Recommendations for the management of acute immune thrombocytopenia in children. A Consensus Conference from the Italian Association of Pediatric Hematology and Oncology

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Background - Immune thrombocytopenia (ITP) is an acquired immune-mediated bleeding disorder characterized by isolated thrombocytopenia. Its estimated yearly incidence in the pediatric population is 1.9-6.4/100,000. ITP in children is usually a self-limiting and benign disorder. The clinical management of children with ITP often remains controversial, as robust randomized trials on the management of this disorder are lacking. Treatments vary widely in clinical practice and existing guidelines from hematology societies on clinical management offer indications based largely on expert opinion rather than strong evidence.

Materials and methods - The Coagulative Disorder Working Group of the Italian Association of Pediatric Hematology and Oncology (AIEOP) developed this document to collect shared expert opinions on the management of newly diagnosed ITP, updating previous guidelines and providing recommendations to pediatricians. Each statement has been given a score expressing the strength of evidence, appropriateness and agreement among participants.

Results - Clear-cut definitions of the clinical phases of the disease and clinical response are stated. Recommendations are given regarding the classification of bleeding symptoms, evaluation of bleeding risk, diagnosis, and prognostic factors. Specific recommendations for treatment include indications for first-line (intravenous immunoglobulins, steroids) and second-line (combined therapy, thrombopoietin receptor agonists, immunosuppressive drugs, rituximab) therapeutic agents, as well as hemorrhagic emergency and supportive treatment, including emergency splenectomy. The optimal follow-up schedule, the relation between ITP and vaccines and health-related quality-of-life issues are also discussed.

Discussion - The panel achieved broad consensus on issues related to how to treat children with newly diagnosed ITP, providing a comprehensive review of all relevant clinical aspects.

Keywords: *ITP, children, management, quality of life, therapy.*

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INTRODUCTION

Immune thrombocytopenia (ITP) is an acquired immune-mediated disorder characterized by isolated thrombocytopenia, due to platelet destruction and impaired platelet production. The estimated yearly incidence in the pediatric population is 1.9-6.4/100,000[1]. ITP is usually a self-limiting and benign bleeding disorder in children. Since robust randomized trials on the management of ITP are lacking, treatments vary widely in clinical practice. Indeed, existing guidelines from hematology societies[2,3] on the clinical management offer indications based largely on expert opinion rather than strong evidence and the clinical management of children often remains controversial.

The Coagulative Disorder Working Group of the Italian Association of Pediatric Hematology and Oncology (AIEOP) developed this Consensus document with the aim of updating previous guidelines[4] and providing recommendations to pediatricians. These recommendations are not intended to be standards or fixed rules but rather a tool to support pediatricians in the management of the diagnostic work-up and treatment of children with newly diagnosed ITP.

MATERIALS AND METHODS

The design and methodology were similar to those adopted for AIEOP Consensus Guidelines on acquired aplastic anemia[5], autoimmune hemolytic anemia[6-7], congenital and acquired neutropenias[8], and immune thrombocytopenias[9], whose procedures were validated by the AIEOP board. Furthermore, the methodology fulfills the AGREE reporting checklist[10].

Twenty-four representatives (22 pediatric hematologists, 1 hematologist, 1 psychologist) from 18 centers participated in the "Acute ITP Committee". Questions to be addressed in the Recommendations were identified by the whole Committee; they included the diagnostic work-up, various treatment interventions, comparison among different options, possible outcomes and health care context. 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.

For the pre-guideline documents, authors extracted evidence from literature searched for in the Medline and Google Scholar databases (from January 1, 2008 to February 28, 2019, and then updated in December 2022 during the compilation of the final draft). Search terms included: immune thrombocytopenia, immune thrombocytopenic purpura, idiopathic thrombocytopenia, idiopathic thrombocytopenic purpura, autoimmune thrombocytopenia, autoimmune thrombocytopenic purpura, and ITP. The search was also extended to older papers, specifically retrieved following cited references, and to hematology textbooks. The target population consisted of patients with acute ITP aged 0-18 years. Every piece of collected evidence was attributed a strength that was scored using the level of evidence criteria reported in **Table I** (modified from George JN *et al.*[11]).

