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# Management strategies for newly diagnosed immune thrombocytopenia in Italian AIEOP Centres: do we overtreat? Data from a multicentre, prospective cohort study

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**Background** - The aim of the present study was to assess management strategies for immune thrombocytopenia (ITP) among Italian paediatric haematologists, and to compare these with those of recent international guidelines. Predictors of early remission or disease chronicity were also evaluated.

**Materials and methods** - During a period of 1 year, 205 children (age: 1 month-18 years) with newly diagnosed ITP were prospectively enrolled by 16 centres belonging to the Italian Association of Paediatric Haematology and Oncology (AIEOP). We collected the subjects demographic data, history, clinical symptoms, platelet count and treatment at presentation and at subsequent visits.

**Results** - Of the 205 patients, 47 (23%) were initially managed with a wait-and-see approach. Compared to these patients, children administered platelet-enhancing therapies were significantly younger (median age: 4.75 vs 7.96 years;  $p < 0.001$ ) and had lower platelet counts. At the 3-month follow-up, 92/202 patients (46%) had persistent ITP. Recovery within 3 months was predicted by younger median age (5.3 vs 7.8 years;  $p < 0.001$ ), and recent viral infection ( $p < 0.001$ ). At 1 year, 56 patients had chronic ITP, which was associated with older median age (7.54 vs 5.35 years;  $p < 0.001$ ), and a family history of autoimmunity ( $p < 0.05$ ; relative risk: 1.81; 95% confidence interval: 1.09-2.98). In total, 357 pharmacological treatments were recorded (216 intravenous immunoglobulins, 80 steroids). Response to intravenous immunoglobulins did not have an effect on remission rate at 12 months.

**Discussion** - Paediatric hematologists in Italian Centre treat over three-quarters of patients with newly diagnosed ITP, despite recent international guidelines. Almost 80% of patients with mild clinical symptoms received pharmacological treatment at diagnosis, which was significantly associated with younger age. Chronicity at 12 months was not affected by different therapeutic approaches at diagnosis or response to therapy.

**Keywords:** *immune thrombocytopenia, IVIG, steroids, children, ITP.*

## **INTRODUCTION**

Primary immune thrombocytopenia (ITP) -previously termed idiopathic thrombocytopenic purpura and immune thrombocytopenic purpura- is the most common childhood haematological disease. This acquired immune-mediated disorder is characterised by isolated thrombocytopenia, defined as a peripheral blood platelet count of  $<100 \times 10^9/L$ , with no apparent underlying cause. In children, ITP is usually benign and spontaneously resolves 6-18 months after diagnosis in the majority of patients. However, 20-30% of patients develop chronic ITP<sup>1</sup>.

Signs and symptoms vary widely. Many patients have either no symptoms or minimal bruising, whereas others experience severe bleeding<sup>2</sup>. Under the assumption that ITP treatment does not affect the natural course of the disease, recent guidelines for childhood ITP management from haematology societies<sup>3,4</sup> recommend that first-line therapies (i.e., intravenous immunoglobulins [IVIg] and steroids) be used in only a minority of paediatric patients who have active bleeding, with the aim of alleviating symptoms and/or preventing major bleeding. In general, physicians are advised to treat signs of bleeding rather than platelet counts. However, the management of children with newly diagnosed ITP remains controversial<sup>5</sup>.

In the present observational study, we assessed management strategies for children with newly diagnosed ITP among Italian paediatric haematologists in tertiary-care paediatric centres. Our primary aim was to report the appropriateness of treatment according to the published guidelines<sup>6</sup>. Our secondary aim was to assess the response rates to various first-line therapies, both at diagnosis and during the overall follow-up period of 12 months from diagnosis, as well as predictors of early remission or chronicity.

