IL4 (lower cytokine expression) in cITP.	Skewed Th1 vs Th2 immunologic response	African (Egypt)	Makhlouf et al. Lab Med 2014
ABCB1/Pgp	C1236T G2677T/A C3435T	471 adult/pediatric, a/cITP; 383 controls	Prospective case-control	homozygous G2677T/A mutation is associated with better steroid responsiveness	Increased glucocorticoid bioavailability and improved pharmacokinetic	Asian (China)	Xuan et al. Human Immunology 2014
STAT1	rs10208033, rs12693591, rs1467199	183 paediatric aITP 64 paediatric cITP 220 controls	Prospective case control	CC homozygosity at rs1467199 is associated with chronic course of ITP, GG homozygosity is associated with acute course of ITP	Dysregulation of IFN-g-dependent signaling pathway	Asian (China)	Chen et al. Autoimmunity 2015
FCGR3A, FCGR2A, FCGR2B, FCGR2C	FCGR3A: F158V, FCGR2A: H131R, FCGR2B: I232T and promoter haplotype, FCGR2C: stop vs ORF in exon 3	138 paediatric aITP randomised to either observation or IVIg 199 controls	Randomized controlled trial and prospective case-control	ORF at FCGR2C and VV genotype at FCGR3A are associated with ITP. Patients carrying both the 2B.4 promoter haplotype and the II genotype at FCGR2B showed better rate of both spontaneous and IVIg -induced platelet recovery.	Increased phagocytes- and NK-mediated ADCC. Increased immunosuppressive reactivity mediated by FCGR2B. See main text for further discussion	Caucasian (Netherlands)	Laarhoven et al. 2015 (doctoral thesis)

IL6, IL10, IL17F, TNF-a, IL1Ra	IL6: -174, IL10: -1082, IL17F: rs763780, TNF-a: -308, IL1Ra: intron 2-VNTR	20 paediatric aITP 30 paediatric cITP 50 controls	Prospective/retrospective case-control	Overexpression of CC genotype at IL6, GG genotype at IL10, and CC genotype at IL17F in ITP cases. Lower-expression A1A1 variant at IL1Ra associated with cITP. AA genotype at IL10 correlates with worse response to steroids (all cases). No association between the polymorphisms studied and IVIg response.	Skewed Th1 vs Th2 immunologic response	African (Egypt)	Mokhtar et al. Blood Coagul Fibrinolysis 2016
VDR	Cdx-2, FokI, BsmI, ApaI, TaqI	37 paediatric aITP 7 paediatric cITP 100 controls	Retrospective case-control	GG homozygosity at Cdx-2 is associated with ITP	Reduced immunomodulatory effect of vitamin D secondary to a reduction in VDR transcription	Turkish	Yesil et al. Pediatr Int 2017
IL-17A, IL-17F	IL-17A: rs2275913, IL-17F: rs763780	80 paediatric aITP 55 controls	Prospective case-control	TT homozygosity at IL-17F rs763780 is associated with aITP	Excessive Th1-mediated immune response driven bu increased IL-17 levels	African (Egypt)	Aziz et al. OJBD 2018
FCGR2B	232 I/T	200 paediatric aITP randomised to either observation or IVIg	RCT	Patients carrying the TT genotype showed no IVIg response at 1 week. Patients carrying the I/T genotype showed no spontaneous platelet recovery at 1 week. Non association with disease duration more than 12 months.	Reduced immunosuppressive activity mediated by FCGR2B	Caucasian (Netherlands)	Heitink-Polle´ et al. Blood 2018

FCGR3A, FCGR2A, FCGR2B	FCGR3A: F158V, FCGR2A: H131R , FCGR2B: I232T	FCGR3A: 436 paediatric ITP, 779 controls; FCGR2A: 381 paediatric ITP, 765 controls; FCGR2B: 203 paediatric ITP, 285 controls	Meta-analysis of 17 studies (1998-2018)	VV genotype at FCGR3A and RR genotype at FCGR2A are associated with ITP independent of ethnicity. No study reported association with disease severity. 2 study reported a dubious association between wild type FCGR2A and longer disease duration. 1 study reported an association between T allele at FCGR2B and cITP.	Increased phagocytosis of antibody-coated platelet. See main text for further discussion	Mixed	Li et al. Scand J Immunol 2019

This table summarizes only positive outcomes: many other reports did not find any association between the studied polymorphism and ITP. The following SNP where tested and not found to be significantly associated with ITP in children: CTLA4 (2 studies), DNMT3B (3 studies), IL4 intron 3 VTR (1 study), TGF-b1 (1 study), TIM-3 (1 study), CD72 (1 study), IFN-g (1 study), HLA (2 studies). Abbreviations: ITP = Immune Thrombocytopenic Purpura (a = acute, c = chronic), VNTR = Variable Number Tandem Repeats, FCGR = Fc Gamma Receptor, ORF = Open Reading Frame, NK = Natural Killer cells, ADCC = Antibody-Dependent Cellular Cytotoxicity, CB2 = cannabinoid receptor type 2, SDF-1 = Stromal-derived factor-1, TPO = Thrombopoietin, IL = interleukin, Pgp = P glycoprotein, ABCB1 = ATP- binding cassette sub-family B member 1, STAT1 = Signal transducer and activator of transcription 1, IFN-g = interferon-gamma, IVIg = IntraVenous ImmunoGlobulines, VDR = Vitamin D Receptor.

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8. Prognostic factors
Marco Spinelli

The available literature dealing with the identification of prognostic factors capable of predicting the evolution toward a chronic course of ITP is based mainly on case series and retrospective reviews. Therefore, the strength of the reported evidence is weak.

Factors that have been identified by different reports as related to chronic evolution are **older age at diagnosis**, **female gender**, **higher initial platelet count**, **absence of mucosal bleeding**, **absence of preceding infection or vaccination, absence of an increase in immunoglobulin** (Glanz et al, 2008, Donato et al, 2009, ElAfy et al, 2010, Kubota et al, 2010, Evim et al, 2014). Although none of these studies has been specifically designed to specifically address such issue, and the osservational-retrospective nature of the studies limits the power of the evidence, yet the concordance of the reports on the avove mentiond factors allows un unpgrade of the level of evidence.

A single report, with very low statistical power, points at low initial lymphocyte count as an indicator of chronic outcome (Deel et al. 2013).

Initial pharmacological treatment and particularly **the use of IVIg** has been related to disease resolution at 6, 12 or 24 months (Tamminga et al, 2009, Bennet 2018).

Infants <1 year of age are a special group with a brief course and very high recovery rate that are not influenced by other prognostic factors (Donato et al, 2009).

The exploration of a possible role of FcγRIIa and FcγRIIIa polymorphisms in the pathogenesis, chronicity and therapeutic result of childhood ITP, yelded no significant results (Papagianni et al, 2013).

Recommendation

27. Prognostic factors of chronic ITP in children are **female gender**, **age > 11** years at presentation, **absence of preceding infection or vaccination**, **higher platelet count** at presentation **(V-Moderate quality 7.9-A)**.

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9. Indications for treatment – wait and see versus first-line treatments in newly diagnosed ITP
Piero Farruggia

Which patients with acute ITP should be treated?

Under the assumption that ITP treatment does not affect the natural course of the disease, recent guidelines for childhood ITP management from hematology societies (Neunert et al, 2011) recommend first-line therapies (i.e. IVIg and steroids) to be used in only a minority of pediatric patients who have active bleeding, with the aim of alleviating symptoms and/or preventing major bleeding: "**Children with no bleeding or mild bleeding (defined as skin manifestations only) be managed with observation alone regardless of platelet count (grade 1B)"**. (Neunert et al, 2011)

Available data on the incidence of severe hemorrhage derive from observational studies and no high-quality studies have been carried out; the evidence points at the rarity of the severe events and the lack of correlation with treatment.

In fact, in a prospective comparative study of 2540 children with newly diagnosed ITP, only 3 episodes (0.17%) of ICH were reported. All 3 patients had a platelet count < 20 x10^9/L at diagnosis and 2/3 had been treated at ITP onset (Kuhne et al, 2003).

Among 685 acute ITP children with platelets < 20 x10^9/L at diagnosis, 22 (3%) presented severe hemorrhage (1 ICH), 158 (23%) presented moderate hemorrhage and 505 (74%) no or mild bleeding: among these latter ones 3 presented severe bleeding and 9 moderate bleeding during the subsequent 28 days; no relationship was found between the initial treatment in children with no to mild bleeding at diagnosis and subsequent severe hemorrhage (Neunert *Blood 2008;112:4003)*

However, the management of children with newly diagnosed ITP remains still controversial**.**

In a recent randomized trial children with newly diagnosed ITP, platelet counts $\leq$ 20 x 10^9/L and score 0-3 bleeding were randomly assigned to receive either a single infusion of 0.8 g/kg IVIg or careful observation: **platelet counts < 100 x 10^9/L at 12 months were detected in 10% and 12% of patients of the IVIg group and the observation group respectively,** even though **complete response rates in the first 3 months significantly higher in the IVIg group**; **grade 4 - 5 bleeding was observed 1% and 9% of patients of the IVIg group and the observation group respectively**; 7/42 patients in the observation group with grade 3 bleeding at diagnosis developed severe bleeding in the first month and one of them presented an intracranial hemorrhage (ICH) 16 days after diagnosis. In the IVIg group only 5 adverse events were registered (1 allergic reaction and 4 nausea or vomiting or headache) (Heitink-Pollé 2018).

Psychological and emotional aspects may be of more concern in children and their families (Cooper, 2014). In the light of a more liberal and personalized approach, some authors propose not to restrict new treatments to symptomatic patients but to consider health-related quality-of-life issues for decision making regarding treatment in pediatric ITP (Parodi et al, 2021).

Examples of clinical conditions that may require treatment, irrespective of platelet count, are listed in table I.

