Heterogeneity of terminology and clinical definitions in adult idiopathic thrombocytopenic purpura: a critical appraisal from a systematic review of the literature

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ABSTRACT

Clinical definitions and terminology vary greatly in clinical studies on idiopathic thrombocytopenic purpura (ITP). An objective assessment of this heterogeneity may be of interest, providing a basis for standardizing ITP terminology. A systematic review of the recent literature on ITP in adults was carried out. The following items were extracted from the articles for comparison: platelet count cut-off values to decide treatment and type of response; timing for evaluating the response to treatment; evaluation of bleeding symptoms; criteria to define initial, chronic and refractory forms. A total of 79 papers, among those published or referenced from 2000 to 2006, were considered eligible. No consensus among the different authors was found on several issues, including:platelet count for definition of ITP; grading of severity; definition of chronic ITP; platelet threshold to start treatment; platelet count to define response to treatment and timing for evaluating the response to therapy. There was only major consensus for the length of disease duration required to diagnose chronic ITP, the criteria for splenectomy and the definition of refractory ITP. Confusing terminology and an unacceptable heterogeneity of clinical definitions used for management decisions and to describe outcomes were evident in recent ITP literature. This makes it very difficult to compare different studies and to share data and clinical experiences. A standardization of terminology and definitions used in ITP is urgently needed.

Key words:idiopathic thrombocytopenic purpura, ITP, systematic review, diagnosis, therapy, terminology.

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Introduction

Idiopathic (or immune) thrombocytopenic purpura (ITP) is an acquired disease characterized by a decrease of the platelet count due to platelet auto-antibodies and, in its more severe forms, by bleeding symptoms.[1-4] Although ITP has been known for many years, there are still many unresolved issues about pathogenetic mechanisms, epidemiology, diagnosis and management. Notably, for the most part, the treatment of ITP is not based on evidence, due to the lack of clinical trials. Consequently, the few published guidelines are inevitably based only on expert opinions.[5-7] Recently, systematic reviews and meta-analysis have been produced[8-10] to obtain more accurate and consistent evaluations on the short and long-term outcomes after splenectomy, therapy for refractory cases or anti CD 20 antibody treatment. Unfortunately, all of these reviews had intrinsic weaknesses in the analysis due to the great variability of clinical definitions used by the different authors. To objectively assess the scale of this heterogeneity, a systematic review of the recent literature was carried out, providing a preliminary step towards a common and shared set of clinical definitions and terminology in ITP.

Search strategy

Full-paper articles on ITP published from 1 January 2000 to 15 August 2006 were searched on Medline database, using the Medical Subjects Heading term *purpura, thrombocytopenic, idiopathic* and the textwords *purpura*; *immune*; *thrombocytopenic*; *thrombocytopenia*, with explosion modality. Articles published prior to the year 2000 were included in this preliminary search only if referenced in one of the more recent articles retained for final analysis and fulfilling the elegibility criteria described below. Bibliography of relevant articles was manually searched.

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Eligibility criteria and study selection

The search was limited to papers written in English, including articles with original data and reviews or guidelines with secondary observations. Initially, titles and abstracts of all articles were evaluated by two authors (MR and SF). Complete articles were retrieved when they were judged potentially pertinent to the aims of this revision. Articles were then retained for final analysis if they included al least one of the clinical definitions or decisional criteria described in Table 1. In addition, original studies had to contain more than 10 cases.

Data extraction and results evaluation

The pertinent data were extracted and collected from articles retained for final analysis. To summarize the results, main clinical settings were identified, including definition of ITP, initial treatment, chronic disease, splenectomy and refractory disease. Taking into account the nature of the data under investigation, no statistical analysis was planned, but an arbitrary percentage cut-off of 75% of concordance for the pooled data, was chosen *a priori* to indicate a significant agreement between different authors. Given the nature of this revision, aimed at assessing the scale of variability of definitions and terminology in ITP, the same strength was assigned to all types of papers (randomized trials, prospective cohorts, case series, reviews or guidelines).

