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

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

Emilia Parodi[1], Giovanna Russo[2], Piero Farruggia[3], Lucia D. Notarangelo[4], Maria T. Giraudo[5], Margherita Nardi[6], Fiorina Giona[7], Paola Giordano[8], Ugo Ramenghi[1], and the "AIEOP-ITP Study Group" (Appendix 1)

[1]*Haematology Unit, Departmentof Paediatric and Public Health Sciences, University of Turin, Turin;*

[2]*Paediatric Haematology and Oncology Unit, "Policlinico-Vittoro Emanuele" Hospital, University of Catania, Catania;*

[3]*Paediatric Haematology and Oncology Unit, A.R.N.A.S. Civic Hospital, Palermo;*

[4]*Onco-Haematology and BoneMarrow Transplantation Unit,Children's Hospital, Brescia;*

[5]*Department of Mathematics, University of Turin, Turin;*

[6]*Paediatric Haematology Oncology, Bone Marrow Transplant, "S. Chiara" University Hospital, Pisa;*

[7]*Department of Translational and Precision Medicine, "Sapienza" University, Rome;*

[8]*Department of Biomedical Sciences and Human Oncology,Pediatric Section, "A. Moro" University of Bari, Bari; Italy*

Background - The aim of the present study was to assess managementstrategies for immune thrombocytopenia (ITP) among Italian paediatric haematologists, and to compare these with those of recent internationalguidelines. 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 3months was predicted by younger median age (5.3 *vs* 7.8 years; $p<0.001$), andrecent viral infection ($p<0.001$) . At 1 year, 56 patients had chronic ITP, whichwas associated with older median age (7.54 *vs* 5.35 years; $p<0.001$), and afamily 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 - Pediatric 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 bydifferent 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 <100×109/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[1].

Signs and symptoms vary widely. Many patients have either no symptoms or minimal bruising, whereas others experience severe bleeding[2]. Under the assumption that ITP treatment does not affect the natural course of the disease, recent guidelines for childhood ITP management from haematology societies[3,4] 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[5].

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[6]. 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 alsoaskedtoreportthetreatmentsadministered, classifiedinto 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/kgfor 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 to60 min bolus injection for 3 days; (vi) combined approach (IVIg + intravenous methylprednisolone, as recentlydefined[7]); or (vii) other treatments.

Definitions

According to the current nomenclature proposed in 2009by 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 ≥12 months)[2]. Responsesto treatments were evaluated according to both historical criteria and the new IWG criteria proposed in 2009 (*OnlineSupplementary Content*, **Table SI**)[2].

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) andtheir 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 at3 months and 200 had a follow-up visit at ≥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 remainingpatients 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 4.75years *vs* 7.96 years; p<0.001) and had a significantly lowermedian platelet count (6×10^9/L vs 46×10^9/L; p<0.001) (**Figure 1**).
Ten patients with a platelet count of $>30\times10^9$/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 ($n \times 10^9$/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
Bleeding at diagnosis					
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	
Sex					
Male (n=103)	29	28	74	72	0.073
Female (n=102)	18	18	84	82	
Diagnosis					
During week (n=167)	42	25	125	75	0.112
During weekend (n=38)	5	13	33	87	

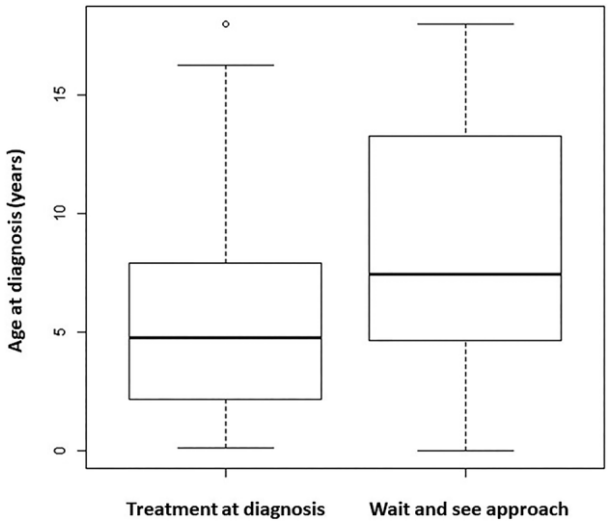

Figure 1 - Age at diagnosis among patients treated with platelet-enhancing therapies (n=158) and in patients managed with a wait-and-see approach (n=47)

Whether a patient received treatment was significantlycorrelated 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 tobleeding 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 treatment1 month and 6 months after diagnosis.