Each draft was reviewed by the entire Committee and modified accordingly after exhaustive discussion. The Committee prepared statements that were then subjected to validation during the Consensus Conference, held in Turin on July 4, 2019, during which 24 participants (15 pediatric hematologists, 2 hematologists, 2 pediatric residents, 1 psychologist, 1 pediatric anesthesiologist, 1 pediatric surgeon, 1 nurse, 1 pharmacist) scored the final items. Another 26 participants (19 pediatric hematologists, 4 pediatricians, 2 pediatric oncologists, 1 pediatric resident), who could not attend in presence, scored all the items via an on-line questionnaire. Patients' associations could not be involved, since there are no national patients' associations for pediatric ITP.

The strength of each statement is expressed by three domains. The first domain, represented by a Roman number from **I** (highest) to **V** (lowest), reports the strength of supporting evidence[11]; the second, represented by an Arabic number form **1** (lowest) to **9** (highest), reports the mean score expressed by the Consensus; the third domain, represented by a letter from **A** (highest) to **D** (lowest), reports the level of agreement among participants, scored by evaluating the distribution of the standard deviations (SD) within each statement. Details of the three indices are reported in **Table I**.

RESULTS

Definitions

For childhood ITP the Consensus panel recommends the following:

- adopting the International Working Group (IWG) definition for ITP preserving the acronym ITP,

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Table I - *Scoring scale for recommendations*

Literature level of evidence	Study design
I (strongest)	Prospective randomized trial with high statistical value
II	Prospective randomized trial with low statistical value
III	Non-randomized study with concurrent control group
IV	Non-randomized study with historical control group
V (weakest)	Case report(s), guideline, meta-analysis, reviews
Mean Consensus score	
1-3 (weakest)	Inappropriate practice
3.01-6.99	Uncertain appropriateness
7-9 (strongest)	Appropriate/necessary practice
Agreement among Consensus	
A (strongest)	Strong agreement (variation more than 1 SD below the average of the variances, in logarithmic scale).
B	Moderate agreement (variation less than 1 SD below the average of the variances).
C	Moderate disagreement (variation less than 1 SD above the average of the variances).
D (weakest)	Strong disagreement (variation more than 1 SD above the average of the variances)

SD: standard deviation.

replacing I (idiopathic) by Immune, T and P (purpura) by ThrombocytoPenia, with thrombocytopenia defined as a platelet count below 100×10^9/L (**V- 8.2-A**)[12];

- adopting 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 (**V- 8.6-A**)[12];
- adopting the IWG definition for severity of ITP defining severe ITP based on 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 (**V- 8.0-A**)[12];
- adopting the IWG definition for response to treatment, based on a quantitative platelet count together with a bleeding outcome, defining:

a) complete response as resolution of bleeding symptoms, and a platelet count of at least 100×10^9/L;
b) partial response as no clinically relevant bleeding and a platelet count between 30 and 100×10^9/L, at least doubling of the baseline count;
c) no response as a platelet count lower than 30×10^9/L or less than doubling baseline count or continued clinically relevant bleeding (**V- 7.9-B**)[12].

The Consensus panel underlines that IWG criteria for defining refractory ITP (failure to respond to splenectomy) cannot be adopted for newly diagnosed and persistent ITP in childhood given the declining rate of splenectomy in pediatric ITP. Splenectomy is very rarely indicated in childhood ITP and should only be considered in children >5 years of age who have failed all available medical therapies, are having thrombocytopenia-related bleeding, and whose life is at risk or whose health-related quality of life (QoL) is substantially impaired.