Results

A total of 1,468 articles were initially retrieved. 1,057 papers were preliminarly excluded, on the basis of their abstract, not being pertinent, or only reporting laboratory data, or regarding childhood patients or describing 10 or less cases. The remaining 411 articles were carefully read to select those studies which completely fulfilled eligibility criteria. Finally, 59 articles were considered eligible for this revision. Twenty additional articles published before 2000 and fulfilling our eligibility criteria were retained from the references of the most recent articles. In this way, all major papers pertinent to the scope of our review and referred to in the most recent literature were also included. A total of 79 papers[1,5-9,11-83] were considered for this revision: 17 prospective cohort studies with active therapeutic intervention; 9 observational studies; 19 retrospective cohort studies; 8 short reports; 6 randomized trials; 1 case-control study; 17 reviews; 2 guidelines. The definitions extracted from the papers were pooled in the different categories to summarize the results (Table 2). Platelet counts were grouped in $5x10^9$/L classes for values < $50x10^9$/L and in $10x10^9$/L classes for values > $50x10^9$/L; time was ranked in month classes. Complete detailed results are available in Tables 1-13 of the *Online Supplementary Appendix*.

Diagnosis of ITP: platelet count threshold, time interval from presentation to definite diagnosis, grading of severity and criteria to start treatment

The level of thrombocytopenia required for ITP diagnosis was reported in 10 papers ranging from <150 and ≤100×10^9/L. In another 58 articles, a vague adherence to *standard criteria* was indicated. In 8 papers the minimum time interval from presentation to definite diagnosis was also reported, ranging from ≥2 months to ≥6 months; in two papers a confirmation of thrombocytopenia in two separate platelet assays was required. The grade of disease severity at diagnosis was based only on the platelet count. The platelet count thresholds to define *severe* (21 papers, ≤5-100×10^9/L), *moderate* (3 papers, from ≥30 to ≤30-100×10^9/L) or *mild* (3 papers, from ≥30 to ≤90×10^9/L) ITP showed a wide range of platelet cut-off values. A total of 23 papers were available regarding the criteria to start treatment. When the initial treatment was suggested on the basis of the platelet count even in the absence of significant bleeding symptoms, the decisional range varied between ≤10 to ≤50×10^9/L. However, the majority of authors agreed to treat patients with a platelet count ≤30×10^9/L if some active bleeding was present.

Initial treatment: bleeding evaluation

Only one article reported the use of a bleeding score to assess the severity of the disease before therapy and to evaluate the grade of response.[11] Otherwise, bleeding is only referred in generic terms as present, minor or major.

Table 1. Clinical definitions or decisional criteria scrutinized in the literature.

Phase of disease	*Data extracted from the articles*
Definition of ITP (bleeding score)	Platelet count used for definition; platelet count used for severity grading; bleeding assessment
Criteria used to decide initial treatment	Platelet count; qualification of bleeding symptoms
Criteria to evaluate and classify the response to initial treatment	Platelet count; timing of assessment; durability of response
Definition of chronic ITP	Platelet count used for definition; time period from initial therapy
Criteria for splenectomy indication	Clinical criteria, minimum platelet count for a safe surgery
Criteria to evaluate and classify the response to splenectomy	Platelet count; timing of assessment; durability of response
Definition of refractory ITP	Platelet count used for definition; clinical criteria
Criteria used to decide treatment of refractory ITP	Platelet count; bleeding assessment
Criteria to evaluate and classify the response to therapy of refractory ITP	Platelet count; timing of assessment; durability of response

Table 2. Agreement of major definitions in the principal clinical settings of ITP.