Follow-up analysis and predictors of remission Figure S2 (*Online Supplementary Content*) outlines the dataregarding the follow-up analyses at 3 and 12 months afterdiagnosis. At 3 months after diagnosis, 92/202 patients(46%) had persistent ITP, while the remaining 110 hadrecovered within the first 3 months after diagnosis.**Table II** reports the differences between these twogroups of patients. Compared to those with persistentITP, 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 foundto 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 patientswith complete follow-up (n=200) and 60% of the patients who had persistent ITP at 3 months (n=92). The remainin 34 patients recovered between 3 and 12 months afterdiagnosis. **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 predictorof 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*), thepercentage of patients with persistent and chronic ITP was higher among children whose platelet count at diagnosis was $>20\times10^9$/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 duringthe 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 >100×109/Lat 3 months (n=110)		Platelet count <100×10⁹/Lat 3 months (n=92)		p value
	media n	(range)	media n	(range)	
Platelet count at diagnosis (n×10⁹/L)	7	(1-100)	11	(1-97)	0.5791
Age at diagnosis (years)	5.3	(0-16)	7.8	(0.35-18)	0.0006
	n	**(%)**	**n**	**(%)**	**p value**
Bleeding at diagnosis					
Absent	8	7	15	16	
(n=23) Type	62	56	46	50	
A (n=108)	40	36	29	31	0.176
Type B	0	0	2	2	
(n=69)					
Type C					
(n=2)					
Sex					
Male (n=102)	62	56	40	43	
Female (n=100)	48	44	52	57	0.068
Family history of autoimmunity					
Yes (n=33)	13	12	20	22	
No (n=134)	78	71	56	61	0.151
Not available (n=35)	19	17	16	17	
Recent immunisation					
Yes (n=12)	7	6	5	5	
No (n=158)	86	78	72	78	0.95
Not available (n=32)	17	15	15	16	
Recent viral infections					
Yes (n=104)	69	63	35	38	
No (n=89)	39	35	50	54	0.0006
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 boththe 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 <100×10^9/L at the 12-month follow-up) occurred in 13/46 patients managed with a wait-and-seeapproach, 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 >100×109/Lat 12 months (n=144)**		**Platelet count <100×10^9/Lat 12 months (n=56)**		**p value**
	median	**(range)**	**median**	**(range)**	
Platelet count at diagnosis (n×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
	n	**(%)**	**n**	**(%)**	**p value**
Bleeding at diagnosis					
Absent	11	8	12	21	
(n=23)	80	56	27	48	
Type A	53	37	15	27	0.2921
(n=107)	0	0	2	4	
Type B					
(n=68)					
Type C					
(n=2)					
Sex					
Male	76	53	25	45	
(n=101)	68	47	31	55	0.301
Female					
(n=99)					
Family history of autoimmunity					
Yes (n=33)	19	13	14	25	
No (n=132)	101	70	31	55	0.041
Not available (n=35)	24	17	11	20	
Recent immunisation					
Yes (n=12)	8	6	4	7	
No (n=157)	113	78	44	79	0.886
Not available (n=31)	23	16	8	14	
Recent viral infections					
Yes (n=102)	84	58	18	32	
No (n=89)	55	38	34	61	0.003643
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 notinfluenced by the response (complete or any, accordingto 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[8], the management of paediatric patients with newly diagnosed ITP remains a controversialtopic. In recent years, haematological societies have recommended that physicians treat bleeding signs rather than platelet counts[3]; 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 thesubsequent course of the disease, and chronicisation at 12 months*

