STANDARDIZATION OF BLEEDING ASSESSMENT IN IMMUNE THROMBOCYTOPENIA: REPORT FROM THE INTERNATIONAL WORKING GROUP

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Abstract

In a previous publication on new terminology, definitions and outcome criteria for immune thrombocytopenia (ITP), the International Working Group (IWG) on ITP acknowledged that response to treatment should consist of clinically meaningful endpoints, like bleeding manifestations, and that platelet count may not be the ideal parameter to capture the benefits of therapy. The IWG now proposes a consensus based ITP-specific bleeding assessment tool (ITP-BAT) with definitions and terminology consistent with those adopted for other bleeding disorders. Bleeding manifestations were grouped into three major domains: Skin (S), visible Mucosae (M) and Organs (O) with Gradation of severity (SMOG). Each bleeding manifestation is assessed at the time of examination. Severity is graded from 0 to 3 or 4, with grade 5 for any fatal bleeding. Bleeding reported by the patient without medical documentation is graded 1. Within each domain, the same grade is assigned to bleeding manifestations of similar clinical impact. The “worst bleeding manifestation since the last visit” (observation period) is graded (a suitable data-base collection form is provided). Then, the highest grade within each domain is recorded. The SMOG system provides a consistent description of the bleeding phenotype in ITP and the IWG unanimously supports its adoption and validation in future clinical studies.
INTRODUCTION

The International Working Group (IWG) on Immune Thrombocytopenia (ITP) recently described new terminology, uniform definitions and outcome criteria for the diagnosis and management of ITP in children and adults (1). These proposals were adopted in recent guidelines and consensus reports and are in widespread use (2, 3). ITP was defined as “severe” when the presence or recurrence of bleeding manifestations was sufficient to mandate treatment, regardless of the platelet count. The use of terms like “mild” or “moderate” ITP was discouraged because of their vagueness. The IWG recommendations for evaluating the effectiveness of treatments are based on the platelet count as an objective surrogate, although the group acknowledged that a platelet count threshold is inadequate as the sole parameter to make such decisions. The reason underlying this choice was the lack of standardized bleeding and quality of life (QoL) assessment tools for ITP. The IWG noted that none of the few bleeding assessment tools available in the literature could be easily adopted and/or were validated for ITP. Therefore, any further investigation focusing on bleeding events and their relationship with platelet counts or other individual attributes would be fraught with difficulties.

This document describes an ITP-specific Bleeding Assessment Tool – version 1.0 (ITP-BAT in short) based on a more precise definition of bleeding manifestations and on the grading of their severity. A standardized data collection form has also been developed in order to facilitate collection of information and communication among physicians and investigators.
METHODOLOGY

The IWG on ITP holds annual conferences during the American Society of Hematology (ASH) and European Hematology Association (EHA) meetings. In 2008 the group agreed that standardization of bleeding assessment should receive priority. During the 2010 ASH meeting in Orlando, a first half-day conference was formally convened. After a focused review of the available literature, the IWG concluded that due to the lack of robust evidence to support any specific existing scale, a consensus-based approach was preferable. The widely used World Health Organisation (WHO) scale (4) (and its many variations) designed to grade bleeding in patients with chemotherapy-induced thrombocytopenias, which has often been adopted in recent clinical trials, has limited sensitivity and accuracy when it comes to accurately describing the bleeding phenotype of ITP patients. It is prone to excessive subjective interpretations and uses broad and overlapping categories of unequal clinical intervals. Impact of bleeding at single sites versus global impact is not measurable with this scale (5). It was also concluded that none of the BATs devoted to congenital hemostatic disorders (6, 7) was entirely suitable for ITP.

Three other IWG meetings on this topic were convened during the EHA 2011 and 2012 meetings in London and Amsterdam and ASH 2011 meeting in San Diego.

The IWG concluded that a single BAT should be produced for use in both children and adults with ITP. It should be easily adapted to the different phases of the disease and amenable for use in clinical trials. The ITP-BAT should have a construction compatible with the clinical aspects of the disease in terms of content and face validity, avoid ambiguous definitions and terminology, and be usable in both a clinical and research context. In addition, the grading of severity of each bleeding manifestation should encompass few points, so that reproducibility among investigators would be enhanced. The panel therefore agreed that a standardized data collection form would be useful to
maintain consistency in reporting and for comparative studies. The ITP-BAT should be useful to define bleeding events and to make correlations with quality of life (QoL) measures, other bleeding determinants, risk factors and platelet counts, among different patients or for the same patient over the course of the disease and its different treatments. A subcommittee was assigned the duty of preparing a preliminary draft of the manuscript and supplemental material based on the progressive consensus reached among the members during face-to-face conferences and several rounds of Delphi-like questionnaires. A draft of the manuscript was approved at a conference held during the 2012 EHA meeting. Changes were subsequently implemented with the approval of all authors. Three external experts provided further review of the manuscript to ensure that the proposal was intrinsically logical, consistent, clear and applicable to ITP. None of IWG members and external reviewers received honoraria or travel support. For more detailed information, please refer to Supplemental Appendix 1 – Methodology.