Table I. "Special needs": examples of clinical conditions that may require treatment, irrespective of platelet count

- Toddler
- Pubertal girls at risk for menorrhagia
- Adolescents with potential risky behavior
- Upcoming procedures associated with a risk of bleeding
- Coexistence of other risk factors
- Co-morbidities, such as neuro-psychiatric disorders

- Low socio-cultural environment
- Long traveling distance from hospital
- Strong wish of parent or patients

Recommendations

28. In children with newly diagnosed ITP who have no or mild bleeding (skin manifestations) only, **the management as an outpatient is favored** over admission to the hospital, unless conditions such as uncertainty about the diagnosis, social concerns, distance from the hospital, and difficulties for follow-up, make admission to the hospital preferable. **(EO-Moderate quality 7.9-A)**
29. In case of Buchanan & Adix **score 0-2** (equivalent to SMOG S0-3 M0 O0) at onset (no symptom or skin bleeding alone), **irrespectively of the platelet counts**, the initial approach should be **observation alone (II-EO- High quality 7.5-B)**
30. In case of Buchanan & Adix **score >=3** (equivalent to SMOG S0-3 M>=2 O>=1) at onset (at least mucosal bleeding), irrespectively of the platelet counts, **the patient should be treated (EO- Moderate quality 8.0-A)**
31. In case of **subsequent appearance** of Buchanan & Adix **score >=3** (equivalent to SMOG S0-3 M>=2 O>=1) (at least mucosal bleeding), patients initially observed alone (score 0-2) **should be treated (EO- Moderate quality 8.8-A)**
32. In case of patients with Buchanan & Adix score 0-2 (equivalent to SMOG S0-3 M0 O0) (no symptom or skin bleeding alone) and platelet count < 20 x109/L **who may benefit from higher platelet counts** (table 1 "special needs", i.e. toddlers with high tendency to fall, pubertal girls at risk for menorrhagia, risk behavior in adolescents, upcoming procedures associated with a risk of bleeding, not acceptable traveling distance from hospital) or in case of strong wish of parents or patients, after having counselled regarding risks and benefits of therapy, **treatment can be offered (EO- Very low quality 8.2-A)**

Which is the preferable treatment in patients with moderate (score 3) mucosal bleeding?

Possible alternatives as first line therapy in patients with moderate mucosal bleeding are IVIg, oral/ intravenous steroids or anti-D immunoglobulin (anti-D).

ASH Guidelines report that for pediatric patients requiring treatment, a single dose of IVIg (0.8 to 1 g/kg) or a short course of corticosteroids are to be used as first-line treatment. IVIg can be used if a more rapid increase in the platelet count is desired. (Neunert et al, Blood 2011;117:4190)

In a randomized trial 53 children with acute ITP, and platelet counts < 20 x 10^9/L, were randomly assigned to receive IVIg 1 gr/kg per day for 2 consecutive days, oral prednisone 4 mg/kg per day with tapering and discontinuation by day 21, or no therapy. **The time taken to achieve a platelet count of > 50 x 10^9/L was significantly faster in patients treated with IVIg** (median, 2 days; range, 1-34 days) than in those receiving prednisone (median, 4 days; range, 2 -13 days; p < 0.001) or no therapy (median, 16 days; range, 2 - 132 days; p < 0.001). (Blanchette et al, 1993).

Also in another prospective, randomized study, 146 children with acute ITP were randomized to receive IVIg 1 g/kg on 2 consecutive days, IVIg 0.8 g/kg once, anti-D 25 micrograms/kg on 2 consecutive days, or oral prednisone 4 mg/kg per

day with tapering and discontinuation by day 21. **The fastest recovery of platelet count was in the groups treated with IVIg.** Moreover, the Authors observed that the lower dose of IVIg achieved an equivalent short-term platelet response when compared with the higher dose of 1 g/kg on 2 consecutive days (Blanchette et al, 1994).

Patients with a platelet count of <10 x 10^9/L or 10-29 x 10^9/L and mucosal bleeding were randomly assigned to receive IVIg 1 to 2 g/kg, oral prednisolone (o-PSL) 2 mg/kg for 2 weeks, parenteral methylprednisolone 5 mg/kg for 5 days, or pulsed parenteral methylprednisolone 30 mg/kg for 3 days. In these patients IVIg offered the fastest recovery. (Fujisawa et al, 2000).

A metanalysis comparing treatment with IVIg and corticosteroids proved that children treated with corticosteroids were 26% less likely to achieve platelet count > 20 x10^9/L at 48 hours from diagnosis (Beck et al, 2005)

Regarding anti-D (that can be administered only in Rh positive patients) it has been proven that acute ITP patients treated with anti-D present a higher decrease in hemoglobin compared with those receiving IVIg. (Son et al, 2008; Tarantino et al, 2006) and that anti-D 50 mcg/kg dose is less effective than IVIg and less effective than the anti-D 75 mcg/kg dose to increase platelets to > 20 x109/L at 24 hours from diagnosis (Tarantino et al, 2006).

Moreover, serious and fatal intravascular hemolysis and disseminated intravascular coagulation after anti-D have been reported: FDA provided warning on this aspect (Gaines et al, Blood. 2005). Anti-D for ITP is not marketed in Italy and is not available in most if not all European countries: in June 2009 the manufacturer notified the European Medicines Agency the decision to withdraw all marketing authorizations in Europe because of concerns about the benefit-to-harm balance in the ITP therapy.

Recommendation

33. In patients with moderate Buchanan & Adix **score 3** (equivalent to SMOG S0-3 M1-3 O0-1) (mucosal bleeding) **the initial approach should be a single dose of 0.8 g/kg IVIg (II- High quality 8.5-A)**

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10. Therapy with steroids
Simone Cesaro, Chiara Garonzi

About 80% of patients who develop ITP achieve a complete sustained remission within a few weeks to a few months from initial presentation, **irrespective of any given therapy**. Nevertheless, the treatment is acceptable to prevent the risk of intracranial hemorrhage that occurs in less than 1% of cases especially in patients with very low platelet counts (<20 x 10^9/L). The aim of the treatment is to increase quickly and stabilize the platelet count to value > 20 x 10^9/L that is in general not associated to severe mucosal or internal bleeding. Effective treatment strategies are single-dose intravenous immunoglobulin (IVIg; approximately 0.8-1 g/kg) and medium to high-dose corticosteroids, administered orally or parenterally. **Several randomized studies showed that IVIg at the dose of 0.8-1 g/kg for 1-2 days (or 0.4-0.5 g/kg for 4-5 days) were more effective than steroids used at different dose and schedule in achieving a platelet count > 20 x 10^9/L by 48 hours** (Beck et al, 2005) **although no difference was found in terms of 6-month overall response rate and relapse incidence**.

Several different schedules have been used for initial treatment with steroids. In 4 randomized trials different doses of prednisone were compared: - prednisone 1 mg/kg/day for 3 weeks vs. 0,25 mg/kg/day for 3 weeks (Bellucci et al, 1988); - 1.5 mg/kg/day vs. 0.5 mg/kg/day until positive response (Mazzucconi et al, 1985); -prednisone 2 mg/kg vs. methylprednisolone 5 mg/kg/day iv for 5 days or 30 mg/kg/day for iv. r 3 days (Fujisawa et al, 2000); - methylprednisolone 30 mg/kg/day for 7 days vs. 50 mg/kg/day for 7 days (Albayrak et al, 1994). In general, no difference in terms of response rate was found with high dose of steroids ($\geq$ 2 mg/kg/day) whereas low dose of prednisone resulted as effective as intermediate dose (0.25 mg/kg/day vs. 1 mg/kg/day) (Bellucci et al, 1988) in one study and less effective in another study (0.5 mg/kg/day vs.1.5 mg/kg/day) (Mazzucconi et al, 1985).

Four randomized studies in adult patients compared short high-dose treatment with dexamethasone 40 mg/day for 4 days for 1-3 courses in 6 months with intermediate dose of prednisone at the dose of 1 mg/kg/day for 4 weeks (Wei et al, 2016; Bae et al, 2010; Din et al, 2015; Mashhadi et al, 2012) showing that **1 or 2 initial course with dexamethasone was associated with overall and complete response compared with prednisone** (Wei et al, 2016); moreover, a higher response rate was observed in patients receiving also a maintenance treatment with 0.035 mg/kg/day of dexamethasone during the interval between courses (Din et al, 2015). Although the long-term response rate was not different among these four trial, high-dose of dexamethasone was associated with improved platelet count by day 14 , fewer bleeding episodes and less toxicity. In particular, Cushing syndrome and weight gain was reported in more than 10% of patients in the prednisone arm whereas other adverse events observed in more than 5% of patients were for the dexamethasone arm mood disorders and insomnia, and for the prednisone arm, dizziness, hyperglicemia, hypertension, insomnia, peptic ulcer (Wei et al, 2016, Mithoowani et al, 2016). This makes the use of dexamethasone preferable in patients where a rapid increase of platelet count is searched.

Recommendations

34. When corticosteroids are chosen as initial treatment for ITP, **intermediate-high dose of prednisone** or **methylprednisolone** have the **same efficacy (I- High quality 8.3-A)**
35. The use of high-dose steroids for **short term** period is associated with **fewer adverse effects** whereas long-term corticosteroids should be avoided in children with ITP because of side effects **(EO- Moderate quality 8.3-A)**

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11. Therapy with IVIg (intravenous immunoglobulin)

Maddalena Casale, Francesca Rossi

When a treatment is indicated for newly diagnosed children with ITP, intravenous immunoglobulin (IVIg) has been recognized as a first line therapy (Neunert et al2011). Treatment with IVIg has proved to be safe and effective in children with ITP. It is generally well tolerated with transient headaches, nausea, vomiting and fever as the most common side effects.

Platelet counts rise within 48 hours in 70-80% of patients with a peak in 2-7 days (Rodeghiero et al, 2009) **and this effect lasts for two to four weeks** (Blanchette et al, 1993; Blanchette et al, 1994; Fujisawa et al, 2000; Duru et al, 2002; Ancona et al, 2002).