We therefore suggest at this time defining ITP as "refractory" in a child with more severe and difficult-to-treat disease, i.e., a child with persistent, clinically relevant, active bleeding and persistent low platelet count despite first-line treatments or rescue therapy (other immunosuppressant agents or thrombopoietin receptor agonists [TPO-RA] or splenectomy) or a child who requires frequent courses of therapy to maintain a sustained clinical response, developing worsening disease and medication-induced toxicities (**V-7.8-A**).

Classification of bleeding symptoms and evaluation of bleeding risk

The identification of possible risk factors can help when deciding whether treatment is indicated.

Reported risk factors for severe bleeding include wet purpura (in the mouth, hematuria, prolonged epistaxis, gastro-intestinal bleeding, or other pronounced mucosal bleeding), trauma, exposure to antiplatelet medications (e.g., aspirin, ibuprofen, other nonsteroidal anti-inflammatory drugs) and anticoagulants (eg, heparin, warfarin), very low platelet count (defined as platelet count $<10\times10^9$/L) (**V-8.1-A**)[13].

The present Consensus panel recommends using a uniform bleeding assessment tool (BAT) at diagnosis and follow-up visits both for grading severity of bleeding and for evaluating response to therapy (**V-8.3-A**); however, the Consensus panel was uncertain on whether to recommend

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Table II - *Clinical data and their relation with a diagnosis of immune thrombocytopenia*

Supportive	Not supportive
• 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 live vaccine)	• Family history of thrombocytopenia, cataract, deafness, renal failure, myelodysplasia, dysmorphic 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
• Normal or slightly elevated mean platelet volume	• Giant or very small platelets

Table III - *Clinical data suggesting congenital/hereditary thrombocytopenia*

Clinical data
• Family history of thrombocytopenia
• Family history of acute myeloid leukemia
• No response to steroid and/or intravenous immunoglobulin therapy
• Thrombocytopenia onset at birth or during the first months of life
• Lack of previous normal platelet count
• Casual finding of thrombocytopenia (>20×10^9/L)
• Long-term persistence of thrombocytopenia >20×10^9/L
• Giant platelets, or very small platelets, as indicated by the mean platelet volume value and/or the blood smear
• Other non-hematological findings, i.e., short stature, arm/hand malformations, eczema, skin spots, deafness, cataract, kidney impairment

the easy and quick Buchanan-Adix score (**V-6.9-C**) or the thorough and precise (SMOG) score (**V-4.3-C**)[14,15].

Diagnosis of immune thrombocytopenia

Primary ITP remains a diagnosis of exclusion and the differential diagnosis is often not easy[16]. 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 recent infection is often described in pediatric ITP, usually about 2 weeks before the onset[17]. A history of recent vaccinations, especially against measles, mumps and rubella, can also be found.

There are features 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 signs of chronic disease (**Tables II** and **III**).

Diagnostic tests

ITP patients are characterized by isolated thrombocytopenia, expressed by a platelet count <100×10^9/L, as recently redefined by an international working group, which abandoned the previously considered cut-off of 150×10^9/L, since non-Caucasian population may have lower platelet levels, without any bleeding risk (**V-8.2-A**)[12].

Evaluation of a peripheral blood smear is indicated in order to exclude inherited and/or secondary thrombocytopenia (**V-7.8-B**). Some large platelets are typically found, but an excessive number of giant platelets, as well as small platelets, should point to other diagnoses[16,18].

Although platelet autoantibodies are thought to be the major underlying cause of ITP[19] testing for platelet autoantibodies is not currently recommended for the diagnosis of ITP because of the poor accuracy of the current tests (**V-7.7-A**)[20].

There is no indication for bone marrow aspiration at the onset of ITP in newly diagnosed children with a typical presentation (**V-8.2-A**). However, this investigation should be considered prior to the administration of steroids, but may safely be omitted in patients with a recent history of complete response to intravenous immunoglobulins (IVIg) (**V-7.4-B**).

The following tests, aiming at recognizing possible underlying conditions, have been considered not indicated in newly diagnosed ITP, whereas they become appropriate in persistent ITP: anti-ENA and ANA screening (**V-8.0-A**); screening of thyroid function and/or for anti-thyroid antibodies (**V-7.6-A**); screening for celiac disease (**V-7.6-B**) is indicated in patients not responding well to therapy or in older children

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(>10 years) or if there is a positive family history for autoimmune diseases.