LITERATURE REVIEW

An analysis of the literature was carried out by two of us (MR and RS). Papers relevant to the evaluation of bleeding manifestations in ITP were identified among those listed in the systematic literature review carried out by Ruggeri et al (8), which initially included publications available up to 2006. Papers published subsequently, up to the end of 2011, were identified using the same criteria. Papers reporting on bleeding assessment in patients with thrombocytopenia secondary to chemotherapy were also considered. For more detailed information, please refer to Supplemental Appendix 1 – Methodology. Some examples of bleeding scales are shown in Supplemental Appendix 2.
RECOMMENDATIONS

Harmonization of terminology and definitions of bleeding in ITP

One of the main aims of this proposal is to provide a terminology for hemorrhagic manifestations in ITP that integrates and is consistent with the terminology already adopted for other bleeding disorders and that is relevant for the purpose of developing an ITP-specific bleeding assessment. The IWG recognized that standard medicine textbooks differ in the terms used to describe bleeding manifestations, particularly for skin and visible mucosae, and that adherence to single definitions is limited.

As platelets are essential for primary hemostasis, bleeding in ITP results most commonly from failure to prevent leakage of blood from small blood vessels. The most frequent hemorrhagic manifestation in ITP is purpura. Purpura broadly encompasses any kind of mucocutaneous bleeding; it is commonly referred to as “dry” when bleeding is confined to the skin and “wet” when mucous membranes are also involved. The IWG recommends against the use of these terminologies because they lack precision. A more precise definition of bleeding symptoms affecting the skin and visible mucous membranes is given in table 1 and we recommend that reporting complies with this set of definitions. For other bleeding manifestations (e.g. melena, gastrointestinal bleeding, hematuria, etc.) standard definitions should be adopted. A complete list of bleeding manifestations is available in Supplemental Appendix 3, along with explanatory definitions and their relevance to ITP.

Grading severity of bleeding

Bleeding symptoms are grouped into three major domains: Skin (S), visible Mucosae (M) and Organ (and internal mucosae) (O), as shown in table 2. The table also defines the grades of severity of the various types of bleeding in each domain and is harmonized with a data collection form, suitable for database processing, which is available in
Supplemental Appendix 4. The data collection form is a guide to fill in the classification and grading in table 2. Although it can be skipped by examiners familiar with this tool, it could be useful to implement an electronic version of the ITP-BAT and for subsequent database processing.

The bleeding grade should be assigned by a physician or trained nurse at presentation and at each follow-up visit. For each type of bleeding, only the worst incident bleeding manifestation occurring during the interval since the previous evaluation should be recorded. Grading ranges from 0 to 4 for epistaxis and for bleeding in the organ domain, except ocular and intracranial bleeding (grade 0 and 2 to 4). For the remaining bleeding sites (in skin and mucosal domains) four grades (0 to 3) were deemed sufficient. Grade 5 is assigned to any fatal bleeding. The IWG recommends providing a short description of any fatal bleeding. By taking the highest grade for each domain, the SMO Grade (SMOG) index is obtained. For example, if during the period under evaluation, the highest grade is 2 for the skin domain, 2 for the mucosal domain and 0 for the organ domain, the index is S2M2O0. A major effort was made by the IWG to ensure that the different bleeding manifestations are graded consistently from the least to the most severe and that, within the same domain, an identical grade corresponds to a similar clinical impact. This consensus was based on the clinical judgment of the IWG members. For example, to receive a grade > 1, all non-open skin and non-open mucosal bleeding (petechiae, ecchymoses, subcutaneous hematomas, subconjunctival hemorrhages) should be visible and assessable at the time of visit. In fact, the IWG decided that for these types of bleeding, patient self-assessment or assessment by the patient’s general practitioner would not have sufficient accuracy and reproducibility to be reliable. Furthermore, these manifestations may remain visible for days or even weeks and be easily captured at scheduled follow up visits, even if the patient is not seen when they arise. For open-skin and open-mucosal bleeding (minor skin wounds, epistaxis, gum, bleeding from bites to lips...
and tongue or after loss/extraction of deciduous teeth) and all organ bleeding, medical records based on direct observation by the attending physician should also be included. Such medical records are acceptable to assign a grade 3 to open-skin and open-mucosal bleeding. For bleeding in the organ domain and internal mucosae, medical reports are of critical importance and should be considered for grading, as detailed in table 2.

