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Acute childhood idiopathic thrombocytopenic purpura: AIEOP consensus guidelines for diagnosis and treatment

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ABSTRACT

Background and Objectives. **A recent evaluation carried out by the *Associazione Italiana di Ematologia e Oncologia Pediatrica* (AIEOP) about practice management of acute childhood idiopathic thrombocytopenic purpura (ITP) revealed a remarkable difference of behaviors among the different AIEOP centers. A need for common practice guidelines for this frequent illness arose from this observation. Our aim was to make the diagnosis and treatment of childhood ITP uniform. In the future we will evaluate the influence of these guidelines on practice behaviors.**

Data sources and Methods. **Our main reference was the 1996 document produced by the American Society of Hematology (ASH). Their recommendations were updated with information from literature searched for in the MEDLINE database (June 1996-October 1998); search terms included: thrombocytopenia, ITP, diagnosis, therapy, children. The computerized search retrieved 83 articles. *Data extraction*: the scientific validity of the literature was evaluated by a panel of members using published guidelines. The strength of the evidence was assessed using *level of evidence* criteria. Only data from level I and level II studies were taken in account. Only one study out of the 83 retrieved articles met these selection criteria and it was considered in addition to the 11 out of 581 articles selected in the ASH ITP guidelines. This preliminary work pointed out each issue about ITP not addressed by clinical studies and all participants in a Consensus Conference expressed their opinion about these issues.**

Results. **Diagnosis is essentially based on history, physical examination, a complete blood count and an examination of the peripheral blood smear. Treatment is recommended taking into account the clinical picture and number of platelets. The main difference between these guidelines and those from ASH are: AIEOP guidelines rely on the opinion of the members of the consensus conference, ASH ones on a panel of experts; therapeutic options include only products available in Italy; the indications to treatment rely more on clinical picture than on platelet number.**

Interpretation and Conclusions. **These are explicitly developed, evidence-based practice guidelines to assist Italian pediatricians in making decisions about diagnosis and appropriate health care for patients with acute childhood ITP.**

Key words: ITP, guidelines, diagnosis, treatment, childhood

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A recent evaluation carried out by *Associazione Italiana di Ematologia e Oncologia Pediatrica* (AIEOP) about practice management of acute childhood idiopathic thrombocytopenic purpura (ITP) revealed a remarkable differences of behavior among the different AIEOP centers.[1] A need for common practice guidelines for this frequent illness (3-10 cases/year every 100,000 subjects < 16 years) arose from this observation.

The following guidelines were produced to fill this need. They are explicitly developed, evidence-based practice guidelines, to assist Italian pediatricians in making decisions about diagnosis and appropriate health care for acute childhood ITP.

Recommendations in these guidelines are not intended to be *standards* or inflexible rules.[3] Adher-

ence to the guidelines will not ensure a successful outcome in every case. The ultimate choice regarding each patient should be made by the patient's physician in the light of the individual data and the available diagnostic and treatment options.

It will be useful to evaluate the impact of these guidelines on practice behavior and patient outcome in AIEOP centers, and to update guidelines incorporating new evidence.

Design and Methods

With a mandate from the AIEOP coagulation study group and according to recently reported indications for development of guidelines[3,4] a preliminary document was produced by a narrow group of AIEOP pediatric hematologists one of whom was expert in practice guideline methodology.

This document was discussed and modified during a *Consensus Conference* held in Ospedaletto, Pisa, Italy, November 30, 1998. All the adopted procedures were previously validated by the AIEOP board (President A. Pession).

Literature review and assessment of evidence

Data sources: the main reference was the *American Society of Hematology* document.[5] The recommendations in this document were updated with information from literature reports searched for in the Medline® database (June 1996-October 1998); search terms included thrombocytopenia, ITP, diagnosis, therapy, children. The computerized search retrieved 83 articles. *Data extraction*: the scientific validity of the literature studies was evaluated by a panel of members using published guidelines,[6-8] the strength of the evidence was assessed using *level of evidence* criteria reported in Table 1. Only data from level I and level II studies were taken in account. Only one study[9] out of the 83 retrieved articles met these selection criteria and it was considered in addition to the 11 out of 581 articles selected in the ASH document (see Table 9 of reference #5 for details).

Consensus conference

Preliminary work pointed out each issue about ITP not adressed by clinical studies. All participants in the Consensus Conference expressed their opinion about these issues. The strength of their opinion was quantified on a 1 to 9 scale; "9" represented strong agreement with the appropriateness and necessity of the practice and "1" represented strong disagreement.

A mean score was calculated for each statement: mean scores of 1 to 3 were indicative of an *inappropriate* practice, 3.01-6.99 of a practice of *uncertain appropriateness*, and 7-9 of an appropriate/necessary action. The level of unanimity was evaluated as reported in Table 2.