Chronic disease (platelets <100×10⁹/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)	10	16	0.283	**CR + R (n=81)**	15	18	0.748
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 beappropriate only in children with mild bleeding (i.e., skin manifestations only, type A) and with a platelet count oF $>20\times10^9/L$[6]. Our present study was specifically designedto evaluate the choices of experienced physicians when managing children with newly diagnosed ITP, and theircurrent 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)[9], our study enrolled approximately 70% of all children with newly diagnosedITP in Italy during the study period. The remaining cases were likely managed in general paediatric units. The adhoc-designed database enabled completion of 12 monthsof follow-up for 97% (200/205 patients) of the enrolledcohort, which is a higher rate than in previous studies[10]. In our cohort of patients, the overall treatment rate atdiagnosis was 77%, which is slightly higher than therates reported at AIEOP centres between 2000 and2003[11]. The decision to start treatment at diagnosis wassignificantly associated with lower platelet count, severityof bleeding, and younger age. Only three patients receivedplatelet-enhancing therapies at diagnosis based on plateletcount alone, in the absence of bleeding symptoms. Incontrast to recent guidelines, a pharmacological approachwas used in almost 80% of children with mild clinicalsymptoms (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[12].

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 slowinfusion (over 18 hours), in contrast to the recent report by Heitink-Polle' *et al.*[13]. 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 subsequentdisease course. This result is consistent with the recently reported findings of Heitink-Polle´ *et al.*[13], who randomly assigned patients with mild-moderate bleeding to be managed by observation alone at diagnosis. No severebleeds (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 Registry14, 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[14,15]. 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[16]. 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[3,4]. 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[6], 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[17,18]. 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 parentsto evaluate the benefit-to-harm balance of treatment *vs* observation[19]. 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 nationalguidelines.

ACKNOWLEDGEMENTS

The Authors are grateful to: Serena Antonelli, BSC, Milan,Italy, for her irreplaceable and precious help with the database creation and management.

AUTORSHIP CONTRIBUTIONS

EP and GR contributed equally.

EP and GR gave substantial contribution to conception and design, drafted the article, reviewed and revisedthe manuscript. PF and LDN contributed to conceptionand desgin, reviewed and revised the manuscript. MTGanalysed data, reviewed and revised the manuscript.MN, FG and PG collected data, reviewed and revised the manuscript. UR supervised data collection and criticallyreviewed and revised the manuscript. All the members of the "AIEOP ITP Study Group" contributed to conception ofthe study and collected data. All Authors and members of the "AIEOP ITP Study Group" approve the filnal version ofthe manuscript as submitted and agree to be accountablefor 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.

BIBLIOGRAPHY

1. Kuhne T, Imbach P, Bolton-Maggs PH, et al. Newly diagnosed idiopathic thrombocytopenic purpura in childhood: an observational study. Lancet 2002; **358**: 2122-5.
2. RodeghieroF, Stasi R, Gernsheimer T, etal. Standardizationofterminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Blood 2009; **113**: 2386-93.
3. Neunert C, Terrell DR, Arnold DM, Buchanan G, et al. American Society of Hematology 2019 guidelines

for immune thrombocytopenia. Blood Adv 2019; **3**: 3829-66.