For particular bleeding manifestations, objective diagnosis is mandatory, as specified in table 2. It is critical to consider all bleeding that occurred in the interval period, including that ongoing at the time of the visit. Residual findings of previously reported bleeding (e.g., petechiae or ecchymoses appearing blue or yellowish green and not red) should be excluded from the assessment.

**Refinement of the SMOG index**

The IWG recommends against summing up the worst manifestations in all domains to obtain a total sum score, instead of generating a SMOG index (separately reporting each of the 3 scores). The total sum score will provide little clinical relevance. For example, it is self evident that organ bleeding usually trumps bleeding manifestations in all the remaining domains. So, for example, a total sum score of 4 produced by a combination of domain grades such as S1M1O2 is certainly of more descriptive and of major clinical relevance when compared to a total sum score of 4 that may be derived from a different combination of domain grades, such as S2M2O0, where there is no organ bleeding.

For particular purposes, provided that the different domains are always treated separately, other modalities of reporting are possible with the SMOG system. For instance, all worst manifestations for each (or selected) bleeding listed in table 2 could be recorded and graded (e.g. petechiae 2, ecchymosis 1, mouth bleeding 1, epistaxis 2, and heavy menses 2). This approach might be useful for very detailed analyses e.g. to evaluate the
relationship of particular bleeding manifestations with some determinants of the disease, like platelet count, or to assess the impact on QoL or in particular for a clinical trial. The value of summing up all worst grades for all manifestations within each domain remains of uncertain utility and of ambiguous interpretation, and the IWG discourages this form of analysis. Despite its overall rarity, but considering the lifelong potential functional impairment caused by intracranial bleeding, the IWG recommends that all intracranial bleedings be reported, irrespective of their grade. For example, if a woman had S2 (subcutaneous hematoma) M2 (epistaxis) O3 (menorrhagia) and an intracranial bleeding grade 2 (post trauma, requiring hospitalization), the SMOG index is S2M2O3 (intracranial 2). If the same patient also had intracranial bleeding grade 3, the SMOG index is S2M2O3 (intracranial 3).

Averaging the grades in each domain over repeated visits in a defined period or phase of the disease could be used to evaluate improvement or worsening of the bleeding severity, either in individual patients or in a cohort of subjects.

The grading scale, the electronic version of the data-collection forms and a series of illustrative pictures taken from patients with ITP or other causes of thrombocytopenia, are available on the website of the Hematology Project Foundation (http://itpbat.fondazioneematologia.it/).

The IWG also proposed a provisional grading to assess the severity of bleeding after hemostatic challenges or surgery (table 3). This scale could be useful to guide the description of bleeding in order to identify a minimal platelet threshold that provides hemostasis for a specific procedure. Table 3 is not part of the SMOG.

A pilot study on 50 ITP patients from 5 different centers was conducted to assess the SMOG’s feasibility, the readability and lack of ambiguities and inaccuracies in the data collection forms and in understanding and applying the grading scale. Concordance
between two observers (an expert physician and a trained nurse or a young investigator), separately investigating the same patient, was evaluated in 40 cases. The time needed to complete the questionnaire ranged from 5 to 20 minutes (< 15 minutes in 45/50 cases, without considering dressing and undressing and any objective investigation required for the assessment), depending on the type and multiplicity of bleeding manifestations. This time could be significantly shortened by examiners familiar with this tool and so able to skip the data collection form and directly use table 2. The rate of concordance among observers (two for each assessment) was 100% for SMOG grading and above 80% for the single items in the various domains.