Autoimmune lymphoproliferative syndrome (ALPS)/ ALPS-like syndromes and common variable immunodeficiency should be considered as underlying causes of acute ITP in patients with a personal/family history of autoimmunity, lymphoproliferation, or other signs of immune-dysregulation (**V-7.9-A**).

The diagnostic work-up of patients with acute ITP associated with signs/history of immune dysregulation should include lymphocyte subset count (including T-cell receptor $\alpha\beta^{+}CD8^{-}CD4^{-}$ T cells), serum immunoglobulin level, antibody titers to prior vaccinations, and screening for autoimmunity before administration of steroids/IVIg (**V-7.8-A**).

Patients with newly diagnosed ITP and a history of autoimmune hemolytic anemia and/or neutropenia should be considered as having Evans syndrome and investigated for ALPS/ALPS-like and common variable immunodeficiency (**V-8.0-A**).

Prognostic factors

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. Identified prognostic factors of chronic ITP in children are female gender, age >10 years at presentation, absence of preceding infection or vaccination, and platelet count $>20\times10^9$/L at presentation (**V-7.9-A**)[21-24].

Recently, a novel clinical prediction tool has been developed to predict transient *versus* persistent ITP disease courses in children with newly diagnosed ITP at the time of diagnosis[25]. Authors recommend its use for research and training purposes only.

Indications for treatment

About 80% of patients with ITP achieve a complete sustained remission within a few weeks to a few months after the initial presentation, irrespective of any given therapy. Consequently, pharmacological treatment is indicated to prevent the risk of severe bleeding, including intracranial hemorrhage that occurs in less than 1% of cases[26]. The aims of the treatment are to increase the platelet count quickly and stabilize it at a value $>20\times10^9$/L in those patients who are considered at risk of developing severe mucosal or deep-organ bleeding.

Therefore, the indications for initial treatment depend on the severity:

a) in children with newly diagnosed ITP who have no or mild bleeding only (Buchanan & Adix score 0-2 (equivalent to SMOG S0-3 M0 O0), the Consensus panel proposes the following statements:

- management as an outpatient is favored over admission to 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 (**V-7.9-A**);
- irrespectively of the platelet count, the initial approach should be observation alone (**II-7.5-B**); however, treatment can be offered to children who may benefit from a higher platelet count, in the case of "special needs", i.e., toddlers with a high tendency to fall, pubertal girls at risk of menorrhagia, risk behavior in adolescents, upcoming procedures associated with a risk of bleeding, not acceptable traveling distance from hospital, or in the case of a strong wish of parents or patients, after having counselled them regarding risks and benefits of therapy (**V-8.2-A**).

b) in the case of a Buchanan & Adix score ≥3 (equivalent to SMOG S0-3 M≥2 O≥1), i.e., at least severe spontaneous mucosal bleeding, at onset of ITP, irrespectively of the platelet count, the Consensus panel offers the following statements:

- the patient should receive treatment (**V-8.0-A**);
- in the case of subsequent appearance of a Buchanan & Adix score ≥3 (equivalent to SMOG S0-3 M≥2 O≥1) (at least mucosal bleeding), patients who were initially observed alone (score 0-2) should be treated (**V-8.8-A**).