Clinical setting	*Definition*	*N. papers*	*Parameter range*		*Most agreed parameter value*		*Agreement percentage (n. papers)*
			Platelet count (×10⁹/L)	*Time*	*Platelet count (×10⁹/L)*	*Time*	
Definition	Platelet level for definition	10	<150 – ≤100	–	<150	–	50 (5)
	Definition of severe ITP	21	<90 – ≤30	–	≤30	–	38 (8)
Initial treatment	Platelet level to start therapy	23	≥50 – ≤10	–	≤30	–	60 (14)
	Definition of CR	18	≥150 – ≥100	–	≥150	–	56 (10)
	Definition of PR	18	≥30 – <150	–	≥50 – <150	–	33 (6)
	Definition of NR	19	≥50 – ≤20	–	≤50	–	53 (10)
	Timing for response assessment	13	–	3 d-9 m	–	3-7 d*	38 (5)
	Durable response	14	–	3 w-12 m		1 m	29 (4)
Chronic ITP	Platelet level	11	≥50 – ≤150	–	≤≤50	–	45 (5)
	Minimum time from initial therapy	25	–	≥ 3-6 m	–	≥ 6 m	76 (19)
Splenectomy	Indication	48			See footnote§		89 (43)
After splenectomy	Definition of CR	24	≥50 – ≥150	–	≥150	–	54 (13)
	Definition of PR	20	≥30 – <150	–	≥50 – <150	–	45 (9)
	Definition of NR	16	≤≤50 – ≤30	–	≤50	–	70 (11)
	Timing for response assessment	11	–	3 d- 6 m	–	After 1 m	18 (2)
	Durable response	13	–	1 m-12 m	–	1 m	38 (5)
Refractory ITP	Definition	49			See footnote#		100 (49)
	Platelet level for definition	7	≤20 – ≤100	–	≤20	–	43 (3)
	Platelet level to start therapy	24	≤10 – ≤90	–	≤30	–	45 (11)
	Definition of CR	31	≥100 – ≥190	–	≥150	–	39 (12)
	Definition of PR	27	≥30 – <150	–	≥50 – ≤100	–	16 (5)
	Definition of NR	25	≤50 – ≤10	–	≤50	–	40 (10)

*CR: complete response; PR: partial response; NR: no response; d: day; w: week; m: month; *: paper evaluating IV Ig response; §: Adult patients with a diagnosis of chronic ITP, after failure of first-line therapy or need of unacceptably high dosage of steroids to maintain a safe platelet count. #Low platelet count persisting after splenectomy and requiring active treatment to maintain a safe platelet count.*

Criteria to assess the response to initial treatment

These criteria involved three parameters: the platelet count, the timing for platelet count evaluation, the duration of response. The response to therapy was commonly defined as complete (CR), partial (PR), minimal (or any) (MR) or absent (NR) depending on platelet count reaching a pre-defined level. In the 18 articles reporting criteria for CR, this was defined as an increase of platelet count above 150×10⁹/L in the majority of cases (55.6%); for PR (18 papers) the most frequently indicated range was ≥30 to ≤150×10⁹/L; for NR, a count of ≤50×10⁹/L was chosen in 10/19 studies (52.5%). Some authors defined the doubling of the initial platelet count as an additional requirement to obtain a response. For all these types of responses, many different times to assess the platelet threshold were indicated, ranging from 2 days to 9 months from the start of therapy. Alternatively, *last control* or *the end* of the therapy was indicated. Furthermore, some authors established a minimum interval time (usually from 3 weeks to 6 months) to define the response as durable.

Chronic disease: definition (platelet threshold and timing of assessment); criteria for splenectomy, criteria for response to splenectomy

The diagnosis of chronic ITP commonly requires two criteria: the platelet threshold, defining the failure of the initial therapy, and the length of the disease. A wide range of platelet counts (≤10×10⁹/L to ≤150×10⁹/L) was indicated as threshold in the 11 papers available, similar to the values used for the assessment of the initial treatment. In 19/25 (76%) papers a minimum of 6 months of observation was required before diagnosing chronic ITP. There was a general consensus (43/48, 89% papers) indicating splenectomy in all adults with a diagnosis of chronic ITP after failure of first-line therapy or need of unacceptably high doses of steroids to maintain a *safe* platelet count. However, different platelet count values and time intervals from initial treatment to surgery (from 14 days in the most severe situations for non-responsive or early relapsing patients to 3-6 months) were indicated. Furthermore, a wide range of minimal platelet count required to carry out splenectomy safely, from ≥30 to ≥100×10⁹/L, was indicated in 7 papers.