**Frequency of bleeding**

In clinical studies or trials, the bleeding assessment should be always made at pre-established intervals, even if the patient was seen or received treatment before the end of the pre-determined interval, to assure consistent assessment. The IWG acknowledged that, as a consequence, the frequency of bleeding manifestations might be underestimated, but concluded that registering all signs and symptoms irrespective of their grade was of limited utility and very demanding in practice. Moreover, by choosing a shorter interval between follow up visits, the overall bleeding picture of the patient would be captured in terms of both severity and types of signs and symptoms. The interval between visits is left to the physician’s discretion and may vary depending on phase of disease, drug tested, patient’s needs and purpose of recording. However, it is mandatory that in clinical trials, an identical between-visits-interval is chosen for the investigational and comparator arm(s). The incidence rate of worst bleeding manifestations occurring during the observation period can be normalized to patient’s exposure time. As intervals between follow up visits becomes shorter (e.g. daily) this rate will approximate the true incidence of the “signs/symptoms” under investigation.
The IWG suggests that the follow-up schedule should reflect the different phases of the disease and be adjusted to capture any significant effect on bleeding due to change in the type of treatment or dose modification. A general suggestion is that the intervals between monitoring visits range from a week to a month, depending on the context and the aim of the trial. For cohort studies investigating the natural history of the disease or the long-term efficacy of some treatments such as rituximab or splenectomy, longer intervals, e.g. from 3 months to 1 year, may be acceptable.

Assessing response to treatments and severity of disease

In its previous report (1) the IWG defined new criteria for assessing response to ITP treatments. These criteria were based on a minimal threshold platelet count and absence of bleeding. With the availability of the proposed ITP-BAT, a more precise definition of “absence of bleeding” can be provided. The IWG proposes that, for the purpose of response assessment, the single occurrence of grade 1 bleeding symptoms in the skin domain is not considered as “the presence of bleeding”. This decision was made to avoid consideration of minor symptoms, sometimes of uncertain significance or dubious relationship with ITP, which could lead to spuriously classifying patients as non-responsive while not requiring treatment based of their platelet count.

The panel also agreed that regardless of the phase of the disease, the term “severe” ITP should be used only in patients who have “clinically relevant bleeding” and that the ability to maintain a platelet count sufficient to prevent “clinically significant bleeding” could be considered as response to treatment in refractory ITP. Clinically relevant or significant bleeding was defined by the presence of symptoms at presentation sufficient to mandate treatment or by the occurrence of new bleeding symptoms requiring additional therapeutic intervention with a different platelet-enhancing agent or an increase in dose of current
therapy. This operational definition can now be more precisely defined using the proposed ITP-BAT. The IWG agreed that a bleeding manifestation can generally be labeled as “severe or clinically relevant” if it is grade 3 for skin and 2 or higher for mucosal domains and/or higher than 1 for organ domain (S>2 and/or M>1 and/or O>1).

For the purpose of classification and potential comparison, all bleedings graded at least 3 for mucosal and organ domains (irrespective of the grade in the skin domain) can generally be considered to correspond to bleeding previously classified as major/severe in the WHO scale. No other particular SMOG combination has been linked to descriptive terms like “mild” or “moderate” ITP. In particular, any proposed SMOG combination for the purpose of prognostication or decision-making should be validated by prospective studies.

CONCLUSIONS

Several BATs specific for ITP or other thrombocytopenias have been proposed (5), but so far none has gained sufficient popularity or consensus for widespread adoption (see Supplemental Appendix 2). The most widely used scale dates back to 1981, stemming from a WHO initiative (4). It was produced as a recommendation for the standardization of reporting acute and subacute toxicity related to cancer treatment. Grading was based on clinical appreciation of the severity of bleeding manifestations. A recommendation was also made to avoid attaching any clinical significance to a particular grade (e.g. debilitating and not life-threatening). In particular, hemorrhage was graded 0 (none), 1 (petechiae), 2 (mild blood loss), 3 (gross blood loss), 4 (debilitating blood loss). This scale was used in recent registration and extension studies with eltrombopag and, slightly modified to include fatal cases in similar studies with romiplostim (9-12). While fortunately major bleeding in ITP is very infrequent, it is possible that the lack of sensitivity and standardization in bleeding assessment when these scales are employed may have contributed to the failure
of these studies to demonstrate a significant reduction in major bleeding compared to placebo (13).

The IWG concluded that none of the few scoring systems available in the literature can be adopted as a simple, reproducible and clinically meaningful tool to describe the bleeding manifestations of ITP and unanimously decided that a new system based on the consensus of clinicians expert in adult and pediatric ITP should be proposed.

Two basic aspects characterize the proposed ITP-BAT: the enumeration and precise definition of the bleeding manifestations relevant to ITP (tables 1 and 2) and the production of a scale to grade their severity (table 2).