Therapy with first-line agents

Effective treatment strategies are single-dose intravenous immunoglobulin G (IVIg 0.8-1 g/kg) or medium to high-dose corticosteroids administered orally or parenterally, i.e., prednisone 1-2 mg/kg/day for 15 days orally; methyl-prednisolone 5-10 mg/kg/day for 3 days intravenously; dexamethasone 0.6 mg/kg/day for 4 consecutive days[3,20]. 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 various doses and schedules, in achieving a platelet count $>20\times10^9$/L by 48 hours[27]; children with mucosal bleeding at diagnosis or treatment with IVIg

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alone have been recently shown to develop chronic ITP less often[28], even though these findings need confirmation in prospective, randomized trials. Therefore:

- IVIg is a first-line therapy in children with newly diagnosed ITP (**I-8.8-A**).
- The recommended dose is 0.8 g/kg in a single dose, with possible repetition (**II-8.6-A**).
- When corticosteroids are chosen as initial treatment for ITP, an intermediate-high dose of prednisone or methylprednisolone has the same efficacy (**I-8.3-A**).
- The use of high-dose steroids for a brief period is associated with fewer adverse effects whereas long-term corticosteroids should be avoided in children with ITP because of side effects (**V-8.3-A**).

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 of the decision to withdraw all marketing authorizations in Europe because of concerns about the benefit-to-harm balance in ITP therapy.

Therapy with second-line agents

Combined therapy

Combining first-line treatments is appropriate in an emergency setting: prednisone and IVIg are recommended for the emergency treatment of patients with uncontrolled bleeding (**V-8.2-A**). High-dose methyl-prednisolone may also be useful in this setting[29].

Patients who do not have an adequate response to initial therapy with first-line agents may also benefit from additional courses of first-line agents in combination (**V-7.6-B**)[30].

The recommended schedule for combined therapy is IVIg 0.4 g/kg daily on days 1 and 2, and methyl-prednisolone 20 mg/kg daily on days 1-3 (**V-7.1-B**).

Thrombopoietin receptor agonists

TPO-RA are a highly effective and well-tolerated treatment for achieving hemostatic platelet counts (>50×10^9/L) in children with ITP[31-36].

They are currently approved for patients with chronic ITP, 1 year of age or older who are refractory to other treatments (e.g., corticosteroids, IVIg). Romiplostin is approved for refractory ITP, independently of time, only in adults. In children TPO-RA agents can be used in newly diagnosed ITP, only as off-label therapy, in selected patients with severe bleeding symptoms, refractory to IVIg and steroids (**V-7.9-B**), and in patients with persistent ITP and a bleeding score >2 or a bleeding score 0-2 in the presence of "special needs" (**V-7.9-A**).

Immunosuppressive drugs

Immunosuppressive drugs, such as mycophenolate mofetil and sirolimus, offer a treatment option in patients with persistent/chronic ITP thanks to promising results shown in both adult and pediatric populations (52% and 64% response, respectively)[37,38]. Selected populations of patients with an underlying ALPS-like disorder or with Evans syndrome had an even better outcome (73% and 81%, respectively).

Recently, a randomized controlled study of steroids *versus* steroid plus mycophenolate mofetil in adults showed a definite benefit from the addition of mycophenolate mofetil in the initial treatment[39].

Sirolimus has been shown to be effective in patients with ALPS and other primary or secondary autoimmune cytopenias[40-41].

In patients with persistent ITP and a bleeding score >2 or a bleeding score 0-2 in the presence of special needs, mycophenolate mofetil and sirolimus can be considered as treatment options, especially in the context of ALPS/ALPS-like syndromes (**V-8.1-A**).

Rituximab

Several uncontrolled, open-label studies support the use of rituximab in pediatric patients with chronic ITP, suggesting an initial response rate of approximately 40 to 50%, falling to approximately 25% over a follow-up of 2 to 5 years; adolescent females are more likely than younger children and males to achieve remission[42-44].

Mild, transient side effects (urticaria, headache, fever, scratchy throat, and chills) may occur during the infusion. Serum sickness has been reported in 5 to 10% of children with ITP treated with rituximab. Progressive multifocal leukoencephalopathy has been reported as a very rare but extremely serious complication of rituximab therapy, too[45,46].

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 (**V-7.6-A**) or to avoid or postpone splenectomy (**V-7.5-B**).

Figure 1 proposes a therapy flow chart, identifying the most suitable treatment options, according to bleeding score.