Initial response to IVIg is reported as more rapid as that seen with high dose parental glucocorticoids or other treatments (Ancona et al, 2002; Fujisawa et al, 2000; Lioger et al, 2019). For this reason, it was suggested to prefer IVIg for patients that may benefit from higher platelet counts during the first weeks after diagnosis, for example toddlers with a higher tendency to fall and bump or pubertal girls with a risk of menorrhagia, or patients who need surgery (Heitink-Pollé et al, 2018).

Several dosing regimens have been used in the treatment of ITP, varying between 0.4-1.0 gram per kilogram bodyweight per day for 1-5 days, but in the most recent American Society of Hematology guidelines (Neunert et al, 2011) and in the previous AIEOP guidelines (De Mattia 2000) **a single dose of 0.8-1.0 gram per kilogram is recommended**, due to the lower cost and the fewer side effects with similar efficacy compared to other dosing regimens.

Observational studies (Bruin et al, 2004; Tamminga et al, 2009) and a meta-analysis (Heitink-Polle et al, 2014) suggested **a lower incidence of chronic ITP in children that were treated with IVIg**, but **in a recent multicenter randomized trial** (Treatment with or without IVIg for Kids with ITP trial – TIKI trial), **IVIg treatment at the onset of the disease did not result in a lower rate of chronic ITP** compared to the no-treatment group. However, this study reported an higher early complete response rates and less bleeding events in the IVIg group (Heitink-Pollé et al, 2018).

Furthermore, an association between the response to IVIg treatment and leucocyte IgG-Fc receptor gene polymorphisms has been reported, **as no patient homozygous for the FCGR2B-232T responded to treatment**, while all complete responders to IVIg displayed the FCGR2B-232I allele (Heitink-Pollé et al, 2018). In the light of this observation, **in non-responder patients to a first treatment with IVIg, analysis of Fc receptor gene polymorphisms is advisable** in order to avoid repeated and useless IVIg treatments in those patients with genetic variations observed in non-responder patients (Heitink-Pollé et al, 2018).

Although IVIg treatment may increase platelet counts in most children with newly diagnosed ITP, risks, costs and benefits of treatment should be carefully weighed. Although total admission was longer in patients treated with corticosteroids, the total costs related to the IVIg treatment have been reported higher than corticosteroid use in children with ITP (Okubo et al, 2018).

Recommendations

36. **IVIg** is a **first line therapy** in children with newly diagnosed ITP **(I- High quality 8.8-A)**
37. IVIg treatment can be used if a rapid increase in the platelet count is needed during the first weeks after diagnosis **(I- High quality 8.7-A)**
38. The recommended dose is **0.8 g/kg** in a single dose, with possible repetition **(II-EO- High quality 8.6-A)**

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12. Therapy with Anti-D (Anti-D Immunoglobulin)
Antonio Marzollo

Anti-D Immunoglobulin (anti-D) is a preparation of human immunoglobulin directed against the Rh(D) antigen. The Rh(D) molecule is present in the surface of red blood cells (RBC) of individuals carrying a Rh(D)-positive blood group, which represent 85% of the Italian population (comprising either RhDd or RhDD individuals). The anti-D is derived from human plasma obtained from donors with a high anti-D titer (Cooper 2009). The main clinical use of anti-D is the prevention of Rh(D) isoimmunization in Rh(D)-negative individuals exposed to Rh(D)-positive RBC by feto-maternal hemorrhage or transfusion and this is the only currently approved indication for anti-D in Europe (Rhophylac Prescribing information, 2016).

Since the 1990s, several clinical trials demonstrated that anti-D is effective also in the treatment of acute and chronic ITP in patients with Rh(D)-positive blood group and this indication is currently approved in the USA by the Food and Drug administration (FDA) (Blanchette et al, 1994; WinRho ® Prescribing information, 2010). The proposed mechanism of action involves the **binding of the anti-D to the surface of RBCs**. Anti-D causes **a preferential clearance of opsonized RBCs rather than the antibody-bound platelets**, resulting in the blockade of the reticuloendothelial system and **increase in platelet count**. Due to this mechanism, the administration of anti-D may result in a positive direct antiglobulin test (Ware & Zimmerman 1998; WinRho ® Prescribing information, 2010; Despotovic et al, 2012).

Treatment with Anti-D in children with acute ITP results in a **complete response in around 70-80% patient**s and a **mean duration of response of 21-46 days** (Scaradavou et al, 1997; Cooper 2009; Papagianni et al, 2011; Kane et al, 2010; Celik et al, 2013; Despotovic & Neunert, 2013). Several studies and a recent meta-analysis suggest that **anti-D is significantly inferior to IVIg** at increasing platelet counts, but the difference is small and of uncertain clinical significance (Table I) (Blanchette et al, 1994; Shahgholi et al, 2008; Lioger et al, 2019). A factor influencing the response might be the RHD zygosity, with hemizygous patients (RhDd) responding better than homozygous subjects (RhDD) (Despotovic et al, 2013). A longer response as compared to IVIg has been reported in a small clinical trial involving patients with HIV-associated acute ITP (Scaradavou et al, 2007).

The proposed doses of anti-D for patients with acute ITP range between 50 and 75 µg/kg, with **75 µg/kg being the most frequently employed dose** in the clinical practice (O'Brien et al, 2019). A dose of 75 µg/kg results in a more rapid and prolonged increase in platelet count than 50 µg/kg, without a significant worsening of the rate of adverse events (Newman et al, 2001; Tarantino et al, 2006; Swain et al, 2016). Anti-D is administered as **a brief intravenous infusion** (slow IV push over 3-5 minutes) and can be repeated every 2-4 weeks (WinRho® Prescribing information, 2010). Subcutaneous administration has been proposed but is rarely used for patients with ITP (Meyer et al, 2004; Kjaersgaard et al, 2009; Thompson et al, 2013). The most frequent adverse events are systemic reactions and hemolysis. The systemic reaction (fever, chills, nausea, headache) occur less frequently with anti-D than IVIg (25% vs 31%) and are usually self-limited or controlled with symptomatic treatment (Long et al, 2012; Eghbali et al, 2016; Lioger et al, 2019). **Hemolysis is very frequent** in patients receiving treatment with anti-D Ig and is due to the destruction of anti-D coated red blood cells by the reticuloendothelial system (Garratty, 2009). In the days following the administration of anti-D, a decrease in Hb concentration of 0,5 – 2 g/dL of Hb is observed in most patients but does not generally lead to clinically significant adverse events (Celik *et al*, 2013). In some patients the hemolytic reaction might be exaggerated (resulting a fall in Hb concentration > 2g/dL) and result in disseminated intravascular coagulation, acute kidney injury, acute respiratory failure and potentially death (Gaines, 2005). **The incidence of severe acute hemolytic reaction (AHR) is estimated in 1:1115**

patients (0.02-0.04%). Risk factors for AHR include underlying autoimmune hemolytic anemia, renal insufficiency, malignancy, cirrhosis, other autoimmune disorders, and active infection (in particular acute or recent EBV infection) (Despotovic *et al*, 2012; Cooper, 2014; Kossiva *et al*, 2013; Yacobovich *et al*, 2016). Considering these side effects, the FDA has issued a black-box warning on the risks of intravascular hemolysis, DIC, and acute renal failure (ARF) in March 2010, which led to a reduction in the use of the anti-D in the US (WinRho ® Prescribing information, 2010; Long *et al*, 2012; Thompson *et al*, 2013).

Anti-D for ITP is not marketed in Italy and is not available in most if not all European countries: in June 2009 the manufacturer notified the European Medicines Agency the decision to withdraw all marketing authorizations in Europe because of **concerns about the benefit-to-harm balance** in the ITP therapy.

Table I. Advantages and disadvantages of anti-D for acute ITP, as compared to IVIg

Pros	**Cons**
Shorter infusion time	Can be used only in Rh(D)-positive patients
Lower incidence of systemic reaction	Risk of severe acute hemolytic reaction
Lower cost	Modestly inferior in increasing platelet count
	Not licensed for ITP in Italy

Table II. Suggested tests prior to the administration of anti-D. Adapted from Despotovic et al, 2012.

Test	**Rationale**
Personal history and physical examination	Screening for malignancy, organ failure, active infections, autoimmune disorders
Complete Blood Count and reticulocytes	Screening for pre-existing anemia
Serology for EBV or EBV-DNA	Screening for active EBV infection
Direct antiglobulin test and other autoantibodies	Screening for autoimmune hemolytic anemia and other autoimmune disorders
Urinalysis	Screening for renal disorders and hemoglobinuria
Renal and hepatic function testing	Screening for renal and hepatic dysfunction

Table III. Suggested follow-up after anti-D infusion, suggested by FDA (WinRho ® Prescribing information, 2010) and adapted from Despotovic et al, 2012; Cooper, 2014.

Suggested action	**Time from anti-D administration**
Information to the caregiver regarding signs of hemoglobinuria, anemia, renal and liver failure	Not applicable

Monitoring in a healthcare setting and full bio-chemical and hematological work-up in case of signs of AHR	8 h since the administration
Urinalysis/dipstick	+ 2 h, + 4h, + 8h
Complete blood count	1-3 days

Recommendations

39. Anti-D at the dose of 50-75 mg/kg is an efficacious option for **Rh(D)-positive** children with acute ITP **(II- High quality),** particularly **indicated** in patients with **HIV-associated ITP (V- Low quality 7.0-B)**

40. Anti-D treatment **is contraindicated in patients at high risk for AHR** (Acute Hemolytic Reaction; see table 2 in the text), and patients receiving anti-D should be monitored for AHR (see table 3 in the text) **(EO- Very low quality 7.8-B)**

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13. Combined therapy

Emilia Parodi

The International consensus report on the investigation and management of primary immune thrombocytopenia states that **combining first-line therapies is appropriate in emergency setting: prednisone and IVIg are recommended for the emergency treatment of patients with uncontrolled bleeding**. High-dose methylprednisolone (HDMP) may also be useful in this setting. (Provan et al, 2010).