To overcome the intrinsically arbitrary nature of any system of grading, the IWG agreed that grading of bleeding severity should be grounded on the highest consensus within the panel when assigning identical clinical importance to a particular bleeding manifestation. Furthermore, skin bleeding, although of high personal impact, is in general less dangerous than bleeding from mucosae, which may require blood transfusion, and organ bleeding is the most severe as it may potentially lead to major functional impairment or a life threatening situation. The IWG concluded that these three anatomical domains should be considered separately (table 2). For the sake of simplicity and consistency, the highest grade in each domain during the period of observation should be indicated in the SMOG index. However, as discussed above, alternative modalities of reporting are possible. The SMOG alpha-numeric system can be easily adapted to an electronic database, with an automatic calculation of grading and bleeding score from patients’ data collection forms. This system could also serve as a template for similar BATs to be used in other clinical situations characterized by thrombocytopenia.

The IWG recommends the adoption of the ITP-BAT v1.0 in future clinical studies investigating the effectiveness of old and new treatments. The ability of the SMOG format
to describe bleeding manifestations in terms that are amenable to statistical analysis may also lend itself to investigations involving the natural course of the disease. To exemplify, the S, M and O components could be adopted to investigate the correlation between bleeding manifestations and platelet counts, to the quality of life outcomes in prospectively evaluated cohorts, or to explore the impact of additional risk factors on the severity and type of bleeding.

This tool will require validation by appropriately designed, prospective clinical studies before widespread adoption in clinical practice. Further modifications of the ITP-BAT v1.0 are envisaged, based on the outcome of such studies and of other data reported. The recent finding that a simple scoring system based primarily on physical examination and grading of severity (14, 15) (see also Supplemental Appendix 2) showed a linear relationship between increased scores at presentation and subsequent failure to “adequately” respond to romiplostim (14) suggests that additional prospective studies will help determine whether the proposed ITP-BAT can also be used in decision making or in prognostication.
ACKNOWLEDGEMENTS

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A dedicated website where interested people will be able to see a series of illustrative pictures and download the grading scale and the electronic version of the data-collection forms is available at http://itpbat.fondazioneematologia.it/.

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AUTHORSHIP

Contribution: F.R. coordinated the project, chaired the meetings and wrote the manuscript; M.M., T.G., and R.S. wrote the manuscript; M.R. acted as scientific secretariat of the meetings and wrote the manuscript; J.B.B., D.B.C., A.G., and R.K. contributed to specific parts of the manuscript; V.B., N.C., B.G., P.I., M.K., T.K., H.L., M.G.M., A.N., I.P. and A.T. were active members of the International Working Group. All reviewed the final version of the manuscript and gave their approval.

CONFLICT OF INTEREST

F.R. is member of advisory boards and speaker for Amgen, GlaxoSmithKline, Eisai, LFB.
M.M. is member of advisory boards for Amgen and GlaxoSmithKline and received research funding from Roche. He participated as a speaker to symposia for Amgen, GlaxoSmithKline, Roche and Bristol Myers Squibb.
T.G. is consultant for Amgen, Symphogen, GlaxoSmithKline.
M.R. received honoraria from Amgen Italy and GlaxoSmithKline Italy for speaking engagements.
V.B. pending
J.B.B. receives clinical research support from the following companies: Amgen, Cangene, GlaxoSmithKline, Genzyme, IgG of America, Immunomedics, Ligand, Eisai, Inc, Shionogi and Sysmex. His family owns stock in Amgen and GlaxoSmithKline. He has participated in Advisory Boards for Amgen, GlaxoSmithKline, Ligand, Shionogi, Symphogen and Eisai. He also had a one day consult with Portola.
D.B.C. is a member of medical advisory boards for Amgen, GlaxoSmithKline and Eisai.
N.C. received honoraria from Amgen and GlaxoSmithKline for speaking at educational meetings and consultancy work.
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R.K. pending
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H.L. is consultant for Bristol Myers Squibb, Eisai, Janssen (J&J) and Sanofi and received research support from Bristol Myers Squibb, Eisai, GlaxoSmithKline and Sanofi
M.G.M. is a consultant for Amgen and GlaxoSmithKline.
A.N. acted as consultant for Amgen, GlaxoSmithKline and Pangenetics. He participated in advisory boards and/or as a speaker at medical education events supported by Amgen, Baxter, Celgene, GlaxoSmithKline and Roche and received research support from Amgen, Eisai, Genetech and GlaxoSmithKline.
I.P. is member of advisory boards and speaker for Amgen and GlaxoSmithKline and received an unrestricted research grant from GlaxoSmithKline
A.T. None
R.S. has served as a consultant for Amgen, GlaxoSmithKline, and Suppremol and has participated on advisory boards and/or as a speaker at medical education events supported by Amgen, GlaxoSmithKline, Nycomed, Symphogen, Novo, Bayer, and Baxter.
REFERENCES