Results

Definition of clinical entity to treat

ITP is a bleeding disorder characterized by isolated low platelet count ($< 150\times10^9$/L) in the absence of other clinically apparent causes of thrombocytopenia such as HIV infection, autoimmune disorders, lymphoproliferative disorders, myelodysplasia, cancer, immunodeficiency states, drug-induced, allo-immune thrombocytopenia, non-immune congenital thrombocytopenia. Acute ITP is the term given to the disease in its first 6 months. These guidelines were developed for subjects between 6 months and 17 years and 11 months of age.

Table 1. Levels of evidence for studies evaluating effectiveness of treatment.

Level of evidence	*Study design*
I (Strongest))	Randomized trials with high statistical value
II	Randomized trials with lower statistical value
III	Non-randomized studies with concurrent control group
IV	Non-randomized studies with historical control group
V (Weakest)	Case series without a control group

Modified from ref. #5 .

Table 2. Consensus level.

A	Strong agreement (variance more than 1 SD below the mean variance)
B	Moderate agreement (variance less than 1 SD below the mean variance)
C	Moderate disagreement (variance less than 1 SD above the mean variance)
D	Strong disagreement (variance more than 1 SD above the mean variance)

SD = Standard deviation

Diagnosis

History and physical examination

The main elements of the history and physical examination are reported in Table 3. In this regard literature suggests that the spleen may be palpable in 12% of children with ITP.[10,11]

Necessary tests

A complete blood count and an examination of the peripheral blood smear are essential in ITP. A pseudothrombocytopenia due to *in vitro* platelet agglutination in presence of EDTA ought to be distinct from true thrombocytopenia. The principal findings of the examination of a blood smear are listed in Table 4. An iron deficiency anemia, *activated* lymphocytes or eosinophilia can be found rarely.[5]

Other laboratory data

Bone marrow aspiration: this is not unanimously recommended (strength of recommendation 5.5 – D) in all cases at diagnosis. It is appropriate before starting glucocorticoid treatment for the first time (strenght of recommendation 8.9 – B).

In cases with a history, physical examination, initial blood count and smear compatible with the diagnosis of ITP other tests at the onset of the disease are not necessary.

In this regard, outside a reaserch program, an assay for antiplatelet antibodies is not considered as nec-

Table 3. Principle elements of the history and physical examination of a child with suspected ITP.

History
- Bleeding symptoms: type, site, severity, duration of bleeding; hemostasis with prior invasive procedures
- Systemic symptoms, especially of recent viral illness or exposure to viruses such as varicella, or recurrent infections suggesting immunodeficiency; symptoms of autoimmune disorder
- Recent live virus immunization
- Medications, including heparin, quinidine/quinine, and sulfonamides, which may cause thrombocytopenia, and aspirin, which may exacerbate bleeding
- Risk factors for HIV infection, including maternal HIV status
- Family history of thrombocytopenia or hematologic disorder
- Comorbid conditions, which may increase the risk of bleeding
- Lifestyle, including vigorous and potentially traumatic activities

Physical examination
- Bleeding signs: type of bleeding (including retinal hemorrhages); severity of bleeding
- Liver, spleen, and lymph nodes
- Evidence of infection
- Presence of dysmorphic features suggestive of congenital disorders, including skeletal anomalies, auditory acuity

Specific congenital syndromes to exclude
- Fanconi's syndrome
- Thrombocytopenia-absent radius
- Wiskott-Aldrich's syndrome (and its variants)
- Alport syndrome (and its variants)
- Bernard-Soulier syndrome
- May-Hegglin anomaly
- Gray platelet syndrome
- Hereditary thrombocytopenia

Modified from ref. #5.

Table 4. The peripheral blood smear in ITP.

Consistent with the diagnosis of ITP
1. Thrombocytopenia. Platelets are normal in size or may appear larger than normal, but consistently giant platelets (approaching the size of red blood cells) should be absent.
2. Normal red blood cell morphology.
3. Normal white blood morphology.

Not consistent with the diagnosis of ITP
1. Predominant giant platelets.
2. Polychromatophilia (unless response to bleeding), macrocytes, nucleated red blood cells.
3. Leukocytosis or leukopenia, with immature or abnormal cells (although *activated* lymphocytes and eosinophilia may occur in children with ITP).

Modified from ref. #5.

essary. In fact although the sensitivity of an elevated platelet associated IgG (PAIgG) in diagnosing ITP is approximately 90%, the specificity of this assay is less than 30%;[12] on the other hand assay of antiplatelet antibodies directed against specific platelet target glycoprotein complexes shows a sensitivity of 50% and a specificity of 80%.[12]

Nevertheless other tests could be considered appropriate in those case in which the above mentioned first evaluations do not yield usual values (e.g. altered mean platelet volume) or suggest other etiologies.