Combination treatment is more effective in immediately raising the platelet count than any one of these treatments alone (Boruchov et al, 2007)**.**

If life-threatening haemorrhage occurs, other therapies that work rapidly include platelet transfusion, possibly in combination with IVIg, and emergency splenectomy (Provan et al, 2010, Neunert & Cooper 2018).

TPO-Ras agents have little impact on the acute bleeding event (usually there is a five-to-seven-day delay before a response is seen); however, they may boost and prolong the platelet response in the days following the bleeding event which may reduce the risk of re-bleeding. Romiplostim with rituximab (Contis et al, 2013) and eltrombopag with dexamethasone (Gómez-Almaguer et al, 2014) have been used in combination with other immunosuppression in acute disease in adults with good responses and these are likely to be used more frequently also in pediatric patients, even though this practice is not standardized, yet.

Also, **patients who don't have an adequate response to initial therapy with first-line agents may benefit from additional courses of first-line agents in combination**. In the AIEOP experience combined therapy (IVIg 0.4 g/kg daily on days 1 and 2, and methylprednisolone 20 mg/kg daily on days 1-3) was administered to 7 patients with newly diagnosed ITP who did not respond to the administration of a single therapy (either intravenous immunoglobulins or steroids) and to 22 children with persistent and chronic disease who required frequent administrations (i.e. more frequently than every 30 days) of either immunoglobulins or steroids (at the same standard dosages) in order to control active bleeding. A response (i.e., rise in platelet count >50×10 ^{9}/L and remission of active bleeding) was observed in more than 2/3 patients with newly diagnosed ITP and patients in the chronic/persistent phase of disease had a significantly longer median period of remission from symptoms compared with the previous longest period of remission. (Parodi et al, 2014)

Combined approach with cytotoxic drugs has been used as second-line approach in refractory symptomatic adult patients (Boruchov et al, 2007). Due to the limited experience in children, the use of such drugs is not recommended in pediatric patients.

Recommendations

41. We recommend using combined therapy in the emergency setting in **patients with uncontrolled bleeding (EO- Very low quality 8.2-A)**
42. Also, children **who don't have an adequate response to initial therapy with a single first-line agent** (IVIg or steroids) may benefit from additional courses of first-line agents in combination **(V- Very low quality 7.6-B)**
43. We recommend **IVIg 0.4 g/kg daily on days 1 and 2**, and **methylprednisolone 20 mg/kg daily on days 1-3 (V- Low quality 7.1-B)**

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14. Therapy with thrombopoietin receptor agonists
Giuseppe Lassandro, Giuseppe Palumbo

Thrombopoietin receptor agonists (TPO-RAs) are the only therapeutic option for ITP that increases platelet production. In addition to promoting platelet production from existing megakaryocytes, TPO-RAs may also enhance proliferation of megakaryocytes in bone marrow, as suggested by in vitro studies and clinical trials in patients with aplastic anemia. Importantly, TPO-RAs may reduce platelet destruction by restoring Treg and regulatory B-cell activity, thereby attenuating the autoimmune response to platelets. Moreover, preliminary evidence suggests that autoantibody levels in patients with ITP may progressively decrease with TPO-RA treatment, which may contribute to restoration of immune tolerance to platelets. TPO-RAs provide a non-immunosuppressive option for children who require an increased platelet count. (Zufferey et al, 2017).

TPO-RAs represent **a highly effective and well-tolerated treatment** for achieving hemostatic platelet counts (higher than 50×10^9/L) in children with ITP (Tarantino et al, 2016; Bussel et al, 2011; Elalfy et al, 2011; Grainger et al, 2015; Bussel et al, 2015)

Two TPO-RAs agents, romiplostim (subcutaneous, competitive agonist) and eltrombopag (oral, non-competitive agonist), are currently European Medicine Agency (EMA) approved for chronic (more than 12 months from diagnosis) ITP patients, one year of age or older who are refractory to other treatments (e.g., corticosteroids, immunoglobulins). Eltrombopag has also been approved to be used six months after diagnosis. TPO-RAs agents can be used in newly diagnosed ITP only as off label therapy.

Analyzing Eltrombopag, the main issue is the dietary limitations. A person who assumes eltrombopag must structure his diary supply on a strict diet: no food 2 hours before and after the meal and no calcium or iron 4 hours before and after the meal. Avatrombopag is similar to eltrombopag in relation to the bond with the TPO-receptor in the transmembrane domain and about being available orally. Potentially, it is not only highly effective, but it can also be assumed on a daily bases by mouth and does not have dietary restrictions. Development of avatrombopag has been complicated due to management complications. As a result, long-term studies are not actually available, despite the initial trial of Avatrombopag in ITP have begun more than 5 years ago (Bussel et al, 2014).

Despite the absence of large data in literature regarding the use of TPO-RAs in children with a newly diagnosed ITP, specialists are prescribing TPO-RAs to pediatric patients off-label and outside clinical trials, as reported in retrospective data. (Neunert et al, 2016).

A similar study underlined the role of Eltrombopag in newly diagnosed ITP in an adult cohort. (González-López et al, 2017).

The review of the literature showed that some authors tried the use of TPO-RAs in newly diagnosed ITP for severe refractory cases. These experiences are reported only for adult population (Rashidi et al, 2016; Tripathi et al, 2014).

Gómez-Almaguer in two trials proposed a starting therapy for ITP with TPO-RAs in association with dexamethasone and or rituximab as frontline treatment. Although a complete response at 6 months (platelets $\geq 100 \times 10^9$/L) was achieved in about 50% of patients is premature to start similar pediatric trials because approximately pediatric ITP is usually of short duration with at least two-thirds of patients recovering spontaneously within 6 months. In fact, the improvement of platelet production with eltrombopag may enhance the outcomes of ITP therapies: added to standard first-line therapy, it increased the durability of response and decreased the relapse rate. Thus, in patients with newly diagnosed ITP, when used as frontline therapy, eltrombopag may help reduce the need for additional courses of steroid or IVIg (Gómez-Almaguer et al, 2014; Gómez-Almaguer et al, 2016).

In addition, a relatively short duration of eltrombopag treatment early in the disease may increase Treg activity, thereby potentially altering the natural course of the disease without the need for continued administration (Bao et al, 2010).

Recommendations

44. Patients with **bleeding score 0-2** after first line treatment can be managed with **observation alone**, irrespective of the platelet count. **Frequent platelet counts should be avoided** to improve QoL. **(EO-Low quality 8.0-B)**
45. The use of **second line agents (TPO-RA, MMF and sirolimus) in newly diagnosed ITP** children **must be limited to selected patients** with **severe bleeding symptoms**, refractory to IVIg and steroids **(EO-Low quality 7.9-B)**
46. In patients with **persistent ITP** and **bleeding score > 2** or **bleeding score 0-2** in the presence of **special needs (see table "Special needs"), TPO-RA can be considered** as treatment option **(V-Moderate quality 7.9-A)**
47. The use of TPO-RAs **in association with other complementary therapies** (e.g., immunosuppressive agents) could improve the platelet rise in selected patients **(EO- Very low quality 7.0-B)**

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15. Therapy with immunosuppressive drugs
Maurizio Miano

Immunosuppressive drugs offer a treatment option in patients with persistent/chronic ITP thanks to promising results shown both in adult and in pediatric population. Mychofenolate mofetile (MMF) is an immunosuppressor which reduces T and B-cells proliferation by inhibiting the inosine monophosphate dehydrogenase (Allison, 2000). In the largest reported cohort of adults treated with **MMF** for ITP, **response to the treatment was obtained in 52%** of patients and was complete in 33% (Taylor et al, 2015). Experiences on pediatric population showed even better results as shown the largest reported series of **children** which achieved a **response in 64%** of cases that was complete in 46% (Miano et al, 2016). The same study also showed that selected populations of patients with an underlying **"ALPS-like" disorder** or with **Evans Syndrome** had an even better outcome (**73% and 81%,** respectively) thus suggesting that children with an underlying immune-dysregulation may particularly benefit from immunosuppressive treatment. These data are in line with what previously published by Rao et al (Rao, 2005) on the efficacy of MMF in patients with ALPS. However, very few patients were reported as receiving immunosuppression during the acute phases of the disease.
Sirolimus is a mTOR inhibitor that targets the PI3K/AKT/mTOR pathway thus modulating B- and T-lymphocyte proliferation and, more specifically, abnormal T-cells. Contrary to MMF, it also promotes the proliferation of regulatory T-cells. It has been shown to be effective in patients with Autoimmune Lymphoproliferative Syndrome (ALPS) and other primary or secondary autoimmune cytopenias (Miano et al, 2016). A prospective multi-institutional trial showed that **sirolimus** was effective and safe in refractory cytopenias including few cases of ITP (Bride et al, 2016).
Two cohort of children with chronic persistent ITP and Evans syndrome have been reported in 2 retrospective studies on 17 and 19 cases, respectively, showing an overall **response in 68-78%** of patients being complete in 50-53% (Jasinski et al, 2017, Miano et al, 2018). In one of these studies, patients were rescued after failure of MMF therapy and showed that **response rate was higher** in patients with an underlying **ALPS-like** immune-dysregulation (89%) compared with the ones with primary disease (50%) (Miano et al, 2018). However very few data are available on patients treated within the first 3 months.