Table 1. Definition of bleeding manifestations based on physical examination

<table>
<thead>
<tr>
<th>Site of bleeding</th>
<th>Manifestation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin (epidermis and dermis)</td>
<td>Petechiae</td>
<td>Red (recent) or purplish (a few days old) discoloration in the skin with a diameter between 0.5 mm to 3 mm that does not blanche with pressure and is not palpable</td>
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<tr>
<td></td>
<td>Ecchymosis (purpuric macule, bruises or contusions)</td>
<td>Flat, rounded or irregular, red, blue, purplish or yellowish green patch, larger than a petechia. Elevation indicated spreading of an underlying hematoma into the superficial layers of the skin</td>
</tr>
<tr>
<td>Skin (subcutaneous tissue)</td>
<td>Hematoma</td>
<td>Bulging localized accumulation of blood often with discoloration of overlying skin</td>
</tr>
<tr>
<td>Visible mucous membranes</td>
<td>Petechiae, purpuric macules and ecchymosis</td>
<td>As for skin</td>
</tr>
<tr>
<td></td>
<td>Bulla, vesicle and blister</td>
<td>Visible raised, thin-walled, circumscribed lesion containing blood. Each bulla is larger than a vesicle (&lt; 5 mm). Bullae, vesicles and blisters should be counted together as bulla</td>
</tr>
<tr>
<td></td>
<td>Epistaxis</td>
<td>Any bleeding from the nose—may be anterior or posterior and unilateral or bilateral</td>
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<td></td>
<td>Gingival bleeding</td>
<td>Any bleeding from the gingival margins</td>
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<td></td>
<td>Subconjunctival hemorrhage</td>
<td>Bright red discoloration underneath the conjunctiva at onset; may assume the appearance of an ecchymosis over time</td>
</tr>
<tr>
<td>Muscles and soft tissues</td>
<td>Hematoma</td>
<td>Any localized collection of blood visible, palpable or revealed by imaging. May be dissect through fascial planes</td>
</tr>
</tbody>
</table>
Table 2. Grading of bleeding symptoms at presentation and at each subsequent evaluation

<table>
<thead>
<tr>
<th>Type of bleeding</th>
<th>GRADES BASED ON THE WORST INCIDENT EPISODE SINCE LAST VISIT</th>
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<tbody>
<tr>
<td></td>
<td>0</td>
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<tr>
<td>SKIN</td>
<td></td>
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<tr>
<td>Petechiae (does not include steroid–induced or senile purpura)</td>
<td>[ ] No</td>
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<tr>
<td></td>
<td>[ ] Any number if reported by the patient</td>
</tr>
<tr>
<td>Ecchymoses</td>
<td>[ ] None or up to 2 in the same body area, but smaller than a patient’s palm-sized area, if a) spontaneous or b) disproportionate to trauma/constriction</td>
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<tr>
<td>Condition</td>
<td>[ ] Yes or No</td>
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<tr>
<td>-----------------------------------</td>
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<tr>
<td>Subcutaneous hematomas</td>
<td>[ ] No</td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>Bleeding from minor wounds(^6)</td>
<td>[ ] No</td>
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<tr>
<td>MUCOSAL</td>
<td>[ ] No</td>
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<tr>
<td>Epistaxis(^7)</td>
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<tr>
<td>Oral cavity – gum bleeding</td>
<td>No</td>
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<td>----------------------------</td>
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</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral cavity – hemorrhagic bullae or blisters</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral cavity – bleeding from bites to lips &amp; tongue or after deciduous teeth loss</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Subconjunctival hemorrhage (not due to conjunctival disease)</td>
<td>[] No</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>ORGAN (and internal mucosae)</td>
<td></td>
</tr>
<tr>
<td>GI bleeding not explained by visible mucosal bleeding or lesion: Hematemesis, Melena, Hematochezia, Rectorrhagia</td>
<td>[] No</td>
</tr>
<tr>
<td>Condition</td>
<td>[ ] No</td>
</tr>
<tr>
<td>--------------------</td>
<td>--------</td>
</tr>
<tr>
<td>Lung bleeding</td>
<td>[ ] No</td>
</tr>
<tr>
<td>Hematuria</td>
<td>[ ] No</td>
</tr>
<tr>
<td>Menorrhagia</td>
<td>[ ] No</td>
</tr>
</tbody>
</table>
### Intramuscular hematomas