4. Provan D, Arnold DM, Bussel JB, et al. Updated international consensus report on the investigation and management of primary immune thrombocytopenia. Blood Adv 2019; **3**: 3780-817.
5. Kuhne T. Idiopathic thrombocytopenic purpura in childhood: controversies and solutions. Pediatr Blood Cancer 2006; **47**: 650-2.
6. De Mattia D, Del Principe D, Del Vecchio GC, et al. Acute childhood idiopathic thrombocytopenic purpura: AIEOP consensus guidelines for diagnosis and treatment. Associazione Italiana di Ematologia e Oncologia Pediatrica. Haematologica 2000; **85**: 420-4.
7. Parodi E, Giordano P, Rivetti E, et al. Efficacy of combined intravenous immunoglobulins and steroids in children with primary immune thrombocytopenia and persistent bleeding symptoms. Blood Transfus 2014; **12**: 340-5.
8. Stasi R, Evangelista ML, Stipa E, et al. Idiopathic thrombocytopenic purpura: current concepts in pathophysiology and management. Thromb Haemost 2008; **99**: 4-13.
9. Yong M, Schoonen WM, Li L, et al. Epidemiology of paediatric immune thrombocytopenia in the General Practice Research Database. Br J Haematol 2010; **149**: 855-64.
10. Rosthøj S, Hedlund-Treutiger I, Rajantie J, et al. Duration and morbidity of newly diagnosed idiopathic thrombocytopenic purpura in children: a prospective Nordic study of an unselected cohort. J Pediatr 2003; **143**: 302-7.
11. Del Vecchio GC, De Santis A, Giordano P, et al. Management of acute childhood idiopathic thrombocytopenic purpura according to AIEOP Consensus Guidelines: Assessment of Italian Experience. Acta Haematol 2008; **119**: 1-7.
12. Jones L, Koch T, Stanek J, O'Brien SH. Patterns of Emergency Department care for newly diagnosed immune thrombocytopenia in United States children's hospitals. J Pediatr 2017; **190**: 265-7.
13. Heitink-Pollé KMJ, Uiterwaal CSPM, Porcelijn L, et al. Intravenous immunoglobulinvs observation in childhood immune thrombocytopenia: a randomized controlled trial. Blood 2018; **132**: 883-91.
14. Bennett CM, Imbach P, Neunert C, et al. Predictors of remission in children with newly diagnosed immune thrombocytopenia : data from the Intercontinental Cooperative ITP Study Group Registry II participants. Pediatr Blood Cancer 2018; **1**: 1-7.
15. Revel-Vilk S, Yacobovich J, Frank S, et al. Age and duration ofbleeding symptoms at diagnosis best predict resolution of childhood immune thrombocytopenia at 3, 6, and 12 months. J Pediatr 2013; **163**: 1335-9.
16. Lambert MP. Intravenous immunoglobulin use in children with ITP does not affect development of chronic disease. J Pediatr 2019; **204**: 320-3.
17. Flores A, Klaassen RJ, Buchanan GR, Neunert CE. Patterns and influences in health-related quality of life in children with immune thrombocytopenia: a study from the Dallas ITP Cohort. Pediatr Blood Cancer 2017; **64**: 8.
18. Trotter P, Hill QA. Immune thrombocytopenia: improving quality of life and patient outcomes. Patient Relat Outcome Meas 2018; **9**: 369-84.
19. Giordano P, Lassandro G, Giona F, et al. ITP-QoL questionnaire for children with immune thrombocytopenia: Italian version validation's. Pediatr Hematol Oncol 2014; **31**: 534-47.

APPENDIX 1

The "AIEOP ITP Study Group"

Angelica Barone, MD; Department of Paediatric Onco-Haematology, University Hospital, Parma, Italy;

Gianluca Boscarol, MD; Department of Paediatrics,

Central Teaching Hospital Bolzano, Bolzano, Italy;

Simone Cesaro, MD; Paediatric Haematology Oncology,

University Hospital, Verona, Italy;

Francesca Fioredda, MD; Clinical and Experimental Unit, "G. Gaslini" Children's Hospital, Genoa, Italy;

Saverio Ladogana, MD; Department of Haematology, "IRCCS Casa Sollievo della Sofferenza", San Giovanni

Rotondo, Italy;
Maria Licciardello, MD; Paediatric Haematologyand Oncology Unit, “Vittorio Emanuele” Polyclinic, University of Catania, Italy;
Francesca Rossi, MD; “Santobono Pausilipon” Hospital, Naples, Italy;
Laura Rubert, MD; Paediatric Haematology Oncology Fondazione IRCCS Policlinico San Matteo, Pavia, Italy;
Marco Spinelli, MD; MBBM Foundation, Department of NPaediatrics, University of Milano-Bicocca, Monza, Italy;
Fabio Tucci; Department of PaediatricOnco-Haematology,Meyer Children's Hospital, Florence, Italy.