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Hemorrhagic emergency and supportive treatment

Symptoms or signs suggestive of organ- or life-threatening hemorrhage require action to ensure a prompt increase of circulating platelets. Recommendations for emergency treatments have already been proposed by AIEOP, the American Society of Hematology and an Indian group with few differences (**Table IV**)[10,20,47].

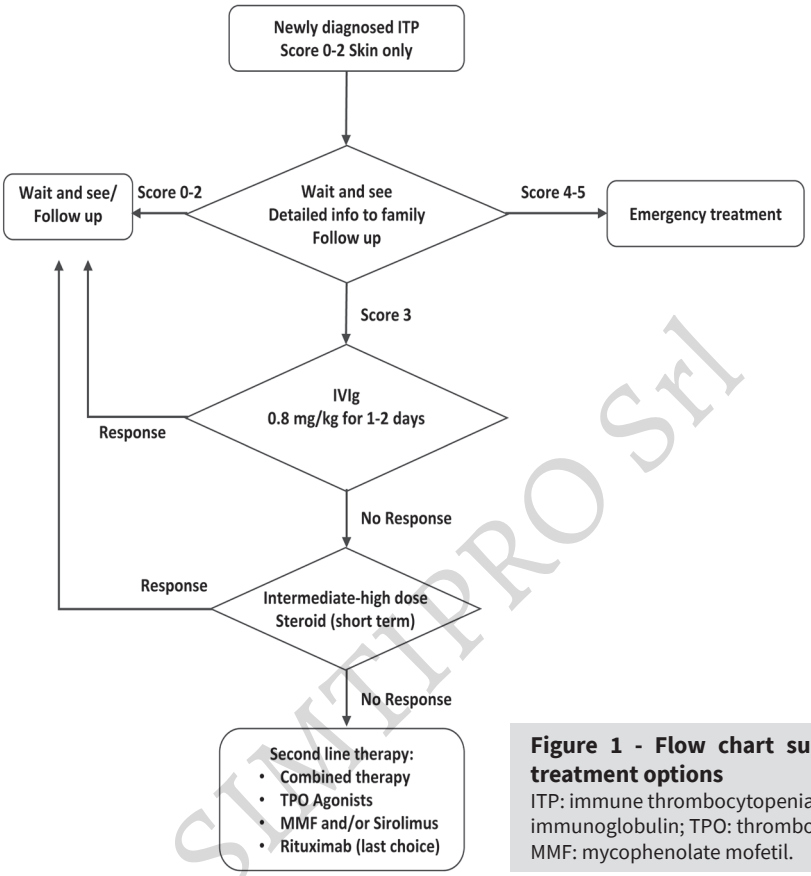

Figure 1 - Flow chart summarizing the treatment options
ITP: immune thrombocytopenia; IVIg: intravenous immunoglobulin; TPO: thrombopoietin; MMF: mycophenolate mofetil.

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Table IV - *Previously published recommendations for emergency treatments*

Severe/life-threatening bleeding	AIEOP recommendations	American guidelines	Indian guidelines
First-line therapy	IVIg at a dose of 0.8 g/kg	Immediate IV administration of m-PDN (30 mg/kg, maximum dose 1 g) + platelet transfusion	m-PDN in combination with IVIg or anti-D. m-PDN and IVIg may be repeated for at least 1-2 days, based on response. Platelet transfusions are indicated only in the setting of life-threatening bleeds
First-line alternatives	m-PDN at a dose of 15-30 mg/kg/day is administered for 3 days	Combined therapy: after administration of IV m-PDN and platelets, an infusion of IVIg (1 g/kg)	
In selected cases	Combined treatments and add platelet transfusion	Continuous infusion of platelets may be beneficial in selected cases. 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 factor VIIa has been used in intracranial hemorrhage refractory to platelet-enhancing agents as "off-label" use at a dose of 90- 120 µg/kg

AIEOP: Italian Association of Pediatric Hematology and Oncology; IVIg: intravenous immunoglobulin; IV: intravenous; m-PDN: methyl-prednisolone.