Recommendations

48. In patients with **persistent ITP** and **bleeding score > 2** or bleeding score 0-2 in the presence of **special needs** (see table "Special needs"), **MMF and Sirolimus** can be considered as treatment option, especially in the context of **ALPS/ALPS-like syndromes (V-Moderate quality 8.1-A)**

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16. Therapy with Rituximab
Emilia Parodi

Rituximab is a chimeric humanised IgG1/j monoclonal antibody first developed for the treatment of adult B-cell non-Hodgkin lymphoma. It targets the CD20 antigen on the surface of normal and malignant premature and mature B lymphocytes and induces B cells destruction by means of both complement mediated lysis and antibody-dependent cellular cytotoxicity (Golay et al 2000). Induction of apoptosis has also been demonstrated. On the assumption that selective B-cell depletion stops the production of autoantibodies, in the past 15 years the use of rituximab has been extended to the treatment of autoimmune diseases (Ghanima et al 2015).

Several uncontrolled open-label studies support its **use in pediatric patients with chronic ITP**, suggesting **an initial response rate of approximately 40 to 50 %**, **falling to approximately 25 %** over follow-up of two to five years; adolescent females are more likely than younger children and males to achieve remission (Parodi et al 2009; Parodi et al 2006; Patel et al 2012).

Mild, transient side effects (urticarial rash, headache, fever, scratchy throat, and chills) may occur during the infusion. Serum sickness has been reported in 5 to 10 percent of children with ITP treated with rituximab Progressive multifocal leukoencephalopathy has been reported as a very rare but very serious complication of rituximab therapy, too (Arnold et al 2007; Liang et al 2012).

The International consensus report on the investigation and management of primary immune thrombocytopenia and the 2011 ASH ITP guidelines consider **Rituximab as a second-line agent** generally reserved for patients with ITP lasting ≥3 to 6 months whose symptoms and risks are not adequately controlled using standard therapies (Neunert et al, 2011). **However, second-line therapies may be used sooner in rare cases that fail to achieve control with first-line therapies**.

Published guidelines, however, do not clearly state define the priority of use of rituximab compared to other second-line drugs such as thrombopoietin receptor agonists and alternative immunosuppressive agents (Neunert et al 2011; Provan et al 2010). The choice among these options is complex and highly dependent on the values and preferences of the patient and family. Sometimes, in adolescent female patients and patients with other autoantibodies rituximab is the preferred choice (expert opinion).

Recommendations

49. Rituximab can be considered in **selected** patients with **persistent** ITP with **severe bleeding symptoms**, refractory to first line agents (IVIg and steroids) and TPO-RA **(EO-Very low quality 7.6-A)**
50. Rituximab can be an option to **avoid splenectomy. If Rituximab fails, the splenectomy should be postponed until reconstitution of immune response is achie**ved **(EO-Very low quality 7.5-B)**

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17. Hemorrhagic emergency and supportive treatment
Fiorina Giona and Alessandra Tolva

Emergency treatments

Bleeding manifestations in patients with immune thrombocytopenia (ITP) range from mild skin bruises to life-threatening intracranial hemorrhage (ICH). Severe bleeding is distinctly uncommon when the platelet count is >30 × 10^9/L and usually only occurs when the platelet count falls <10 × 10^9/L. Different studies analyze the management of severe bleeding in ITP. A large data study showed no relationship between the initial treatment in children with no to mild bleeding at diagnosis and subsequent severe hemorrhage (Neunert et al, Blood 2008). An interesting study conducted by Segel et al, showed an important association between life-threatening bleeding, including intracranial hemorrhage, often associated with "wet purpura" (as manifested by mucosal bleeding) and the concomitant use of anti-platelet agents such as aspirin or dipyridamole, or head trauma. The study also underlines how the complications of treatment may exceed the complications of the disease at platelet levels above 10 x 10^9/L in children with ITP (Segel et al, 2009). It is also observed that the **platelet transfusion** should be performed only in a life-threatening bleeding. In fact, although the platelet count may not increase substantially, bleeding often can be controlled.

Former AIEOP recommendations are:

-In ITP patients with massive and/or life-threatening bleeding is recommended **IVIg** at a **dose of 0.8 g/kg**.

- Alternatively, intravenous **methylprednisolone at a dose of 15–30 mg/kg/day** is administered for 3 days (maximally 1 g).

- In select cases, it is possible to **combine treatments** and **add platelet transfusion**.

-The second choice of treatment is intravenous anti-D (recommended dose 50 mcg/kg) in Rh-positive and non-splenectomized patients. (De Mattia et al, 2010).

On other hand, it is interesting to underline the differences in the management and treatment of severe bleeding ITP in other non-European centers of reference, confirmed by the 2011 American guidelines (Blanchette et al, 2010; Neunert et al, 2011): the axiom is that management of symptoms or signs suggestive of organ- or life-threatening hemorrhage should involve measures that have the potential to increase the circulating platelet count rapidly. These measures include:

- Immediate **IV administration of methylprednisolone** (30 mg/kg, maximum dose 1 g) + **platelet transfusion**. After administration of IV methylprednisolone and platelets, an infusion of **IVIg (1 g/kg**) should be started with IVIg and methylprednisolone repeated daily as indicated clinically, generally for at least 1 to 2 days. **Survival of transfused donor platelets may be improved after IVIg therapy**.

- **Continuous infusion of platelets** may be beneficial in selected cases.

- Depending on the specific clinical circumstances, an **emergency splenectomy** may need to be considered.

- Experience with recombinant factor VIIa is limited but this hemostatic agent can be administered rapidly and should be considered in critical situations (Larsen et al 2013; Gurion et al, 2012; Salama et al 2009).

A large review conducted by an Indian center (Bansal et al, 2014), led to similar results with some slight difference and specification:

- **Methylprednisolone in combination with IVIg or anti-D**. IVIg and methylprednisolone may be repeated for at least 1–2 days, based on response.
- **Platelet transfusions** are indicated only in the setting of life-threatening bleeds, at least 2–3 fold higher dose of platelets is administered to temporarily increase the circulating platelet count.

Survival of transfused platelets may be improved with concurrent IVIg therapy. Continuous infusion of platelets may be beneficial in selected cases.

- Splenic artery embolization is performed to achieve a prompt rise in platelet count before splenectomy in patients unresponsive to conventional treatment.
- **Splenectomy** is indicated in life threatening bleeds unresponsive to first-line drugs or in a patient who is acutely ill and will benefit from an immediate rise in platelet count.
- In case of ICH, mechanical ventilation may be indicated.
- In case of **massive ICH** and raised intrachranial pressure (ICP), where neurosurgical intervention for evacuation of hematoma or decompression craniotomy may be urgently indicated, **splenectomy followed by craniotomy** in one sitting under the same anesthesia may offer the best chance.
- **Recombinant VIIa** has been used in ICH refractory to platelet enhancing agents as 'off-label use' at a **dose of 90– 120 µg/kg**, q 2–3 h, till the cessation of bleeding.
- Severe acute menorrhagia (defined as bleeding that requires >1 pad or tampon per hour or change in vital signs, indicating hypovolemia): **intravenous estrogens** and platelet enhancing drugs. Supportive management with tranexamic acid and iron supplementation is important.

Arnold (2015) underlines how patients with severe thrombocytopenia (<20 x 109/L) and significant bleeding **should be hospitalized.**

Table I. Recommendations for emergency treatments

Severe/life-threatening bleeding	**AIEOP GUIDELINES**	**AMERICAN GUIDELINES**	**INDIAN GUIDELINES**
1st line therapy	**IVIg** at a **dose of 0.8 g/kg**	Immediate **IV administration of methylprednisolone** (30 mg/kg, maximum dose 1 g) + **platelet transfusion.**	**Methylprednisolone in combination with IVIg or anti-D**. IVIg and methylprednisolone may be repeated for at least 1–2 days, based on response. **Platelet transfusions** are indicated only in the setting of life-threatening bleeds.
1st line alternatives	Intravenous **methylprednisolone at a dose of 15–30 mg/kg/day** is administered for 3 days	Combined therapy: After administration of IV methylprednisolone and platelets, an infusion of **IVIg (1 g/kg**).	
In select cases	**combined treatments** and **add platelet transfusion**	**Continuous infusion of platelets** may be beneficial in selected cases. an **emergency splenectomy** may also need to be considered.	**Splenic artery embolization** is performed to achieve a prompt rise in platelet count before **splenectomy** in patients unresponsive to conventional treatment. **Recombinant VIIa** has been used in ICH refractory to platelet enhancing agents as 'off-label use' at a **dose of 90– 120 µg/kg**
2nd line therapy	**intravenous anti-D** (recommended dose 50 mcg/kg) in Rh-positive and non-splenectomized patients		

Supportive treatment

Antifibrinolytic agents has been shown to reduce bleeding in many surgical and medical settings including trauma, cardiovascular operations, orthopedic arthroplasty, liver transplantation and menorrhagia. To our knowledge, only one previous study has reported on antifibrinolytic drugs in immune and non-immune thrombocytopenia.

From our own experience and of others (personal communication), tranexamic acid (TA) has been frequently used in the management of children with severe ITP, above all in very young children and in adolescent females. Apart from a single case report in a child after dental extraction, the use of TA in ITP is only mentioned in isolated reviews on ITP treatment.

Due to the paucity of the evidence, the use of antifibrinolytic agents (**tranexamic/caproic acid**) is **optional**.

In patients with persistent epistaxis, menstrual, or gastrointestinal bleeding, aminocaproic acid may be a useful adjunct to treatment, and can be given orally or intravenously. **When the bleeding is life threatening, platelet transfusions should be given**. Although the platelet count may not increase substantially, bleeding often can be controlled (Segel et al, 2009). Tranexamic acid is preferred due to longer half-life, higher potency, and lower toxicity. The dose of **tranexamic acid is 25–50 mg/kg q 6–8h**. Aminocaproic acid is administered as a stat dose of 100– 200 mg/kg (maximum: 10 g), followed by 50–100 mg/kg/ dose q 6 hourly (maximum dose: 5 g). **Antifibrinolytic agents are contraindicated in hematuria**; formation of clots can result in colic and obstruction of outflow from the renal pelvis.

Persistent epistaxis (>20 minutes): anterior nasal pack that remains in situ for ≤48 h, without prophilactic antibiotics.