## **MATERIALS AND METHODS**

### Patients

In the 1-year period from January 1, 2014 to December 31, 2014, all children with newly diagnosed ITP were prospectively enrolled in this study by 16 Italian Association of Paediatric Haematology and Oncology (AIEOP) centres. Patients aged  $<1$  month or  $>18$  years were excluded. This study was approved by the Coagulation Defects Study Group of AIEOP, and by the ethics committee of each participating institution. Informed written consent was obtained for all patients from their parents or legal guardians. Every patient was treated in accordance with the clinical decisions of their local physician. Laboratory testing intervals were not defined. Follow-up clinical visits and platelet count assessments were locally recommended in relation to clinical conditions.

### Data collection

Immediately after diagnosis, the participating investigators registered their patients using web-based data transfer. Assisting physicians collected data concerning sex, date of birth, and date of diagnosis, as well as the subject's clinical history including information on any recent viral illness (within 3 weeks of the onset of ITP), recent immunisation, and family history of autoimmune diseases. Platelet count was determined at diagnosis, and during each subsequent clinical visit. At presentation and during the subsequent follow-up visits, assisting physicians were asked to classify each patient's clinical symptoms into one of three categories, as specified in the AIEOP guidelines: (i) type A: few *petechiae* and some bruises, without mucosal bleeding; (ii) type B: several *petechiae*, bruises, and mucosal haemorrhages; and (iii) type C: severe mucosal bleeding symptoms, as well as retinal haemorrhage, intracranial haemorrhage, other severe internal haemorrhages, and/or non-controlled or life-

threatening bleeding. The assisting physician was also asked to report the treatments administered, classified into seven main categories, as defined in the AIEOP guidelines:

(i) no therapy (wait-and-see approach); (ii) intravenous immunoglobulins (IVIg), 0.8 g/kg for 1 day; (iii) IVIg 0.8 g/kg for 2 days; (iv) oral prednisone at 1-2 mg/kg daily for 30 days (long course) or 4 mg/kg/day for 4 days (short course); (v) intravenous methylprednisolone 15-30 mg/kg as a 30 to 60 min bolus injection for 3 days; (vi) combined approach (IVIg + intravenous methylprednisolone, as recently defined<sup>7</sup>); or (vii) other treatments.

## Definitions

According to the current nomenclature proposed in 2009 by members of the International Working Group (IWG), ITP was classified based on duration into newly diagnosed (duration of 0-3 months), persistent (duration of 3-12 months), and chronic (duration  $\geq$  12 months)<sup>2</sup>. Responses to treatments were evaluated according to both historical criteria and the new IWG criteria proposed in 2009 (*Online Supplementary Content, Table SI*)<sup>2</sup>.

## Statistical analysis

All patients had a minimum of 1 year of follow-up. Data are expressed as medians and ranges for quantitative variables, and as absolute frequencies and percentages for qualitative variables. We used chi-square or Fisher's exact tests to assess independence between categorical variables, and non-parametric Mann-Whitney U tests to compare continuous variables. A p value of less than 0.05 was considered statistically significant. For significant variables, we also computed relative risks (RR) and their 95% confidence intervals (95% CI). Analyses were performed according to the intention-to-treat principle. Multivariable logistic regression was performed to analyse predictors of chronic disease. Cohen's kappa coefficient was used to evaluate the concordance of classifications obtained following different criteria. Analyses were performed using the software R, release 3.2.1.

## **RESULTS**

### Patients' characteristics at diagnosis

For this study, we enrolled 205 patients with newly diagnosed ITP, of whom 202 had a follow-up visit at 3 months and 200 had a follow-up visit at  $\geq$  1 year. The patients' characteristics at diagnosis are reported in the *Online Supplementary Content, Table SII*.