- **(compared to pre-ITP or to a phase of disease with normal platelet count)**
  - Pads or tampons in last cycle compared to pre-ITP or to a phase of disease with normal platelet count
  - Score $> 100$ using PBAC in the last cycle, if normal score in pre-ITP cycles or in a phase of disease with normal platelet count
- **(requiring hospital admission or endometrial ablation)**
  - Requiring combined treatment with antifibrinolytics and hormonal therapy or gynecological investigation (either at this visit or described in a medical report)
  - Menorrhagia more frequently than every 2 hrs. or clot and flooding
  - Transfusion or Hb drop $> 2\text{g/dL}$

### Hemarthrosis

- **(compared to pre-ITP or to a phase of disease with normal platelet count)**
  - Post trauma, diagnosed at this visit, if judged disproportionate to trauma
  - Spontaneous, diagnosed at this visit
  - Spontaneous or post trauma (if judged disproportionate to trauma), diagnosed at this visit and requiring hospital admission or surgical intervention
- **(requiring hospital admission or endometrial ablation)**
  - Transfusion or Hb drop $> 2\text{g/dL}$

### Infrapatellar bursitis

- **(only if diagnosed by a physician with an objective method)**
  - No
  - Diagnosed at this visit, function conserved or minimally impaired
  - An equivalent episode if described in a medical report

### Intramuscular hematomas

- **(only if diagnosed by a physician with an objective method)**
  - No
  - Diagnosed at this visit, if judged disproportionate to trauma
  - An equivalent episode if described in a medical report

### Hemarthrosis

- **(only if diagnosed by a physician with an objective method)**
  - No
  - Diagnosed at this visit, function conserved or minimally impaired
  - An equivalent episode if described in a medical report

### Intramuscular hematomas

- **(only if diagnosed by a physician with an objective method)**
  - No
<table>
<thead>
<tr>
<th>Ocular bleeding (only if diagnosed by a physician with an objective method)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Any post trauma vitreous or retinal hemorrhage involving one or both eyes with or without impaired/blurred vision present at this visit if judged disproportionate to trauma</td>
<td>Spontaneous vitreous or retinal hemorrhage involving one or both eyes with impaired/blurred vision present at this visit</td>
<td>Spontaneous vitreous or retinal hemorrhage with loss of vision in one or both eyes present at this visit</td>
</tr>
<tr>
<td></td>
<td>An equivalent episode if described in a medical report</td>
<td>An equivalent episode if described in a medical report</td>
<td>An equivalent episode if described in a medical report</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intracranial bleeding: intracerebral, intraventricular, subarachnoidal, subdural,</th>
<th>No</th>
<th>Any post trauma event requiring hospitalization</th>
<th>Any spontaneous event requiring hospitalization in presence of an underlying</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>An equivalent episode if described in a medical report</td>
<td>An equivalent episode if described in a medical report</td>
<td>An equivalent episode if described in a medical report</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Extradural (only if diagnosed with an objective method at the visit or described in a medical report provided by the patient)</th>
<th>Intracranial lesion</th>
<th>Intracranial lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other internal bleeding: hemoperitoneum, hemopericardium, hemothorax, retroperitoneal bleeding, hepatic and splenic peliosis with organ rupture, retroorbital bleeding, metrorrhagia, etc. (only if diagnosed with an objective method at the visit or described in a medical report provided by the patient)</td>
<td>[ ] No</td>
<td>[ ] Any event requiring hospitalization &lt; 48 hrs.</td>
</tr>
</tbody>
</table>
Grading is based on physical examination at the time of the visit by the physician or expert nurse or on patient’s history supplemented by available medical reports. Bleeding manifestations reported by the patient but not visible at the time of data collection are graded 1. Grade 5 is assigned to fatal bleeding.

In addition to the guidance offered in the table, it is advised to refer to the Supplemental Appendix 3 for more detailed definitions and to the data collection form in Supplemental Appendix 4. Illustrative examples are available on the website of the Hematology Project Foundation (http://itpbat.fondazioneematologia.it/)

To receive a grade > 1, all non-overt skin and non-overt mucosal bleeding (petechiae, ecchymoses, subcutaneous hematomas, vescicles/bullae subconjunctival bleeding) should be visible at the time of visit for grading by the physician or expert nurse taking the history.