For post-splenectomy response, in 13/24 papers (54%) CR was defined as a platelet count ≥150×10⁹/L ; PR (20 papers) was indicated within a wide range of platelet counts; a platelet count ≤50×10⁹/L was adopted to define no response in 11/16 papers (68.8%). The timing to assess the response ranged from 3 days to 6 months. Notably, mild cases, with a persistent thrombocytopenia not requiring treatment (e.g. incidentally discovered borderline thrombocytopenic subjects)[84] are not usually indicated as chronic ITP.

Criteria to define refractory disease and response to "second line" therapy

From 49 articles, a common definition of chronic refractory (or simply refractory) ITP emerged as the condition characterized by a low platelet count persisting after splenectomy and by the need of active treatment to maintain a *safe* platelet count. In 7 papers significantly different platelet cut-off values were proposed (from ≤ 20×10^9/L to ≤50×10^9/L). In a single paper, focusing on the laparoscopic splenectomy outcomes, patients with a platelet count < 100×10^9/L were considered refractory to the intervention.[12]

Discussion

The results of our critical appraisal of recent literature confirm that the authors often use very different criteria to evaluate patient's characteristics and to report treatment outcomes (Table 2). Notably, a general consensus exists only in the following three issues: the persistence of thrombocytopenia for a minimum of 6 months to diagnosis chronic ITP, the appropriateness of splenectomy in cases with chronic ITP, after failure of medical treatment or need of steroids at unacceptably high doses to maintain a durable *safe* platelet count and the definition of refractory ITP as a condition of low platelet count persisting after splenectomy and with a need for active treatment to maintain a *safe* platelet count. For all the other clinical definitions, a great heterogeneity was found, with a distinct lack of standardization in diagnosis and management, wide discrepancies in operative terminology, and uncertainty regarding platelet thresholds and timing to start treatment and to assess the efficacy of therapy. All these unresolved issues could be addressed in prospective studies that have sample size and adequate follow-up, using homogeneous and well-defined outcomes. A useful consensus should be based on sound clinical background. Firstly, the aims of treatment should be considered and agreed on.

Clinically relevant treatment outcomes should use end-points sensitive to the impact of bleeding symptoms in terms of their frequency and severity rather than to platelet count itself. Furthermore, the characteristics of other outcomes, like the quality of life, the use of health resources, and the morbidity and mortality in the different phases of the disease should also be part of the evaluation. Secondly, criteria for response to treatment should be differentiated for the various treatments (treatment-dependent criteria). For example, criteria for short-term response should be appropriate for the intra venous high dose Ig or anti-D Ig, while new criteria should be considered for the emerging thrombopoietin receptor agonists usually requiring continuous administration. By contrast, long term response criteria seem to be appropriate for splenectomy, an approach aimed at modifying the natural course of the disease.

Finally, it would be desirable to differentiate the assessment criteria with regard to the personal risk profile (patient-dependent criteria), such as age, sex, concomitant therapies, previous trauma or surgery, arterial hypertension, and bleeding diathesis. For example, a post-treatment stable platelet count of 40- 50×10^9/L may be considered a *complete* response in an old patient without other risk factors for hemorrhage, *partial* in a young patient, with very active life-style, or *minimal* in a patient with severe risk factors for bleeding, e.g. needing anticoagulant therapy. Despite the difficulties of the proposed approach, a wide consensus on critical clinical definitions and specific terminology seems a fundamental prerequisite to plan informative studies and to speak a common language in ITP.

Authorship and Disclosures

MR: conception and design of the study, literature search, interpretation of data, writing the article; SF: literature search, acquisition of data, analysis of data; FR: conception and design of the study, interpretation of data, writing and drafting the article, final approval for publication. A preliminary version of this work was presented at the 2nd Intercontinental Childhood ITP Study Group (ICIS) Expert Meeting on "Critical Issues and Future Research of ITP", September 16-18, 2006, in Yverdon-les-Bains, Switzerland, and published in part on Supplement 5 of Pediatric Blood & Cancer 2006, 47:649-745.

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