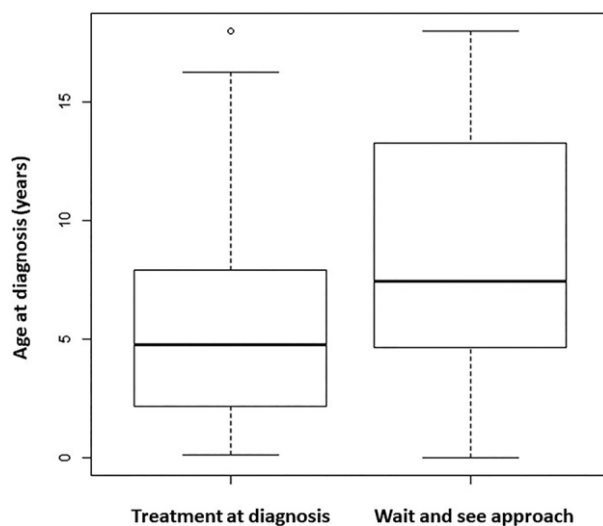
### Clinical management at diagnosis

The overall treatment rate at diagnosis was 77%. Of the 205 patients, only 47 (23%) were observed and received no pharmacological treatment at diagnosis (i.e., wait-and-see approach). **Table I** reports the differences between patients who were or were not treated at diagnosis. Of the 158 patients treated at diagnosis, 146 (93%) received first-line therapies: IVIg (n=132) or steroids (n=14). The remaining patients received other treatments as the first approach. Only patients who received IVIg were always hospitalised, because the Italian protocols recommend a very slow infusion (over 18 hours). Compared to the patients managed with a wait-and-see approach, the patients treated with platelet-enhancing therapies were significantly younger (median age of 4.75 years vs 7.96 years;  $p < 0.001$ ) and had a significantly lower median platelet count ( $6 \times 10^9/L$  vs  $46 \times 10^9/L$ ;  $p < 0.001$ ) (**Figure 1**).

Ten patients with a platelet count of  $> 30 \times 10^9/L$  at onset received treatment: IVIg (n=3), steroids (n=4), or a combined approach (n=3). The decision regarding treatment was unrelated to whether the diagnosis was made in the weekend or on a week day

**Table I - Differences between patients given or not given treatment upon diagnosis**

Parameters	Wait-and-see approach (n=47)		Treatment (n=158)		p value
	Median	(range)	median	(range)	
Platelet count at diagnosis (n×10 <sup>9</sup> /L)	46	(4-100)	6	(1-46)	0<0.001
Age at diagnosis (years)	7.96	(0.76-18)	4.75	(0.14-18)	0<0.001
	n	(%)	n	(%)	p value
<b>Bleeding at diagnosis</b>					
Absent (n=23)	20	87	3	13	0<0.001
Type A (n=111)	22	20	89	80	
Type B (n=69)	5	7	64	93	
Type C (n=2)	0	0	2	100	
<b>Sex</b>					
Male (n=103)	29	28	74	72	0.073
Female (n=102)	18	18	84	82	
<b>Diagnosis</b>					
During week (n=167)	42	25	125	75	0.112
During weekend (n=38)	5	13	33	87	



**Figure 1 - Age at diagnosis among patients treated with platelet-enhancing therapies (n=158) and in patients managed with a wait-and-see approach (n=47)**

Whether a patient received treatment was significantly correlated with the clinical symptoms at diagnosis ( $p<0.001$ ). Among the 23 patients who did not have bleeding symptoms at diagnosis, only three (13%) were treated with a pharmacological approach: IVIg (n=1) and/or steroids (n=3). Among those with mild clinical symptoms (type A, n=111), 89 (80%) received pharmacological treatment: IVIg (n=74), steroids (n=8), or a combined approach (n=4) (*Online*

*Supplementary Content, Figure S1*). (NB: 74+8+4=86, not 89) Of the 47 children managed using the wait-and-see option, only five (11%) required pharmacological treatment due to bleeding during the subsequent 12 months. Of these five children, three received parenteral therapy (IVIg) within the first week following diagnosis (3, 4, and 7 days after diagnosis), and the other two patients received treatment 1 month and 6 months after diagnosis.

**Follow-up analysis and predictors of remission Figure S2** (*Online Supplementary Content*) outlines the data regarding the follow-up analyses at 3 and 12 months after diagnosis. At 3 months after diagnosis, 92/202 patients (46%) had persistent ITP, while the remaining 110 had recovered within the first 3 months after diagnosis. **Table II** reports the differences between these two groups of patients. Compared to those with persistent ITP, children who had recovered by the 3-month follow-up were significantly younger (median age at diagnosis 5.3 years, range 0-16.8 years vs 7.8 years, range 0.35-18 years;  $p < 0.001$ ). Recent viral infection was also found to be a predictor of early recovery ( $p < 0.001$ ; RR: 0.60; 95% CI, 0.43-0.83).