For bleeding from minor wounds and overt-mucosal bleeding (epistaxis, gum, bleeding from bites to lips & tongue or after deciduous teeth loss/extraction) and all organ bleeding, a medical record describing the symptom or indicating a specific intervention/prescription should be also taken into account for grading.

Requirement for ITP specific treatments and antifibrinolytics (apart from menorrhagia) was not considered for grading, due to their subjective nature and their adoption not only to control actual bleeding but also to reduce the “risk” of impendent or future bleeding (see supplemental appendix 1).

1 In case of patients examined for the first time, all types of bleeding occurring at the visit and in the 15 days preceding the visit should be considered.

2 Each type of bleeding should be graded based on the worst bleeding manifestation that occurred during each observation period or in the 15 days preceding the first visit.

3 Patient’s own palm size is commonly considered to be proportional to body surface area. Palm = The inner surface of the hand stretching between the distal crease of the wrist and the bases of the fingers (fingers surface excluded).

4 Body areas include: face, neck, right and left upper limbs (considered separately), right and left lower limbs (considered separately), trunk, abdomen, and recumbent areas (for the ambulatory patient means the area below the knees).

5 Bleedings considered proportionate to trauma/constriction on a clinical ground should not be reported for skin domain

6 Minor wound means superficial skin cuts (e.g., by shaving razor, knife, or scissors).

7 Epistaxis and gum bleeding are also reported in some normal subjects. Thus, a critical judgment is required in grading these manifestations: they should be reported only if judged more severe when compared with pre-ITP bleeding, if any.

8 Any endoscopic investigations should be considered for grading only if performed for therapeutic purpose and not solely for diagnostic purpose.

9 In girls at menarche grade 1 cannot be assigned, lacking comparison with previous cycles.

10 Intracranial bleeding should always be reported, irrespective of its grade. For example, if a woman had S2 (subcutaneous hematoma) M2 epistaxis) O3 (menorrhagia) and an intracranial bleeding grade 2 (post trauma, requiring hospitalization), the SMOG index is S2M2O3
intracranial 2). If the same patient also had intracranial bleeding grade 3, the SMOG index is S2M2O3 (intracranial 3) (see text)

Table 3. Reporting of bleeding after hemostatic challenges or surgery°.

<table>
<thead>
<tr>
<th>Type of Intervention/Procedure</th>
<th>Grades of Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Permanent or deciduous tooth extraction^</td>
<td>Platelet counts before and during</td>
</tr>
<tr>
<td>Date</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>[ ] No</td>
</tr>
<tr>
<td></td>
<td>[ ] No</td>
</tr>
<tr>
<td></td>
<td>[ ] No</td>
</tr>
<tr>
<td></td>
<td>[ ] No</td>
</tr>
</tbody>
</table>

Invasive procedures/Surgery

Date

[ ] _________ Date ________
[ ] _________ Date ________
[ ] _________ Date ________

[ ] No
[ ] Present but not requiring revisiting or protracted observation
[ ] Requiring return to operating room or causing organ damage or occurring in critical areas (e.g. CNS)
[ ] Requiring critical care or directly contributing to death
<table>
<thead>
<tr>
<th>Parturition Date __________</th>
<th>[ ] _______ Date _______</th>
<th>[ ] No</th>
<th>[ ] Present</th>
<th>[ ] Requiring iron therapy or prolonged in hospital stay</th>
<th>[ ] RBC transfusion or Hb drop &gt; 2g/dL</th>
<th>[ ] Requiring critical care or surgical intervention</th>
</tr>
</thead>
</table>

*These criteria are proposed as provisional and are not used to calculate the patient’s SMOG and are provided to help in the description of bleeding after hemostatic challenges.

^Spontaneous loss of a deciduous tooth is considered in table 2.
*Biopsy, epidural anesthesia, catheter insertion, etc.
Standardization of bleeding assessment in immune thrombocytopenia: report from the International Working Group

Francesco Rodeghiero, Marc Michel, Terry Gernsheimer, Marco Ruggeri, Victor Blanchette, James B. Bussel, Douglas B. Cines, Nichola Cooper, Bertrand Godeau, Andreas Greinacher, Paul Imbach, Mehdi Khellaf, Robert J. Klaassen, Thomas Kühne, Howard Liebman, Maria Gabriella Mazzucconi, Adrian Newland, Ingrid Pabinger, Alberto Tosetto and Roberto Stasi

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