Menorrhagia in an adolescent with ITP is commonly managed with oral contraceptive pills containing estrogen and progestogen or cyclic high dose progestins. (Bansal et al, 2014)

Recommendations

51. **IVIg** (1-2 g/kG) is proven to have the most rapid onset of action and should be considered along with **high-dose corticosteroids** with the aim of increasing the platelet count **(I- High quality 8.4-)**
52. **Platelet transfusions** are indicated in the setting of life-threatening bleeds. Survival of transfused platelets may be improved with **concurrent IVIg therapy**. **Continuous infusion of platelets** may be beneficial in selected cases. Although the platelet count may not increase substantially, bleeding often can be controlled **(EO- Very low quality 8.0-A)**
53. Administration of **recombinant factor VIIa** should be considered in critical situations, but the treatment is off label and with very limited experience **(EO- Very low quality 6.8-B)**
54. In case of **massive ICH** and raised intracranial pressure (ICP), where **neurosurgical intervention** for evacuation of hematoma or decompression craniotomy may be urgently indicated, **splenectomy** in the same surgical sitting may offer the best chance **(EO- Very low quality 6.8-B)**
55. Control of **bleeding from mucosal surfaces**, particularly epistaxis, gum bleeding and menorrhagia can be aided with antifibrinolytic agents. **Tranexamic acid is preferred** due to longer half-life, higher potency and lower toxicity. The dose of tranexamic acid is 25–50 mg/kg q 6–8h. **Antifibrinolytic agents are contraindicated in hematuria**; formation of clots

can result in colic and obstruction of outflow from the renal pelvis **(V- Very low quality 8.0-A)**

56. **Menorrhagia** in an adolescent with ITP is commonly managed with **oral contraceptive** pills **(V- Very low quality 7.5-B)**

Emergency splenectomy

Splenectomy is considered inappropriate for children with newly diagnosed or persistent ITP (Kuhne et al, 2013). It is generally deferred for as long as possible (Bhatt et al, 2018; Neunert et al, 2018).

Some different considerations can be made in case of emergency conditions, as organ or life-threatening situations in children, as with adult patients. **In special circumstances, emergency splenectomy should be considered** (Blanchette et al, 2008; Provan et al, 2010; Arnold et al, 2015). **It may be indicated in life-threatening bleeds unresponsive to first-line drugs or in a patient who is acutely ill and will benefit from an immediate rise in platelet count** (Bansal et al, 2014).

Emergency management of thrombocytopenia-associated bleeding in ITP requires a combination of treatments, at least two, including splenectomy, which is generally not the first choice, to improve the platelet count quickly and maintain safe platelet levels at least until the bleeding subsides. (Mithoowani et al, 2017).

In truly life-threatening bleeding, emergent splenectomy (with or without IVIg and/or corticosteroids, usually in concert with platelet transfusion) has been reported. This treatment should be regarded as heroic given the dangers of unplanned surgery, lack of immunization, risk of surgical bleeding and risk of managing bleeding while preparing a patient for major abdominal surgery (Neunert et al, 2011). Over the past 30 years, the literature search found few case reports or case series of adult and children patients with ITP complicated by life-threatening bleeding (mostly significant spontaneous gross hematuria or gastrointestinal bleeding or intracranial hemorrhage, ICH) who underwent successful emergency splenectomy (Zerella et al, 1978; Wanachiwanawin et al, 1989; Gural et al, 1998; Trimmings et al, 2009; Aladjidi et al, 2012; Sharma et al, 2012; Marescaux et al, 2013; Mithoowani et al, 2017). **Emergency splenectomy rate in pediatric newly diagnosed ITP is however low**.

Splenectomy is curative for ITP by removing both the primary site of platelet destruction and an important site of antiplatelet antibody production (Ghanima et al, 2011). The removal of spleen is still the more effective intervention targeting multiple pathophysiological mechanisms of ITP and the only one able to substantially modify the course of the autoimmune process (Rodeghiero, 2018). In children with chronic ITP, response rates are around 70-80% (Provan et al, 2010; Cooper 2014). A survey of severe bleeding, in particular ICH, in childhood ITP in the United States identified forty patients with ICH and 80 matched ITP control subjects were accrued. The patients with severe life-threatening bleeding received aggressive treatment and **emergency splenectomy was not associated with a better outcome** compared to other emergency treatment (Psaila et al, 2009).

Being emergency splenectomy an unplanned surgery, **the risk of surgical bleeding and the risk of managing bleeding while preparing the patient for intervention are very high** (Neunert et al, 2011). Despite first-line therapies, several patients will still have very low platelet count at the time of splenectomy (Bansal et al, 2013). Some more recent series demonstrate the feasibility and safety of laparoscopic splenectomy in patients with a preoperative very low platelets counts ($<1x10^9$/L), if normal prothrombin time and activated partial thromboplastin time (Wu et al, 2011) and meticulous

surgical technique is used (Cai et al, 2014). Rapid-effect medication should be used if the operation is an emergency, and it is necessary to urgently increase the platelet count in the preoperative period. IVIg (single dose or two doses) and/or corticosteroids (Rodeghiero 2018), usually in concert with platelet transfusion, is the most frequently chosen combination (Provan et al, 2010; Neunert et al, 2011).

Emergency splenectomy should not be delayed in view of severe thrombocytopenia, as risk of surgical bleeding is often exaggerated (Sharma et al, 2012). **An orchestrated teamwork with commitment of pediatric surgeon (sometimes also neurosurgeon), anesthetist, intensivist, and pediatric hematologist, with a case-by-case approach, is the key for such a life-saving procedure**.

Emergency splenectomy may be performed, in ITP patients with life-threatening bleeding, as an open or laparoscopic surgery. All types of surgical procedures may be performed in patients with an ITP diagnosis. The critical factor is whether the decision for the surgical procedure is emergency or elective. Both laparoscopic splenectomy and open splenectomy offer similar efficacy (Neunert et al, 2011; Li et al, 2017) and there is no association with the development of post-splenectomy infection based on operation type (Khasawneh et al, 2019). However, since the first laparoscopic splenectomy was reported in 1991 (Delaitre et al, 1991), this technique has gradually replaced traditional open splenectomy (Zheng et al, 2016). Laparoscopic splenectomy is widely used the preferred approach because it has fewer overall complications: it is less traumatic, engenders less postoperative pain and is associated with fewer wound infections, shorter hospitalization, faster recovery, and decreased cost (Ghanima et al, 2011; Cooper 2014; Chaturvedi et al, 2018).

If expertise is available, splenic artery embolization could be considered as a faster and safer bridge procedure prior to splenectomy. Splenic artery embolization is typically performed by interventional radiologist and it consists in nonsurgical intervention characterized by the transcatheter occlusion of the splenic artery and/or its branch vessels using metallic coils or other embolic devices and it takes about 30 minutes. There is often a prompt rise in platelet count, as in splenectomy. However, the infarcted spleen has to be surgically removed within the next few days to avoid complications of pain and fever. It benefits by controlling bleeds in a patient with severe thrombocytopenia and decreases the need for platelet transfusion during subsequent splenectomy. Data regarding the use of splenic artery embolization in ITP related life-threatening bleeding is limited (Molica M et al, 2016; Imbach 2010).

In adults, splenectomy-related complications include infection, bleeding, thrombosis, and relapse (Ghanima et al, 2012). In children, complications and risks of splenectomy are different compared to adults and include infectious diseases particularly in young children, with the potential of fast deterioration and septic shock, mainly caused by encapsulated bacteria (*Streptococcus pneumoniae, Neisseria meningitidis, Haemophilus influenzae type B)*. This risk is also higher in young children compared with adolescents. The risk of overwhelming sepsis is up to 3% in children (Kuhne et al; 2013, Provan et al, 2010; Anguita et al, 2016).

Since 1952, it has been evident that asplenic patients are at increased risk of infection (Thomsen *et al*, 2009), because the spleen is the largest accumulation of lymphoid tissue in the body. The spleen has an abundance of lymphoid tissue, including splenic macrophages that attack encapsulated organisms. In their absence, the ability to fight off these pathogens is severely diminished. The spleen is also a major site of early immunoglobulin M production, which is important in the acute clearance of pathogens from the bloodstream (Sinwar 2014). Moreover, surgical morbidity and mortality is of concern. The risk of infection is the major cause of mortality after splenectomy (Nomura 2016).

In emergency splenectomy, it is not possible organize preoperative vaccinations. Vaccinations against encapsulated bacteria should be performed after surgery. **It is optimal to start immunizations at least two weeks postsplenectomy, because the vaccine response is lower in the two first weeks after splenectomy because of the immunosuppressive effects of surgery** (Buzelè et al, 2016;

Gent L et al, 2017). However, the benefit of waiting two weeks post-splenectomy must be carefully weighed against the possibility that the patient may not be vaccinated at all; sometimes the best choice is to vaccinate the child before discharge from hospital. (Salvadori et al, 2014, Rubin et al, 2014). **Yearly seasonal influenza vaccine is recommended**, starting at six months of age, to lower the risk of secondary bacterial infections. All asplenic patients travelling to less developed areas of the world may be at risk of *Salmonella typhi* infection and should be immunized for *Salmonella typhi*. Other preventive measures include avoiding malarial areas, avoiding dog bites. Parents and household contacts of asplenic children should receive all age-appropriate vaccines and the yearly influenza vaccine (Salvadori et al, 2014).

Prophylactic antibiotic therapy post-splenectomy with penicillin or alternative antibiotics in the case of penicillin allergy is recommended based on expert opinion rather than evidence. The duration of such therapy including lifelong prophylaxis is not proven (Kunhe et al, 2013). **Antibiotic prophylaxis is recommended until the child is five years of age post-splenectomy** and **for a minimum of two years for children older than 5 years** of age post-splenectomy and for a longer period if there has been a previous episode of severe infection or are conditions of particular infectious (Salvadori *et al*, 2014; Dionne *et al*, 2017). The greatest risk of serious infections was observed in the first years after splenectomy (Thomsen e*t al*, 2009). In the large Italian cohort of asplenic patients, 50% of serious infections were reported in the first 2 years after splenectomy, confirming the need for very close supervision particularly in the first years after splenectomy (Casale et al, 2014). However, the risk of infection persists throughout life, so it is recommended to **educate patients and family members about the risks associated with asplenia**, preventive measures that can be taken and interventions that are necessary when a child develops a febrile illness.