At 12 months after diagnosis, 56 patients had chronic ITP; these 56 patients constituted 28% of the total patients with complete follow-up ( $n=200$ ) and 60% of the patients who had persistent ITP at 3 months ( $n=92$ ). The remaining 34 patients recovered between 3 and 12 months after diagnosis. **Table III** reports predictors of recovery within 12 months. Compared to those with normal platelet counts at the 12-month follow-up, children with chronic ITP were significantly older at diagnosis (median age at diagnosis: 7.54 years vs 5.35 years;  $p < 0.001$ ). A positive familial history of autoimmunity was also associated with the disease becoming chronic (RR: 1.81; 95% CI: 1.09-2.98;  $p < 0.05$ ). Recent viral infection was found to be a predictor of disease resolution at 12 months (RR: 0.46; 95% CI, 0.28-0.76;  $p < 0.05$ ). As reported in **Table SIII** (*Online Supplementary Content*), the percentage of patients with persistent and chronic ITP was higher among children whose platelet count at diagnosis was  $> 20 \times 10^9/L$  than among children with lower platelet counts at diagnosis; however, this difference was not statistically significant ( $p=0.351$ ). Multivariable analysis confirmed results for both the 3-month and 12-month univariate models (data not shown).

#### Treatment rates during the follow-up

During the 12-month follow-up period, a total of 357 pharmacological treatments were recorded. Among 216 courses of IVIg, 134 were administered at a dosage of 0.8 g/kg for 1 day, and 82 were administered at a dosage of 0.8 g/kg for 2 days. There were no recorded hospital readmissions due to therapy-related adverse events in the IVIg group.

A total of 80 courses of steroids were recorded during the 1-year follow-up period, comprising 38 courses of intravenous methylprednisolone and 42 courses of oral prednisone. Of the 42 courses of prednisone, 33 were administered at a dosage of 1 mg/kg/day for 30 days, and nine at a dosage of 4 mg/kg/day for 4 days. All patients who received steroid administration underwent bone marrow aspiration before starting treatment.

**Table II - Predictors of remission at 3 months**

	Platelet count >100×10 <sup>9</sup> /Lat 3 months (n=110)		Platelet count <100×10 <sup>9</sup> /Lat 3 months (n=92)		p value
	media n	(range)	media n	(range)	
Platelet count at diagnosis (n×10 <sup>9</sup> /L)	7	(1-100)	11	(1-97)	0.579 1
Age at diagnosis (years)	5.3	(0-16)	7.8	(0.35-18)	0.000 6
	n	(%)	n	(%)	p value
<b>Bleeding at diagnosis</b>					
Absent (n=23)	8	7	15	16	0.176
Type A (n=108)	62	56	46	50	
Type B (n=69)	40	36	29	31	
Type C (n=2)	0	0	2	2	
<b>Sex</b>					
Male (n=102)	62	56	40	43	0.068
Female (n=100)	48	44	52	57	
<b>Family history of autoimmunity</b>					
Yes (n=33)	13	12	20	22	0.151
No (n=134)	78	71	56	61	
Not available (n=35)	19	17	16	17	
<b>Recent immunisation</b>					
Yes (n=12)	7	6	5	5	0.95
No (n=158)	86	78	72	78	
Not available (n=32)	17	15	15	16	
<b>Recent viral infections</b>					
Yes (n=104)	69	63	35	38	0.000 6
No (n=89)	39	35	50	54	
Not available (n=9)	2	2	7	8	

Overall response rate to treatments

**Table IV** summarises the response rates to treatments, according to both historical criteria and the new IWG criteria. The overall response rates according to both the historical and IWG criteria were higher following 2 days of IVIg administration (87% and 78%, respectively) than after 1 day of IVIg (71% and 68%, respectively) ( $p < 0.005$ ).