The Consensus panel agrees on the following statements:

- 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-8.4-A**).
- 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 can often be controlled (**V-8.0-A**).
- Recombinant factor VIIa has been used in patients with intracranial hemorrhage refractory to platelet-enhancing agents as an "off-label" treatment at a dose of 90-120 µg/kg, every 2-3 h, until the cessation of bleeding[48-51]. Therefore, recombinant factor VIIa can be considered in critical situations (**V-6.8-B**), but the treatment is "off label" and there is very limited experience with it.
- In the case of massive intracranial hemorrhage and raised intracranial pressure, when neurosurgical intervention for evacuation of hematoma or decompression craniotomy may be urgently indicated, splenectomy in the same surgical session may offer the best chance (**V-6.8-B**).
- Control of bleeding from mucosal surfaces, particularly epistaxis, gum bleeding and menorrhagia, can be aided with antifibrinolytic agents. Tranexamic acid is preferred due to its longer half-life, higher potency and lower toxicity. The dose of tranexamic acid is 25-50 mg/kg every 6-8 h. Antifibrinolytic agents are contraindicated during hematuria; formation of clots can result in colic and obstruction of outflow from the renal pelvis (**V-8.0-A**).
- Menorrhagia in adolescents with ITP is commonly managed with oral contraceptive pills and tranexamic acid (**V-7.5-B**).

Emergency splenectomy

Splenectomy is considered inappropriate for children with newly diagnosed or persistent ITP[4].

However, emergency splenectomy may be considered in special circumstances, in the case of severe thrombocytopenia and life-threatening bleeding (**V-7.2-B**). 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 (**V-7.7-B**).

If expertise is available, splenic artery embolization could be considered as a faster and safer bridge procedure prior to splenectomy, although data regarding the use of splenic artery embolization in ITP-related life-threatening bleeding are limited[52,53].

The risk of infection is the major cause of mortality after splenectomy[53]. Therefore, measures to prevent infection are recommended. Vaccinations against encapsulated bacteria (*Streptococcus pneumoniae, Neisseria meningitidis, Haemophilus influenzae* type B) should be performed promptly after emergency surgery, at least 2 weeks after splenectomy. Yearly seasonal influenza vaccine is recommended (**V-8.3-A**).

Prophylactic antibiotics should be administered after splenectomy until the child is 5 years of age, for a minimum of 2 years after splenectomy for children older than 5 years of age and for a longer period if there has been a previous episode of severe infection or there are other infective risks (**V-7.9-A**). The risk of infection persists throughout life, so it is recommended that patients and families be educated about the risks associated with asplenia, the preventive measures that can be taken and the correct management of post-splenectomy episodes of fever (**V-8.7-A**).

Follow-up

The management of follow-up in patients with ITP is complex and various aspects such as age, potential co-morbidities and co-medications, activities as well as health-related QoL and psychic, social and economic aspects must be considered in decision making.

The present Consensus panel recommends managing the patient with a bleeding score 0-2 and favorable prognostic factors with observation alone, limiting needle sticks after the first-line treatment (**V-8.1-A**).

Immune thrombocytopenia and vaccines

The Consensus panel underlines that all the vaccines included in the pediatric vaccinations' schedule are recommended even in the case of previous thrombocytopenia (possibly related or not to vaccine) (**III-8.3-A**).

Although the possibility of ITP onset after measles-mumps-rubella (MMR) vaccination is well

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recognized, the global incidence of ITP after MMR vaccination has been demonstrated to be lower than that reported after native infection (0.087-4/100,000 per vaccine dose compared to 6 to 1,200/100,000 cases); moreover, ITP after vaccination has been reported to be favorable, with a more self-limited clinical course and complete resolution in >90% of patients after 6 months[54-58]. In children who have had an episode of thrombocytopenia within 6 weeks after the MMR or MMR-varicella vaccination, the possibility of avoiding the administration of a second dose should be considered, evaluating the anti-measles antibodies (**V-7.5-B**).