Finally, the initial reactive thrombocytosis immediately following a splenectomy is to be monitored and very high trombocytosis (greater than 1.000.000 platelets/mm^3) may deserve treatment by aspirin. (Dionne et al, 2017). Other potential long term complications of splenectomy in adulthood include thromboembolic events and pulmonary hypertension, but they have not been described in childhood (Sarpatwari et al, 2010).

The long-term consequences of splenectomy are not well known (Cooper 2014).

Recommendations

57. In special circumstances, in presence of severe thrombocytopenia and **life-threatening bleeding**, emergency splenectomy may be considered for children and adolescents with ITP **(EO- Very low quality 7.2-B)**

58. Emergency splenectomy should be considered heroic, given the **dangers of unplanned surgery, lack of immunization, risk of surgical bleeding, and risk of managing bleeding** while preparing a patient for major abdominal surgery **(EO- Very low quality 7.7-)**

59. Emergency splenectomy should be evaluated on a case-by-case basis, by a team including at least pediatric surgeon, anesthetist, intensivist, and pediatric hematologist **(EO- Very low quality 8.4-A)**

60. **Vaccinations** against encapsulated bacteria (Streptococcus pneumoniae, Neisseria meningitidis, Haemophilus influenzae type B) should be performed promptly after emergency surgery, at least **two weeks postsplenectomy**. Yearly seasonal influenza vaccine is recommended **(EO- Very low quality 8.3-A)**

61. **Prophylactic antibiotics** should be administered **until the child is five years** of age post-splenectomy and **for a minimum of two years** for children older than 5 years of age post-splenectomy and for a **longer period if there has been a previous episode of severe infection** or are other **infective risk (EO- Very low quality 7.9-A)**

62. The risk of infection persists throughout life, so it is recommended to **educate patients and families about the risks associated with asplenia**, the preventive measures that can be taken and the correct management of post-splenectomy fever episodes **(EO- Very low quality 8.7-A)**

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18. Follow-up
Marco Spinelli

The management including diagnostic procedures, prophylaxis, treatment and follow-up of patients with primary immune thrombocytopenia (ITP) in childhood is controversial due to limited clinical data, difficulties in the estimation of individual bleeding risk and heterogeneity of pathophysiology potentially causing various treatment responses. We report the available evidence from the literature, derived from case series or reviews.

"The management of patients with ITP is complex and thus prevents the development of a straightforward management based on a simple algorithm. There are various aspects when considering treatment decisions, such as age, activities, health-related quality of life, potential co-morbidities and co-medications, psychic, social and economic aspects." (Kuhne et al*,* 2013).

"At 6 months' follow-up, 32% had a persistent platelet count $<150\times10^9$/L, but only 4.8% had a count <20." (Grainger et al, 2012).

"Although most children with immune thrombocytopenia (ITP) have a short duration of the disease, the very rare but significant complications of the disease often cause fear and anxiety among families of children with ITP. Identification of predictors of recovery would be beneficial for improving treatment decisions and QoL of both children and families." (Yacobovich et al, 2013).

"Current recommendations on management and information from recent studies are summarized with the goal of decreasing variable practice among providers and **improving patient-centred care**. Options for initially managing young patients with ITP who experience bruising, petechiae, or occasional mild epistaxis not interfering with daily living include **observation without pharmacotherapy as a first-line option**." (Friedman et al, 2019).

Although current guidelines suggest that most patients are just observed, children still receive platelet-enhancing therapies for fear of bleeding complications. Labrosse *et al*, in a controlled study (**IV**), showed tha following a standardised protocol achieved a 34% decrease in the hospitalisation rate ($p < 0.001$) at diagnosis. Prednisone treatment duration at diagnosis was also significantly reduced (13.1 versus 5.8 days, $p = 0.004$). Children over 3 years of age were 3.8 times less likely to be hospitalised (95% CI 1.94-7.61) and 2.3 times less likely to receive treatment (95% CI 1.2-4.3). There was no difference in the rate of persistent ITP (38% versus 30%, $p = 0.43$) or serious bleeding complications (7% versus 5%, $p = 0.70$). (Labrosse et al, 2017).

"The high rate of recovery from ITP between 7 to 12 months demonstrates, that the cut-off point of 6 months for the definition of chronic ITP does not adequately differentiate chronic from acute ITP. Most children with ITP have variable time to recovery with gradual improvement of platelet counts and disappearance of bleeding signs". (Imbach et al, 2006).

Recommendation

63. After the first-line treatment, the patient with bleeding score 0-2 and favorable prognostic factors should be managed with **observation alone (V- Moderate quality 8.1-A)**

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19. ITP and vaccines
Lucia Notarangelo

A viral infection precedes the onset of ITP in approximately two-thirds of pediatric patients (Blanchette et al, 2010) with **a possible molecular mimicry mechanism** in which self antigens are recognized as being similar to those of the viruses, provoking the production of autoantibodies (Perricone et al, 2014). With the same pathogenetic explanation, **a link between some vaccines and the onset of ITP** has been postulated, with a different risk depending on the type of vaccine (O'Leary et al, 2012; Okazaki et al, 2011; Rinaldi et al, 2014). In addition to antiviral cross-reacting antibodies against platelets antigens, other consituents of vaccines (for example the adjuvants) could elicit an immune response (Perricone et al, 2014). The real incidence of ITP after vaccine injection has been evaluated in several prospective and case-control studies, both in pediatric and adult patients, with no documented effect on ITP onset in the latter (Grimaldi-Bensouda et al, 2012). In pediatric age, **while the possibility of ITP onset after measles-mumps-rubella (MMR) vaccination is well recognized, the real incidence of ITP after vaccines other than MMR included in the pediatric vaccine schedule is not known, but it is considered negligible** (Rajantie et al, 2007; Cecinati et al, 2013; O'Leary et al, 2012; Cines et al, 2009). A 4-6 week period after vaccination was considered at risk of thrombocytopenia in most studies, with a median onset of 2 weeks (Sauvé L et al, 2009; Mantadakis et al, 2010). Particular attention has been paid to relatively recent vaccines (papilloma virus, HPV) as well as to those used more extensively over the years (influenza). The safety of HPV vaccine was questioned due to adverse events reported in relation to autoimmune phenomena (Baker et al, 2015) but these data were not confirmed in a large, prospective case-referent study (Grimaldi-Bensouda et al, 2017). Regarding influenza vaccines, some clinical case-reports highlight a possible association between new onset ITP and vaccination as well as a relapse of ITP following influenza vaccine (Hamiel et al, 2016); however, several epidemiological studies concerning the possible side effects of the influenza vaccine did not show a significant correlation between this vaccination and ITP (Halsey et al, 2015; Grimaldi-Bensouda et al, 2012; O'Leary et al, 2012).

MMR vaccine and the more recent measles-mumps-rubella-varicella (MMRV) vaccine are strongly recommended for the prevention of these viral diseases associated with a high risk of severe complications (Mc Lean et al, 2013). A decreased platelet count is a well-known, possible side effect of live virus vaccines containing measles (Oski et al, 1966). A meta-analysis, based on 12 studies performed with different methods (passive or active surveillance, retrospective, nested case-control studies), investigated: the incidence of ITP after MMR vaccination compared to the incidence of ITP after actual infections, its clinical course and outcome, the probability of recurrence of ITP after MMR vaccination (first shot or boost) in patients previously unvaccinated – or (with) MMR-associated ITP and the effect of MMR vaccine in patients affected by chronic ITP (Mantadakis et al, 2010). The global incidence of ITP after MMR vaccination ranged between 0.087 to 4/100,000 (per) vaccine doses (median 2.6) that is less than the incidence reported post measles or rubella infection (6 to 1,200/100,000 cases). **The outcome of ITP after vaccination was favorable, with a complete resolution in 93% of patients after 6 months** (Nieminen et al, 1993; Jonville-Bera et al, 1996; Rajantie et al, 2007; France et al, 2008; Jadavji et al, 2003). The clinical picture was comparable to that of post infectious ITP, with a slightly shorter hospitalization and a more self-limited clinical course. Only one fatal event was reported due to intracranial hemorrhage after an accidental closed head trauma (Jadavji T el al, 2003). **The safety of MMR vaccination (first dose or subsequent boost) in children with previous ITP, related or not to MMR vaccine, has been reported in several studies** (Miller et al, 2001; Black et al, 2003; France et al, 2008; Rajantie et al, 2007; Stowe et al, 2008; Bibby et al,

2008); **no patient, out of the 131 examined, presented a recurrence of ITP after 6 months from the MMR vaccine**.

MMRV vaccine has been compared to MMR vaccine + Varicella vaccine (V) injected separately the same day, about possible adverse events (Klein et al, 2015). **Concerning ITP, no increased risk was found between MMMR and MMR+V**; furthermore, MMRV was found to be associated with a similar probability of ITP as MMR. (Sauvé et al, 2010; Klein et al, 2015).

A recent document from the Italian Ministry of Health provides information on ITP and vaccinations in different scenarios (Gallo et al, 2018). Considering all the vaccines included in the pediatric schedule but MMRV, they are all recommended even in case of previous thrombocytopenia (possibly related or not to vaccines) with the foresight to postpone the vaccination for a few weeks in the presence of thrombocytopenia. **In children who have had a thrombocytopenia episode within 6 weeks after the MPR or MPRV vaccination, the possibility of avoiding the administration of a second dose should be considered evaluating the anti-measles antibody titer**. In case protection has already been achieved, the boost may be omitted. In children who do not have a proven seroconversion, the benefit of vaccination is considered to outweigh the risk, therefore the vaccination is recommended, given that the frequency of thrombocytopenia after the second dose is less than the one reported after the first shot.