Treatment options at diagnosis and development of chronic disease

Different therapeutic approaches at diagnosis did not influence the chronicity rate at 12 months. Chronic

disease (platelet count  $<100 \times 10^9/L$  at the 12-month follow-up) occurred in 13/46 patients managed with a wait-and-see approach, 36/132 children treated with IVIg, and 3/14 children treated with steroids ( $p=0.878$ ).

**Table III - Predictors of remission at 12 months**

Parameters	Platelet count $>100 \times 10^9/L$ at 12 months (n=144)		Platelet count $<100 \times 10^9/L$ at 12 months (n=56)		p value
	media n	(range)	media n	(range)	
Platelet count at diagnosis ( $n \times 10^9/L$ )	6.5	(1-78)	11	(1-97)	0.43230
Age at diagnosis (years)	5.35	(0-16)	7.54	(0.14-18)	0.002557
	<b>n</b>	<b>(%)</b>	<b>n</b>	<b>(%)</b>	<b>p value</b>
<b>Bleeding at diagnosis</b>					
Absent (n=23)	11	8	12	21	0.2921
Type A (n=107)	80	56	27	48	
Type B (n=68)	53	37	15	27	
Type C (n=2)	0	0	2	4	
<b>Sex</b>					
Male (n=101)	76	53	25	45	0.301
Female (n=99)	68	47	31	55	
<b>Family history of autoimmunity</b>					
Yes (n=33)	19	13	14	25	0.041
No (n=132)	101	70	31	55	
Not available (n=35)	24	17	11	20	
<b>Recent immunisation</b>					
Yes (n=12)	8	6	4	7	0.886
No (n=157)	113	78	44	79	
Not available (n=31)	23	16	8	14	
<b>Recent viral infections</b>					
Yes (n=102)	84	58	18	32	0.003643
No (n=89)	55	38	34	61	
Not available (n=9)	5	3	4	7	



Treatment response to intravenous immunoglobulins and development of chronic disease  
 The probability of remission at 12 months was not influenced by the response (complete or any, according to IWG criteria) or lack of response to IVIg, administered as first therapy or in the subsequent course of the disease (Table V).

## **DISCUSSION**

Despite significant progress in understanding the pathophysiology of ITP<sup>8</sup>, the management of paediatric patients with newly diagnosed ITP remains a controversial topic. In recent years, haematological societies have recommended that physicians treat bleeding signs rather than platelet counts<sup>3</sup>; however, published Italian

**Table IV - Response rate to different treatments according to historical criteria and new International Working Group criteria**

Treatments	Response: Hist-C		Response: IWG-C		Kramer's coefficient
	n	(%)	n	(%)	
All treatments (n=357)	255	77	237	66	
IVIg all courses (n=216)	166	77	156	72	0.566 (p=0.1805)
IVIg 0.8 g/kg for 1 day (n=134)	95	71	92	68	
IVIg 0.8 g/kg for 2 days (n=82)	71	87	64	78	
Steroids all courses (n=80)	54	68	53	66	0.634 (p=0.2633)
m-PDN (n=38)	25	66	25	66	
PDN 1-2 mg/kg/day for 30 days (n=33)	24	73	24	73	
PDN 4 mg/kg/day for 4 days (n=5)	5	56	4	55	

Hist-C: historical criteria; IWG-C: International Working Group criteria; IVIg: intravenous immunoglobulins; m-PDN. Intravenous methylprednisone; PDN: oral prednisone.