The vaccination is recommended in children who do not have proven seroconversion, as it is considered that the benefit of vaccination outweighs the risk of a possible thrombocytopenia (**V-7.9-A**).

The Consensus panel reminds that in the case of previous use of blood-derived 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 IVIg) to prevent the eventual interference of passively transmitted antibodies (**V-7.5-B**).

Health-related quality of life

Health-related QoL issues should be considered while making decisions on management in childhood ITP[3,20]. Physical symptoms of ITP itself, social limitations, parents' anxiety and specific medical-related factors (i.e., duration, complications, inconvenience of treatments, need for invasive interventions) may all adversely affect the child's and family's quality of life[59,60]. Fatigue, defined by extreme and persistent tiredness, weakness or exhaustion, possibly associated with decreased functioning, has been reported as an important health-related QoL issue by 54% of children and 62% of adolescents with ITP[60].

The Consensus panel recommends that QoL be evaluated using specific tools at diagnosis and at defined intervals for each treatment (**IV-7.8-A**)[61]. Fatigue should be measured with specifically dedicated tools (**V-7.8-A**)[62]. Moreover, the influence of ITP burden on QoL should be

Table V - *Differences between previous and current AIEOP recommendations and international guidelines*

	AIEOP 2000 recommendations	AIEOP current recommendations	ASH current guidelines
Definitions: phase of the disease	Acute ITP <6 months Chronic >6 months	According to IWG: • newly diagnosed (<3 months), • persistent (3-12 months, • chronic (>12 months)	According to IWG: • newly diagnosed (<3 months), • persistent (3-12 months), • chronic (>12 months)
Definitions: response to treatment	Not provided	According to IWG: • complete response: PLT >100×10^9/L • partial response: PLT 30-100×10^9/L (at least doubling of baseline count) • no response: PLT <30×10^9/L Refractory to "specific treatment indicated": persistent active bleeding, persistent low PLT count, despite first-line or rescue therapy	According to IWG: • complete response: PLT >100×10^9/L • partial response: PLT 30-100×10^9/L (at least doubling of baseline count) • no response: PLT <30×10^9/L Refractory: failure to splenectomy
Indications for treatment	Platelet count bleeding signs	Bleeding signs special needs	Bleeding signs special needs
First line - treatments	Steroids or IVIg	IVIg	Steroids
Second-line treatments	Not considered	Combined therapy TPO agonists immunosuppressive drugs rituximab	TPO agonists immunosuppressive drugs rituximab
Bone marrow biopsy at diagnosis	Mandatory prior to steroid administration	Suggested prior to steroid administration	Not recommended
Assessment of HRQoL issues	No	Yes	Yes

AIEOP: Italian Association of Pediatric Hematology and Oncology; ASH: American Society of Hematology; ITP: immune thrombocytopenia; IWG: International Working Group; PLT: platelets; IVIg: intravenous immunoglobulin; TPO: thrombopoietin; HRQoL: health-related quality of life.

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considered when deciding on treatment and follow-up for children/adolescents with ITP (**V-8.0-A**).

CONCLUSIONS

The present report represents a valuable effort to support pediatricians with guidance for the management of diagnosis and therapy of newly diagnosed and persistent ITP in children. The Consensus panel achieved broad sharing of issues related to how to treat newly diagnosed children with ITP, yielding a comprehensive review of all relevant clinical aspects.

Table V reports a comparison of current recommendations with previous AIEOP guidelines published in 2000[4] and international guidelines[2,3].

An extensive version of the current recommendations, which includes a detailed description of the background supporting all the statements, can be accessed on the AIEOP website: https: //www.aieop.org/web/operatori-sanitari/linee-guida-consensum/.

Information given to parents can be accessed on the AIEOP website: https: //www.aieop.org/web/famiglie/schede-malattia/piastrinopenia-immune-itp/.

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ETHICAL CONSIDERATION

The manuscript does not involve human or animal subjects or records of human patients. Therefore, no ethical approval was asked for.

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