Clinical classification

The site and extent of bleeding symptoms can allow three different clinical types to be differentiated:

Type A: asymptomatic-paucisymptomatic ITP, clinical symptoms ranging from no bleeding to few petechiae and some bruises without mucosal hemorrhages.

Type B: intermediate ITP, clinical picture with more petechiae, bruising and mucosal hemorrhages.

Type C: severe ITP, clinical picture with severe cutaneous and mucosal bleeding symptoms with at least one of the followings: retinal hemorrhages, intracranial hemorrhage, other severe internal hemorrhages, hemorrhagic shock, life-threatening bleeding. In other and more general words a clinical picture characterized by severe bleeding symptoms with severe organ impairment or life-threatening conditions.

Treatment

Treatment recommendations take into account the clinical picture and platelet count. Because the association between these two aspects is not always evident, clinical bleeding symptoms are considered more important that platelet count in the single case.

In general the treatment of acute ITP is aimed at curing clinical symptoms and reducing the risk of hemorrhages; therefore from a general point of view it is appropriate to treat forms B and C and form A with platelet count $< 20\times10^9$/L because at this level of platelets there is a high risk of intracranial hemorrhage.[12] Moreover it should be considered that most evidence regarding the efficacy of treatment of ITP is inferred by measuring a surrogate outcome, platelet count, rather than bleeding resolution or mortality.

There are very few studies with level I and II evidence; treatment recommendations, therefore also rely on the opinion of the members of the consensus conference (see relative section).

Finally, treatment with anti-RhD immunoglobulins was not considered because these products are not available in Italy with a licensed indication for ITP.

Type of treatment

The therapeutic options are the followings.

No therapy: no therapy (drug) implies the need to explain the clinical course of ITP to the parents of the affected child. In particular it is important to indicate temporary restriction on motor activities, avoidance of some procedures (e.g. dental extractions) and avoidance of the use of some drugs (e.g. aspirin) that can worsen bleeding symptoms. It must be stressed that in patients with major risk factors for bleeding (e.g. elevated blood pressure, ulcer disease, vigorous lifestyle) a policy of not treating becomes inappropriate also in type A ITP with a platelet count $> 20\times10^9$/L and especially for those patients with platelet counts between $20\text{-}50\times10^9$/L.

Glucocorticoids: randomized clinical trials (level I and II) demonstrated that glucocorticoid therapy increases the platelet count more quickly than when no specific treatment is administered.[5] The mechanism of

action of glucocorticoids in ITP is thought to be multifactorial: they can increase vascular stability, and increase platelet survival, an effect attributed to both decreased production of antiplatelet antibodies and decreased clearance of opsonized platelets.[12] The potential side effects of corticosteroid therapy include: Cushingoid facies, acne, psychosis, fluid retention, hyperglycemia, hypertension, cataracts, pseudotumor cerebrii, osteoporosis and growth retardation. These effects are dependent on the dose and duration of treatment, the most severe side effects usually resulting from use for more than a month.[12]

The recommended regimens are the following: *conventional-dose oral glucocorticoids:* 2 mg/kg/d or 60 mg/m^2/d of oral prednisone for 14 days, followed by a tapering down dose and discontinuation on day 21; maximum dose 80 mg/d;[13] *high-dose oral glucorticoids:* 4 mg/kg/d of oral prednisone in three divided doses, for 7 days, followed by a 50% reduced dose in the second week, and then by a tapering down dose and discontinuation on day 21, max dose 180 mg/d in the first week.[14] These two oral regimens have not been compared with each other in level I and II studies, however a high-dose of glucocorticoids might induce a more rapid increase in platelet count than a conventional dose.

Parenteral glucocorticoids: 15-30 mg/kg of intravenous (i.v.) methylprednisolone as a 30-60 minute bolus injection, for 3 days; max dose 1 g/d.[15,16]

Platelet count recovery achieved by using high-dose parenteral glucocorticoids is faster than that obtained by oral glucorticoids and is as rapid as that seen with intravenous immunoglobulins.[15-17]

Intravenous immunoglobulins with intact Fc fragment (IVIG): one level I study has shown that initial IVIG treatment of children with acute ITP increases the platelet count more rapidly than no specific treatment and than oral glucorticoid therapy.[18]