**Table V - Response, according to International Working Group criteria, to intravenous immunoglobulins administered as first therapy or in the subsequent course of the disease, and chronicisation at 12 months**

Chronic disease (platelets <100×10 <sup>9</sup> /L) at 12 months							
IVIg as first therapy (n=132)							
Response	n	(%)	p value	Response	n	(%)	p value
CR (n=72)	18	25	0.665	CR + R (n=97)	27	28	0.567
R + NR (n=60)	17	28		NR (n=35)	8	23	
Only IVIg therapy (n=95): better response							
Response	n	(%)	p value	Response	n	(%)	p value

CR (n=63)	1 0	16	0.28 3	CR + R (n=81)	1 5	18	0.74 8
R + NR (n=32)	8	13		NR (n=14)	3	21	

IVIg: intravenous immunoglobulins; CR: complete response; R: response; NR: no response.

guidelines still consider the wait-and-see approach to be appropriate only in children with mild bleeding (i.e., skin manifestations only, type A) and with a platelet count of  $>20 \times 10^9/L$ <sup>6</sup>. Our present study was specifically designed to evaluate the choices of experienced physicians when managing children with newly diagnosed ITP, and their current rate of implementing the Italian guidelines 15 years after their publication.

Our study population was an observational cohort enrolled in Italian tertiary care paediatric haematology centres, and case management decisions were made at the discretion of the treatment provider. Based on the age-specific incidence of ITP among paediatric patients (4.2 per 100,000 person-years)<sup>9</sup>, our study enrolled approximately 70% of all children with newly diagnosed ITP in Italy during the study period. The remaining cases were likely managed in general paediatric units. The ad hoc-designed database enabled completion of 12 months of follow-up for 97% (200/205 patients) of the enrolled cohort, which is a higher rate than in previous studies<sup>10</sup>. In our cohort of patients, the overall treatment rate at diagnosis was 77%, which is slightly higher than the rates reported at AIEOP centres between 2000 and 2003<sup>11</sup>. The decision to start treatment at diagnosis was significantly associated with lower platelet count, severity of bleeding, and younger age. Only three patients received platelet-enhancing therapies at diagnosis based on platelet count alone, in the absence of bleeding symptoms. In contrast to recent guidelines, a pharmacological approach was used in almost 80% of children with mild clinical symptoms (type A bleeding).

The problem of non-adherence to evidence-based guidelines is great in all countries; Lones *et al.* recently reported a high hospitalisation rate in the USA among children with newly diagnosed immune thrombocytopenia, even in the absence of documented bleeding symptoms<sup>12</sup>.

The vast majority of patients in our cohort received IVIg as both the first therapeutic approach and during the subsequent disease course, with over 200 IVIg courses administered overall. No readmissions or prolonged admissions due to adverse effects of IVIg were recorded, likely because the Italian protocols recommend a very slow infusion (over 18 hours), in contrast to the recent report by Heitink-Polle' *et al.*<sup>13</sup>. The treatment response rates were higher with IVIg than with steroids, according to both historical response criteria (considering only the platelet count as the primary outcome) and the new IWG criteria for response (also considering remission of bleeding).

Among the patients initially managed with observation alone, only about 10% required hospital admission and/or pharmacological treatment during their subsequent disease course. This result is consistent with the recently reported findings of Heitink-Polle' *et al.*<sup>13</sup>, who randomly assigned patients with mild-moderate bleeding to be managed by observation alone at diagnosis. No severe bleeds (type C, including intracranial haemorrhage) were registered among our patients. However, it is challenging to compare these two cohorts of children directly, since our observation group comprised mostly children without bleeding symptoms (n=20) or with mild bleeding (type A, n=22).

With regards to follow-up analysis, over 50% of patients exhibited recovery within 3 months after diagnosis. Among the patients with persistent ITP at 3 months, 40% recovered within 12 months. Thus, almost 30% of patients with a complete 1-year follow-up had chronic ITP at 12 months. These data are consistent with findings previously reported by the Intercontinental Cooperative ITP Study Group Registry<sup>14</sup>, and confirm the good prognosis of ITP during childhood. We found that younger age at diagnosis and recent viral infection were associated with both early recovery and resolution at 12 months. Furthermore, a positive family history of autoimmunity was weakly associated with a higher risk of chronicisation. Predictors of disease remission were detected in both univariable and multivariable analyses, in accordance with previous studies<sup>14,15</sup>. The development of chronic disease was not influenced by different therapeutic approaches at diagnosis, response to IVIg administered as first therapy, or better response in patients who received only IVIg during the 1-year follow-up period, as recently demonstrated<sup>16</sup>. Interestingly our present results demonstrated that paediatric haematologists in Italian Centres continue to treat over three-quarters of patients with newly diagnosed ITP, regardless of recent international guidelines<sup>3,4</sup>. Almost 80% of patients with mild clinical symptoms were managed with a pharmacological approach, and the decision to start treatment at diagnosis was significantly associated with younger age. Although the administration of IVIg has not been proven to affect the natural history of the disease, it is preferred over steroids probably because IVIg quickly increases platelet count and ameliorates bleeding symptoms without significant side effects.