Furthermore, it should be remembered that, **in case of previous use of blood products, it is necessary to postpone live-virus vaccinations (at least 6 months for unwashed red blood cells, 7 months for platelets and 11 months for high dose-intravenous Immunoglobulins)** in order to prevent that antibodies eventually present could interfere with the viral replication, with a subsequent reduction in the immune response (Gallo et al, 2018).

Recommendations

64. **All the vaccines** included in Pediatric vaccinations' schedule **are recommended** even in case of previous thrombocytopenia (possibly related or not to vaccine) **(III- Moderate quality 8.3-A)**
65. In children who have had an episode of thrombocytopenia within 6 weeks after the MPR or MPRV vaccination, **the possibility of avoiding the administration of a second dose** should be considered evaluating the anti-measles antibodies **(EO- Very low quality 7.5-B)**
66. **In children who do not have a proven seroconversion**, it is considered that the benefit of vaccination outweighs the risk of a possible thrombocytopenia, therefore **the vaccination is recommended (EO- Very low quality 7.9-A)**
67. In case of **previous** use of **blood products or Immunoglobulins, it is necessary to postpone live-virus vaccinations** (at least **6 months for unwashed red blood cells, 7 months for platelets and 11 months for High dose-intravenous Immunoglobulins)** in order to prevent that antibodies eventually present could interfere with the viral replication **(EO-Very low quality 7.5-B)**

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Health Related Quality of Life (HRQoL)
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Recent management guidelines state that HRQoL issues should be considered while making decisions on management in childhood ITP. However, these statements are based on clinical experience rather than results of research since HRQoL studies in childhood ITP are scarce.
Specific medical-related factors that may adversely affect the child's and family's quality of life are: anxiety while the child is thrombocytopenic, complications of treatments, duration of treatment, need for invasive interventions, costs or inconvenience of the treatment. Furthermore, many aspects of ITP itself and its treatments may affect HRQoL. Patient concerns include physical symptoms (e.g. visible bruising, epistaxis etc.), social limitations (e.g. adjustments to life due to physician visits, intravenous therapies, other issues with treatments e.g. the need to have an empty stomach in order absorb eltrombopag, etc.) and the fear of bleeding in public e.g. epistaxis, and psychological effects (e.g. negative body image, fear of bleeding, social limitations, fatigue (Hill QA et al, 2015; Sestøl et al, 2018).
Regarding pediatric patients, parents' anxiety may add further pressure on the HRQoL, since parents frequently put their children in a "protective bubble", irrespective of medical recommendations.
Fatigue is reported as an important HRQoL issue by ITP patients; it is defined by extreme and persistent tiredness, weakness or exhaustion, possibly associated with decreased functioning. It has been reported by 12-39% of ITP patients; it may influence many of the above-mentioned concerns and limitations (*Sestøl et al,* 2018).
Studies suggest an association between ITP and fatigue or irritability in children (Barnard et al, 2003; Blatt *et al*, 2010).
Although there are studies showing that HRQoL is low in ITP patients, Physicians are often not fully aware of the impact of diminished HRQoL on the life of their ITP patients. Moreover, **it is not clear whether improving the platelet count is sufficient to remediate decreased HRQoL, and it is unknown how treatments influence HRQoL**

Tools
Treatment side effects can be substantial and are often perceived by patients as worse than the symptoms of the disease. Traditionally, the assessment of a patient's response to the chosen treatment has been exclusively made by clinicians based on platelet count and clinical bleeding. However, given that many patients with very low platelet counts do not bleed, it is emphasized that treatment choice should rely more on symptoms, underscoring the importance of incorporating the patient's perspective by using patient-reported outcomes (PROs). As a future trend, several institutions facilitate real-time electronic PRO (e-PRO) symptom reporting and combine them with electronic health records. (Kirsch et al 2013). At present, the systematic use of PRO instruments in clinical care and research is rare.
A disease-specific instrument for the assessment of HRQoL in children with ITP has been developed: the Kids' ITP Tools (KIT). The KIT is available in three questionnaire versions for children aged 7–17.99 years (child self-report: Child KIT, fig. 1), for parents to complete on behalf of their child aged 2–17.99 years (parent proxy report: Proxy KIT) and for parents to complete for themselves (parent impact: Parent KIT); the latter focuses on the effect of the disease on the parent, otherwise known as "parental burden".

Figure 1. KIT (Kids' ITP): child

KIT (Kids' ITP): child

1. Were you bothered because you could not do the activities you like?
2. Did you feel sick?
3. Did you have a headache?
4. Did you feel tired?
5. Did you feel upset?
6. Were you bothered by your bruises?
7. Were you bothered by how you looked?
8. Did having your blood tests bother you?
9. Did staying in the hospital bother you?
10. Did getting your treatment through an IV bother you?
11. Did taking medicine bother you?
12. Were you upset that you could not do things with your friends?
13. Were you bothered by missing school?
14. Were you bothered because your parents watched you too much?
15. Were you bothered because you did not know enough about ITP?
16. Did you worry about your platelet count?
17. Did you mind not knowing how long your ITP will last?
18. Did you worry about your ITP coming back?
19. Did you feel cranky?
20. Was your appetite increased?
21. Did you feel more anxious?
22. Were you more frustrated with your parents than usual?
23. Were you upset that you could not do anything to make your ITP better?
24. Did your round face bother you?
25. Did having a bone marrow test bother you?
26. Did you worry about having a serious disease?

Figure 2. KIT (Kids' ITP): parent

KIT (Kids' ITP): parent

1. Did you wish you understood more about your child's ITP?
2. Did your child's bruising bother you?
3. Did leaving your child with a sitter bother you?
4. Did your child's ITP change your usual planning for activities?
5. Did you worry that your child had a serious disease such as leukemia?
6. Did you worry about possible serious viral or other infections caused by your child' s treatment?
7. Did you find it hard to protect your child against injury?
8. Were you bothered when your child could not do her/his usual activities?
9. Did you find it difficult/stressful to limit your child's activities?
10. Were you worried/frightened by the possible side effects of your child's treatment of ITP?
11. Did you find your child's changes in emotions or behavior stressful?
12. Did you worry when your child's platelet count was <20,000?
13. Did you worry about protecting your child against injury?
14. Did you need to know your child's platelet count frequently?
15. Did you find not knowing your child's platelet count stressful?
16. Did you feel your child was more likely to be seriously hurt than another child?
17. Did you feel that you had to be constantly watching out for your child?
18. Did you worry about what ITP could mean for your child's future?
19. Did you find it hard to deal with not knowing what the course of your child' s ITP would be?
20. Were you bothered that your child looked well but had a health problem?
21. Were you upset when your child had a bone marrow test?
22. Did you worry about a bleed into your child's head?
23. Did you spend time worrying if your child would get better?
24. Were you upset when your child needed an intravenous infusion (IV)?
25. Did you worry about your child's ITP coming back?
26. Did you feel that other parents who do not have a child with ITP

An Italian version "ITP QoL questionnaire" has been *validated (Giordano et al, 2014)* **(III).**
For the assessment of fatigue, there is a dedicated tool, FACIT-F (Functional Assessment of Chronic Illness Therapy) Questionnaire (fig. 3). However, this is not specific for ITP. Recently, an Italian questionnaire "La piastrinopenia ti stanca?" has been launched.

Fig. 3. FACIT-F (Functional Assessment of Chronic Illness Therapy) Questionnaire

		Per niente	Un po'	Abba-stanza	Molto	Moltis-simo
HI7	Mi sento affaticato/a.....	0	1	2	3	4
HI 12	Mi sento molto indebolito/a	0	1	2	3	4
An1	Mi sento svogliato/a	0	1	2	3	4
An2	Mi sento stanco/a.....	0	1	2	3	4
An3	Sono così stanco/a che ho difficoltà a iniziare qualunque cosa.....	0	1	2	3	4
An4	Sono così stanco/a che ho difficoltà a finire quello che ho cominciato	0	1	2	3	4
An5	Ho energia	0	1	2	3	4
An7	Sono in grado di svolgere le mie attività abituali (lavorare, andare a scuola, fare la spesa, svolgere attività durante il tempo libero, ecc.).....	0	1	2	3	4
An8	Ho bisogno di dormire durante il giorno.....	0	1	2	3	4
An 12	Mi sento troppo stanco/a per mangiare	0	1	2	3	4
An 14	Ho bisogno di aiuto per svolgere le mie attività abituali...	0	1	2	3	4
An 15	Sono frustrato/a perché sono troppo stanco/a per fare le cose che desidero fare.....	0	1	2	3	4
An 16	Devo limitare la mia vita sociale perché sono stanco/a.....	0	1	2	3	4

Comments

In conclusion, HRQoL in children with ITP is not influenced by bleeding severity or treatment modality, but only by the clinical course of the disease. Parental education and support along the course of the disease may contribute to an improvement of HRQoL.

Future studies and registry data should include HRQoL as an important outcome measure and explore the possible reasons for failure of treatment to improve HRQoL. Ideally, HRQoL should be recorded before and after any treatment is administered.

Though treatment in children with newly diagnosed ITP has not been shown to improve HRQoL, it may lessen parent disease burden in children with persistent/chronic ITP.

Data suggest that the burden of disease falls mostly on parents, not necessarily their child with ITP.

Recommendations

68. QoL should be evaluated using **specific tools** at **diagnosis** and **at defined intervals** for each treatment. **(IV – Low quality 7.8-A)**
69. The **influence of ITP burden on QoL should be considered** when deciding on treatment and follow up for children/adolescents affected with ITP **(EO – Very low quality 8.0-A).**

70. **Fatigue should be measured** with specifically dedicated tools **(EO – Very low quality 7.8-A).**

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