The immunomodulatory mechanism of action of IVIG is not understood, although it is likely to involve IgG occupation of the Fc receptors on reticuloendothelial cells, resulting in survival of the opsonized platelets. Another mechanism proposed to play a role in the action of IVIG is the presence of anti-idiotypic antibodies in the pooled IgG preparations. These antibodies may bind to circulating autoantibodies, rendering them ineffective for platelet opsonins, and may also suppress the B-cells that produce the offending autoantibodies.[11] Adverse effects of IVIG are common (15% to 75%) but generally mild, and include headache, backache, nausea, and fever. Rare reported complications include aseptic meningitis, alloimmune hemolysis and hepatitis C infection. However, no hepatitis C infections have been reported with viral inactivated products.[5,11] The recommended regimen is the following: 0.8 g/kg of IVIG for 1 day. In very severe cases a total dose of 2 g/kg divided in 2-5 days can be used.[14, 19] It is advisable to take care over the infusion velocity. The 0.8 g/kg posology achieves the same results as the formerly used dose of 400 mg/kg for 5 consecutive days but costs less and may have fewer side effects.[14]

Platelet transfusion: platelet transfusion has little benefit in ITP, since platelet autoantigens are public antigens, present on all normal platelets. After a transfusion there usually is no significant rise in platelet count, although exceptions can occur. Thus, in the case of life-threatening hemorrhage, intermittent (2-4 U/m^2 every 6-8 hours) or continuous (0.5-1 U/m^2 per hour) platelet transfusions have been given in

Table 5. Treatment option in acute ITP, asymptomatic-paucisymptomatic cases (type A).

Platelet count ($n \times 10^9$/L)	*Appropriate* (mean scores 7-9)	*Appropriateness uncertain* (mean scores 3.1-6.9)	*Inappropriate* (mean scores 1-3)
> 20	No treatment* (8.7-B)	Hospitalization (3.3-C) Oral glucocorticoids (4.0-B)	Parenteral glucocorticoids (1.6-B) IVIG (1.8-B)
≤ 20	Hospitalization° (7.0-D)	Oral glucocorticoids (6.5-C) Parenteral glucocorticoids (4.3-D) IVIG (4.1-C)	No treatment° (1.0-A)

*In brackets consensus level; *in absence of other major risk factors for bleeding; °mainly at onset.*

Table 6. Treatment option in acute ITP, intermediate and severe cases (types B and C).

Clinical type	*Appropriate* (mean scores 7-9)	*Appropriateness uncertain* (mean scores 3.1-6.9)	*Inappropriate* (mean scores 1-3)
Type B	Hospitalization (9.0-A) Parenteral glucocorticoids (8.2-B) IVIG (7.3-C)	High-dose oral glucocorticoids (6.4-D) Conventional-dose oral glucocorticoids (4.4-D)	No treatment (1.1-B)
Type C	Hospitalization (9.0-A) IVIG (8.9-B) Parenteral glucocorticoids (8.7-B) Platelet transfusion (7.7-B) (differently combined)		No treatment (1.0-A) Oral glucocorticoids (1.5-B)

In brackets consensus level.

order to control hemorrhage.[20]

Hospitalization: by hospitalization (see Tables 5 and 6) we intend full hospitalization as an in-patient, not *day-hospital* care.

The indications for all the aforementioned strategies are reported in Tables 5 and 6. Each treatment option in these tables is intended to be used alone.

A special note should be made for severe ITP in which appropriate interventions include platelet transfusions, high-dose parenteral glucocorticoids and IVIG, in different combinations.

All the above mentioned treatments can be considered for every single episode of ITP within 6 months from the onset of the disease. At the end of each treatment (the day after the last administration of the drug or the 11th day in the case of no drug) the patient's clinical picture and platelet count should be reassessed. If the need to treat persists or a new episode occurs within 6 months from the onset of the original disease it is recommended that treament options are alternated.

Implementation, assessment and revision

To increase the diffusion and use of these guidelines they were discussed, during a specific *consensus conference,* by the interested members of AIEOP centers. Specific assessments by questionnaire will be carried out to evaluate any effective changes in clinical practice. These guidelines may need to be modified taking into account new evidence and suggestions from the questionnaires.

Contributions and Acknowledgments

DDM and DDP were responsible for designing guideline preparation and writing the paper. GCDV and MJ were responsible for methodological aspects and data analysis. AA, PG, AM, PM, MZ and AP were responsible for literature review and assessment of evidence. The AIEOP ITP Study Group members actively participated in the consensus conference. All the authors gave critical contributions to the paper and approved its final version. The name order was a joint decision, considering the role of each author.

Disclosures

Conflict of interest: none.

Redundant publications: this publication is, in part (>50%), reiterative (cfr. Rivista Italiana di Pediatria 1999; 25:41-51). However, the previous paper, aimed at pediatricians, was published in Italian in a journal without international diffusion and it was published without the benefits of peer-review and suggestions. Although the contents of the two papers are simlar, the target audience reached by Haematologica is very different and much larger.

Manuscript processing

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