A comparison of economic aspects of IVIg vs steroids has not been made, in part because of the difficulty of comparing costs and refunds from the National Health System which may fluctuate in different regions. Another discordance from current international guidelines regards bone marrow aspiration. The existing Italian guidelines consider bone marrow aspiration to be appropriate before starting steroid treatment<sup>6</sup>, and the real-life data collected are consistent with such recommendation; even though bone marrow aspirate is an invasive procedure that requires additional medication and sedation, Italian paediatricians working in Paediatric Onco-Haematology Units frequently prefer to perform it mainly for the purpose of excluding leukaemia and so completely reassuring the child's family.

The question remains: do we overtreat, or do we have a different attitude regarding newly diagnosed paediatric ITP? Even in the earliest stages of the disease, patients often report additional burdens, including fatigue and lack of energy, restrictions to activity, medication side effects, hospital admissions, and frequent blood sampling. Parents' greatest concerns for their children are focused on fears of bleeding and injury, and are inversely proportional to the patient's age<sup>17,18</sup>. Toddlers, who have a high tendency to fall, can benefit from increased platelet counts during the first weeks after the onset of ITP, even though younger age is associated with a higher frequency of early remission. Additionally, social embarrassment due to visible signs of bruising (and potential suspicion of physical violence and efforts at bruise concealment) may also lead both children and their families to prefer treatment, even when symptoms are very rare or completely absent.

## **CONCLUSIONS**

The real-life treatment choices that we registered were in line with published Italian recommendations but

resulted “overtreatment” according to current international guidelines, as recently reported. These choices may be explained with the motivation of maintaining a better quality of life in the acute phase of the disease also in less severe cases: fear of major bleeding and the family's anxiety are still critical issues, especially with infants and younger children whose exposure to trauma cannot be controlled.

We strongly believe that in clinical practice there is an urgent need for shared medical decisions focusing also on patient/family-centred outcomes (including parental anxiety); thus, it is essential to assess the health-related quality of life of children with ITP and their parents to evaluate the benefit-to-harm balance of treatment vs observation<sup>19</sup>. Moreover, there is an urgent need for dissemination and implementation among paediatric haematologists of current guidelines: education and repeated publication of the evidence can change the attitude of both families and doctors.

It is our intention to take all these critical issues into serious consideration for all the necessary review and amendment in an up-to-date edition of our national guidelines.

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## **AUTORSHIP CONTRIBUTIONS**

EP and GR contributed equally.

EP and GR gave substantial contribution to conception and design, drafted the article, reviewed and revised the manuscript. PF and LDN contributed to conception and design, reviewed and revised the manuscript. MTG analysed data, reviewed and revised the manuscript. MN, FG and PG collected data, reviewed and revised the manuscript. UR supervised data collection and critically reviewed and revised the manuscript. All the members of the “AIEOP ITP Study Group” contributed to conception of the study and collected data. All Authors and members of the “AIEOP ITP Study Group” approve the final version of the manuscript as submitted and agree to be accountable for all aspects of the work.

## **DISCLOSURE OF CONFLICTS OF INTEREST**

*The Authors declare no conflicts of interest. The Authors declare that Serena Antonelli, referenced in the Acknowledgments section, gave her voluntary help for database creation and management and that she has no conflict of interest or financial interests in the work to declare.*

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## **APPENDIX 1**

The "AIEOP ITP Study Group"

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